Plasma Fibrinogen and Ischemic Heart Disease Risk Factors

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The association between risk factors for ischemic heart disease and plasma fibrinogen level was analyzed in a cross-sectional population study. All 51-year-old men living in a certain area within the county of Copenhagen were invited; 439 of 542 (81%) participated in the study. Data were collected via questionnaire and at health examinations. The following independent variables were analyzed: social variables, which included social class, marital status, and job strain; psychological and psychosomatic variables, which included abdominal pain, personal and economic problems, self-assessed state of health, and degree of loneliness; behavioral variables, which included smoking, drug consumption, physical activity, use of sugar, and alcohol consumption; and physiological variables, which included high density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol, physical fitness, fasting glucose level, waist-to-hip ratio, and systolic blood pressure. In the multivariate analyses, the following variables showed an independent positive association with plasma fibrinogen level: one social variable (low social class); two psychological variables (abdominal pain index and personal/economic problems); two behavioral variables (smoking and physical inactivity during leisure time); and three physiological variables (low HDL cholesterol, low physical fitness, and high LDL cholesterol). The strongest independent associations with plasma fibrinogen level were found for smoking, social class, LDL cholesterol, and HDL cholesterol. These analyses suggest that smoking is a major risk factor for an elevated plasma fibrinogen level, but that other factors such as social class, cholesterol level, physical inactivity/physical fitness, and psychological problems also influence plasma fibrinogen level. (Arteriosclerosis and Thrombosis 1991;11:344-350)

During the years 1980-1989, results were reported from four prospective epidemiological studies on fibrinogen as a possible risk factor for cardiovascular disease. These studies included the Gothenburg 1913 Study,1,2 in which 792 men were followed up for 18.5 years; the Framingham Study,3,4 comprising 554 men and 761 women and extending over 14 years; the Northwick Park Heart Study,5-6 on results from a 10-year follow-up of a cohort of 1,511 men; and the Leigh Clinical Research Unit Study,7 in which a cohort of 297 men from one general practice was followed for an average of 7.3 years.

All four studies showed a clear association between fibrinogen level and the incidence of ischemic heart disease in the follow-up period. In the Gothenburg 19131,2 and Framingham3,4 studies, a significant positive association between fibrinogen level and stroke was found in men, but not in women (although the number of stroke events among the latter was low).

In all four studies, the association between fibrinogen level and cardiovascular disease was present, independent of the well-known endogenous risk factors for cardiovascular disease such as high blood pressure, high serum cholesterol level, and glucose intolerance. This association was of the same order of magnitude or higher than those for the other risk factors.

On the basis of their results, all the authors of these studies concluded that a high fibrinogen level was an independent risk factor for cardiovascular disease and that fibrinogen plays an especially important role in the thrombotic processes in the pathogenesis of cardiovascular disease.

If fibrinogen were accepted as an independent risk factor for cardiovascular disease, it would be of great importance, from both a scientific and preventive point of view, to know what factors influence fibrinogen level. A number of studies have already
examined this question, but as yet it has not been fully elucidated.

The association between smoking and fibrinogen level has been examined in a rather large number of studies. All studies except one found a strong positive association between smoking and fibrinogen level, and several concluded that fibrinogen level probably explained a considerable part of the causal association between smoking and cardiovascular disease.

The other risk factors for cardiovascular disease have also been found to be associated with fibrinogen level, although not quite so convincingly and in fewer studies. This applies to body mass index, serum cholesterol level, blood pressure, heart rate, oral contraceptive use, glucose intolerance, blood sugar, hereditary disposition, and age. Furthermore, it has been found that fibrinogen level is positively correlated with the proportion of energy intake derived from protein and negatively correlated with cereal fiber and alcohol intake.

In only one study was fibrinogen level found to be positively correlated with occupational stress. The authors of this study concluded that fibrinogen was a possible link in the causal chain connecting low social class with increased risk of cardiovascular disease. Also, Meade et al and Rosengren et al found a negative correlation between social class and fibrinogen level.

In our study, we examined the association between most of the above-mentioned risk factors and fibrinogen level in a cohort of 51-year-old Danish men. As with most of the previously mentioned studies, this one is cross sectional. We will later examine the association between fibrinogen level and the incidence of cardiovascular disease, together with changes in fibrinogen level over time.

