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Fibrinogen: a possible link between social class and coronary heart disease

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Abstract

Mortality from coronary heart disease in civil servants in the lowest grade of employment has been found to be about three times that of men in the highest grade of employment. As part of an investigation of this finding several haemostatic variables were measured in a sample of 29 men in lower grades of employment and 45 men in higher grades. There was a significant difference in plasma fibrinogen concentrations between men in lower grades of employment and those in higher grades (mean 3.39 g/l v 2.95 g/l, respectively; $p < 0.01$) but not in other haemostatic variables. Multiple regression analyses showed significant independent associations of fibrinogen concentration with smoking ($p < 0.05$) and grade of employment ($p < 0.05$). The size of the observed difference between the grades of employment was similar to that between those dying of coronary heart disease or surviving during longitudinal study; it may therefore be an important part

of the mechanism underlying social class differences in coronary heart disease.

The statistical relation between fibrinogen concentrations and other characteristics that may be concerned in the aetiology of coronary heart disease was examined. A summary measure of job stress was significantly related to fibrinogen concentration ($p < 0.01$) and made a substantial contribution to explaining the differences between grades of employment. Behaviour type and a score of physical activity were not significantly related to fibrinogen concentration.

Introduction

In England and Wales mortality from coronary heart disease in 1971 was 26% higher in social class V than social class I.¹ The Whitehall study of London civil servants showed larger differences in mortality from coronary heart disease between different grades of employment: the relative risk was more than three times greater in the lowest grade of employment (predominantly messengers) compared with the highest grade of employment (administrators).² Much of this difference remained unexplained after the effect of other measured risk factors (plasma total cholesterol concentration, smoking, blood pressure, glucose tolerance, and obesity) had been taken into account.³

The new Whitehall (Department of Environment) study was set up in 1978 to seek other explanations for the difference in mortality from coronary heart disease between the different grades of employment, including possible differences in haemostatic variables.

Clinical studies have implicated poor fibrinolytic activity⁴ and higher plasma fibrinogen concentration⁵ in the onset of thromboembolic disease, but epidemiological studies of the role of haemostatic variables are few. The Northwick Park heart study showed an association between high concentrations of plasma fibrinogen and clotting factors VII and VIII and subsequent risk of death.

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from cardiovascular disease.⁶ Additional evidence implicating fibrinogen as a risk factor for cardiovascular disease has come from two other longitudinal studies.^{7,8}

We report an investigation of the relation between these and other haemostatic variables and the grade of employment in a subsample of participants from the Department of Environment study.

Subjects and methods

The Department of Environment study comprised 1274 male and female civil servants aged between 35 and 54 working in the Department of Environment in London and Croydon in April 1978. The 75 subjects in our investigation were a random subsample of participants from the Department of Environment study, stratified by grade of employment and whether they smoked. The following outline relates only to procedures relevant to our investigation.

Subjects initially received a health screening questionnaire with questions on physical activity, consumption of alcohol, and medical history. They were then invited for an examination, including electrocardiography, various blood tests—for example, determination of plasma total cholesterol concentration—and administration of a questionnaire concerned with life style relevant to health with questions relating to behaviour type and job stress. The three questions selected to comprise a summary score of job stress were concerned with characteristics of the job that had previously been shown to identify increased risk of coronary heart disease.^{9,10}

About 18 months later 435 men still employed in these offices were recalled for further procedures, including determination of weight and whether they smoked and the collection and checking of a detailed record of all food and drink consumed over a three day period, which was completed on the Thursday, Friday, and Saturday before attendance at the appointment. The proportion of men responding at this final stage of the study had fallen to 69% in higher grades of employment and 36% in lower grades.

At this final examination haemostatic tests were performed on the blood of 45 men in higher grades of employment (corresponding to administrative and professional and executive grades in the Whitehall study) and 29 men in lower grades of employment (corresponding to clerical and "other" grades in the Whitehall study). Blood from one subject clotted and was not analysed.

Recruitment of the subjects was spread over the course of 10 months. Venepuncture, without application of a tourniquet, was performed mid-morning after subjects had rested on a couch for a short time.

