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Association between Plasma Fibrinogen Concentration and Five Socioeconomic Indices in the Kuopio Ischemic Heart Disease Risk Factor Study

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The association between five socioeconomic indices (lifetime occupation, education, income, ownership of material possessions, and childhood socioeconomic status) and plasma fibrinogen levels was investigated in middle-aged Finnish men who were part of the Kuopio Ischemic Heart Disease Risk Factor Study. The Kuopio Ischemic Heart Disease Risk Factor Study is based on a representative age-stratified sample of 2,682 men aged 42, 48, 54, and 60 years. The data were collected between 1984 and 1989. The present analysis is restricted to the 2,011 men for whom information on fibrinogen and all covariates was available. The covariates were alcohol consumption, body mass index, physical fitness, smoking, coffee consumption, high density lipoprotein cholesterol, low density lipoprotein cholesterol, blood leukocyte count, and prevalent disease (at least one sign of ischemic heart disease, hypertension, diabetes, or previous stroke). An age-adjusted inverse association was found between levels of plasma fibrinogen and four of the five socioeconomic indices: current income, education, lifetime occupation status, and current material possessions. After adjustment for the covariates, the association persisted for education, current income, and lifetime occupation. Analysis of the joint effect of childhood and adult socioeconomic status indicated that those who were economically disadvantaged at both times had the highest fibrinogen levels, but the fibrinogen levels of those who were not poor as adults had no variation by childhood socioeconomic status. *Am J Epidemiol* 1993;137:292–300.

cardiovascular diseases; fibrinogen, analysis; men; middle age; risk factors; social class; socioeconomic factors

A consistent association has been observed between socioeconomic factors and a variety of diseases ever since the first studies were conducted in 19th century England and France (1). While socioeconomic factors (2–4) appear to be of major etiologic importance in cardiovascular disease morbidity and mortality, the underlying biologic mechanisms that mediate this association are unknown. Existing studies, such as the Whitehall study of civil servants (5), have suggested that the association between socioeconomic factors and cardiovascular disease is not fully explained by the higher levels of

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smoking, lipids, hypertension, or other factors among those in lower socioeconomic levels. With increasing interest in the role of hemostatic factors in coronary heart disease, it is important to examine the association between such factors and measures of socioeconomic level. Recent evidence suggests that fibrinogen, a blood protein related to clotting, is of particular importance. Fibrinogen has been identified as an important independent risk factor (6) for cardiovascular diseases because of its probable relation to endothelial cell injury, platelet aggregation, or fibrous plaque formation (7). Indeed, epidemiologic evidence based on prospective (8–13), case-control (14–16), and cross-sectional studies (17, 18) supports an important association between plasma fibrinogen and cardiovascular diseases.

In this study, we examined the relation between fibrinogen and socioeconomic factors in eastern Finland, an area with one of the highest rates of ischemic heart disease in the world (19), yet with quality health care largely unrelated to socioeconomic level. The subjects were an age-stratified random sample of middle-aged Finnish men who participated in the baseline examination of the Kuopio Ischemic Heart Disease Risk Factor Study, a longitudinal study designed, in part, to identify the underlying biologic mechanisms that mediate between psychosocial factors and cardiovascular disease. The Kuopio Ischemic Heart Disease Risk Factor Study data allowed us to adjust for the following previously identified risk factors that have been associated with serum fibrinogen levels (20–26): age, alcohol consumption, body mass index, physical fitness, smoking, coffee consumption, high density lipoprotein cholesterol, low density lipoprotein cholesterol, blood leukocyte count, prevalent disease, and season of the year.