**Methods**

A cohort of all men born in 1936 and living in four municipalities served by Glostrup Hospital in the county of Copenhagen has been followed since 1976. The participation rate was 87%, corresponding to 504 men. In 1987, the health examination was repeated, with a participation rate of 76% (439 men). Thirty-five men had died or emigrated. Remaining were 103 nonrespondent men. A special questionnaire sent to these nonresponders was returned by 56. Among nonresponders, significantly more were living alone (p<0.001), were blue-collar workers (p<0.05), and had been admitted to hospital since 1981 (p<0.05). The other variables showed no significant differences.

In this study, only cross-sectional data from the study in 1987 have been used, since fibrinogen level was not determined in 1976. Follow-up of the cohort with regard to the incidence of ischemic heart disease will continue.

The social class of the participants was determined on the basis of the method developed by the Danish National Institute of Social Research. Three criteria were employed: occupation, education, and number of subordinates. Stratum 1 consists of university graduates, self-employed with more than 20 employees, and salaried employees with more than 50 subordinates. Stratum 2 consists of self-employed with six to 20 employees and salaried employees with 11 to 50 subordinates, or those with a medium-long education. Stratum 3 consists of self-employed with a maximum of five employees and salaried employees with one to 10 subordinates, or those in specialized work. Stratum 4 includes lower-level salaried employees and skilled manual workers. Stratum 5 consists of unskilled manual workers.

Cohabitation was determined according to whether the subject was cohabiting (90%) or not (10%).

Job strain was defined according to Karasek, where high job strain results from a combination of high job demands and low job decision latitude.

Nine questions concerning abdominal pain and indigestion were combined in an "abdominal index." Two questions concerning personal and/or economic problems within the previous month were used to classify respondents as having "problems," if the subject had at least one problem (17%), "no" if not (83%).

Self-assessed state of health was classified on the basis of a four-category question describing the subject's own health.

Loneliness was determined on the basis of a four-category question whether, within the last month, the subject had felt lonely.

Of the participating men, 54% were smokers and 46% were nonsmokers. Exsmokers (23%) were included under nonsmokers.

At the health examinations, the participants were interviewed as to drug consumption. In our analyses, we included consumption of tranquilizers. Those men who were characterized as users took tranquilizers at least once a month (9%).

The intensity and duration of leisure time physical activity was characterized by a four-category question as 1) fully sedentary; 2) at least 4 hours of walking, biking, or other activity per week; 3) some fitness sports training or other strenuous activities for at least 3 hours per week; and 4) regular competitive sports.

If a subject used sugar in his tea or coffee, he was termed a "sugar user" (32%).

Alcohol consumption was analyzed as a continuous variable in which the unit of measurement was the number of drinks per week. One drink was defined as equal to a glass of wine (0.15 l) or one beer (0.33 l). The average consumption was 14.8 drinks/week.

Physical fitness was estimated from a graded submaximal bicycle exercise test, and physical working capacity was measured by the Astrand and Ryhming method for indirect measurement of maximal oxygen uptake (ml · kg⁻¹ · min⁻¹). Men who were taking cardiovascular drugs or who, for physical reasons, could not perform strenuous exercise were excluded from the test (five men). In a further 45 men, physical fitness could not be determined since submaximal heart rate was not reached or was not constant over 6 minutes.
Waist-to-hip ratio was chosen as a measure of obesity since recent studies have shown this ratio to be a better predictor of ischemic heart disease than body mass index.

The measurements of blood pressure were standardized according to World Health Organization recommendations. Blood pressure was determined as the mean of two measurements in the supine position after 10 minutes of rest. We used the London School of Hygiene and Tropical Medicine Sphygmomanometer with a 12×33-cm cuff. At the study, all measurements were performed by the same person and with the same apparatus.

For all blood samples, the participants had been fasting for 12 hours and had rested in a supine position for 10 minutes. If possible, no vein stases were used.

High density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol levels were determined enzymatically (Boehringer Mannheim, Mannheim, F.R.G.) at our laboratory. The laboratory is standardized against the Prague laboratory.

A gravimetric method was used to measure the concentration of clottable fibrinogen. One of the 439 analyses failed, so the results are based on the values for the remaining 438 men.

