Impact of Traditional and Novel Risk Factors on the Relationship Between Socioeconomic Status and Incident Cardiovascular Events

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Background—Persons of lower socioeconomic status have greater cardiovascular risk than those of higher socioeconomic status. However, the mechanism through which socioeconomic status affects cardiovascular disease (CVD) is uncertain. Virtually no data are available that examine the prospective association between novel inflammatory and hemostatic CVD risk indicators, socioeconomic status, and incident CVD events.

Methods and Results—We assessed the relationship between 2 indicators of socioeconomic status (education and income), traditional and novel CVD risk factors (high sensitivity C-reactive protein, soluble intercellular adhesion molecule-1, fibrinogen, and homocysteine), and incident CVD events among 22,688 apparently healthy female health professionals participating in the Women’s Health Study. These women were followed up for 10 years for the development of myocardial infarction, ischemic stroke, coronary revascularization, and cardiovascular death. More educated women were less likely to be smokers; had a lower prevalence of hypertension, diabetes, and obesity; and were more likely to participate in vigorous physical activity than less educated women. At baseline, median total cholesterol, low-density lipoprotein, triglyceride, C-reactive protein, intercellular adhesion molecule-1, fibrinogen, and homocysteine levels for women in 5 categories of education (4 years of nursing education, 2 to <4 years of nursing education, a bachelor’s degree, a master’s degree, and a doctoral degree) and 6 categories of income ($<19,999, $20,000 to $29,999, $30,000 to $39,999, $40,000 to $49,999, $50,000 to $99,999, and $100,000) decreased progressively with increasing education or income levels (all \(P<0.001\), whereas an opposite pattern was observed for high-density lipoprotein \(P<0.001\). Overall, in age-adjusted Cox proportional hazards models, the relative risk of incident CVD events decreased with increasing education (1.0, 0.7, 0.5, 0.4, and 0.5; \(P\) for trend <0.001) and income (1.0, 1.0, 0.9, 0.7, 0.6, and 0.4; \(P\) for trend <0.001) categories. In multivariate models that assessed the impact of traditional and novel CVD risk factors on the relationship between education/income and CVD events, the relative hazard of incident CVD associated with a 1-category-higher level of education changed from 0.79 in age- and race-adjusted analysis to 0.89 in fully adjusted analysis. The 11% lower risk per 1 category of education remained significant \(P\) for trend =0.006), suggesting that controlling for both novel and traditional risk factors could not explain the protective effect of education. A similar analysis for income revealed that its relationship with CVD events was explained largely by these noted risk factors.

Conclusions—In this prospective analysis, we observed a decrease in incident CVD events with increasing levels of education and income. In contrast to the relationship between income and CVD events, the relationship of CVD events with education controlling for both novel and traditional risk factors could not explain the protective effect of education.

Key Words: atherosclerosis ■ cardiovascular disease ■ inflammation ■ social class

Socioeconomic status (SES) as defined by education, income, occupation, social status, and neighborhood environment is an important contributor to health. Although low SES is associated with an increased prevalence of cardiovascular disease (CVD) risk factors and poorer health outcomes than high SES, the mechanism underlying this relationship remains uncertain. Proposed pathways through which SES likely affects cardiovascular disease include access to or use of care, chronic stress, and biological, environmental, and behavioral issues. Relatively few studies have examined the relationship among markers of inflammation, SES, and CVD despite the understanding of the crucial role of inflammation in the pathogenesis of atherosclerotic heart disease. For exam-
ple, Owen et al. evaluated the relationship between C-reactive protein (CRP), immune factors, and SES among healthy volunteers from the Whitehall II study and found that higher CRP levels were associated with lower SES. Jousilahti et al. found a similar relationship between SES, CRP, serum amyloid A, and fibrinogen levels; mean levels of the aforementioned inflammatory markers decreased significantly with increasing SES. These data are limited, however, by their cross-sectional nature and focus on male subjects. Moreover, it remains unclear whether control for markers of inflammation and hemostasis will attenuate apparent relationships of SES with risk of CVD and whether SES remains substantially related to risk of CVD after these markers are controlled for. Thus, whether reported effects of SES on blood pressure, high-density lipoprotein (HDL), fibrinogen, and CRP are causes or consequences is largely unknown. As a result, we sought to prospectively evaluate the relationship between traditional and novel (CRP, intercellular adhesion molecule-1 [ICAM], fibrinogen, and homocysteine) CVD risk factors, SES (education or income), and incident cardiovascular events among middle-aged women.

