

The Relation of C-Reactive Protein Levels to Total and Cardiovascular Mortality in Older U.S. Women

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PURPOSE: To determine whether serum C-reactive protein levels, a sensitive indicator of inflammation, are associated with the risk of cardiovascular mortality among older women.

METHODS: We conducted a case-cohort study within the Study of Osteoporotic Fractures, a population-based study involving 9704 women aged ≥ 65 years from four U.S. centers. We randomly selected 400 women from the entire cohort plus an additional random sample of 92 women from the 1125 women in the cohort who had died during the first 6 years of follow-up. Baseline serum C-reactive protein levels were measured using a high-sensitivity immunoassay. Cause-specific mortality was ascertained by review of death certificates and hospitalization records. Multivariable Cox proportional hazards regression was used to determine the association between C-reactive protein levels and cardiovascular mortality.

RESULTS: During 6 years of follow-up, 150 of the 492 women

died, including 52 who died of cardiovascular disease. After adjusting for potential confounders, women with C-reactive protein levels in the highest quartile (>3.0 mg/L) had a 8.0-fold (95% confidence interval [CI]: 2.2 to 29) greater risk of cardiovascular mortality than those in the lowest quartile (≤ 1.0 mg/L). The association remained strong in women who did not smoke or take estrogen, and when early deaths were excluded. Women who smoked and whose C-reactive protein levels were above the first quartile had a very high risk of cardiovascular mortality (relative risk [RR] = 13; 95% CI: 3.4 to 47). C-reactive protein levels were not associated with noncardiovascular mortality (RR = 0.92; 95% CI: 0.4 to 2.1).

CONCLUSION: C-reactive protein level was an independent predictor of cardiovascular mortality in older women. *Am J Med.* 2003;114:199–205. ©2003 by Excerpta Medica Inc.

Conventional risk factors explain approximately half of the variability in the risk of cardiovascular events (1–3) but are less useful in older women, in whom lipid levels are less strongly associated with atherosclerosis (4). C-reactive protein, a sensitive marker of inflammation, has been proposed as an independent risk factor for cardiovascular disease (5,6). Both laboratory and pathology data suggest that inflammation is important in atherosclerosis (7). Previous studies have demonstrated an association between elevated C-reactive protein levels and myocardial infarction in patients with stable or unstable angina (8–10), as well as in healthy men (11).

Women and older patients have frequently been excluded from studies of cardiovascular disease. The first two major reports of the relation between C-reactive protein level and cardiovascular disease involved men (11,12), although the association has been confirmed in both men and women (13,14). Studies involving women have focused on middle-aged women and nonfatal outcomes (15). In women, however, most cardiovascular deaths occur in the older age ranges. We hypothesized that older women with elevated C-reactive protein levels would be at an increased risk of dying of cardiovascular disease, but not other causes. We tested this hypothesis in older women participating in the Study of Osteoporotic Fractures, a population-based cohort study.

METHODS

Study Sample

We enrolled 9704 women living in four geographic regions (Baltimore, Maryland; Pittsburgh, Pennsylvania; Minneapolis, Minnesota; and Portland, Oregon) between September 1986 and October 1988. The women were 65 years or older, ambulatory, and living independently at enrollment. African American women were excluded because of their low risk of hip fracture. The institutional review boards at the four clinical sites and the coordinating center approved the study protocol. All participants gave informed consent.

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Data Collection

All participants underwent an extensive examination at enrollment. The baseline questionnaire obtained information on age, education, health status, use of certain medications (e.g., diuretics, estrogens, steroids), use of alcohol and tobacco products, and physical activity. Blood pressure measurements were taken in the right brachial artery according to a standard protocol (16). Height and weight were measured, and body mass index was calculated as the weight in kilograms divided by the square of the height in meters. Waist and hip girths were measured with a steel tape, and the ratio of waist to hip measurements was used as an indicator of body fat distribution. Hypertension was defined as systolic blood pressure >160 mm Hg, diastolic blood pressure >90 mm Hg, or the use of diuretics.

