Relation of Educational Level to Inflammation-Sensitive Biomarker Level

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It is a well-established finding that cardiovascular morbidity varies among groups of different socioeconomic status. Inflammatory processes have been proposed as a possible mediator of this variance. Level of education is an important indicator of socioeconomic status, inversely related to levels of inflammatory biomarkers. Whether this association was significant in a subpopulation of highly educated individuals was questioned. This cross-sectional study enrolled attendees of an executive health screening program intended specifically for executive and high-wage personnel from September 2002 to November 2007. A detailed questionnaire, anthropometric measurements, and laboratory data were used to determine self-reported years of education and cardiovascular risk factors. Linear regression models included high-sensitivity C-reactive protein, fibrinogen, erythrocyte sedimentation rate, and white blood cell count as dependent variables and were adjusted for multiple potential confounders. Data for 8,998 subjects (5,757 men, 3,241 women) with a mean age of 44 years (range 18 to 84) were analyzed. More than two-thirds reported ≥14 years of schooling, and >2,900 reported ≥17 years of schooling. We found a statistically significant inverse association between number of school years and high-sensitivity C-reactive protein, fibrinogen, and erythrocyte sedimentation rate. Higher levels of education were associated with lower prevalences of diabetes and current smoking in both genders and lower prevalences of hypertension and dyslipidemia in women. In conclusion, level of education was inversely associated with inflammatory biomarkers and prevalence of cardiovascular risk factors, even within highly educated populations. **(Am J Cardiol 2008;102:1034–1039)**

We analyzed the association between years of schooling and various inflammatory variables, as well as cardiovascular risk factors, in a large survey of apparently healthy subjects. Level of education is perhaps the most important predictor of socioeconomic status (SES), such that when controlled for, the association between income inequality and health across nations disappears.[1] This survey was held as part of an executive health screening program offered by workplaces and intended specifically for executive and high-wage personnel. The presumed level of education for this cohort thus was higher than that of the general population, enabling us to explore whether the inverse association of schooling on inflammatory biomarkers and prevalence of cardiovascular risk factors remains significant within a subpopulation of a higher educational level.

Methods

We analyzed data collected through the Tel-Aviv Medical Center Inflammation Survey (TAMCIS), a registered data bank of the Israeli Ministry of Justice.[2–8] This relatively large survey was composed of apparently healthy persons attending the medical center for periodic health examinations.

All patients attending the Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel, for routine health examinations from September 2002 to November 2007 were invited to participate in the TAMCIS. Subjects were recruited during routine annual health checkups and gave their written consent in accordance with the guidelines of the Institutional Ethics Committee. A total of 12,251 subjects gave their informed consent (7,702 men, 4,549 women).

Level of education was assessed using self-reported years of schooling from a questionnaire. The cohort was initially analyzed as a whole, and significant associations were found between level of education and inflammatory biomarkers (not shown). To minimize the effect of some important confounders, we excluded 2,204 subjects based on their medical findings, including malignant conditions, immunosuppressive therapy, known inflammatory disease (e.g., arthritis, inflammatory bowel disease, and psoriasis), pregnancy, steroidal or nonsteroidal treatment (except for aspirin ≤325 mg/day), and acute infection or invasive procedures (e.g., surgery or catheterization) during the past 6

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Table 1
Mean anthropometric variables, laboratory findings, and inflammation-sensitive biomarkers by tertile of school years for men