Methods

Participants

Clinical and demographic information and baseline blood samples were collected from participants in the Women’s Health Study, a randomized, placebo-controlled trial of vitamin E and aspirin for the primary prevention of cardiovascular events and cancer among apparently healthy female health professionals (75% registered nurses, 15% licensed practical/visiting nurses, 8% other health professionals such as dietitians and pharmacists). Written informed consent was received from all participating women, and the trial was approved by the institutional review board of Brigham and Women’s Hospital. Education and income are used as indicators of SES. Data on education, income, other demographic, clinical, CRP, ICAM, fibrinogen, and homocysteine measurements are available for 22,688 women who form the basis of this analysis. Cardiovascular events over a 10-year follow-up period included nonfatal myocardial infarction, nonfatal ischemic stroke, cardiovascular death, and revascularization procedure (coronary artery bypass grafting and percutaneous transluminal coronary angioplasty). Relevant end points were reported via follow-up questionnaires, letters, and telephone calls. Deaths were reported by ascertaining from the National Death Index or reports from family members or postal authorities. Medical records were acquired from hospitals and from the National Death Index or reports from family members or catch, Inc (Seattle, Wash). All blood samples were blinded and measured with a validated, high-sensitivity Denka Seiken (Tokyo, Japan) assay. Lipid levels were performed in a certified Centers for Disease Control and Prevention laboratory (Roche Diagnostics, Indianapolis, Ind.). ICAM was measured with an ELISA assay (R&D Systems, Minneapolis, Minn) that uses a quantitative sandwich enzyme immunoassay technique. Fibrinogen concentration was determined with a Roche Diagnostics immunoturbidimetric assay on a Hitachi 917 analyzer using reagents and calibrators from Kamiya Biomedical Company (Seattle, Wash), and homocysteine was measured with an enzymatic assay with reagents and calibrators from Catch, Inc (Seattle, Wash). All blood samples were blinded and randomly analyzed in triplicate to minimize systemic bias and interassay variation.

Evaluation of Socioeconomic Status

Women were grouped in 5 categories of education level beyond high school: ≤2 years of health professional education, 2 to <4 years of health professional education, a bachelor’s degree, a master’s degree, and a doctoral degree (doctor in philosophy and/or medical degree). Because annual household income (doctor) was reported in ranges of income, participant income range was converted to the midpoint income for the respective reported range. Income is reported in 6 categories of US dollars (≤$19,999, $20,000 to $29,999, $30,000 to $39,999, $40,000 to $49,999, $50,000 to $99,999, and ≥$100,000).

Statistical Analyses

Baseline CVD risk factors are reported as means or proportions, and the significance of any differences was assessed by ANOVA or the χ² statistic. As a result of skewness in the distribution of CRP, ICAM, fibrinogen, and homocysteine, we report median levels and associated interquartile ranges and log-transformed these novel cardiovascular markers in regression analyses. The Kruskal-Wallis test was used to determine the significance of any differences in the distribution of CRP, ICAM, fibrinogen, and homocysteine. Partial correlation analysis that adjusted for age was used to evaluate the relationship between individual CVD risk factors and increasing levels of education and income. The relative risks of CVD events were calculated in increasing categories of education (referent, <2 years of health professional training) and income (referent, ≤$19,999) using age- and race-adjusted Cox proportional-hazards models and models adjusted for the traditional (age, race, smoking status, presence/absence of type II diabetes [diabetes], HDL, low-density lipoprotein, triglycerides, hormone use, history of hypertension, alcohol use, physical activity, body mass index, family history of myocardial infarction before 60 years of age) and novel (CRP, ICAM, fibrinogen, and homocysteine) CVD risk factors. Trends across categories of education and income were tested by use of a single ordinal term for the category in the Cox regression model. Kaplan-Meier curves were constructed to illustrate event-free survival according to the various categories of education and income. To test for deviation from linearity, we compared age-adjusted models that contained education or income indicators with those containing a linear term for either education or income in a likelihood ratio test with 3 and 4 df, respectively. We also evaluated the impact of the traditional and novel risk factors for CVD on the linear terms for education/income using Cox proportional hazards models. In addition, we tested for interactions between inflammatory parameters and education/income categories. All probability values are 2 tailed.