Blood was collected between 8:00 AM and 2:00 PM after fasting or a nonfat breakfast. Serum was stored for up to 1 week at -20°C and shipped on dry ice to Biomedical Research Institute (Rockville, Maryland) for subsequent storage in liquid nitrogen (-190°C). All assays were performed blinded to vital status. C-reactive protein level was measured by a high-sensitivity enzyme-linked immunosorbent assay based on purified protein and polyclonal anti-C-reactive protein antibodies (Calbiochem, La Jolla, California) (17). This assay was the standard against which the major commercial high-sensitivity C-reactive protein assay was compared (18). The C-reactive protein assay was standardized according to the World Health Organization First International Reference Standard and had a sensitivity of 0.08 mg/L, with a standard reference measure between 0.05 and 2.5 mg/L. Serum total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels were measured using an automated chemistry analyzer; low-density lipoprotein (LDL) cholesterol levels were estimated using the Friedewald formula. Fructosamine levels were measured using a standard calorimetric assay (Endocrine Sciences, Calabasas Hills, California); the upper limit of normal was 285 $\mu\text{mol/L}$.

We obtained the hospital records and death certificates for all women who died. Cause of death was assigned by the clinical site principal investigator and reviewed by one of the coordinating center investigators (WB). In cases of disagreement, the coordinating center adjudication was final. Cause of death, coded according to study protocol using the *International Classification of Diseases, Ninth Revision, Clinical Modification*, was classified as due to cardiovascular diseases (codes 394 to 440), coronary heart disease diseases (codes 410 to 414), or stroke (codes 431 to 438). Mortality data were 99% complete through 6 years of follow-up.

Selection of Cases and Controls

A case-cohort sampling design was used for efficiency (19,20). From the cohort of 9704 women, we randomly

selected 400 women, of whom 58 had died. An additional 92 women were randomly selected from the 1125 women who had died during the first 6 years of follow-up. Fifty-two of the 150 deaths in the final sample were due to cardiovascular disease.

Statistical Analysis

We compared cases and noncases using the Student *t* test for continuous variables and the chi-squared test for categorical variables. Because C-reactive protein values were highly skewed, the median was used as a measure of central tendency, and differences in medians were evaluated using the Wilcoxon rank sum test.

We used Cox proportional hazards regression, modified to account for the case-cohort sampling design (19), to study the association between C-reactive protein levels and cardiovascular mortality. Results are presented as relative risks and 95% confidence intervals. Proportionality assumptions were checked using log-log plots and interaction terms with time to death. C-reactive protein levels were analyzed by quartiles (≤ 1.0 mg/L, 1.1 to 1.8 mg/L, 1.9 to 3.0 mg/L, >3.0 mg/L) in the primary analysis to allow for potential nonlinear associations between C-reactive protein and time to death. Our analysis suggested a threshold effect at the first quartile of C-reactive protein. A dichotomous variable at this cutoff was used for further analyses. Covariates known to be associated with cardiovascular disease were included in multivariable models as potential confounders. Cardiovascular mortality rates were calculated as the number of deaths divided by the person-years of follow-up adjusted for the case-cohort design.

Subgroup analyses were performed to assess whether the association of C-reactive protein level with cardiovascular mortality could be explained by covariates known to increase C-reactive protein levels. We excluded women who smoked, to address the hypothesis that C-reactive protein is primarily a surrogate for smoking (21,22). Women taking estrogen were also excluded in a second subgroup analysis, because estrogens have been reported to increase C-reactive protein levels (23,24), and hormone therapy may affect cardiovascular disease event rates. Because elevated C-reactive protein levels may only identify women who were ill and at an increased risk of dying in the short term, subgroup analyses included women who reported good or excellent health and excluded deaths occurring within 2 and 4 years of the baseline examination. We also analyzed the association of C-reactive protein level with noncardiovascular mortality to assess whether the association was specific to cardiovascular disease or all-cause mortality. Analyses were performed using STATA Release 7 (StataCorp, College Station, Texas). A *P* value <0.05 (two-sided) was considered statistically significant.

