



Published in final edited form as:

*Am J Cardiol.* 2005 December 1; 96(11): 1506–1511. doi:10.1016/j.amjcard.2005.07.059.

## Relation of Low Socioeconomic Status to C-Reactive Protein in Patients With Coronary Heart Disease (from the Heart and Soul Study)

Lindsey A. Lubbock, BA<sup>a</sup>, Anne Goh, MD, MPH<sup>a</sup>, Sadia Ali, MD, MPH<sup>a</sup>, James Ritchie, PhD<sup>c</sup>, and Mary A. Whooley, MD<sup>a,b,\*</sup>

<sup>a</sup>Department of Veterans Affairs Medical Center, University of California, San Francisco, California

<sup>b</sup>Departments of Medicine and Epidemiology and Biostatistics, University of California, San Francisco, California

<sup>c</sup>Department of Pathology, Emory University School of Medicine, Atlanta, Georgia.

### Abstract

Low socioeconomic status (SES) is associated with poor health outcomes in patients who have coronary heart disease (CHD). Inflammation is a potential mechanism by which low SES may lead to adverse cardiovascular outcomes, but it is not known whether low SES is associated with inflammation in patients who have CHD. We measured high-sensitivity C-reactive protein (CRP) levels in a cross-sectional study of 985 adults who had CHD. Income and education were determined by self-report. We used ordinal logistic regression to examine the association of income and education with CRP. Of the 985 participants, 390 had high CRP levels (>3 mg/dl). The proportion of participants who had high CRP levels ranged from 30% (103 of 340) in those who had a college degree to 51% (65 of 127) in those who had less than a high school degree ( $p < 0.0001$ ). The proportion of subjects who had a high CRP level ranged from 28% (52 of 183) in those who had annual income >\$50,000 to 42% (199 of 974) in those who had an annual income <\$20,000 ( $p < 0.001$ ). After adjustment for traditional cardiovascular risk factors and other potential confounding variables, lower income and education remained associated with higher CRP levels. In conclusion, low SES is associated with high CRP levels in patients who have CHD. This observation raises the possibility that inflammation may contribute to the adverse cardiovascular outcomes associated with low SES.

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To determine the relation between socioeconomic status (SES) and level of C-reactive protein (CRP), we assessed income and education and measured CRP in a cross-sectional study of 985 adults who had coronary heart disease (CHD). We hypothesized that lower income and education would be associated with higher CRP levels after adjusting for demographic characteristics, traditional CHD risk factors, medical co-morbidities, medication use, and other clinical indicators.

### Methods

#### Participants

The Heart and Soul Study is a prospective cohort study that examines the influence of psychosocial factors on health outcomes in patients who have coronary artery disease. Methods have been described previously.<sup>1,2</sup> Patients who had coronary artery disease were recruited by

using administrative databases from 2 Departments of Veterans Affairs Medical Centers (Veterans Affairs Medical Center, San Francisco, and the Veterans Affairs Palo Alto Health Care System, Palo Alto, California), 1 university-based medical center (University of California, San Francisco), and 9 public health clinics in the Community Health Network of San Francisco. Eligibility requirements included a history of any of the following: myocardial infarction, angiographic evidence of  $\geq 50\%$  stenosis in  $\geq 1$  coronary vessel, coronary revascularization, a diagnosis of coronary disease that was documented by an internist or cardiologist, or evidence of exercise-induced ischemia by treadmill or nuclear testing.

A total of 15,438 eligible patients was mailed an invitation to participate, and 2,495 responded that they would be interested. Of the 2,495 patients whom we attempted to contact by telephone to schedule a study appointment, 505 could not be reached and 596 declined to participate. An additional 370 patients were excluded because they had a history of myocardial infarction in the previous 6 months, deemed themselves unable to walk 1 block, or were planning to move out of the local area within 3 years.

Between September 2000 and December 2002, 1,024 participants enrolled and attended a day-long appointment at the Veterans Affairs Medical Center in San Francisco. For this cross-sectional study, we excluded 39 subjects from whom we could not obtain serum samples, leaving 985 participants for analysis. This study protocol was approved by the appropriate institutional review boards, and all participants provided written, informed consent.

#### **Predictor variable: SES**

We evaluated SES by measuring education and income. To assess education, we asked participants, "What is the highest level of education that you have completed?" Multiple-choice responses were grade  $\leq 8$ , grades 9 to 11, high school graduate or equivalent, some college or vocational school, college degree, or graduate or professional degree. For analysis purposes, we categorized participants as having less than a high school education, a high school diploma, or a college or graduate degree.