After collection blood was taken to Northwick Park Hospital for immediate analysis or storage. The following haemostatic variables were measured: concentrations of clotting factors II, VII, VIII, and X, clottable fibrinogen, and antithrombin III (by an immunological method¹¹); aggregation of platelets using adenosine diphosphate¹²; and fibrinolytic activity. Clotting factors II and X were assayed by automated modifications of the methods described by Denson.^{13,14} A clot weight method was used to measure the concentration of clottable fibrinogen.¹⁵ Other clotting variables were measured by methods previously described.¹⁵

Concentrations of fibrinogen and clotting factors II, VII, VIII, and X tend to be log normally distributed, and statistical analyses were therefore performed on log transformed values. Means presented for these variables are geometric means, and thus the standard deviations are approximate.

Comparison of mean concentrations of fibrinogen was performed by Student's *t* test. Correlations presented are Pearson product-moment coefficients. Because of correlations between the characteristics under consideration multiple regression analyses were performed using the natural logarithm of fibrinogen as the dependent variable.

Results

Comparison between grades of employment showed significant differences in plasma fibrinogen concentration but in no other haemostatic variable (table I).

Table II shows the effects of smoking and age on fibrinogen concentration. The difference between the different grades of employment was present and of similar size (0.40 g/l) in each of the four categories. Numbers were small and no difference between the grades reached significance.

Table III shows the results of a multiple regression analysis with log fibrinogen concentration as the dependent variable. In addition to grade of employment, terms are included for characteristics previously shown to be significantly related to fibrinogen concentration: age,^{16,17} smoking,^{16,18} obesity (expressed as the body mass index, calculated as weight/(height)²),¹⁶ and plasma total cholesterol concentration.¹⁸ A regression including all these characteristics explained about 26% of the total variance in log fibrinogen concentration. Data on consumption of alcohol¹⁶ and intake of cereal fibre¹⁹

TABLE I—Details of subjects studied and values of haemostatic variables according to grade of employment

	High grade of employment (n=45)	Low grade of employment (n=29)
Mean (SD) age (years)	47.3 (5.9)	48.0 (5.1)
Mean (SD) weight (kg)	75.5 (8.8)	74.5 (11.3)
No of smokers (%)	16 (36)	16 (55)
<i>Haemostatic variables</i>		
Clotting factors (% of standard):		
II	121.3 (24.3)	124.2 (24.0)
VII	99.9 (19.5)	100.2 (20.7)
VIII	107.7 (34.3)	100.1 (32.9)
X	110.7 (20.4)	109.2 (23.5)
Mean (SD) fibrinogen (g/l)	2.95* (0.50)	3.39 (0.71)
Mean (SD) fibrinolytic activity (100/lysis time (hours))	11.5 (7.1)	10.0 (7.3)
Mean (SD) antithrombin III (%)	90.0 (10.6)	91.5 (8.9)
Mean (SD) platelet aggregation (median effective dose) (× 10 ⁻⁷ M)	9.8 (4.1)	10.4 (6.9)

*Compared with subjects in low grades of employment *p*<0.01.

TABLE II—Plasma fibrinogen concentrations (g/l) by grade of employment, age, and smoking habit. Values in parentheses are numbers of subjects

	Low grade of employment	High grade of employment
<i>Aged <50</i>		
Non-smokers	3.13 (8)	2.73 (15)
Smokers	3.53 (7)	3.14 (13)
<i>Aged ≥50</i>		
Non-smokers	3.38 (5)	2.99 (14)
Smokers	3.52 (9)	3.13 (3)

TABLE III—Multiple regression of log_e (fibrinogen) in relation to other variables (n=74)

	Regression coefficient (B)	Standard error	p Value
Age (years)	0.006	0.004	0.10
Smoking (non-smokers=0; smokers=1)	0.10	0.04	0.03
Body mass index (kg/m ²)	0.012	0.009	0.17
Grade of employment (high=0; low=1)	0.10	0.04	0.03
Plasma total cholesterol (mmol/l)	0.024	0.021	0.24
Intercept	0.31	0.26	

Conversion: SI to traditional units—Cholesterol: 1 mmol/l≈39 mg/100 ml.