Education (yrs)	Tertile 1 (n = 1,780)	Tertile 2 (n = 2,069)	Tertile 3 (n = 1,908)	ANOVA p Value	p Value for Trend
	12–14	15–16	≥17		
Age (yrs)	43 ± 13	43 ± 11	46 ± 10	<0.001	<0.001
Waist circumference (cm)	95 ± 11	95 ± 11	96 ± 10	0.001	0.003
Body mass index (kg/m^2)	27 ± 7	27 ± 4	27 ± 4	0.621	0.874
Systolic blood pressure (mm Hg)	125 ± 15	124 ± 14	125 ± 14	0.019	0.160
Diastolic blood pressure (mm Hg)	78 ± 8	78 ± 8	78 ± 8	0.830	1.000
Plasma glucose (mg/dl)	96 ± 22	94 ± 15	94 ± 14	<0.001	0.001
High-density lipoprotein cholesterol (mg/dl)	50 ± 10	51 ± 10	51 ± 11	0.019	0.013
Low-density lipoprotein cholesterol (mg/dl)	119 ± 33	122 ± 32	124 ± 31	<0.001	<0.001
Triglycerides (mg/dl)	112 ± 2	112 ± 2	114 ± 2	0.435	0.212
Alcohol consumption (glasses/wk)	1.2 ± 2.3	1.3 ± 2.2	1.4 ± 2.4	0.006	0.001
Physical activity (h/wk)	2.6 ± 3.5	2.4 ± 2.8	2.3 ± 2.5	0.009	0.003
hs-CRP (mg/L)	1.5 ± 2.8	1.4 ± 2.8	1.3 ± 2.7	0.001	<0.001
Fibrinogen (mg/dl)	282 ± 61	277 ± 56	279 ± 54	0.043	0.123
ESR (mm/h)	10 ± 9	10 ± 7	10 ± 7	0.075	0.240
White blood cell count (10^3 cells/μl)	6.8 ± 1.7	6.7 ± 1.6	6.7 ± 1.5	0.011	0.003

Values expressed as mean ± SD.
ANOVA = 1-way analysis of variance.

Table 2
Mean anthropometric variables, laboratory findings, and inflammation-sensitive biomarkers by tertiles of school years for women

Education (yrs)	Tertile 1 (n = 1,164)	Tertile 2 (n = 1,038)	Tertile 3 (n = 1,039)	ANOVA p Value	p Value for Trend
	12–14	15–16	≥17		
Age (yrs)	46 ± 11	43 ± 11	46 ± 10	<0.001	0.441
Waist circumference (cm)	84 ± 12	81 ± 11	82 ± 11	<0.001	<0.001
Body mass index (kg/m^2)	26 ± 5	25 ± 5	25 ± 4	<0.001	<0.001
Systolic blood pressure (mm Hg)	119 ± 16	116 ± 15	116 ± 15	<0.001	0.001
Diastolic blood pressure (mm Hg)	74 ± 8	73 ± 8	73 ± 7	<0.001	<0.001
Plasma glucose (mg/dl)	93 ± 22	89 ± 14	90 ± 14	<0.001	<0.001
High-density lipoprotein cholesterol (mg/dl)	62 ± 14	65 ± 15	65 ± 15	<0.001	<0.001
Low density lipoprotein cholesterol (mg/dl)	122 ± 34	118 ± 33	116 ± 31	<0.001	<0.001
Triglycerides (mg/dl)	99 ± 2	88 ± 2	88 ± 2	<0.001	<0.001
Alcohol consumption (glasses/wk)	0.4 ± 1.2	0.6 ± 1.3	0.7 ± 1.6	<0.001	<0.001
Physical activity (h/wk)	1.9 ± 3.1	1.8 ± 2.7	2.0 ± 2.5	0.462	0.407
hs-CRP (mg/L)	2.0 ± 3.2	1.5 ± 3.3	1.4 ± 3.2	<0.001	<0.001
Fibrinogen (mg/dl)	315 ± 60	303 ± 9	302 ± 56	<0.001	<0.001
ESR (mm/h)	20 ± 11	18 ± 9	18 ± 10	<0.001	<0.001
White blood cell count (10^3 cells/μl)	6.9 ± 1.8	6.7 ± 1.7	6.7 ± 1.7	0.054	0.023

Values expressed as mean ± SD.
ANOVA = 1-way analysis of variance.

months. One hundred sixty-two subjects were later excluded from our study because of missing data for 1 of the inflammatory biomarkers, and an additional 350 subjects were excluded because of missing data for educational level. An additional 135 non-Jewish subjects were excluded from our cohort because of the significant acknowledged ethnic variation in inflammatory markers[9,10] and their relatively small group size, preventing us from analyzing them as a separate group. Finally, an additional 402 subjects with an incomplete high school education were excluded from our study because of their relatively small group size and to eliminate bias in the lower education-level group. After these exclusions, the final sample included 8,998 subjects (5,757 men, 3,241 women).

