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Fibrinogen, viscosity and the 10-year incidence of ischaemic heart disease

The Caerphilly and Speedwell Studies

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Aims To use the ten year follow-up of the Caerphilly and Speedwell studies to assess the contributions of fibrinogen and viscosity to the prediction of risk of ischaemic heart disease.

Methods and Results Caerphilly and Speedwell are prospective studies based on representative samples of middle-aged males. Ischaemic heart disease morbidity and mortality were defined using hospital notes, repeat electrocardiographs and death certificates. There were 603 incident events among the 4860 men. Age-adjusted relative odds of ischaemic heart disease increased to 3·3 and 3·4 in the 20% of men with the highest levels of fibrinogen and viscosity, respectively. After standardizing for the major cardiovascular risk factors, these relative odds were 2·2 (95% confidence interval 1·6 to 3·1) for fibrinogen and 2·3 (95% confidence interval 1·7 to 3·2) for viscosity. When fibrinogen and viscosity were entered jointly, both remained significant ($P<0·01$) predictors. Incidence of ischaemic heart disease increased with increasing fibrinogen at every level of viscosity, and vice versa. Interactions with lipids were also examined. There was no support for the suggestion that risk is independent of cholesterol level when fibrinogen is low.

Conclusions Fibrinogen and viscosity are powerful, long term and independent predictors of the risk of ischaemic heart disease.
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Key Words: Fibrinogen, viscosity, ischaemic heart disease, prospective study, interactions, cholesterol.

Introduction

Fibrinogen has been shown to be a risk factor for ischaemic heart disease by a number of prospective studies[1–3]. A meta-analysis[4] of six such studies showed that although event rates differed between the six studies, there was a consistent pattern of increasing risk with increasing level of fibrinogen. The summary relative odds comparing risk in the top third of the distribution of fibrinogen with that in the bottom third were 2·3, with a 95% confidence interval of 1·9 to 2·8. The average length of follow-up of the six studies varied from 2 years to nearly 14 years. The three largest of the six studies had follow-up periods of 5 years or less. One of those studies was the Caerphilly/Speedwell study[5] and we now report the 10-year follow-up for that study. One advantage of this longer follow-up is that if a factor predicts risk over the longer period then it is more likely the association is causal.

High fibrinogen levels are thought to increase the risk of ischaemic heart disease through at least four pathways[6], one of the most important probably being the contribution that they make to increased viscosity. We showed[5] in the shorter follow-up that viscosity was predictive of risk, independent of fibrinogen. In the absence of corresponding data from other prospective studies, this 10-year follow-up provides many more cases on which to assess the contribution of viscosity to ischaemic heart disease risk.

Recently, two studies[7,8] have claimed that low fibrinogen levels are associated with low levels of coronary risk even when total or low-density lipoprotein cholesterol are high. That claim was later withdrawn[9] for one of the studies. Reliable information on such interactions requires large numbers of events[10,11] and both these studies were based on less than 90 events. We now present similar data based on over 500 events.

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Methods

Study population and recruitment survey methods

These have been described in detail elsewhere[5]. Briefly, in both areas men were recruited from geographically defined populations. Recruitment took place between 1979 and 1983 when the Caerphilly men were aged 45–59 years and the Speedwell men 45–63 years. In Caerphilly, 2512 men were recruited, 89% of the 2818 men who were found to be eligible. In Speedwell, 2348 men were recruited, 92% of the eligible cohort of 2550. The combined cohort thus numbers 4860 men. The two studies had a common core protocol. At an afternoon or evening clinic a standard medical and smoking history was obtained; the London School of Hygiene and Tropical Medicine chest pain questionnaire[12] was administered; height, weight and blood pressure were measured, and a 12-lead electrocardiogram (ECG) was recorded. Detailed methods are described elsewhere[13]. The men returned, after an overnight fast, to an early morning clinic where a blood sample was taken with minimal venous stasis. Fasting samples were obtained from 4641 men. Fibrinogen and plasma viscosity were estimated by the same laboratory for the two studies; fibrinogen by a nephelometric method[14] after heat precipitation in buffered saline and plasma viscosity by a Harkness viscometer[15]. Cholesterol was measured using enzymatic procedures[16].