To determine income, we asked participants, "Which of the following categories best describes your total combined household income for the previous 12 months?" ( $< \$10,000$ ,  $\$10,000$  to  $\$19,000$ ,  $\$20,000$  to  $\$29,000$ ,  $\$30,000$  to  $\$39,999$ ,  $\$40,000$  to  $\$50,000$ , or  $> \$50,000$ ). For analysis purposes, we categorized participants into 1 of 4 income groups ( $< \$20,000$ ,  $\$20,000$  to  $\$29,999$ ,  $\$30,000$  to  $\$50,000$ , or  $\geq \$50,000$ ).<sup>3</sup>

#### **Outcome variable: CRP**

Participants were instructed to fast for 12 hours (except for medication, which they were to take with water), not to take aspirin for 1 week, and not to smoke for 5 hours. Fasting venous blood samples were obtained, and serum was frozen at  $-70^{\circ}\text{C}$  until the time of the CRP assay. We used the Roche Integra high-sensitivity assay (Roche, Indianapolis, Indiana) to measure CRP in 229 participants and (due to a change in the laboratory) the Beckman Extended Range high-sensitivity CRP assay (Beckman, Galway, Ireland) to measure CRP in the remaining 756 participants. We categorized participants by CRP levels  $< 1$ , 1 to 3, and  $> 3$  mg/L, which corresponded to low, moderate, and high levels of cardiovascular risk, respectively.<sup>4</sup>

The Roche Integra high-sensitivity CRP assay is an immunoturbidimetric assay that uses latex particles that are coated with monoclonal anti-CRP antibody. When the CRP of the sample agglutinates with these particles, a precipitate is formed and the amount is determined turbidimetrically at 522 nm. This assay has been standardized against the World Health Organization reference and compared with the Dade nephelometric method, with a correlation

coefficient of 0.997. The interassay coefficient of variation is 3.2%, and the lowest detectable measurement of this assay is 0.025 mg/dl.

The Beckman Extended Range CRP assay is also an immunoturbidimetric assay that uses latex particles and a near-infrared particle immunoassay that is measured with a laser diode at 940 nm, with a detection limit of 0.20 mg/L and a measuring range of 0.20 to 1440 mg/L. This assay is highly correlated with the Roche Integra assay ( $r = 0.99$  in a sample of 185 patients). The interassay (between-run) coefficient of variation is  $\leq 6.7\%$ , and the intraassay (with-in-run) coefficient of variation is  $< 6.2\%$ .

### Other measurements

Age, gender, ethnicity, smoking, marital status, alcohol use, medical history, angina frequency, and physical activity were determined by a self-report questionnaire. We used the Computerized Diagnostic Interview Schedule, Fourth Edition, to determine the presence of current major depression according to criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.<sup>5,6</sup> Alcohol use was evaluated by using alcohol consumption from the Alcohol Use Disorders Identification Test, with a score  $\geq 4$  to define regular alcohol use.<sup>7</sup>

Participants were instructed to bring all medication bottles to their study appointment, and the research team recorded all current medications. All participants completed echocardiography at rest for measurement of left ventricular ejection fraction and an exercise treadmill test with stress echocardiography. We calculated the wall motion score index at peak exercise as our measurement of ischemia.<sup>8</sup> Body mass index was calculated as weight in kilograms divided by the square of height in meters. We measured systolic and diastolic blood pressures, fasting total cholesterol level, high-density lipoprotein, low-density lipoprotein, and triglycerides (milligrams per deciliter). Creatinine clearance (milliliter per minute) was calculated from 24-hour urine excretion.

### Statistical analysis

This study examined the association of education and income with levels of C-reactive protein. Differences in characteristics of participants by level of CRP ( $< 1$ , 1 to 3, and  $> 3$  mg/L) were compared using analysis of variance for continuous variables and chi-square test for dichotomous variables. We used analysis of covariance to compare mean log CRP by categories of income and education. We also compared the unadjusted frequency of low, moderate, and high CRP levels by categories of education and income by using Cochran-Armitage chi-square test for trend.

To further evaluate the association between low SES and CRP, we used polytomous (ordinal) logistic regression, with category of income or education as the predictor variable and category of CRP ( $< 1$ , 1 to 2,  $> 3$  mg/L) as the ordinal outcome variable. To obtain adjusted risk estimates, we entered all variables listed in Table 1 into a backward elimination logistic regression models that included different levels of education and income as indicator variables. Variables that were associated with high CRP levels (at  $p < 0.05$ ) were retained in the models. We verified the proportional odds assumption for all models. Results are reported as odds ratios with 95% confidence intervals. Analyses were performed with SAS 8 (SAS Institute, Cary, North Carolina).