We employed multiple regression analyses with plasma fibrinogen as the dependent variable. In the initial multivariate analyses, the independent variables were divided into four groups: social, psychological, lifestyle, and physiological, and each group was analyzed separately. The reason for this was to distinguish confounding variables from intermediate ones.

We have, so far as possible, included all variables reported by others to be associated with fibrinogen.

In addition, we have included variables that, in our data, showed a significant ($p<0.05$) univariate association with fibrinogen level. In the single multivariate analyses, we left out, in a stepwise fashion, the variables with the highest $p$ value until all variables in the model had values of $p<0.05$.

In the present material, fibrinogen level generally showed a normal distribution, and no logarithmic transformation was necessary in the multiple regression analyses. In the univariate analyses, Spearman's rank correlation test was used when the independent variables were continuous and the Wilcoxon–Mann–Whitney test when the independent variables were dichotomous. In Table 6 where classed variables are correlated, we used the Goodman–Kruskal $\gamma$ test.

**Results**

Figure 1 shows the distribution of plasma fibrinogen level in the 438 51-year-old men. The mean was 2.73 g/l (SD of 0.52 g/l), and the coefficient of variation was 0.19; the range was 1.3–5.8 g/l, with approximately 90% of the men having values between 2.0 and 3.5 g/l. The distribution is a little skewed to the right, but fairly close to a normal distribution.

Results from the univariate and multivariate analyses of the social variables are presented in Table 1. The univariate analyses show that social class and cohabitation are correlated significantly with fibrinogen, whereas job strain is not. In the multivariate analyses including the three variables, cohabitation decreased to borderline significance ($p=0.08$), but the overall picture was the same as in the univariate analyses: fibrinogen level is higher among men from low social class and among men living alone.
Table 2 gives the results from the analyses of the psychological variables. Abdominal index, problem index, and self-assessed state of health are correlated significantly with fibrinogen in the univariate analyses, whereas in the multivariate analyses, only abdominal index and problem index remain significant. Thus, men with abdominal pain or with social, economic, or individual problems have higher fibrinogen levels.

The behavioral or lifestyle variables analyzed are presented in Table 3. All variables except alcohol consumption show significant p values in the univariate analyses. In the multivariate analyses, however, only smoking and physical activity remained significant. As to the use of sugar, a highly significant p value changed to a nonsignificant value in the multivariate analyses because of a close association with physical fitness. For fasting glucose, the p value in the multivariate analyses is clearly smaller than that in the univariate analyses, without, however, reaching statistical significance at the conventional level.

Table 5 analyzes the variables with p<0.05 in the preceding multivariate analyses. Three physiological, one behavioral, and one social variable remained significant in the final multivariate analysis. Clearly, the lowest p value was found for smoking, with p<0.0001.

Among men with a “low” risk profile (i.e., nonsmokers with high social class and low LDL cholesterol), the plasma fibrinogen level was 2.43 g/l, whereas it was 3.18 g/l among men with the “high” risk profile.

In Table 6, correlations between social and psychological variables are shown. Concerning the three variables included in Table 5, the following correlations are significant: low social class is associated with living alone, having job strain, and being lonely. Having social or psychological problems and having abdominal pain are both associated with poor self-assessed state of health and being lonely.

### Discussion
The present cohort was examined both at age 40 and 51 years. However, fibrinogen level was not determined at the first examination. Consequently, we have been confined to analyzing cross-sectional
TABLE 6. Correlations Between Social and Psychological Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Social class (0=1-2, 4=5)</th>
<th>Cohabitation (0=yes, 1=alone)</th>
<th>Job strain (0=no, 1=strain)</th>
<th>Abdominal index (0=no, 1=pain)</th>
<th>Problem index (0=no, 1=problems)</th>
<th>Subjective health (0=good, 2=poor)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohabitation (0=yes, 1=alone)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>$\gamma$</td>
<td>0.35</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>$p$</td>
<td></td>
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<td></td>
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<tr>
<td>Job strain (0=no, 1=strain)</td>
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</tr>
<tr>
<td>$\gamma$</td>
<td>0.35</td>
<td>0.10</td>
<td></td>
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<tr>
<td>$p$</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal index (0=no, 1=pain)</td>
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<td></td>
</tr>
<tr>
<td>$\gamma$</td>
<td>0.10</td>
<td>0.12</td>
<td>0.02</td>
<td></td>
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<tr>
<td>$p$</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Problem index (0=no, 1=problems)</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>$\gamma$</td>
<td>0.17</td>
<td>0.45</td>
<td>0.21</td>
<td>0.20</td>
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<td></td>
</tr>
<tr>
<td>$p$</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Subjective health (0=good, 3=poor)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>$\gamma$</td>
<td>0.11</td>
<td>0.22</td>
<td>0.14</td>
<td>0.42</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>$p$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loneliness (0=no, 3=lonesome)</td>
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<td></td>
</tr>
<tr>
<td>$\gamma$</td>
<td>0.26</td>
<td>0.82</td>
<td>0.03</td>
<td>0.29</td>
<td>0.54</td>
<td>0.47</td>
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<tr>
<td>$p$</td>
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</tbody>
</table>

