Association of Educational Level with Inflammatory Markers in the Framingham Offspring Study

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Socioeconomic position consistently predicts coronary heart disease; however, the biologic mechanisms that may mediate this association are not well understood. The objective of this study was to determine whether socioeconomic position (measured as educational level) is associated with inflammatory risk factors for coronary heart disease, including C-reactive protein, interleukin-6, soluble intercellular adhesion molecule-1, monocyte chemoattractant protein-1, and P-selectin. The study sample included 2,729 participants (53.4% women; mean age, 62 ± 10 years) from the US Framingham Offspring Study cohort who attended examination cycles 3 (1984–1987) and 7 (1998–2001) and provided educational attainment data. Inflammatory markers were measured in fasting serum samples. Multivariable linear regression analyses were performed, adjusting for potential confounders including age, sex, and clinical risk factors. In age- and sex-adjusted analyses, educational attainment was significantly inversely associated with C-reactive protein ($p < 0.0001$), interleukin-6 ($p < 0.0001$), soluble intercellular adhesion molecule-1 ($p < 0.0001$), and monocyte chemoattractant protein-1 ($p = 0.0004$). After further adjustment for clinical risk factors, educational level remained significantly associated with C-reactive protein ($p = 0.0002$), soluble intercellular adhesion molecule-1 ($p = 0.01$), and monocyte chemoattractant protein-1 ($p = 0.01$). In conclusion, educational attainment is associated with inflammatory risk factors for coronary heart disease. The association provides evidence suggestive of a biologic pathway by which socioeconomic position may predispose to coronary heart disease.

cohort studies; inflammation; risk factors; social class

Abbreviations: IL-6, interleukin-6; MCP-1, monocyte chemoattractant protein-1; sICAM-1, soluble intercellular adhesion molecule-1.
of coronary heart disease. Meta-analyses have shown that elevated concentrations of C-reactive protein (2) and soluble intercellular adhesion molecule-1 (sICAM-1) (3) are prospectively associated with the incidence of coronary heart disease. Several longitudinal studies have demonstrated that, after adjustment for covariates, elevated interleukin-6 (IL-6) concentrations predict cardiovascular events (4–7). Elevated monocyte chemoattractant-1 (MCP-1) levels also have been associated with acute coronary syndromes (8, 9), myocardial infarction, and death (10) in case-control (8, 9) and longitudinal (10) studies. In addition, in prospective nested case-control studies, P-selectin levels have been found to be elevated in patients with prevalent coronary heart disease (11) and in women (12) (but not men (3)) who developed cardiovascular events.

Preliminary findings suggest an association between education and inflammatory markers. Specifically, low educational levels have been significantly associated with elevated C-reactive protein concentrations (13–16), including in British and Greek samples after adjusting for covariates such as sex, age, body mass, smoking, alcohol consumption, compliance with medication, diet, and physical activity (15, 16). To our knowledge, the association between education and inflammatory markers in a North American population, after adjusting for potential confounders, has not yet been determined. Furthermore, to our understanding, the relation between educational level and concentrations of other inflammatory markers or adhesion molecules such as IL-6, sICAM-1, P-selectin, or MCP-1 has not been studied.

We hypothesized that educational attainment is associated with C-reactive protein, IL-6, sICAM-1, P-selectin, and MCP-1 in the Framingham, Massachusetts, community. Furthermore, we aimed to elucidate whether the relations between education and inflammatory markers were independent of clinical cardiovascular disease and its risk factors, as well as depression and income.

MATERIALS AND METHODS

Study sample

The present investigation was based on participants in the Framingham Offspring Study, which began in 1971 with recruitment of 5,124 US men and women who were offspring, or spouses of the offspring, of the original Framingham Heart Study cohort. The design and selection criteria of the Framingham Offspring Study have been described elsewhere (17). All study participants received routine medical history and physical examinations, laboratory assessments of cardiovascular risk factors, and anthropometric measurements. Participants were asked not to eat or drink (except water or decaffeinated black coffee or tea) after 8 p.m. on the evening prior to the examination.