Table 1. Baseline Characteristics of Study Participants

Characteristic	Alive (n = 342)	Deaths (n = 150)	Cardiovascular Deaths (n = 52)
	Number (%) or Mean \pm SD		
Age (years)	71.5 \pm 5	74.9 \pm 6*	75.4 \pm 6*
Education (>12 years)	128 (37)	42 (28) [†]	10 (19) [‡]
Rated health as good or excellent	291 (85)	108 (72)*	36 (69) [‡]
Smoking	29 (8)	21 (14)	10 (19) [†]
Diabetes	28 (8)	19 (13)	9 (17) [†]
Hypertension	125 (37)	74 (49) [‡]	31 (60) [‡]
Estrogen use	33 (10)	14 (10)	1 (2)
Systolic blood pressure (mm Hg)	141 \pm 20	149 \pm 24*	154 \pm 24*
Diastolic blood pressure (mm Hg)	77 \pm 10	78 \pm 11	80 \pm 13
LDL cholesterol (mg/dL)	154 \pm 39	155 \pm 41	163 \pm 31
HDL cholesterol (mg/dL)	53 \pm 16	50 \pm 16	51 \pm 13
Fructosamine (μ mol/L)	254 \pm 37	261 \pm 56	278 \pm 78
Smoking (pack-years)	10 \pm 19	16 \pm 22 [‡]	13 \pm 20
Body mass index (kg/m ²)	26.7 \pm 4.7	26.2 \pm 5.3	26.1 \pm 4.4
Waist-to-hip ratio	0.81 \pm 0.07	0.83 \pm 0.06 [‡]	0.84 \pm 0.06 [‡]

* $P < 0.001$ compared with patients who were alive.

[†] $P < 0.05$ compared with patients who were alive.

[‡] $P < 0.01$ compared with patients who were alive.

HDL = high-density lipoprotein; LDL = low-density lipoprotein.

RESULTS

Among the 52 women in the final sample who died of cardiovascular disease, 22 of the deaths were due to coronary heart disease and 16 were due to stroke. Women who died of cardiovascular disease were older, had less formal education, and reported being in worse health compared with women who were alive after 6 years of follow-up (Table 1). Women who died of cardiovascular disease were also more likely to smoke, have hypertension, and have diabetes, and were less likely to be taking estrogen. Cardiovascular mortality was not associated with HDL or LDL cholesterol levels, but it was strongly associated with waist-to-hip ratio and systolic blood pressure.

Median C-reactive protein levels were higher in women with a higher body mass index and waist-to-hip ratio and in those receiving hormone replacement therapy (Table 2). Women who smoked, however, did not have elevated levels. Levels were higher in women who died of vascular disease than in women who survived at least 6 years (2.1 mg/L vs. 1.8 mg/L, $P = 0.06$), and greatest in women who died of coronary heart disease (2.4 mg/L vs. 1.8 mg/L, $P = 0.05$). Women who died of noncardiovascular diseases or cancer did not have elevated C-reactive protein levels.

Women in the upper three quartiles of C-reactive protein (1.1 to >3.0 mg/L) had a threefold greater risk of dying from cardiovascular disease compared with women in the lowest quartile (≤ 1.0 mg/L) (Figure). Mortality ranged from 8 per 1000 person-years for women in the lowest quartile to 25 per

1000 person-years for women in the highest quartile. Adjusting for known cardiovascular risk factors did not weaken the association between C-reactive protein level and cardiovascular mortality (Table 3). The adjusted relative risk of cardiovascular death in women with a C-reactive protein level in the upper three quartiles was 6.0 (95% confidence interval [CI]: 2.0 to 18; $P = 0.001$) compared with women in the lowest quartile.

Noncardiovascular Mortality

C-reactive protein levels were not associated with the risk of noncardiovascular mortality ($P > 0.1$) before or after adjusting for other risk factors in multivariable-adjusted models (Table 3).

Smoking

The association of C-reactive protein level with cardiovascular mortality was unchanged and remained statistically significant when current smokers were excluded from the analysis (Table 4), and after adjusting for the total pack-year history of cigarette smoking and the number of cigarettes smoked daily.

Estrogen Therapy

Adding estrogen use to the model modestly increased the strength of the relation between C-reactive protein and cardiovascular mortality. However, the relative risk remained large and statistically significant when the analysis was limited to women not using estrogen replacement therapy (Table 4).