Fasting blood samples were drawn during morning hours. Analysis of complete blood count was performed using the Coulter STKS (Beckman Coulter, Nyon, Switzerland) electronic cell analyzer. Fibrinogen concentrations were calculated using the method of Clauss[11] and a Sysmex 6000 (Sysmex Corp., Hyaga, Japan) autoanalyzer. High-sensitivity C-reactive protein (hs-CRP) was measured using a Behring BN II Nephelometer (Dade Behring, Marburg, Germany).[12] Erythrocyte sedimentation rate (ESR) was calculated using the method of Westergren.[13,14]

Findings from the routine health checkups were assessed for atherothrombotic risk using various criteria. Risk factors included diabetes mellitus, defined as fasting glucose ≥126 mg/dl (≥7.0 mmol/L) or regular intake of insulin or an oral

Table 3
Number of subjects with a history of cardiovascular event and risk factors by tertiles of school years for men and women

Education (yrs)	Tertile 1 12–14	Tertile 2 15–16	Tertile 3 ≥17	Chi-Square p Value
	n = 1,780	n = 2,069	n = 1,908	
Men				
Previous atherothrombotic event	70 (4%)	87 (4%)	85 (5%)	0.732
Diabetes mellitus	113 (6%)	78 (4%)	81 (4%)	<0.001
Hypertension	432 (24%)	461 (22%)	473 (25%)	0.144
Dyslipidemia	581 (33%)	679 (33%)	684 (36%)	0.063
Current smoker	381 (22%)	320 (16%)	215 (11%)	<0.001
Past smoker	504 (29%)	548 (27%)	507 (27%)	
	n = 1,164	n = 1,038	n = 1,039	
Women				
Previous atherothrombotic event	45 (4%)	20 (2%)	19 (2%)	0.003
Diabetes mellitus	64 (6%)	31 (3%)	26 (3%)	<0.001
Hypertension	213 (18%)	149 (14%)	131 (13%)	0.001
Dyslipidemia	329 (28%)	230 (22%)	217 (21%)	<0.001
Current smoker	286 (25%)	178 (17%)	150 (15%)	<0.001
Past smoker	212 (19%)	207 (20%)	224 (22%)	

Values expressed as number (percent).

Table 4
Number of subjects using relevant prescription drugs, by tertiles of school years for men and women

Education (yrs)	Tertile 1 12–14	Tertile 2 15–16	Tertile 3 ≥17	Chi-Square p Value
	n = 1,780	n = 2,069	n = 1,908	
Men				
Aspirin	134 (8%)	159 (8%)	175 (9%)	0.123
β Blockers	86 (5%)	89 (4%)	100 (5%)	0.378
Calcium channel blockers	45 (3%)	54 (3%)	51 (3%)	0.963
Angiotensin-converting enzyme inhibitors	71 (4%)	71 (3%)	88 (5%)	0.165
Angiotensin II receptor blockers	14 (1%)	23 (1%)	28 (2%)	0.147
Statins	160 (9%)	206 (10%)	222 (12%)	0.026
Fibrates	20 (1%)	23 (1%)	27 (1%)	0.624
	n = 1,164	n = 1,038	n = 1,039	
Women				
Aspirin	58 (5%)	20 (2%)	33 (3%)	<0.001
β Blockers	67 (6%)	41 (4%)	28 (3%)	0.001
Calcium channel blockers	28 (2%)	13 (1%)	13 (1%)	0.048
Angiotensin-converting enzyme inhibitors	28 (2%)	24 (2%)	19 (2%)	0.620
Angiotensin II receptor blockers	7 (1%)	9 (1%)	6 (1%)	0.668
Statins	96 (8%)	57 (6%)	79 (8%)	0.035
Fibrates	8 (0.7%)	3 (0.3%)	5 (0.5%)	0.411
Oral contraceptives	130 (11%)	175 (17%)	129 (12%)	<0.001
Hormonal replacement therapy	109 (9%)	80 (8%)	115 (11%)	0.032

Values expressed as number (percent).

hypoglycemic; hypertension, defined as blood pressure >140/90 mm Hg in 2 separate measurements or regular use of antihypertensive drugs; dyslipidemia, defined as low-density lipoprotein or high-density lipoprotein cholesterol higher than recommended levels according to risk profile defined by the updated Adult Treatment Panel III recommendations[15] in persons with increased triglycerides >200 mg/dl (>2.26 mmol/L) or use of lipid-lowering medications. The definition of metabolic syndrome was based on the National Cholesterol Education Program Adult Treatment Panel III criteria,[15] with the modified impaired fasting glucose criteria of the American Diabetes Association,[16] as proposed by the updated American Heart Association/National Heart, Lung, and Blood Institute scientific statement.[17]