The authors have had full access to all of the data in the study and take full responsibility for the integrity of the data and the accuracy of the data analysis. All authors have read and agree to the manuscript as written.

Results

Baseline Characteristics

Baseline characteristics of the study population are shown in Table 1. The mean age of participants was 54.1 ± 7.1 years, and 44.9% of the women had attained a college degree or higher. Compared with women with <2 years of health professional
TABLE 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>&lt;2 y of Health Professional Education (n=2771)</th>
<th>2–&lt;4 y of Health Professional Education (n=9726)</th>
<th>BS Degree (n=5422)</th>
<th>MS Degree (n=3502)</th>
<th>Doctorate (n=1267)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>54.1±7.2</td>
<td>54.9±7.4</td>
<td>53.1±6.4</td>
<td>53.3±6.5</td>
<td>54.4±7.7</td>
</tr>
<tr>
<td>Smoking, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>49.4</td>
<td>48.9</td>
<td>53.8</td>
<td>55.2</td>
<td>62.6</td>
</tr>
<tr>
<td>Past</td>
<td>31.5</td>
<td>38.0</td>
<td>37.3</td>
<td>38.2</td>
<td>32.2</td>
</tr>
<tr>
<td>Current</td>
<td>19.0</td>
<td>13.1</td>
<td>9.0</td>
<td>6.6</td>
<td>5.2</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.3±5.5</td>
<td>26.0±5.0</td>
<td>25.7±4.8</td>
<td>25.4±4.8</td>
<td>24.4±4.2</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>32.2</td>
<td>26.6</td>
<td>21.5</td>
<td>20.5</td>
<td>19.3</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>4.8</td>
<td>2.9</td>
<td>2.3</td>
<td>1.8</td>
<td>2.3</td>
</tr>
<tr>
<td>Family history of MI, %</td>
<td>13.5</td>
<td>12.8</td>
<td>13.0</td>
<td>12.3</td>
<td>13.3</td>
</tr>
<tr>
<td>HRT, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>45.2</td>
<td>45.3</td>
<td>47.1</td>
<td>48.6</td>
<td>48.3</td>
</tr>
<tr>
<td>Past</td>
<td>14.9</td>
<td>10.6</td>
<td>8.6</td>
<td>7.8</td>
<td>6.5</td>
</tr>
<tr>
<td>Current</td>
<td>40.0</td>
<td>44.1</td>
<td>44.3</td>
<td>43.8</td>
<td>45.2</td>
</tr>
<tr>
<td>Alcohol use, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rare/never</td>
<td>61.0</td>
<td>46.3</td>
<td>39.0</td>
<td>35.2</td>
<td>33.8</td>
</tr>
<tr>
<td>1–3 drinks per month</td>
<td>12.7</td>
<td>13.0</td>
<td>13.4</td>
<td>14.8</td>
<td>12.1</td>
</tr>
<tr>
<td>1–6 drinks per week</td>
<td>20.6</td>
<td>30.8</td>
<td>36.2</td>
<td>38.1</td>
<td>37.3</td>
</tr>
<tr>
<td>1+ a day</td>
<td>5.9</td>
<td>9.9</td>
<td>11.3</td>
<td>12.1</td>
<td>16.8</td>
</tr>
<tr>
<td>Exercise, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rare/never</td>
<td>48.0</td>
<td>40.1</td>
<td>32.3</td>
<td>29.7</td>
<td>30.6</td>
</tr>
<tr>
<td>&lt;1 time a week</td>
<td>18.2</td>
<td>19.6</td>
<td>20.7</td>
<td>19.2</td>
<td>18.1</td>
</tr>
<tr>
<td>1–3 times a week</td>
<td>26.6</td>
<td>30.2</td>
<td>34.9</td>
<td>36.5</td>
<td>35.0</td>
</tr>
<tr>
<td>4 times a week</td>
<td>7.2</td>
<td>10.1</td>
<td>12.2</td>
<td>14.6</td>
<td>16.3</td>
</tr>
<tr>
<td>Median annual household income (IQR), $</td>
<td>34 500 (24 500, 44 500)</td>
<td>44 500 (34 500, 75 000)</td>
<td>75 000 (50 000, 99 999)</td>
<td>75 000 (50 000, 99 999)</td>
<td>125 000 (100 000, 150 000+)</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; MI, myocardial infarction; and HRT, hormone replacement therapy. Values are mean±SD when appropriate. The interquartile range (IQR) represents the 25th and 75th percentiles.