MATERIALS AND METHODS

Study population

The Kuopio Ischemic Heart Disease Risk Factor Study participants are comprised of two randomly selected samples from the Kuopio region in eastern Finland. The first sample was of men aged 54 years. Of the men chosen, 1,399 were considered eligible (i.e., alive and residing in the sampling catchment area at the time of the examination), and 1,166 participated. An examination date was selected that was near their 54th birthday. All examinations were conducted between March 1984 and June 1986. The second sample was an age-stratified sample of men aged 42, 48, 54, or 60 years. A total of 1,836 men were eligible for the study, and 1,516 participated. They were examined between August 1986 and December 1989 on a date near their birthday. The overall participation rate was 82.9 percent (n = 2,682) of the 3,235 eligible men. The present analysis is based upon 75 percent of the participants (n = 2,011) who had no missing values on either fibrinogen or the covariates (age, smoking, alcohol intake, coffee consumption, physical fitness, body mass index, plasma lipids, and prevalent disease): 271 men were 42 years old (13.5 percent), 288 men were 48 years old (14.3 percent), 1,192 men were 54 years old (59.3 percent), and 260 men were 60 years old (12.9 percent). Of the 671 who were excluded from our analysis, 89.3 percent were missing because of either technical problems in the administration of the exercise test (n = 348) or delay in the start date of the fibrinogen assay (n = 227) or both (n = 24).

Dependent variable

Plasma fibrinogen concentrations were determined in fresh plasma samples based on clotting of diluted plasma with excess thrombin (27) using the Coagulometer KC4 device (Heinrich Amelung GmbH, Lemgo, Germany) after 12-hour abstinence from food and coffee and a 3-day abstinence from alcohol. Blood sampling followed rest in the supine position for 30 minutes. No tourniquet was used. The coefficient of variation describing the day-to-day measurement of variability for serum fibrinogen assays was 5.5 percent.

Socioeconomic measures

Occupation status. Participants were classified into three categories, white-collar, blue-collar, or farmers, on the basis of self-reported lifetime occupation. The white-collar classification included professional and managerial staff as well as low-paid clerical workers. Blue-collar workers were manual laborers in construction, mining, manufacturing, or forestry. Farmers were those who spent most of their employment life in the agricultural sector. Information on lifetime occupation was unavailable for 26 individuals (1.3 percent).

Education level. On the basis of reported lifetime education, participants were classified into one of four categories: less than an elementary education, completion of elementary school, completion of middle school, and completion of high school or above. Information on education was not available for two individuals (<0.1 percent).

Income level. Participants were subdivided into quintiles of income on the basis of reported personal income over the past 12 months. Information on income was not available for 24 individuals (1.2 percent).

Material possessions. A material possession index was based upon self-reports of ownership of the following 12 items: freezer (91 percent), dishwasher (31.4 percent), videocassette recorder (25.5 percent), color television (88.5 percent), telephone (94.6 percent), summer cottage (46.4 percent), motorcycle (12.9 percent), car (87.1 percent), recreational vehicle (2.7 percent), motorboat (34.1 percent), sailboat (1.6 percent), and skimobile (3.6 percent). An individual score was derived by summing all the affirmative responses about ownership of the 12 items and dividing by the total number of item responses. The score was considered missing if the respondent did not provide an answer on six or more items. These scores were divided into approximate quartiles. Information on material possessions was missing for three men (0.1 percent).

Childhood socioeconomic status. Childhood socioeconomic status was based upon the father's education and occupational prestige, the mother's occupational prestige, whether or not the family lived on a farm and the size of the farm, and a rating of the wealth of the family when the respondent was 10 years of age. The scores were divided into approximate tertiles (28). Information on childhood socioeconomic status was available for all 2,011 men.

Covariates

Alcohol consumption. Based on 1-year recall of the average consumption per week using the Nordic Alcohol Consumption Inventory from the Scandinavian drinking survey (29), four categories were formed: nondrinkers and approximate tertiles of drinkers, more than 0.0 to 0.8 g/week, more than 0.8 to 5.7 g/week, and more than 5.7 g/week.

Body mass index. Body mass index was calculated by dividing the participant's weight (in kilograms) by his height (in meters squared).

Physical fitness assessment. To assess physical fitness, we performed a maximal exercise tolerance test on an electrically braked bicycle ergometer. The highest oxygen uptake during the test was scored. The exercise tests were carried out under the supervision of a physician in the exercise laboratory of the Kuopio Research Institute of Exercise Medicine, Kuopio, Finland, with adequate equipment for cardiorespiratory resuscitation (30).

Smoking. Smoking status was divided into three categories: current smoker (smoked in the last month), former smoker, and never smoker.

Coffee consumption. Coffee consumption was assessed by a 4-day diary, and participants were placed into four categories: nondrinkers and approximate tertiles of drinkers, more than 0.0 to 437.5 g/day, more than 437.5 to 675 g/day, and more than 675 g/day.