*p<0.05, †p<0.01, ‡p<0.001.

data. Such analyses have well-known shortcomings in that they lack control with the time dimension. Another shortcoming is that—to some extent, owing to the composition of the study population—it has not been possible to include a number of variables such as sex, age, oral contraceptive use, and hereditary disposition. Furthermore, we have no data on dietary habits.

The mean fibrinogen level in the 51-year-old men was 2.73 g/l. In Table 7, this level in Danish men is compared with that in similar populations in other studies. The lowest levels are seen for Danish men and the cohorts from Münster and Framingham. In all the British studies and in the two Gothenburg Studies, the fibrinogen level is above 3.00 g/l. Apparently, these differences cannot be explained solely by differences in measurement methods. We recommend an international standardization within this area, so that fibrinogen values can become directly comparable.

We find a significant association between social class and fibrinogen in that the men from the lowest social class have the highest fibrinogen level (Table 1). This agrees with the results from the Whitehall Study, the Northwick Park, and the Gothenburg 1933 study. In contrast to the Whitehall Study, we find no association between job strain and fibrinogen level.

Apparently, the relation between cohabitation and fibrinogen has only been examined in the Gothenburg 1933 study, in which Rosengren et al found a negative association between fibrinogen level and the number of people in the household for nonsmokers. It should be noted that this is consistent with the finding in a number of studies, which shows that lack of a social network or support is a risk factor for cardiovascular disease.

TABLE 7. Mean Fibrinogen Level Reported in Epidemiological Studies in Men Aged About 50 Years

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Method</th>
<th>Plasma fibrinogen level (g/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Münster</td>
<td>507</td>
<td>Claus</td>
<td>~2.7</td>
</tr>
<tr>
<td>Framingham</td>
<td>201</td>
<td>Spectrophotometric</td>
<td>2.78</td>
</tr>
<tr>
<td>Leigh</td>
<td>191</td>
<td>Gravimetric</td>
<td>3.04</td>
</tr>
<tr>
<td>Northwick</td>
<td>627</td>
<td>Gravimetric</td>
<td>3.10</td>
</tr>
<tr>
<td>Whitehall</td>
<td>74</td>
<td>Gravimetric</td>
<td>3.12</td>
</tr>
<tr>
<td>Gothenburg 1933</td>
<td>639</td>
<td>Claus</td>
<td>3.12</td>
</tr>
<tr>
<td>Gothenburg 1913</td>
<td>781</td>
<td>Spectrophotometric</td>
<td>3.33</td>
</tr>
<tr>
<td>Caerphilly</td>
<td>134</td>
<td>Nephelometric</td>
<td>3.6</td>
</tr>
</tbody>
</table>
The results in Table 2 show univariate associations between fibrinogen level and four variables of psychological or psychosomatic character. Of these four variables, two are significant in the multivariate analysis. In the Gothenburg 1933 study, a negative association between activity score and fibrinogen level was found. This activity score is comparable with our loneliness variable.

As already mentioned, the literature on fibrinogen as a cardiovascular risk factor is in agreement with the notion that smoking is one of the most important causes of increased fibrinogen level. Consistently, we find in Table 3 a very clear association between smoking and fibrinogen in both the univariate and the multivariate analyses. Furthermore, there was a clearly significant univariate and multivariate association between physical inactivity and fibrinogen level. No such association was found in the Whitehall Study; however, that study population was very small (N = 74). In the Gothenburg 1933 Study, a very significant negative association between physical activity and fibrinogen was found. This association became insignificant in the multivariate analyses. In the Gothenburg 1913 Study, there was a positive univariate association between heart rate and fibrinogen, which, however, became nonsignificant in the multivariate analyses.