education, women with doctorates were less likely to be smokers (5.2% versus 19.0%), overweight (body mass index, 24.4±4.2 versus 27.3±5.5 kg), and diabetic (2.3% versus 4.8%) and to have a history of hypertension (19.3% versus 32.2%). The most educated women also were more likely to be frequent exercisers (4 times a week, 16.3% versus 7.2%), to consume daily alcohol (4 times a week, 7.2% versus 27.3), and to have higher annual median household income ($125 000 versus $34 500) than women in the lowest category of education.

There was a moderate age-adjusted partial correlation between education and income (r=0.38). Small to modest partial correlations also were noted between education and income categories and increasing levels of body mass index (r<education=−0.12, r<income=−0.15), HDL (r<education=0.10, r<income=0.13), triglycerides (r<education=−0.10), physical activity (r<education=0.12, r<income=0.12), and alcohol use (r<education=0.15, r<income=0.21). There were also small to modest associations between baseline log-fibrinogen levels and income (r=−0.11) and between log-ICAM levels and education/income (r<education=−0.12, r<income=−0.12). The partial correlations between log-CRP and education and income were r<education=−0.09 and r<income=−0.08, respectively. The age-adjusted partial correlations between current smoking and education and income categories were −0.12 and −0.11, respectively. All of the above-noted partial correlations were statistically significant.

Distribution of Lipid, Inflammatory, and Hemostatic Markers

Table 2 shows the distribution of baseline total cholesterol, low-density lipoprotein, HDL, CRP, ICAM, homocysteine, and fibrinogen levels according to categories of education and income. Total cholesterol, low-density lipoprotein cholesterol, and triglyceride levels decreased and HDL cholesterol levels increased with increasing categories of education (P<0.001). CRP levels decreased progressively with increasing categories of education and income. Similar to CRP, ICAM, fibrinogen, and homocysteine levels all decreased with increasing levels of education and income, although the degree of difference in homocysteine levels was less striking than that of the other novel risk markers of CVD.

Education, Income, and CVD Events

In multivariate models, we observed a progressive decrease in the relative risk of incident CVD events with increasing education and income categories (Table 3). Over 10 years of follow-up, 620 women developed incident CVD events (myocardial infarction, 151; ischemic stroke, 168; CVD death, 74;
percutaneous transluminal coronary intervention, 139; and coronary artery bypass graft surgery, 88). In models that included increasing education categories and adjusted for age and race, the relative risks for CVD events were 1.0, 0.7, 0.5, and 0.8 (P for trend <0.001). After full adjustment for traditional and novel CVD risk factors (age, race, past and current smoking, current and past hormone use, diabetes, history of hypertension, alcohol, physical activity, body mass index, family history of myocardial infarction, <60 years of age, low-density lipoprotein, HDL, triglycerides, CRP, fibrinogen, ICAM, and homocysteine), the relative risks of CVD events were 1.0, 0.8, 0.7, 0.6, and 0.8. (P for trend=0.006).