There were 3,267 participants who attended the seventh examination cycle and 3,682 participants who completed the supplement to the third examination cycle, at which educational data were collected. A total of 2,901 attended both examinations. Educational data were missing for 172 participants, leaving data on 2,729 for analysis. The inflammatory markers (dependent variables) and covariates were obtained from the seventh examination cycle data.

Educational level

Educational attainment was measured both as a continuous variable (years of school completed) and as an ordinal variable (highest degree earned). For the former, responses ranged from 1 year to 17 years or more. Labels were provided to orient respondents; response options were 1 year (elementary), 7 years (junior high), 12 years (high school), 15 years (college), and so on. The highest degree earned was obtained from the question, “What is the highest degree you earned?” with the response options being 1) high school diploma, 2) associate’s degree, 3) bachelor’s degree, 4) master’s degree, 5) doctorate degree, and 6) none of the above.

Inflammatory markers

Fasting morning serum samples were collected and then stored at −70°C. Serum C-reactive protein was measured once by using a high-sensitivity assay (BN100 nephelometer; Dade Behring, Inc., Deerfield, Illinois); mean interassay coefficient of variation, 3.2 percent on 139 phantom replicates). IL-6, sICAM-1, MCP-1, and plasma P-selectin levels were measured in duplicate and were averaged using commercially available enzyme-linked immunoassay kits (R&D Systems, Minneapolis, Minnesota) following previously described quality control procedures (18, 19). Biomarker measurement reproducibility was good (intraassay coefficient of variation for IL-6, 3.1 (standard deviation, 2.1) percent; for sICAM-1, 3.7 (standard deviation, 2.4) percent; for MCP-1, 1.9 (standard deviation, 1.6) percent; and for P-selectin 3.0 (standard deviation, 2.2) percent).

Covariates

Clinical covariates, except education and income, were classified at examination 7, the same examination at which the biomarkers were ascertained. Current cigarette smoking was determined by self-report if it occurred regularly in the past year. Blood pressure was determined as the average of the two seated blood pressure measurements by the clinic’s physician. Hypertension was diagnosed if systolic blood pressure was ≥140 mmHg or diastolic blood pressure was ≥90 mmHg or the participant was receiving treatment. Prevalent cardiovascular disease (coronary heart disease, stroke, intermittent claudication, congestive heart failure) was documented as previously described (20). Body mass index was calculated as weight in kilograms divided by the square of height in meters (kg/m²). High density lipoprotein and total cholesterol levels were measured by automated enzymatic techniques (21). The Framingham Offspring Study laboratory participates in the lipoprotein cholesterol laboratory standardization program administered by the Centers for Disease Control and Prevention. Depression was measured by using the Center for Epidemiologic Studies Depression (CES-D) scale and was adjusted for in analyses as a continuous variable. Annual family income was measured by self-report from the examination.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Systolic blood pressure (mmHg)</th>
<th>Diastolic blood pressure (mmHg)</th>
<th>Total/HDL‡</th>
<th>Body mass index (kg/m²)</th>
<th>Current smoker (%)</th>
<th>Lipid-lowering medication (%)</th>
<th>Prevalent CVD‡ (%)</th>
<th>Depressive symptoms (CES-D‡ score)</th>
<th>Annual family income ($000s)§</th>
<th>p value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>62.1</td>
<td>127.0</td>
<td>73.8</td>
<td>4.1</td>
<td>28.1</td>
<td>11.9</td>
<td>21.3</td>
<td>13.5</td>
<td>5.4</td>
<td>41.0</td>
<td>0.0001</td>
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<tr>
<td>(n = 2,729)</td>
<td>(n = 1,536)</td>
<td>(n = 295)</td>
<td>(n = 537)</td>
<td>(n = 192)</td>
<td>(n = 124)</td>
<td>(n = 361)</td>
<td>(n = 361)</td>
<td>(n = 499)</td>
<td>(n = 318)</td>
<td></td>
</tr>
<tr>
<td>PE</td>
<td>61.8</td>
<td>126.3</td>
<td>4.0</td>
<td>27.9</td>
<td>10.7</td>
<td>32.6</td>
<td>12.2</td>
<td>5.1</td>
<td>40.2</td>
<td></td>
</tr>
<tr>
<td>95% CI†</td>
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<td>127.7</td>
<td>4.1</td>
<td>28.2</td>
<td>13.1</td>
<td>36.2</td>
<td>14.8</td>
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</tbody>
</table>

* Unless otherwise noted, all point estimates (PE) are expressed as the mean.
† Derived from regression analyses adjusted for age and sex.
‡ CI, confidence interval; HDL, high density lipoprotein; CVD, cardiovascular disease; CES-D, Center for Epidemiologic Studies Depression.