All analyses were performed separately for each gender because of the significant variance in inflammation-sensitive biomarkers between genders and the different factors influencing these biomarkers within each group.[18] All continuous variables were expressed as mean ± SD, whereas

Table 5
Mean change in inflammation-sensitive biomarkers for each additional school year adjusted for multiple confounders for men and women

	Mean Change	95% Confidence Interval	Partial Correlation	p Value
Men				
hs-CRP (%)	−2.3	(−3.2 to −1.3)	−0.064	<0.001
Fibrinogen (mg/dl)	−1.0	(−1.6 to −0.5)	−0.051	<0.001
ESR (%)	−0.6	(−1.4 to 0.2)	−0.021	0.130
White blood cell count (cells/μl)	−5	(−21 to 11)	−0.009	0.536
Women				
hs-CRP (%)	−2.0	(−3.1 to −0.8)	−0.059	0.001
Fibrinogen (mg/dl)	−1.1	(−1.8 to −0.4)	−0.055	0.003
ESR (%)	−1.3	(−2.0 to −0.5)	−0.060	0.001
White blood cell count (cells/μl)	13	(−7 to 34)	0.023	0.207

Table 6
Mean inflammation-sensitive biomarkes by tertiles of school years adjusted for multiple confounders for men and women

Education (yrs)	Tertile 1 12–14	Tertile 2 15–16	Tertile 3 ≥17	ANOVA p Value
	n = 1,780	n = 2,069	n = 1,908	
Men				
hs-CRP (mg/L)	1.7 ± 1.1	1.5 ± 1.1	1.4 ± 1.1	<0.001
Fibrinogen (mg/dl)	284 ± 6	279 ± 6	276 ± 6	<0.001
ESR (mm/h)	8.6 ± 1.1	8.3 ± 1.1	8.2 ± 1.1	0.101
White blood cell count (10^3 cells/μl)	7.5 ± 0.2	7.5 ± 0.2	7.5 ± 0.2	0.482
	n = 1,164	n = 1,038	n = 1,039	
Women				
hs-CRP (mg/L)	3.4 ± 1.2	3.0 ± 1.2	2.8 ± 1.2	<0.001
Fibrinogen (mg/dl)	317 ± 12	311 ± 12	309 ± 12	0.003
ESR (mm/h)	17.2 ± 1.1	16.4 ± 1.1	15.4 ± 1.1	<0.001
White blood cell count (10^3 cells/μl)	8.4 ± 0.3	8.4 ± 0.3	8.5 ± 0.3	0.489

Values expressed as mean ± SEM.
ANOVA = 1-way analysis of variance.

categorical variables were expressed as number and percent of patients within each group. hs-CRP, ESR, and triglycerides did not have normal distributions in this population. A logarithmic transformation was used to convert them to normal distributions for all statistical purposes, such as regressions and analysis of covariance. All hs-CRP, ESR, and triglyceride results are thus expressed as back-transformed geometrical mean ± SD. The 1-sample Kolmogorov-Smirnov test and Q-Q plots were used to test for normality of distributions.

To compare the different educational level groups, we divided our population into tertiles according to number of school years.

For continuous variables, 1-way analysis of variance was performed to compare various parameters between different educational-level groups, as well as to calculate the significance of trends. For all categorical variables, chi-square test was used to assess the overall significance of variance among groups.

Level of education was initially analyzed as a continuous variable. To assess the specific contribution of years of schooling to the variability in inflammation-sensitive biomarkers, we performed linear regression models with the inflammation-sensitive biomarkers as dependent variables and number of school years, as well as various potential confounders, as independent variables. These potential confounders were variables with either known or suspected influence on inflammatory-sensitive biomarkers and included age; waist circumference; body mass index; complete lipid profile, including low-density lipoprotein, high-density lipoprotein, and triglycerides; plasma glucose; diastolic and systolic blood pressure; alcohol consumption habits; physical activity intensity; use of various prescription drugs, including aspirin, β blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, statins, and fibrates; and cardiovascular risk factors, including current and past smoking, diabetes mellitus, history of atherothrombotic event (ischemic heart disease, cerebrovascular event, or peripheral arterial disease); and family history of coronary heart disease. Regular intake of either oral contraceptives or hormone replacement therapy was included as a potential confounder for women.