Similarly, for increasing income categories, the age- and race-adjusted relative risks of CVD events were 1.0, 1.0, 0.9, 0.7, 0.7, and 0.4 (P<0.001), and the traditional and novel CVD risk factor adjusted relative risks were 1.0, 1.2, 1.1, 0.9, 1.0, and 0.8 (P for trend=0.08). Because age could affect the observed relationship between income and CVD events, we also performed age-stratified analyses across income categories (age <65 years: fully adjusted relative risk for CVD, 1.0,

| TABLE 2. Median Levels of Lipid and Novel Markers of CVD Based on Education and Income Categories |
|---------------------------------|---------------------------------|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|
1.7, 1.3, 1.1, 1.2, and 1.0; $P=0.15$; age ≥65 years: fully adjusted relative risk for CVD, 1.0, 0.9, 1.1, 0.6, 0.9, and 0.5; $P=0.23)$. The Figure shows the event-free survival for women based on education or income level.

An evaluation of the accuracy of using Cox proportional hazard models that used a linear term for either education/income to assess the relationship between CVD events and education/income revealed that the use of a linear term instead of education/income categories was appropriate (education: difference in likelihood ratio $\chi^2$ statistic $= 6.5$, $df = 3$, $P = 0.09$; income: likelihood ratio $\chi^2$ statistic $= 5$, $df = 4$, $P = 0.3$). An assessment of the impact of potential confounders of the relationship between education/income and CVD events demonstrated that the coefficient related to education in age- and race-adjusted models decreased by almost 50% after adjustment for the traditional and novel risk factors of CVD (education coefficient, from $0.24 \ [P=0.001]$ to $0.12 \ [P=0.006]$). This corresponded to a 21% decrease in CVD events for each 1-category increase in education for age- and race-adjusted models that was attenuated to an 11% decrease in CVD events with each category increase in education level in fully adjusted models (Table 4). Thus, for the relationship between education and CVD events, only $49\%$ of the relationship between these 2 variables could be explained by taking into account the noted traditional and novel risk factors of CVD. In a similar analysis for income, the relationship between income and CVD events was explained entirely by adjusting for traditional risk factors of CVD (income $\beta$ coefficient, from $-0.076 \ [P<0.001]$ to $-0.026 \ [P=0.09]$). Finally, in a joint-effect model, adding income to a model that included traditional CVD risk factors and novel CVD risk factors did not significantly change the $\beta$ coefficient related to education (education $\beta$ coefficient, from $-0.12 \ [P=0.006]$ to $-0.10 \ [P=0.02]$). Table 5 shows a detailed analysis of the individual contributions of

**TABLE 4. $\beta$ Coefficients Related to Education/Income in the Evaluation of the Association Between CVD Events and Income or Education**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Education</th>
<th>Income</th>
<th>$P^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>$-0.24$</td>
<td>$-0.075$</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Model 2</td>
<td>$-0.12$</td>
<td>$-0.026$</td>
<td>$0.09$</td>
</tr>
<tr>
<td>Model 3</td>
<td>$-0.12$</td>
<td>$-0.027$</td>
<td>$0.08$</td>
</tr>
<tr>
<td>Model 4</td>
<td>$-0.10$</td>
<td>$-0.013$</td>
<td>$0.43$</td>
</tr>
</tbody>
</table>

Model 1 was adjusted for age, race. Model 2 was adjusted for age, race, body mass index, history of hypertension, history of diabetes, low-density lipoprotein cholesterol, HDL cholesterol, triglycerides, physical activity, smoking status, hormone use, family history of myocardial infarction before 60 years of age, and alcohol use. Model 3 was adjusted for age, race, body mass index, history of hypertension, history of diabetes, low-density lipoprotein cholesterol, HDL cholesterol, triglycerides, physical activity, smoking status, hormone use, family history of myocardial infarction before 60 years of age, alcohol use, ICAM, CRP, fibrinogen, and homocysteine. Model 4 was adjusted for variables in model 3 plus education or income. For income, the $\beta$ coefficient represents the relative hazard per $10,000$ increase in income.