Lipids. Lipoprotein separations were carried out from unfrozen plasma samples within 3 days of blood sampling. The high density lipoprotein cholesterol and low density lipoprotein cholesterol fractions were separated from fresh plasma using a combination of ultracentrifugation and precipitation (31). Blood leukocyte count was determined by using the Coulter counter, and cell counts are expressed in Système International units.

Prevalent disease. A single dichotomous variable was created indicating the presence or absence of one of more of the following conditions: prevalent ischemic heart disease (determined by a positive result in the Rose questionnaire (32), the appearance of ischemia or chest pain during the exercise test, history of angina, history of myocardial infarction, regular nitroglycerin or other antiangina medication use, or prior acute myocardial infarction as defined by the Minnesota code (33)), prevalent hypertension (the mean of two sitting systolic blood pressure measurements during the medical examination was ≥160 mmHg, or the mean of two sitting diastolic blood pressure measurements was ≥95 mmHg, or the participant was currently taking antihypertensive medication), prevalent diabetes mellitus (either a fasting plasma glucose ≥8 mmol/liter or a previous diagnosis of diabetes mellitus by a physician), or previous cerebrovascular event (stroke was determined by previous diagnosis by a physician).

Season of the year. Winter, spring, summer, or fall category was assigned based upon the examination date.

Statistical methods

All analyses were performed using the Statistical Analysis System version 5.18 (34). The distribution of fibrinogen was examined to determine normality. The proportion of the study population in each category of the five different socioeconomic measures was calculated. For these measures, dummy variables were created with the presumed lowest risk value defined as the reference category (e.g., white-collar, high education, wealthy, etc.). Dummy variables were created for the alcohol, coffee, and smoking variables with the reference group always being the low-risk stratum (high alcohol consumption, low coffee consumption, and nonsmoker). Analysis of linear trend was done by regressing serum fibrinogen level on each ordinal socioeconomic index adjusting for age and for the covariates. Age- and covariate-adjusted mean fibrinogen levels were calculated for each level of the socioeconomic index, and 95 percent confidence intervals were calculated from the regression coefficients estimated in the models. For each index, the highest socioeconomic level was designated as a reference level. The mean fibrinogen for each of the other levels was compared with that of the reference level by a t test. Model fitting was done using the Statistical Analysis System PROC REG, and t tests were performed using the LSMEANS option on PROC GLM (34). Because the effect of socioeconomic factors on fibrinogen may be modified by prevalent disease, a product term was also included in the GLM models to indicate the interaction between disease and socioeconomic factors. Results are reported if the product term was at least marginally statistically significant ($p < 0.10$).

RESULTS

Plasma fibrinogen values ranged from 1.32 to 6.29 g/liter, with a mean of 3.01 g/liter (standard deviation, ±0.56). The distribution of fibrinogen approximated a Gaussian distribution, but with a skew to the right. Analysis was performed comparing the effect of each socioeconomic index on the untransformed values of fibrinogen, as well as the logarithmic transformed values of fibrinogen, with no appreciable differences in model fit or parameter estimates. Therefore, we report results from the untransformed analysis as these values are easier to interpret.

The proportions of the sample in each category of the socioeconomic indices are listed in table 1. The distributions of covariates were as follows. The mean body mass index was 26.95 (standard deviation, ±3.42), mean maximum oxygen uptake was 30.5 ml/kg/minute (standard deviation, ±

TABLE 1. Characteristics of sample and mean serum fibrinogen (g/liter) by five socioeconomic indices, Kuopio (Finland) Ischemic Heart Disease Risk Factor Study, 1984–1989