Table 2. Baseline Concentration of C-Reactive Protein, by Selected Characteristics

Characteristic	C-Reactive Protein (mg/L)	P Value*
	Median (Interquartile Range)	
Body mass index		<0.0001
Below median (<26.2 kg/m ²)	1.2 (0.7–2.0)	
Above median	2.4 (1.6–3.7)	
Waist-to-hip ratio		<0.0001
Below median (<0.81)	1.4 (0.8–2.6)	
Above median	2.0 (1.4–3.3)	
Estrogen use		0.05
No	1.7 (1.0–2.9)	
Yes	2.1 (1.3–3.2)	
Smoking		0.65
Never	1.7 (1.0–2.9)	
Past	1.8 (1.0–3.3)	
Current	1.5 (1.0–2.7)	

* Using the Mann-Whitney U test.

Current Health Status by Self-Report or Early Death

The relative risk of cardiovascular death among women with elevated C-reactive protein levels who reported their health to be good or excellent was 7.4 (95% CI: 1.9 to 29). The magnitude of the risk relation remained stable and

statistically significant after excluding subjects who died or who were lost to follow-up during the first 2 and 4 years (Table 4).

DISCUSSION

We found that minimally elevated serum C-reactive protein levels were associated with increased mortality from cardiovascular disease for at least 6 years among older women. This association was consistent in women who did and did not smoke. Adjustment for conventional risk factors strengthened the association modestly.

These results are similar to those of previous studies involving men and women (11–15), even though our study comprised the oldest cohort of women and focused on cardiovascular cause of death. In the Multiple Risk Factors Intervention Trial (12), C-reactive protein levels were associated with mortality due to coronary heart disease, but not myocardial infarction; whereas the Physician’s Health Study reported associations only with first myocardial infarction (11). The Cardiovascular Health Study reported an increased risk of new cardiovascular events (angina or myocardial infarction) in older women with C-reactive protein levels >2.78 mg/L, but not in older men (13); a similar observation was made in the Women’s Health Study (15). The Iowa 65+ Rural Health Study found an increased risk of all-cause mortality by quartile of C-reactive protein, with similar trends for

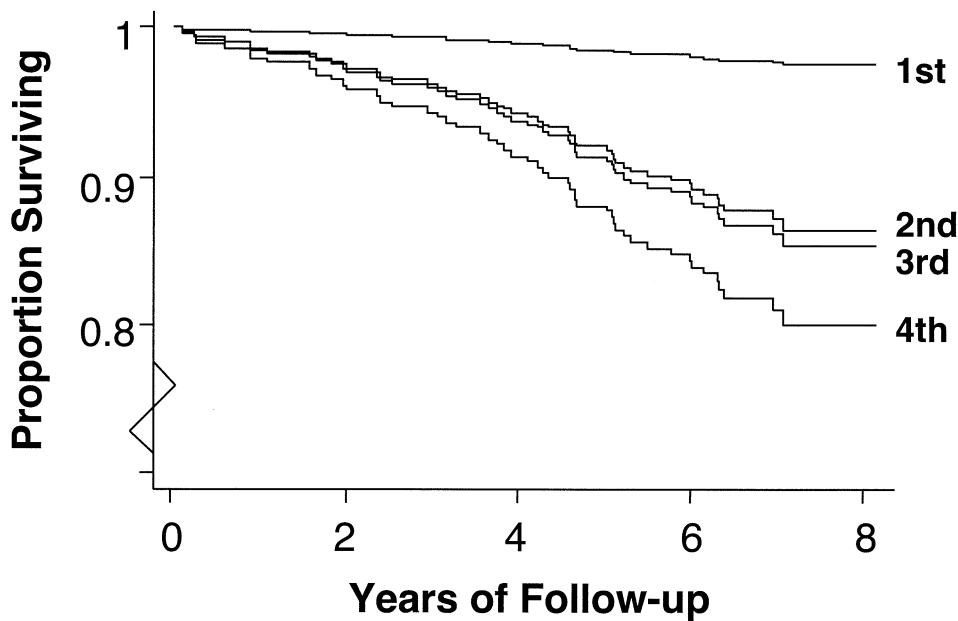


Figure. Survival curves by quartile of C-reactive protein, adjusted for age, hypertension, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, diabetes, smoking, body mass index, estrogen use, education level, and clinical site. 1st = C-reactive protein ≤1.0 mg/L; 2nd = C-reactive protein 1.1 to 1.8 mg/L; 3rd = C-reactive protein 1.9 to 3.0 mg/L; 4th = C-reactive protein >3.0 mg/L.