*Probability value reflects the significance levels for education/income $\beta$ coefficient.
TABLE 5. Evaluation of the Separate Effect of CVD Risk Factors: β Coefficients Related to Education/Income in the Evaluation of the Association Between CVD Events and Income or Education

<table>
<thead>
<tr>
<th>Variable</th>
<th>Education</th>
<th>Income</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index</td>
<td>−0.21</td>
<td>&lt;0.0001</td>
<td>−0.061</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>−0.21</td>
<td>&lt;0.0001</td>
<td>−0.066</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>−0.21</td>
<td>&lt;0.0001</td>
<td>−0.059</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lipids*</td>
<td>−0.18</td>
<td>&lt;0.0001</td>
<td>−0.050</td>
<td>0.001</td>
</tr>
<tr>
<td>Family history of myocardial infarction</td>
<td>−0.24</td>
<td>&lt;0.0001</td>
<td>−0.075</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Novel CVD risk factors†</td>
<td>−0.19</td>
<td>&lt;0.0001</td>
<td>−0.053</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Behavioral risk factors‡</td>
<td>−0.17</td>
<td>&lt;0.0001</td>
<td>−0.050</td>
<td>0.002</td>
</tr>
</tbody>
</table>

All above models include age and race plus the referred-to CVD risk factor (eg, diabetes is a variable for education/income, age, race, and diabetic status). For income, the β coefficient represents the relative hazard per $10,000 increase in income. Probability value reflects the significance levels for education/income β coefficient.

†CRP, ICAM, fibrinogen, and homocysteine.
‡Hormone use, physical activity, smoking status, and alcohol.

Discussion

In this prospective cohort of female health professionals followed up over a 10-year period, we observed a progressive decrease in incident CVD events with increasing levels of education and increasing levels of income. Although approximately half of the relationship between education and events was attributable to differences in traditional CVD risk factors, we found little evidence that biomarkers of inflammation or hemostasis explained much of the remaining effect. In contrast, the relationship of income to incident CVD events in this cohort was almost entirely attributable to traditional risk factors. Our data thus support the hypothesis that the effects of education that protect against CVD are not strictly related to income level. Our findings add information to current literature by demonstrating these findings prospectively in a large cohort of relatively well-educated women and by assessing the impact of inflammatory and hemostatic CVD risk factors on the relationship between education or income and incident CVD events.

The current data concur with previous reports showing that CVD risk decreases with improvements in SES indicators such as occupational grade, education, and income. Moreover, these results demonstrate that education is a powerful determinant of CVD risk, even in a cohort of relatively educated and employed women who all have additional formal education beyond high school. This finding supports the previously observed lack of a threshold effect in the observed SES-mortality gradient. Our data indicate that obtaining a bachelor’s degree confers additional cardiovascular protection. Without the intent to imply causation, education is nonetheless likely a robust measure of SES compared with other measures such as income and occupation because it varies little in adulthood and is measurable with less error than other measures of SES. Furthermore, although theoretically poor childhood health might influence educational attainment, most adults have completed their formal education long before many chronic diseases develop. Our results are similar to those of the landmark Whitehall Study of 17,530 civil servants in England that showed a decrease in CVD mortality with improvements in employment grade; coronary mortality was 3.6 times higher among civil servants who had lower professional grade compared with those who belonged to the professional executive grade. Multiple studies from the United States also indicate an inverse gradient between education and CVD. For example, the US National Longitudinal Study demonstrated that among white and black men and women, higher levels of education were associated with a lower incidence of ischemic heart disease death, a gradient that varied depending on gender and race. Because our present study includes predominantly white females, the joint impact of race/ethnicity and gender on the SES-CVD relationship cannot be reliably assessed. We have, however, adjusted for self-reported race/ethnicity in our analyses.