Sample characteristics			Age-adjusted means			Covariate*-adjusted means		
Variable	No.	%	Mean	95% confidence interval	*p* value†	Mean	95% confidence interval	*p* value†
Occupation								
Farmer	841	42.4	3.06	3.00–3.12	0.004	3.07	3.01–3.13	0.008
Blue-collar	307	15.5	3.06	3.02–3.10	<0.001	3.03	3.00–3.07	0.022
White-collar	837	42.2	2.95	2.91–2.99	Reference	2.98	2.94–3.01	Reference
Income (quintiles)								
1 (low)	349	17.6	3.19	3.14–3.25	<0.001	3.13	3.06–3.17	<0.001
2	380	19.1	3.03	2.98–3.09	<0.001	3.02	2.96–3.07	0.050
3	427	21.5	2.99	2.94–3.05	0.004	2.98	2.94–3.04	0.201
4	416	20.9	3.01	2.96–3.06	0.001	3.04	3.00–3.09	0.004
5 (high)	415	20.9	2.89	2.83–2.94	Reference	2.94	2.90–2.99	Reference
Education								
Less than elementary	181	9.0	3.06	2.98–3.15	<0.001	3.00	2.91–3.06	0.054
Elementary	948	47.2	3.05	3.02–3.09	<0.001	3.03	3.01–3.07	<0.001
Middle school	735	36.6	2.99	2.95–3.03	0.003	3.02	2.98–3.06	0.002
High school or greater	145	7.2	2.84	2.75–2.93	Reference	2.87	2.79–2.96	Reference
Material possessions (quartiles)								
1 (low)	292	14.5	3.12	3.06–3.19	<0.001	3.05	2.97–3.14	0.455
2	816	40.6	3.02	2.98–3.05	0.121	3.01	2.98–3.05	0.715
3	480	23.9	2.99	2.94–3.04	0.423	3.01	2.97–3.07	0.547
4 (high)	420	20.9	2.96	2.91–3.02	Reference	3.00	2.95–3.05	Reference
Childhood socioeconomic status (tertiles)								
1 (low)	686	34.1	3.04	3.00–3.08	0.132	3.03	3.00–3.07	0.400
2	897	44.6	3.01	2.97–3.05	0.470	3.01	2.97–3.04	0.786
3 (high)	428	21.3	2.99	2.93–3.04	Reference	3.00	2.96–3.06	Reference

* Alcohol consumption, body mass index, physical fitness, smoking, coffee consumption, high density lipoprotein cholesterol, low density lipoprotein cholesterol, blood leukocyte count, and prevalent disease (at least one sign of ischemic heart disease, hypertension, diabetes, or previous stroke).

† *p* value for comparison between reference level and other levels of the socioeconomic index.

8.15), mean low density lipoprotein cholesterol was 4.04 mmol/liter (standard deviation, ±1.01), mean high density lipoprotein cholesterol was 1.29 mmol/liter (standard deviation, ±0.30), and mean of blood leukocyte count was 5.66×10^9/liter (standard deviation, ±1.56). In our sample, 32 percent were current smokers, 40 percent were former smokers, and 28 percent were never smokers. Alcohol consumption varied as follows: abstinence (13 percent), light drinkers (21 percent), moderate drinkers (33 percent), and heavy drinkers (33 percent). Coffee consumption varied as follows: abstinence (4 percent), light drinkers (28 percent), medium drinkers (34 percent), and heavy drinkers (34 percent). Finally, the proportion of subjects with any of the disease conditions was 61 percent (37 percent had hypertension, 41 percent had at least one sign of ischemic heart disease, 2 percent had a previous stroke, and 4 percent had diabetes mellitus).

The demographic characteristics of this sample were compared with the demographic characteristics of the originally selected random sample of 2,682 subjects, and no important differences were found.

In the age-adjusted analyses, the variable indicating season of the year was entered in all models, but there was no evidence of confounding. Thus, we removed it from further consideration. The test for linear trend indicated that plasma fibrinogen levels were inversely related to education ($p < 0.001$), income ($p < 0.001$), and material possessions ($p < 0.001$), but not to childhood socioeconomic status ($p = 0.124$).

The differences in the age-adjusted fibrinogen levels between the highest and lowest categories of our five socioeconomic indices were 0.30 g/liter for income, 0.22 g/liter for education, 0.16 g/liter for material possessions, and 0.05 g/liter for childhood socioeconomic status. For the occupation index, the age-adjusted mean for white-collar workers was 0.11 g/liter lower than for farmers and for blue-collar workers. The significance probabilities are reported in table 1.

After adjusting for all covariates (except season), a significant inverse monotonic trend between fibrinogen and income (p = 0.004) and between fibrinogen and education (p = 0.076) was found, but the linear trend was not statistically significant for either material possessions (p = 0.571) or childhood socioeconomic status (p = 0.316).