Table 3. Risk of Death, by C-Reactive Protein Level*

Quartile of C-Reactive Protein (Range in mg/L)	Cardiovascular Mortality				Noncardiovascular Mortality				Total Mortality			
	No. of Deaths [†]	Incidence (Per 1000 Person-Years)	Relative Risk (95% Confidence Interval)	P Value	No. of Deaths	Incidence (Per 1000 Person-Years)	Relative Risk (95% Confidence Interval)	P Value	No. of Deaths	Incidence (Per 1000 Person-Years)	Relative Risk (95% Confidence Interval)	P Value
1st (≤1.0)	5	8	1.0	—	30	46	1.0	—	35	54	1.0 (—)	—
2nd (1.1–1.8)	15	22	5.3 (1.7–17)	0.004	18	27	0.6 (0.3–1.3)	0.2	33	49	1.2 (0.6–2.1)	0.6
3rd (1.9–3.0)	14	23	6.1 (1.7–21)	0.005	18	29	0.6 (0.3–1.3)	0.2	32	52	1.2 (0.6–2.2)	0.7
4th (>3.0)	16	25	8.0 (2.2–29)	0.002	32	49	1.0 (0.5–2.1)	1.0	48	73	1.7 (0.8–3.3)	0.1

* Adjusted for age, hypertension, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, diabetes, smoking, body mass index, estrogen use, education level, and clinical site.

† Two patients who died were not included because of incomplete data. These 2 patients were also excluded from the adjusted analyses of total mortality.

both cardiovascular and noncardiovascular etiologies (14).

The upper limit of the first quartile of C-reactive protein in our study was similar to that in most studies (12–15), except the Physician’s Health Study (11), in which the quartile bounds may have reflected the younger age of that cohort. We found that women in the lowest quartile had a significantly lower risk of death from cardiovascular disease than those in the upper three quartiles. Low C-reactive protein levels indicate a low level of inflammation and may represent plaques that are less prone to rupture. Hence, it is not known whether these women will receive equivalent benefit from aggressive treatment with medications that reduce C-reactive protein levels (25–27), such as aspirin (11) and statins (28), as do women with higher levels.

The pathophysiology underlying the relation between C-reactive protein levels and cardiovascular disease is not understood. It has been suggested that C-reactive protein, a marker for systemic inflammation, may reflect chronic infection with organisms such as *Chlamydia pneumoniae*, *Helicobacter pylori*, or cytomegalovirus (29–31). Atheromatous plaques infiltrated by inflammatory cells may be less stable than quiescent plaques because of collagen disruption from the effects of secreted metalloproteinases. An alternative hypothesis would be that C-reactive protein is a marker for other proteins that are elevated during inflammation and that increase coagulability. C-reactive protein enhances the expression of tissue factor by monocytes and is thus procoagulant (32). C-reactive protein also induces complement activation (33), leading to an increased inflammatory response that could increase the likelihood of lethal arrhythmias or the volume of ischemic tissue. C-reactive protein production by the liver is also stimulated by interleukin 6 (34) and promotes leukocyte adhesion that results in enhanced recruitment of monocytes to atherosclerotic plaques, thus supporting thrombus formation (35).

Our study has several limitations. Cause of death is particularly difficult to ascertain in the elderly; several disease processes often contribute to the death. Autopsy studies have documented that a substantial percentage of deaths due to coronary heart disease are misclassified or missed (36–38). Furthermore, our analyses were based on a single measurement of C-reactive protein. Any woman with trauma or illness in the days preceding study enrollment would have had an acute elevation of C-reactive protein level. The number of deaths due to cardiovascular disease was also relatively small. However, the results were robust to adjustment for confounders, of similar magnitude in multiple subgroups, and similar to those in other studies. The number of women who died of other causes was also low, which limited our ability to identify associations with other specific causes of death, such as lung cancer. In addition, C-reactive protein may