The present study also shows that the traditional risk factors of CVD account for only approximately half of the observed significant relationship between education and CVD risk. This finding is not unlike that noted in the Whitehall study in which only 25% of the SES-CVD gradient could be attributed to traditional CVD risk factors. Whether one should control for these traditional CVD risk factors in the SES-CVD relationship remains a matter of debate because education can affect health behavior. However, adding variables that potentially are on the causal pathway of the association between SES and CVD can elucidate mechanisms by which SES influences CVD risk. Unlike our data for education, controlling for traditional CVD risk factors explained almost the entire effect of income on CVD risk. Although income might influence lifestyle choices and control, income is probably more prone to reporting error and influence from other factors such as family size and variation over time. Wealth rather than income is probably a more accurate measure of SES because it can dictate the ability of an individual or household to respond to stressors. In these data, it also is possible that characteristics of retired women who would have lower income but greater wealth than younger women could confound the multivariate relationship between income and CVD risk. However, our age-stratified analyses across income categories demonstrated that our main income effect remained consistent for women <65 and ≥65 years of age.

Because an essential component of atherosclerosis relates to the role of the inflammatory and coagulation systems, inflammatory and hemostatic markers of coronary artery disease risk might contribute to the observed SES-CVD gradient and thus the inability of traditional CVD risk factors to explain the relationship. The latter is important because, as noted in our data, levels of these novel CVD risk factors generally decrease with improvements in education and income, a finding that suggests they might be causally related to the observed SES-CVD relationship. We therefore controlled for CRP, ICAM, fibrinogen, and homocysteine as potential mediators of the SES-CVD relationship. However, we found that although the novel CVD factors appear to have similar effects on the SES-CVD risk relationship. However, adding variables that potentially are on the causal pathway of the association between SES and CVD can elucidate mechanisms by which SES influences CVD risk. Unlike our data for education, controlling for traditional CVD risk factors explained almost the entire effect of income on CVD risk. Although income might influence lifestyle choices and control, income is probably more prone to reporting error and influence from other factors such as family size and variation over time. Wealth rather than income is probably a more accurate measure of SES because it can dictate the ability of an individual or household to respond to stressors. In these data, it also is possible that characteristics of retired women who would have lower income but greater wealth than younger women could confound the multivariate relationship between income and CVD risk. However, our age-stratified analyses across income categories demonstrated that our main income effect remained consistent for women <65 and ≥65 years of age.

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markers, particularly ICAM, have modest correlations with education and income, controlling for the aforementioned parameters did not further attenuate the education-CVD gradient, suggesting either that these novel CVD risk factors are not major intermediaries of this relationship or that they are capturing elements of the CVD-SES relationship similar to the traditional CVD risk factors.

These data add information to the literature because previous work examining the association between SES indicators and inflammation has been limited to men, cross-sectional studies, and data that used intermediate clinical vascular disease correlates. Lynch et al.27 used income data among Finnish men examined the role of job control on coronary disease risk. For hemostatic markers has not been characterized, but it is plausible the association between these factors and inflammatory and psychosocial stress, social support, and job control. At present, data from the National Health and Nutrition Surveys25 also show a magnitude and direction of association between years of education and CRP levels similar to those in this study. In contrast, data from Kivimaki et al.26 indicate that any association between CRP, socioeconomic position, and carotid atherosclerosis was abolished after control for indexes of adiposity. Testing for interactions between high (CRP \( \geq 3 \) mg/L) or low (CRP \(<3\) mg/L) risk levels and education (\(P=0.3\) for the interaction term) or income (\(P=0.07\)) revealed no significant interaction between CRP and education/income categories in our cohort.