In the covariate-adjusted model, the differences in fibrinogen levels between the upper and lower classes were 0.17 g/liter for income and 0.11 g/liter for education. The covariate-adjusted means for white-collar workers was 0.09 g/liter lower than that for farmers and 0.05 g/liter lower than that for blue-collar workers; differences between the high and low extremes of the other indices were significantly different (table 1). In analyses in which the smoking variable included quartiles of cigarette pack years for current smokers, virtually identical results were found.

In order to evaluate the different results for childhood socioeconomic status and income (as a measure of adult socioeconomic status), an interaction model was fitted including a product term (childhood socioeconomic status × income). This covariate-adjusted model revealed that those who scored in the bottom two tertiles of the childhood socioeconomic status and who were also currently in the lowest income quartile had the highest fibrinogen levels of all ($p < 0.05$). These results are summarized in figure 1.

The mean value of serum fibrinogen for those with prevalent disease was 3.07 g/liter, and for those without prevalent disease it was 2.92 g/liter, a difference of 0.15 g/liter. Although fibrinogen values were consistently higher among those with prevalent disease across levels of each socioeconomic index, there was no important modification in the effect of socioeconomic factors on fibrinogen by prevalent disease status.

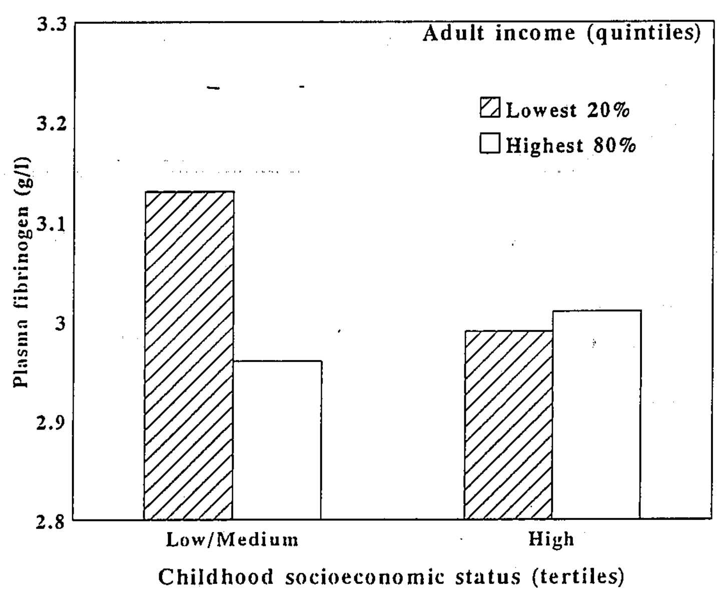

FIGURE 1. Mean plasma fibrinogen by childhood socioeconomic status and adult income, Kuopio (Finland) Ischemic Heart Disease Risk Factor Study, 1984–1989.

DISCUSSION

Several previous studies have examined the association between occupation and fibrinogen levels. The English Civil Servant Study (35) found a monotonic relation between occupational grade and fibrinogen after controlling for potential confounders. Since then, at least three other studies have examined the relation between measures of social class and fibrinogen, including the Scottish Heart Health Study (36, 37), the Gothenburg, Sweden, 1933 Birth Cohort Study (38), and the Copenhagen, Denmark, Study (39), and have reported similar results. Three of the four studies used occupation grade as their only social class index; the fourth, the Copenhagen study, used an index incorporating occupation and education. Many authors have suggested that more than one index of social class should be used in epidemiologic studies. They have noted that different measures of social class often yield dissimilar results (40) because these indices measure distinct aspects of one's social experience.

The advantage of this study is its use of five measures of socioeconomic factors: occupation, education, income, material possessions, and childhood socioeconomic status. For example, childhood socioeconomic status (aged 10 years or less) or highest education level achieved are historical exposures among a middle-aged population and, therefore, may be tapping something quite different from current income or material possessions, both of which measure present circumstances.

The absolute difference in fibrinogen levels between the highest and the lowest categories of each socioeconomic factor differed by the socioeconomic factor, yet a consistent finding was that the highest class always had the lowest fibrinogen. The difference between the highest and the lowest group was significant for all measures except childhood socioeconomic status in the age-adjusted model and for all except material possessions and childhood socioeconomic status in the covariate-adjusted model. When the indices were ranked by the greatest difference in fibrinogen from top to bottom, the income index had the largest difference, followed by education and occupation. Although these ranges could be an artifact of the methods by which the categories were divided (e.g., the white-collar occupational category included low-paid clerical staff), it is striking that the highest social class always had the lowest plasma fibrinogen level.