### Results

Among the 985 study participants, 262 had CRP levels  $< 1$  mg/L, 333 had CRP levels 1 to 3 mg/L, and 390 had CRP levels  $> 3$  mg/L (Table 1). Compared with participants who had low

CRP levels, those who had higher CRP levels were older, less likely to be men or married, and more likely to smoke, to have diabetes, to have congestive heart failure, and to be physically inactive. Participants who had higher CRP levels were also more likely to be taking diuretics, less likely to be taking statins or aspirin, and more likely to be using hormone replacement therapy. They had higher values for blood pressure, low-density lipoprotein, and body mass index and lower values for high-density lipoprotein and creatinine clearance compared with those who had low CRP levels.

Mean  $\pm$  SE log CRP values were  $0.48 \pm 0.07$  mg/dl in the 340 participants who had a college degree,  $0.80 \pm 0.06$  mg/dl in the 516 participants who had a high school degree, and  $0.98 \pm 0.12$  in the 127 participants who had less than a high school degree ( $p < 0.0001$ ). Mean  $\pm$  SE log CRP values were  $0.33 \pm 0.10$  mg/dl in the 183 participants who had an annual income  $>$  \$50,000,  $0.75 \pm 0.09$  in the 189 participants who had an annual income from \$30,000 to \$50,000,  $0.81 \pm 0.11$  in the 133 participants who had an annual income from \$20,000 to \$29,999, and  $0.82 \pm 0.06$  in the 474 participants who had an annual income  $<$  \$20,000 ( $p = 0.0002$ ).

When we divided CRP into categories ( $<1$ ,  $1$  to  $3$ ,  $>3$  mg/dl), lower income and education levels were associated with higher CRP levels (Figure 1, Table 2). The proportion of participants who had high CRP levels ( $>3$  mg/dl) ranged from 30% in those who had a college degree to 51% in those who had less than a high school education ( $p < 0.0001$ ) and from 28% in those who had an annual income  $\geq$  \$50,000 to 42% in those who had an annual income  $<$  \$20,000 ( $p < 0.001$ ). After adjustment for potential confounding variables, lower income and education levels remained associated with higher CRP levels (Table 3).

## Discussion

Our cross-sectional study of outpatients who had CHD associated low SES with higher levels of CRP. Associations of lower education and income were independent of each other and persisted after adjustment for traditional cardiovascular risk factors, marital status, and depression. The observed relation between low SES and CRP raises the intriguing possibility that inflammation may contribute to the adverse cardiovascular outcomes associated with low SES.

Low SES is associated with an increased risk of CHD and with greater morbidity and mortality among patients who have CHD.<sup>9–17</sup> However, the mechanisms by which low SES leads to adverse cardiovascular outcomes are not known. Patients who have low SES are more likely to smoke, to be obese, to have hypertension or diabetes, and to be physically inactive.<sup>18–21</sup> However, even after adjusting for traditional CHD factors, low SES is independently associated with excess morbidity and mortality among patients who had CHD.<sup>22–24</sup> The effect of low SES on mortality after myocardial infarction is equivalent to the effect of many traditional risk factors.<sup>25</sup>

CRP level, a measurement of inflammation, is a well-established and independent predictor of cardiovascular events.<sup>26–29</sup> Previous studies of healthy adults have associated high CRP levels with low social class in childhood,<sup>30,31</sup> low occupational grade,<sup>3</sup> low educational level,<sup>32–34</sup> and low income level.<sup>34</sup> Our findings demonstrate that the association between low SES and CRP that was observed in healthy adults is also present in patients who have CHD. Because high levels of CRP predict CHD events,<sup>26–28</sup> inflammation may be a mechanism by which SES leads to adverse health outcomes.

Other possible pathways by which SES may influence cardiovascular outcomes include the effects of chronic stress,<sup>3</sup> dysregulation of the parasympathetic nervous system,<sup>35</sup> greater insulin resistance,<sup>36</sup> and differences in dietary, lifestyle, and behavior patterns.<sup>37</sup> Limited

education and lack of financial resources may also affect access to quality medical care<sup>38</sup> and decrease adherence to medication.<sup>39</sup> Whatever the mechanism, our findings suggest that patients who have a low income or education level may benefit from more aggressive management of CHD, including treatment of dyslipidemia, hypertension, diabetes, smoking, obesity, and physical inactivity.