The residual protective effect of education on CVD risk might be related to other factors such as access to care, chronic psychosocial stress, social support, and job control. At present, the association between these factors and inflammatory and hemostatic markers has not been characterized, but it is plausible that some relationship exists. To this end, several authors have examined the role of job control on coronary disease risk. For example, Lynch et al.27 used income data among Finnish men from the Kuopio Ischemic Heart Disease Risk Factor Study and demonstrated that control for known CVD risk factors resulted in a substantial reduction in the CVD mortality difference in high-income compared with low-income groups. Additional adjustment for psychological and behavioral factors abolished any difference noted in CVD mortality by income category. Marmot et al.28 also evaluated the impact of job control on incident coronary heart disease in the Whitehall II study and found that the inverse CHD incidence related to improvements in office grade was reversed in men and almost eliminated in women after controlling for multiple CVD risk factors, with the greatest contribution from adjustment of job control. The potential importance of influence of psychosocial factors on the SES-CVD gradient is suggested by findings from the international INTERHEART (effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries) study, which showed that the population-attributable risk for psychosocial factors for acute myocardial infarction was 32.5%.29

The limitations of the present study deserve mention. First, because participants were apparently healthy, middle-aged health professionals who have a relatively narrow range of income and education, generalizability to other populations might be restricted. However, the fact that an inverse SES-CVD gradient is observed even in this well-educated and employed group highlights the power of the SES contribution to CVD events. Additionally, this cohort allows the simultaneous examination of several intertwined SES indicators: income, education, and health profession. Second, because of the relatively small number of women from various race/ethnic backgrounds, our ability to evaluate the SES-CVD gradient and any interrelation between race and gender on the latter is limited. Third, specific reliable data on diet, childhood SES, and neighborhood environment are unavailable for our cohort and could have important effects on the SES-CVD relationship. Despite this, one could hypothesize that because factors such as neighborhood environment contribute to chronic stress, measurement of certain novel markers of CVD risk might result in a more global assessment of such potential risk factors.

Conclusions

Although improvements in education and income were associated with improvements in biochemical indexes, our data demonstrate a strong inverse education-CVD gradient among middle-aged women that was not entirely accounted for by traditional and novel risk factors of CVD. Because inflammation and hemostasis are critical components in the development of ischemic disease, these data add information to the literature by demonstrating that although the examined biomarkers of CVD risk decrease with increasing levels of income and education, these biomarkers do not fully explain the SES-CVD relationship. Furthermore, although education and income are highly correlated, the lack of an independent relationship between income and CVD risk in these data highlights the notion that different measures of SES reflect different aspects of social stratification. Moreover, no one measure sufficiently captures the essence of SES.30,31 From a public health perspective, these data support the need for CVD risk reduction programs and policies that inherently incorporate social and environmental components.

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Disclosures

Dr Ridker is named as a coinventor on pending patents filed by Brigham and Women’s Hospital that relate to use of inflammatory biomarkers in cardiovascular disease. The other authors report no conflicts.

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**CLINICAL PERSPECTIVE**

Although lower socioeconomic status (SES) is associated with poorer cardiovascular outcomes (cardiovascular disease [CVD]), the exact mechanism of this relationship remains unclear. Because SES often dictates health behaviors, access to medical care, and long-term stress, whether moderators of the biochemical stress response such as inflammatory and hemostatic markers play a role in the relationship between SES and CVD is of clinical importance. In this prospective examination of female health professionals, we found that improvements in SES as measured by income and education were associated with lower levels of certain markers of inflammation (C-reactive protein, soluble intercellular adhesion molecule) and hemostasis (fibrinogen and homocysteine) and better cardiovascular outcome. However, although the relationship between income and incident cardiovascular events could be explained by the traditional CVD risk factors, only half of the relationship between education and CVD could be attributed to the traditional CVD risk factors, with little remaining effect of the novel risk factors. These findings suggest that the evaluated novel risk factors either capture elements of the CVD–socioeconomic status relationship similar to the traditional risk factors or are not major mediators of this association. Furthermore, although income and education are correlated, the lack of an independent relationship between income and CVD emphasizes the differential impact of different measures of socioeconomic status on health. From clinical and public health perspectives, these results underscore the point that only targeting CVD traditional risk factor reduction without incorporating programs and policies that address socioenvironmental variables does not address the full response to the CVD burden.
Impact of Traditional and Novel Risk Factors on the Relationship Between Socioeconomic Status and Incident Cardiovascular Events
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