3 cycle (1984–1987), with the following response options: no income (n = 4), <$5,000 (n = 14), $5,000–9,999 (n = 19), $10,000–14,999 (n = 68), $15,000–19,999 (n = 106), $20,000–24,999 (n = 192), $25,000–29,999 (n = 214), $30,000–34,999 (n = 257), $35,000–39,999 (n = 218), $40,000–44,999 (n = 239), $45,000–49,999 (n = 204), and ≥$50,000 (n = 718). The midpoint of each category of family income was calculated (the “≥$50,000” category was set to equal $65,000), and values were treated as continuous variables in the analyses.

The Boston Medical Center Institutional Review Board approved the study. In addition, all subjects provided written informed consent.

Statistical analysis

Descriptive statistics, including means, standard deviations, medians, and interquartile ranges, were generated for continuous variables, and proportions were generated for discrete variables. Because of the nonnormality in the distributions, the inflammatory markers were log-transformed for all analyses. For this paper, we back-transformed the logged values and present summary statistics on the raw scales. Descriptive statistics for study variables were generated, including for each educational group defined by the highest degree earned.

Age- and sex-adjusted, as well as multivariable-adjusted, associations of years of education with each of the inflammatory markers were estimated by using multiple regression analysis. For the multivariable analyses, we constructed three models adjusted for 1) age and sex; 2) age, sex, and income; and 3) age, sex, and clinical risk factors. Clinical risk factors were smoking, systolic blood pressure, diastolic blood pressure, total cholesterol:high density lipoprotein cholesterol ratio, body mass index, lipid-lowering medication, antihypertensive medication, depression, and a history of cardiovascular disease. There was no evidence of effect modification by sex; consequently, data on the sexes were pooled. Analyses were conducted by using the statistical software program SAS, version 8.2 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

The 2,729 Framingham Offspring Study participants were 53.4 percent women, and the mean age was 62.1 (95 percent confidence interval: 61.8, 62.5) years for the examination at which the markers and clinical covariates were assessed (table 1). Increasing educational levels generally were significantly associated with more favorable cardiovascular risk factors. In addition, higher educational attainment was significantly associated with lower prevalence of clinical cardiovascular disease, and fewer depressive symptoms, and with higher annual family income (table 1).

Age- and sex-adjusted analyses showed significant inverse graded associations between highest educational
degree earned and concentrations of C-reactive protein \( (p < 0.0001) \), IL-6 \( (p < 0.0001) \), sICAM-1 \( (p < 0.0001) \), and MCP-1 \( (p = 0.002) \) (table 2). Age- and sex-adjusted analyses in which “years of schooling” was used produced similar findings, with the exception that years of schooling additionally were significantly associated with P-selectin concentrations \( (p = 0.04) \) (table 3). In the models in which we adjusted for age, sex, and annual family income, education was significantly associated with C-reactive protein \( (p < 0.0001) \), IL-6 \( (p = 0.004) \), sICAM-1 \( (p < 0.0001) \), and MCP-1 \( (p = 0.0006) \). Furthermore, after adjusting for clinical risk factors (including age, sex, smoking, systolic blood pressure, diastolic blood pressure, total cholesterol: high density lipoprotein cholesterol ratio, body mass index, lipid-lowering medication, antihypertensive medication, prevalent cardiovascular disease, and depression), education was significantly associated with concentrations of C-reactive protein \( (p = 0.0002) \), sICAM-1 \( (p = 0.01) \), and MCP-1 \( (p = 0.01) \).