Our study has several limitations that should be considered. Income and education were measured by self-report, thus leaving room for inaccuracies in our analysis. Further, our measurement of “overall household income” may not reflect the participants’ personal income. However, it is likely a reasonable reflection of participants’ SES. Although the 2 CRP assays were highly correlated ( $r = 0.99$ ), use of 2 different assays still poses a potential limitation. Moreover, stepwise analysis uses a purely statistical method to select significant variables without necessarily considering biologic confounding. In addition, the investigation involved only a minority of female participants, so our results may not generalize to all populations.

## Acknowledgments

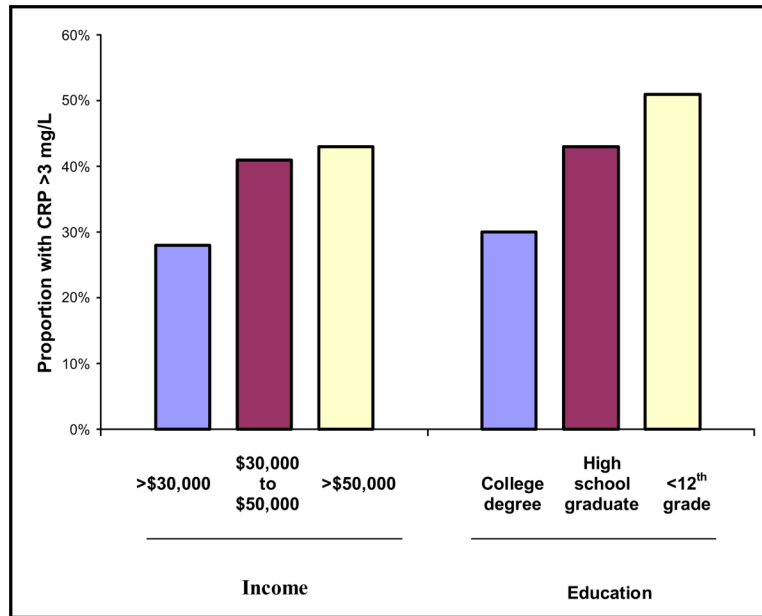
This work was supported by grants from the Department of Veterans Affairs, Washington, DC; the American Federation for Aging Research (Paul Beeson Scholars Program), New York, New York; the Robert Wood Johnson Foundation (Faculty Scholars Program), Princeton, New Jersey; and the Nancy Kirwan Heart Research Fund, San Francisco, California.

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**Figure 1.** Proportion of participants who had high CRP levels according to income and education level (p for trend <0.01).



**Table 1**

Characteristics of 985 participants by level of C-reactive protein (CRP)

Variable	CRP			p Value
	<1 mg/L (n = 262)	1–3 mg/L (n = 333)	>3 mg/L (n = 390)	
Age (yrs)	66 ± 11	68 ± 11	66 ± 11	0.02
Men	224 (86%)	283 (85%)	295 (76%)	0.001
White	151 (58%)	208 (62%)	236 (61%)	0.52
Married	131 (50%)	137 (41%)	153 (39%)	0.02
Current smoking	38 (15%)	50 (15%)	107 (27%)	<0.0001
Regular alcohol use	77 (30%)	100 (30%)	108 (28%)	0.78
Hypertension	176 (68%)	234 (70%)	284 (73%)	0.36
Diabetes mellitus	55 (21%)	95 (29%)	110 (28%)	0.07
Congestive heart failure	33 (13%)	53 (16%)	87 (22%)	0.004
Angina weekly or more	94 (36%)	114 (34%)	146 (38%)	0.65
Previous myocardial infarction	136 (52%)	188 (57%)	203 (52%)	0.37
Previous stroke	34 (13%)	49 (15%)	55 (14%)	0.85
Previous coronary artery bypass grafting	101 (39%)	123 (37%)	125 (32%)	0.18
Previous coronary angioplasty	106 (41%)	133 (40%)	146 (38%)	0.67
Current depression	58 (22%)	75 (23%)	84 (22%)	0.94
Not at all or a little physically active	63 (24%)	112 (34%)	185 (48%)	<0.0001
β-Blocker use	160 (61%)	191 (57%)	214 (55%)	0.29
Renin-angiotensin system inhibitor use	136 (52%)	180 (54%)	189 (48%)	0.31
Diuretics (loop or thiazide) use	57 (22%)	90 (27%)	143 (37%)	0.0001
Statin use	177 (68%)	230 (69%)	226 (58%)	0.003
Aspirin use	216 (82%)	257 (77%)	288 (74%)	0.03
Hormone replacement therapy use	7 (3%)	9 (3%)	30 (8%)	0.001
Ejection fraction (%)	0.62 ± 0.09	0.62 ± 0.10	0.61 ± 0.10	0.33
Wall motion score index	1.14 ± .31	1.17 ± .34	1.19 ± .39	0.22
Systolic blood pressure (mm Hg)	129 ± 20	132 ± 20	136 ± 22	<0.0001
Diastolic blood pressure (mm Hg)	73 ± 12	75 ± 11	76 ± 11	0.005
Total cholesterol (mg/dl)	171 ± 37	177 ± 43	183 ± 46	0.001
High-density lipoprotein (mg/dl)	47.8 ± 15	46 ± 14	44 ± 13	0.004
Low-density lipoprotein (mg/dl)	96.5 ± 26	104 ± 33	110 ± 38	<0.0001
Creatinine clearance (ml/min)	86 ± 28	81 ± 28	78 ± 29	0.001
Body mass index (kg/m <sup>2</sup> )	27 ± 4.1	28 ± 5	30 ± 6	<0.0001
Triglycerides (mg/dl)	136 ± 157	137 ± 120	147 ± 113	0.47