There have been some reports of an association between coronary heart disease and current material possessions. Television ownership in the 1950s in England was reported (41). However, in our study, the effect of current material possessions was very weak after controlling for age, and it disappeared with adjustment for covariates. We believe that in Finland today, an index of current material possessions is a less sensitive indicator of socioeconomic status than is current income.

An association between childhood socioeconomic status and prevalent ischemic heart disease was reported in a previous paper (28). Importantly, a recent report by Barker et al. (42) found an association between infant (aged less than 1 year) growth rate and adult fibrinogen levels. In our study, childhood socioeconomic status was not associated with fibrinogen, however, a combined measure of child and adult socioeconomic status used to assess long-term lower class existence was. This suggests that increased levels of fibrinogen associated with early disadvantage can be overcome by a more favorable adult status and that those who are disadvantaged both as children and as adults are at particularly high risk.

Several case-control studies have reported a higher fibrinogen level among cases of a cardiovascular event than among controls. The mean difference in fibrinogen between cases and controls was as low as 0.30 g/liter for young (aged 45 years or less) treated cases of incident myocardial infarction who had survived 3–6 months after the acute event compared with controls (15), a difference as low as 0.30 g/liter fibrinogen for cases with prevalent ischemic heart disease compared with controls (aged 45–69 years) (14), and a difference of 0.43 g/liter fibrinogen for cases of a transient ischemic attack or a minor ischemic stroke compared with controls (16). However, in these case-control studies, fibrinogen levels may have been affected by prevalent disease or by drug regimens. Prospective epidemiologic studies provide results that are subject to fewer potential biases, yet results are strikingly similar to the case-control studies. The Gothenburg Study (8), the Framingham Study (9, 10) the Northwick Park Heart Study (11, 12), and the Leigh Clinical Research Study (13) all reported higher baseline fibrinogen levels among those who subsequently experienced morbidity or mortality from heart disease than among those who had no such event. For example, in the Gothenberg study, the fibrinogen level of those who experienced a myocardial infarction was 3.30 g/liter, while those who did not experience "no endpoint" (i.e., no myocardial infarction, no stroke, or no "other death") was 3.56 g/liter, for a difference of only 0.26 g/liter. Thus, the risk factor-adjusted differences in point estimates of fibrinogen (up to 0.31 g/liter) between the low and high levels of socioeconomic factors that we report may have both clinical and public health importance.

This brings us to the question of why socioeconomic factors have such a strong independent effect on fibrinogen levels. We have shown that controlling for characteristics that are strongly associated with lower social class (at least in developed countries) and are also risk factors for fibrinogen (as well as cardiovascular disease)—smoking, obesity, high fat diet, poor physical fitness, alcoholism, underlying infection (indicated by leukocyte count), and prevalent disease—does little to lessen the effect of socioeconomic factors on fibrinogen. Of course, measurement error in the covariates could result in incomplete control of confounding (43), with unpredictable results on the association between socioeconomic factors and fibrinogen level. That aside, the consistently strong relation reported between socioeconomic factors and fibrinogen, after adjustment for suspected risk factors for fibrinogen, suggests that psychosocial factors might be partially responsible for the association. Markowe et al. (35) have shown that job strain (high demand, low control) is related to fibrinogen levels. Acute psychosocial stress may also be associated with fibrinogen levels, as fibrinogen is higher during the study time before examinations when compared with the levels following them (44). Chronic psychosocial conditions may be a factor as well, as our evidence suggests that long-term disadvantage predicts adult fibrinogen levels. The inclusion of psychosocial factors in cardiovascular studies could help to clarify their role in the higher levels of fibrinogen among the less advantaged.

In conclusion, in the present data, sizable differences in plasma fibrinogen levels were associated with several socioeconomic measures, and these differences remained after controlling for the major coronary risk factors. In future analyses of the Kuopio Ischemic Heart Disease Risk Factor Study cohort, we will examine to what extent these differences in fibrinogen levels by social class explain the association between socioeconomic factors and subsequent cardiovascular disease morbidity and mortality.

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