TABLE IV—Plasma fibrinogen (mmol/l) by summary score of job stress.* Values in parentheses are numbers of subjects

	Job stress score		
	Low	Medium	High
High grade of employment	2.90 (25)	3.05 (16)	3.14 (3)
Low grade of employment	2.93 (6)	3.27 (9)	3.69 (14)
Combined†	2.90 (31)	3.14 (25)	3.58 (17)

*Summary score based on responses to questions on: (a) use of skills (under use=high stress); (b) control over work (little control=high stress); and (c) job variety (little variety=high stress).

†Information missing on one subject.

were not available for all 74 subjects, and they made only small and non-significant contributions to the regression equation.

Table IV shows the relation between fibrinogen concentration, grade of employment, and job stress score. A trend was present in subjects from both high and low grades of employment of increasing fibrinogen concentration with increasing job stress. On univariate analysis a strong association was present between job stress score and plasma fibrinogen concentration (*r*=0.37; *p*<0.01). Multiple regression analysis including the terms shown in table III showed that job stress made a significant contribution (*p*<0.05) and increased the total variance in log fibrinogen concentration explained to 34%. The regression coefficient for grade of employment diminished by 64% to 0.03, indicating that differences in job stress between the grades of employment could explain (statistically) much of the residual difference between the grades in fibrinogen concentration.

Neither physical activity score (based on responses to three questions on

exercise) nor behaviour type (type A or B)²⁰ was significantly associated with fibrinogen concentration or made a significant contribution when relevant terms were added to the regression equation.

Discussion

Fibrinogen concentrations were significantly higher in men in lower grades of employment than in those in higher grades. No significant differences were found between the grades in other clotting factors.

There are several biological reasons why fibrinogen may be important in the aetiology of coronary heart disease,²¹⁻²⁶ and results from three longitudinal studies have implicated fibrinogen as a risk factor for cardiovascular disease.⁶⁻⁸ Results of our study are therefore consistent with a hypothesis that raised concentrations of fibrinogen could contribute to the increased mortality from coronary heart disease experienced by civil servants in low grades of employment,³ or more generally by the lower social classes.¹ Confirmation will, however, require longitudinal rather than cross sectional study.

The difference in mean fibrinogen concentrations between the different grades of employment was large (3.39 g/l in men in lower grades, 2.95 g/l in men in higher grades) and is comparable with that found in the Northwick Park heart study between subjects subsequently dying of cardiovascular disease and all other surviving subjects (3.32 g/l and 2.93 g/l, respectively).⁶

Bias in selection needs to be considered as a possible explanation for our findings. The poor rate of response in men in the lower grades of employment could have resulted in over-representation of "sick" subjects with pre-existing coronary heart disease or diabetes, both of which may result in high plasma fibrinogen concentrations.^{27,28} Exclusion of such subjects (two from the low grades of employment and one from the high grade), however, produced only a minimal reduction in the difference in fibrinogen concentration between the grades. Variables known to affect plasma fibrinogen concentration were compared in the 74 haemostatic study subjects and in respondents in similar grades of employment in earlier phases of the Department of Environment study. The only difference was a significantly greater proportion of smokers in subjects in high grades of employment in the haemostatic study. This was due to stratification by smoking during the selection of the sample, without which the difference in fibrinogen concentrations between the grades would have been larger. These findings in association with the consistency of the difference between the grades in multiple cross tabulations support the reality of the difference in fibrinogen concentrations between the grades of employment.

Job stress has been implicated as a risk factor for coronary heart disease,^{9,10} and the related characteristic of job dissatisfaction has also been proposed as a possible risk factor.²⁹ Our findings indicate that fibrinogen could be important in the associated mechanism. Blood clotting time has been shown to vary with occupational stress,³⁰ though another study of severe short term stress failed to show a sustained rise in plasma fibrinogen concentration.³¹ The relation between an attribute such as job stress and the development of coronary heart disease is probably complex, and the association found in this study between increased job stress and raised fibrinogen concentration could be confounded with other characteristics not identified so far.

If the large difference in fibrinogen concentrations found in the different grades of employment in this study is representative of the value in the civil service as a whole then applying the mortality experience of the Northwick Park heart study⁶ to our distribution of fibrinogen, we estimate that this factor might account for up to a quarter of the excess risk of mortality from coronary heart disease in

subjects in the lower grades of employment. Our findings suggest that differences in fibrinogen concentration may contribute substantially to social class differences in mortality from coronary heart disease, and they indicate the importance of further epidemiological research in this and other haemostatic variables.

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