Table 4. Subgroup Analyses of Associations between Cardiovascular Death and C-Reactive Protein Levels*

Subgroup	Relative Risk (95% Confidence Interval)	P Value
Never smoked	5.0 (1.4–17)	0.01
No estrogen use	6.1 (2.0–18)	0.001
Good or excellent health	7.4 (1.9–29)	0.004
Event-free at least 2 years	4.8 (1.5–16)	0.008
Event-free at least 4 years	5.0 (1.0–24)	0.05

* Upper three quartiles of C-reactive protein compared with first quartile; adjusted for age, hypertension, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, diabetes, smoking, body mass index, estrogen use, education level, and clinical site.

be a marker for other factors that we did not measure. Finally, our sample comprised women who were older and predominantly white. Nevertheless, they were sampled from four diverse communities across the United States.

Measurement of C-reactive protein level may be useful in predicting a patient's risk of future cardiovascular events, particularly because effective preventive therapies, such as aspirin, beta-blockers, and cholesterol-lowering agents, are available. Whether the identification of older women at low risk of cardiovascular events will be useful in limiting unnecessary medications in the primary prevention of cardiovascular disease remains uncertain.

REFERENCES

- Braunwald E. Shattuck lecture—cardiovascular medicine at the turn of the millennium: triumphs, concerns, and opportunities. *N Engl J Med.* 1997;337:1360–1369.
- Rimm EB, Stampfer MJ, Ascherio A, et al. Vitamin E consumption and the risk of coronary heart disease in men. *N Engl J Med.* 1993;328:1450–1456.
- Stampfer MJ, Hennekens CH, Manson JE, et al. Vitamin E consumption and the risk of coronary disease in women. *N Engl J Med.* 1993;328:1444–1449.
- Manolio TA, Pearson TA, Wenger NK, et al. Cholesterol and heart disease in older persons and women. Review of an NHLBI workshop. *Ann Epidemiol.* 1992;2:161–176.
- Tracy RP. Inflammation in cardiovascular disease: cart, horse, or both? *Circulation.* 1998;97:2000–2002.
- Ridker PM. Evaluating novel cardiovascular risk factors: can we better predict heart attacks? *Ann Intern Med.* 1999;130:933–937.
- Ross R. Atherosclerosis—an inflammatory disease. *N Engl J Med.* 1999;340:115–126.
- Thompson SG, Kienast J, Pyke SD, et al. Hemostatic factors and the risk of myocardial infarction or sudden death in patients with angina pectoris. European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study Group. *N Engl J Med.* 1995;332:635–641.
- Haverkate F, Thompson SG, Pyke SD, et al. Production of C-reactive protein and risk of coronary events in stable and unstable angina. European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study Group. *Lancet.* 1997;349:462–466.
- Liuzzo G, Buffon A, Biasucci LM, et al. Enhanced inflammatory response to coronary angioplasty in patients with severe unstable angina. *Circulation.* 1998;98:2370–2376.
- Ridker PM, Cushman M, Stampfer MJ, et al. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med.* 1997;336:973–979.
- Kuller LH, Tracy RP, Shaten J, Meilahn EN. Relation of C-reactive protein and coronary heart disease in the MRFIT nested case-control study. Multiple Risk Factor Intervention Trial. *Am J Epidemiol.* 1996;144:537–547.
- Tracy RP, Lemaitre RN, Psaty BM, et al. Relationship of C-reactive protein to risk of cardiovascular disease in the elderly. Results from the Cardiovascular Health Study and the Rural Health Promotion Project. *Arterioscler Thromb Vasc Biol.* 1997;17:1121–1127.
- Harris TB, Ferrucci L, Tracy RP, et al. Associations of elevated interleukin-6 and C-reactive protein levels with mortality in the elderly. *Am J Med.* 1999;106:506–512.
- Rifai N, Buring JE, Lee IM, et al. Is C-reactive protein specific for vascular disease in women? *Ann Intern Med.* 2002;136:529–533.
- Dischinger P, DuChene AG. Quality control aspects of blood pressure measurements in the Multiple Risk Factor Intervention Trial. *Control Clin Trials.* 1986;7(Suppl):137S–157S.
- Macy EM, Hayes TE, Tracy RP. Variability in the measurement of C-reactive protein in healthy subjects: implications for reference intervals and epidemiological applications. *Clin Chem.* 1997;43:52–58.
- Rifai N, Tracy RP, Ridker PM. Clinical efficacy of an automated high-sensitivity C-reactive protein assay. *Clin Chem.* 1999;45:2136–2141.
- Prentice RL. A case-cohort design for epidemiologic cohort studies and disease prevention trials. *Biometrika.* 1986;73:1–11.
- Prentice RL. Opportunities for enhancing efficiency and reducing cost in large scale disease prevention trials: a statistical perspective. *Stat Med.* 1990;9:161–170.
- Das I. Raised C-reactive protein levels in serum from smokers. *Clin Chim Acta.* 1985;153:9–13.
- Tracy RP, Psaty BM, Macy E, et al. Lifetime smoking exposure affects the association of C-reactive protein with cardiovascular disease risk factors and subclinical disease in healthy elderly subjects. *Arterioscler Thromb Vasc Biol.* 1997;17:2167–2176.
- Cushman M, Legault C, Barrett-Connor E, et al. Effect of postmenopausal hormones on inflammation-sensitive proteins: the Postmenopausal Estrogen/Progestin Interventions (PEPI) Study. *Circulation.* 1999;100:717–722.
- Cushman M, Meilahn EN, Psaty BM, et al. Hormone replacement therapy, inflammation, and hemostasis in elderly women. *Arterioscler Thromb Vasc Biol.* 1999;19:893–899.
- Farmer JA. Pleiotropic effects of statins. *Curr Atheroscler Rep.* 2000;2:208–217.
- Ridker PM, Rifai N, Pfeffer MA, et al. Long-term effects of pravastatin on plasma concentration of C-reactive protein. The Cholesterol And Recurrent Events (CARE) Investigators. *Circulation.* 1999;100:230–235.
- Ridker PM, Rifai N, Lowenthal SP. Rapid reduction in C-reactive protein with cerivastatin among 785 patients with primary hypercholesterolemia. *Circulation.* 2001;103:1191–1193.
- Ridker PM, Rifai N, Clearfield M, et al. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. *N Engl J Med.* 2001;344:1959–1965.
- Patel P, Mendall MA, Carrington D, et al. Association of *Helicobacter pylori* and *Chlamydia pneumoniae* infections with coronary heart disease and cardiovascular risk factors. *BMJ.* 1995;311:711–714.
- Abdelmouttaleb I, Danchin N, Ilardo C, et al. C-reactive protein and coronary artery disease: additional evidence of the implication