Subanalyses were performed on the relation between family income and inflammatory markers adjusted for age, sex, and education. Income was significantly associated with logarithmic concentrations of C-reactive protein \( (\beta = -0.0029, p = 0.04) \) and IL-6 \( (\beta = -0.0024, p = 0.006) \) and was less strongly associated with sICAM-1 \( (\beta = -0.00058, p = 0.06) \), MCP-1 \( (\beta = -0.00019, p = 0.65) \), and P-selectin \( (\beta = -0.00066, p = 0.17) \) (note that regression coefficient \( \beta \) represents the change in logarithmic concentration of each inflammatory marker per $1,000 change in income). Annual family income and years of education correlated with a coefficient of 0.30 \( (p < 0.0001) \). The statistical significance appeared to be stronger for the association between education and inflammatory markers than between income and inflammatory markers (refer to the results given above compared with those shown in table 3).

**DISCUSSION**

Our study demonstrated that, in age- and sex-adjusted analyses, educational attainment was significantly associated with the inflammatory markers C-reactive protein, IL-6, sICAM-1, and MCP-1. In analyses that additionally...
adjusted for potential confounders that may also mediate the relation between education and inflammatory marker concentrations (i.e., income or clinical risk factors), educational level remained significantly associated with C-reactive protein, sICAM-1, and MCP-1 levels.

Prior literature

There is remarkable consistency in the literature showing that educational levels and C-reactive protein values are inversely associated. The significant negative relation between educational attainment and C-reactive protein levels in our study is in agreement with findings from two European studies that conducted adjusted analyses (15, 16) and with those from two other studies that did not adjust for covariates (13, 14). The findings reported here are, to our knowledge, the first to demonstrate a significant association between education and C-reactive protein concentrations after adjusting for depression or the biologic cardiovascular risk factors systolic blood pressure, diastolic blood pressure, and total cholesterol:high density lipoprotein cholesterol ratio. Although there is now reasonable evidence regarding the relation between educational attainment and C-reactive protein concentrations, to our knowledge this is the first study to date that has investigated the associations between educational attainment and concentrations of the markers IL-6, sICAM-1, MCP-1, and P-selectin.

Measures of socioeconomic position other than educational attainment, such as income and occupation, have also been investigated in relation to inflammatory markers. Specifically, studies have shown a significant association between socioeconomic position and C-reactive protein, whether socioeconomic position was measured as employment grade (16), income (16), or a cumulative score incorporating education and income (22). A study within the Third National Health and Nutrition Examination Study found no association between socioeconomic position and C-reactive protein if socioeconomic position was measured as a poverty index (13). With regard to IL-6, most (23–25) but not all (26) studies have found no significant associations between socioeconomic position and IL-6. However, several studies to date have had sample sizes of fewer than 200 participants and/or binomial categorizations of socioeconomic position that limited statistical power to detect differences between groups. The findings reported in our study agree with those in the majority of papers that found no significant association between socioeconomic position and IL-6. One interesting study by Brydon et al. (23) demonstrated no significant associations between socioeconomic position and IL-6 concentrations at baseline; however, 2 hours after a mental stress test, IL-6 concentrations were significantly higher in participants of low compared with high socioeconomic position. To our knowledge, no studies have linked socioeconomic position to sICAM-1, P-selectin, or MCP-1. An initial indication of possible associations was found in a case-control study by Malik et al. (3) In the Malik report, additionally adjusting for socioeconomic position attenuated the ability of sICAM-1 to predict coronary heart disease and did not attenuate the predictive ability of P-selectin (in fact, it was slightly strengthened) (3). These findings provide support for the results reported in our paper, in that education was significantly negatively associated with sICAM-1 and not P-selectin concentrations.