Linear regression models are presented as mean change in each inflammatory variable with 95% confidence intervals per each additional year of schooling. According to logarithmic transformation of hs-CRP and ESR distributions, the anticipated change in a linear model with these as dependent variables reflects a relative change presented as

percentage of change, rather than an absolute change as presented for fibrinogen and white blood cell count.

The estimated marginal mean values of the inflammation-sensitive biomarkers for the different educational level groups (tertiles) were calculated and adjusted for the same list of potential confounders.

The level of significance used for all analyses was 2 tailed ($p < 0.05$). The SPSS statistical package was used to perform all statistical analyses (SSPS Inc., Chicago, Illinois).

Results

We analyzed data for 8,998 subjects (5,757 men, 3,241 women) with a mean age of 44 ± 11 years (range 18 to 84). Anthropometric characteristics, blood pressure, relevant laboratory studies, inflammation-sensitive biomarkers, sport activity, and alcohol consumption habits of both genders are listed in Tables 1 and 2 according to tertiles of educational level for men and women, respectively. Various cardiovascular risk factors and frequencies of relevant drug intake for both genders are listed in Tables 3 and 4, respectively.

Table 5 lists the multiadjusted net effect of each additional school year on inflammatory biomarkers, and Table 6 lists the multiadjusted estimated marginal means of inflammation-sensitive biomarkers in each of the 3 tertiles. Of note is that after adjustment for multiple potential confounders, we still found statistically significant differences in inflammation-sensitive biomarkers, such as hs-CRP and fibrinogen, across tertiles in both genders, as well as statistically significant differences in ESRs among tertiles within the group of women. All mentioned inflammation-sensitive biomarkers gradually decreased with increase in school years. No difference was found in mean white blood cell counts across tertiles within each group.

Finally, to minimize the potential effect of some of the variables described in previous tables on our results, we further excluded subjects with a history of atherothrombotic event, diabetes mellitus, hypertension, dyslipidemia, or metabolic syndrome, as well as current smokers, from our sample. This cohort of apparently healthy persons was composed of 4,940 subjects (3,087 men, 1,853 women). Mean inflammation-sensitive biomarkers for each tertile of educational level within this healthy cohort showed lower concentrations and smaller differences between groups. However, all previously significant differences in biomarkers remained statistically significant (not shown).

Discussion

We analyzed the association between level of education and inflammation-sensitive biomarkers and prevalence of cardiovascular risk factors in a large sample of apparently healthy, asymptomatic, highly educated subjects. About ⅔ of the subjects in our sample had >14 years of schooling and about ⅓ declared ≥17 years of schooling. No previous large-scale data exist for this type of population. We analyzed this subpopulation with the a priory assumption of a higher educational level. Our results, in accordance with previous reports, confirm the finding that educational level as an indicator of SES has an inverse association with inflammation-sensitive biomarkers.[19–23]

In the present study, as in previous studies in which educational level was dichotomized,[24] divided into tertiles,[25] or displayed as cutoffs correlating to academic institution affiliation,[20,26] we also attributed a linear scale to level of education. Our findings clearly showed that even within this sample of highly educated individuals, higher levels of education correlated with lower inflammatory-sensitive biomarkers. To further emphasize these results, we repeated our analysis excluding from our sample many subjects with co-morbidities that could influence inflammation-sensitive biomarkers. We found that even after exclusion of these subjects from our sample, the inverse association between number of school years and inflammation-sensitive biomarkers remained significant.

Socioeconomic differences in levels of inflammation could stem from several sources. Subjects with lower SES have greater exposure to and are more susceptible to infection,[27] have a greater risk of developing chronic diseases,[28] are more likely to engage in hazardous activities, and experience higher psychological stress.[29] However, these persons have fewer social resources and are more likely to lack access to health care facilities and treatment.[30] Thus, differences in susceptibility, exposure, prevalence, and treatment create an environment in which persons from low socioeconomic backgrounds are more likely to experience both acute and chronic health conditions. Our study focused on highly educated subjects with a presumed higher SES. Thus, the inverse relation observed in it cannot be accounted for using this reasoning.

Our study analyzed a single indicator of SES, focusing on a specific subpopulation. Although these could be major limitations because of a lack of comparison to persons with lower SES and use of other indicators of SES, we believe our results for this specific subpopulation and the use of a single linear noninterchangeable indicator showed the discussed inverse association convincingly.

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