- of an inflammatory process in acute coronary syndromes. *Am Heart J*. 1999;137:346–351.
31. Yudkin JS, Stehouwer CD, Emeis JJ, Coppack SW. C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? *Arterioscler Thromb Vasc Biol*. 1999;19:972–978.
 32. Cermak J, Key NS, Bach RR, et al. C-reactive protein induces human peripheral blood monocytes to synthesize tissue factor. *Blood*. 1993;82:513–520.
 33. Lagrand WK, Visser CA, Hermens WT, et al. C-reactive protein as a cardiovascular risk factor: more than an epiphenomenon? *Circulation*. 1999;100:96–102.
 34. Bataille R, Klein B. C-reactive protein levels as a direct indicator of interleukin-6 levels in humans in vivo. *Arthritis Rheum*. 1992;35:982–984.
 35. Pasceri V, Willerson JT, Yeh ET. Direct proinflammatory effect of C-reactive protein on human endothelial cells. *Circulation*. 2000;102:2165–2168.
 36. Battle RM, Pathak D, Humble CG, et al. Factors influencing discrepancies between premortem and postmortem diagnoses. *JAMA*. 1987;258:339–344.
 37. Burnand B, Feinstein AR. The role of diagnostic inconsistency in changing rates of occurrence for coronary heart disease. *J Clin Epidemiol*. 1992;45:929–940.
 38. Paterson DA, Dorovitch MI, Farquhar DL, et al. Prospective study of necropsy audit of geriatric inpatient deaths. *J Clin Pathol*. 1992;45:575–578.