In the present study, we investigated the relation between income and inflammatory markers in analyses adjusted for age, sex, and education. Education tended to be a stronger predictor than income, likely because of at least two reasons. First, income is fairly high in the Framingham Offspring Study cohort compared with the US population. In 1986 (during the time of the income sampling, 1984–1987), the poverty line was set at $7,138 for a family of two and $11,203 for a family of four living in the United States (27). At that time, according to the US Census Bureau, 13.6 percent of the US population was at or below the poverty line (28). In the current study, only 1.6 percent of participants had an annual family income of less than $10,000 per year, and 4.6 percent of participants had an income below $15,000. The lack of Framingham Offspring Study participants in the lower income categories may have reduced the effect size compared with what would be observed in nationally representative samples. Second, for 648 (22.3 percent) study participants, information on income was missing compared with only 172 (5.9 percent) participants for whom data on education were missing. Consequently, the sample may have been less representative of the Framingham community, and there may have been less statistical power for income analyses compared with the analyses using educational level. Most studies in the United States use educational attainment as a measure of socioeconomic position (1) because there are a number of benefits in doing so. Specifically, education is frequently completed after early adulthood and is consequently less influenced by poor adult health than is income, which may be more influenced by adult illness. Furthermore, participants are typically more likely to be willing to report education than income, thereby reducing response bias. However, measuring income is beneficial in that it is more sensitive than education to current workforce participation and is a measure of participants’ access to goods and services (such as medical care) that may protect against disease. Future studies of cohorts including substantial numbers of low- and high-income-bracket participants may be able to better determine the relation between income and inflammatory markers.

Mechanisms

A major mechanism by which educational attainment may influence inflammatory markers is through health behaviors. A number of studies have demonstrated that, compared with higher educational levels, low educational attainment is associated with a higher prevalence of cigarette smoking, excessive alcohol consumption, and obesity and a lower prevalence of leisure-time physical activity, as reviewed by Kaplan and Keil (1). Cigarette smoking and obesity have been correlated with the inflammatory markers reported in this cohort (19, 29–31) and may be a mechanism by which education influences inflammatory marker concentrations. A second potential mechanism is through psychological distress, such as depression and anxiety. A recent meta-analysis demonstrated that persons of low socioeconomic position,
compared with those of high socioeconomic position, had a 1.81 higher odds of reporting depression (32). Several other studies have reported a negative association between socioeconomic position and anxiety (33). Longitudinal studies suggest that the direction of causality is primarily from socioeconomic position to depression (rather than predominantly due to depression leading to downward socioeconomic mobility or impairing upward mobility) (33). This direction may be due to the greater prevalence of adversity and stress among persons in the lower socioeconomic positions, leading to increased psychopathology (33). A number of reports have demonstrated that major depression and clinical depression are associated with elevated inflammatory markers (including C-reactive protein, IL-6, and ICAM-1 (34, 35)), but the findings on the associations between depressive symptoms and inflammatory markers remain inconsistent (reviewed by Empana et al. (35)). In summary, evidence suggests that health behaviors and psychological distress are two major pathways by which socioeconomic position may influence inflammatory markers. Our analyses—which showed that the strength of association was reduced after adjusting for smoking, body mass index, lipid-lowering medication, antihypertensive medication, and depression—support these factors as potential mediators. However, the fact that the associations typically retained statistical significance suggests that the relation between education and inflammatory markers may be accounted for by other unmeasured variables.

Strengths and limitations

Strengths of the present investigation include the well-characterized community-based cohort in which a wide range of cardiovascular risk factors were routinely ascertained, enabling us to adjust for a large number of potential confounding variables. Limitations of the study include its observational design and the ascertainment of education and income on average 14 years prior to inflammatory markers, resulting in the potential for misclassification of educational attainment and income. Additionally, because the historical design of the Framingham Offspring Study reflected the population of Framingham, Massachusetts, at study onset in 1948, the original and Offspring cohorts are largely composed of White participants. Consequently, the generalizability of our findings to other races/ethnicities and younger individuals is uncertain.

Clinical and research implications

In conclusion, this study provides evidence that educational attainment is associated with inflammatory risk factors for coronary heart disease, including C-reactive protein, IL-6, sICAM-1, and MCP-1. These findings suggest one potential biologic mechanism for the consistently observed associations between educational attainment and coronary heart disease in prospective studies (1). Future research, using racially/ethnically diverse cohorts and other population-and community-based samples, will further clarify the potential effects of socioeconomic position on concentrations of inflammatory markers.

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Conflict of interest: none declared.

REFERENCES