The association between use of sugar and fibrinogen level, which is very clear in the univariate analysis in Table 3, disappears in the multivariate analysis. The reason for this appears to be that sugar users, to a higher degree, are smokers and that smoking therefore is a confounding factor.

Alcohol consumption does not correlate with fibrinogen level in Table 3. This negative finding confirms the results from other studies. However, two studies found a negative association between alcohol consumption and fibrinogen level, namely, the Caurphilly Study and the Northwick Park Study.

The results on HDL and LDL cholesterol levels in Table 4 agree well with those from other studies. On the other hand, no association between fibrinogen and serum cholesterol was found in the Framingham Study, where only total serum cholesterol level was measured.

As previously mentioned, the Gothenburg 1913 Study demonstrated an association between heart rate and fibrinogen level, and the Gothenburg 1933 Study found a negative association between physical activity level and fibrinogen, which is in keeping with the negative association between physical fitness and fibrinogen in Table 4. No other studies have included physical fitness in the analyses of fibrinogen.

The association between fasting glucose and fibrinogen is nonsignificant in both analyses in Table 4, which agrees well with the results from the Gothenburg 1913 and the Münster studies. As to systolic blood pressure, other studies have demonstrated significant univariate associations, but only the Münster Study found a multivariate association, and only among women. As seen in Table 4, we find no association between systolic blood pressure and fibrinogen level, and this agrees with the findings in the Gothenburg 1933 Study.

The last of the physiological variables in Table 4 is waist-to-hip ratio. This variable shows a strong association with fibrinogen in the univariate but not in the multivariate analyses. The results from other studies are not clear, some finding significantly positive associations and others not. The lack of consensus may be due partly to different measures of obesity and partly to lack of control with confounders in the various analyses. Table 4 clearly shows that the p value for the waist-to-hip ratio is considerably higher when adjustments for other physiological variables are made, which emphasizes the importance of control of confounding variables.

Table 5 comprises those variables that in Tables 1–4 have reached significance in the multivariate analyses. In a multivariate analysis, the variables closest in the causal chain to the dependent variable will be "favored," whereas variables occurring earlier in the causal chain often will lose significance. This pattern is apparent in Table 4, in that a number of the social and psychological variables become insignificant. This does not apply, however, to social class, which in this analysis has a p value of 0.003. Smoking, LDL cholesterol, physical fitness, and HDL cholesterol also remain significant.

Even if, as already mentioned, cross-sectional studies like the present one do not allow conclusions as to causal associations, it seems justifiable to frame some hypotheses concerning causes of increased fibrinogen level.

On the basis of the previous discussion of our results as well as the results of others, we consider the following four causal chains probable: 1) Diet → serum cholesterol (HDL and LDL cholesterol) → fibrinogen level. (Diet is not included in our analyses. A detailed discussion is given by Fehely et al. and Rogers et al. 2) Physical activity → physical fitness → fibrinogen level. 3) Smoking → fibrinogen level. 4) Lack of social support/network → psychological problems → fibrinogen level.

All these four causal chains are possibly operative in the association between social class and fibrinogen level. Thus, in most industrialized societies, a high-fat/low-fiber diet, smoking, no or little physical activity, and lack of social support are most frequently seen in the lower social strata. Besides these four causal chains involving social and lifestyle factors, there may be a fifth, namely, hereditary disposition, which, however, is outside the scope of the present study.

For many years, the atherosclerotic process has played a dominant role in research on cardiovascular disease. Recent research on fibrinogen as an independent risk factor for cardiovascular disease has contributed to an increased interest in the thrombogenic processes, thereby supplementing our understanding of the etiology and pathogenesis of cardiovascular diseases.
If the association between fibrinogen level and risk for cardiovascular disease is accepted as a causal one, it then becomes important to ascertain the factors that determine the fibrinogen level. In this connection, the most important finding is the apparently causal association between smoking and fibrinogen level. We recommend that the other causal chains mentioned be examined in future research in this area, especially the role of psychosocial factors.

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