Values are means ± SD or numbers of patients (percentages).

**Table 2**

Socioeconomic status and level of C-reactive protein (CRP) in 985 participants with coronary heart disease

	CRP		p Value
	<1 mg/L	1–3 mg/L	
Education			
Grade ≤8	11	19	220.0002
Grades 9–11	12	20	43
High school graduate	36	55	85
Some college or vocational school	85	118	137
College degree	63	57	54
Graduate or professional degree	54	63	49
Annual income (United States dollars)			
<\$10,000	58	87	1000.002
\$10,000–\$19,000	53	77	99
\$20,000–\$29,999	27	45	61
\$30,000–\$39,999	22	31	40
\$40,000–\$50,000	25	33	38
>\$50,000	75	56	52

Values are numbers of subjects.

Association between socioeconomic status and level of C-reactive protein (CRP) (<1, 1 to 3, >3 mg/L)

Table 3

	Proportion With CRP >3 mg/L	Unadjusted OR (95% CI)	p Value	Adjusted OR (95% CI)*	p Value	Adjusted OR (95% CI) <sup>†</sup>	p Value
Education							
≤11 yrs	51% (65/127)	2.4 (1.6–3.5)	<0.0001	2.2 (1.4–3.5)	0.001	2.2 (1.3–3.6)	0.002
High school degree	43% (222/516)	1.7 (1.3–2.2)	<0.0001	1.4 (1.0–1.9)	0.03	1.5 (1.1–2)	0.02
College degree or higher	30% (103/340)	1	—	1	—	1	—
Annual income							
<\$20,000	42% (199/474)	2.1 (1.5–2.8)	<0.0001	1.4 (.96–2.1)	0.08	1.2 (0.8–1.9)	0.34
\$20,000–29,999	46% (61/133)	2.4 (1.6–3.7)	<0.0001	2.2 (1.4–3.6)	0.001	2.1 (1.2–3.5)	0.006
\$30,000–50,000	41% (78/189)	2.0 (1.3–2.9)	0.0005	1.8 (1.2–2.8)	0.007	1.7 (1.1–2.7)	0.02
≥\$50,000	28% (52/183)	1	—	1	—	1	—

CI = confidence interval; OR = odds ratio.

\* All variables were entered into a backward elimination ordinal logistic regression model with a p value <0.05 for retention. Other variables associated with high CRP level (at p <0.05) in the education model were white ethnicity, smoker, history of congestive heart failure, not currently depressed, little or no physical activity, not using  $\alpha$ / $\beta$  blocker, using hormone therapy, increased systolic blood pressure, high cholesterol level, low high-density lipoprotein level, low creatinine clearance and high body mass index. Other variables associated with high CRP level (at p <0.05) in the income model were white ethnicity, smokers, history of congestive heart failure, not currently depressed, little or not physically activity, not using a  $\beta$  blocker, using hormone therapy, increased systolic blood pressure, low cholesterol level, high low-density lipoprotein level, high triglyceride level, low creatinine clearance, and high body mass index.

<sup>†</sup> Further adjusted for other socioeconomic variable (education or income).