Follow-up procedure and definition of incident ischaemic heart disease

The results reported in this paper refer to the second follow-up in Caerphilly, and the third in Speedwell. These were at nearly constant intervals averaging 120 months in Caerphilly and 112 months in Speedwell. In Caerphilly, 89% of men were seen within ± 6 months of that average, while in Speedwell it was 97%. At each follow-up the chest pain questionnaire was readministered and another ECG was recorded. The chest pain questionnaire was extended to include questions about admissions to hospital with severe chest pain. This, together with hospital activity analysis notifications of admissions coded as 410–414 (ischaemic heart disease) on the International Classification of Diseases was used as the basis for a search of hospital notes for events which satisfied World Health Organisation criteria for definite acute myocardial infarction. For men who had died before follow-up, a copy of the death certificate was received automatically from the National Health Service Central Registry. From this information, three categories of incident ischaemic heart disease were defined: death (cause of death coded as 410–414), clinical non-fatal myocardial infarction (an event satisfying the World Health Organisation criteria) and ECG myocardial infarction (the appearance of major or moderate Q or QS waves, Minnesota codes 1-1-1 to 1-2-5, or 1-2-7 on any follow-up ECG when there were no Q or QS waves, 1-1-any or 1-2-any or 1-3-any on the recruitment ECG).

Statistical methods

Adjusted mean differences between men who developed incident ischaemic heart disease and those who did not were obtained by analysis of covariance using standard multiple regression techniques. The remainder of the analysis was performed using multiple logistic regression with the occurrence, or not, of any one of the three types of incident disease as the dependent variable. Logistic regression takes no account of the duration of follow-up, but this is likely to be immaterial. Within each area the duration was nearly constant. Further, any model involving time would face the problem that no time to event is available for the ECG-defined myocardial infarctions. Cox proportional hazard models[17] fitted to data which included time to event or censoring but excluded the ECG-defined myocardial infarctions as events, gave age-adjusted regression coefficients that were closely similar (within 5%) to those from the corresponding multiple logistic regression.

In the logistic regression analyses, fibrinogen and viscosity were divided into five equal-sized groups using each area's own quintiles, and the results are presented as the odds of incident ischaemic heart disease in each 5th relative to the baseline 5th. Tests for trend were obtained by entering fibrinogen or viscosity as continuous variables, and are summarized as standardized relative odds, the odds associated with a one standard deviation increase in fibrinogen or viscosity.

Ischaemic heart disease at recruitment was assessed by the chest pain questionnaire and the ECG. Three categories of pre-existent disease, namely, angina, history of prolonged severe chest pain and ECG ischaemia, were defined in a standard manner[18]. Among the 4860 men, 1122 (23%) had some evidence of prevalent disease. This prevalence is similar to that found by the British Regional Heart Study[19]. Men with evidence of disease at recruitment have not been excluded from the analysis. Exclusion of such a large group, among whom over 40% of the incident events occur, does not seem satisfactory. The usual practice is to exclude a small group, such as the 261 (5%) who had had an episode of severe chest pain that was considered by a doctor to be ischaemic in origin[20]. It is then assumed, incorrectly, that the remaining subjects are free of ischaemic heart disease. Instead, we have chosen, as did the Regional Heart Study[21], to include all men, but to adjust for the presence of pre-existent disease by including the standard measures of angina, severe chest pain and ECG ischaemia as three covariates in the logistic regression analyses. Baseline fibrinogen and viscosity are higher in men with pre-existent disease. If the association between fibrinogen and viscosity and incident disease is similar for men with and without pre-existent disease, then

Table 1 Mean levels of fibrinogen and plasma viscosity and the 10-year incidence of ischaemic heart disease

	Incident ischaemic heart disease*		Age-standardized differences	
	No (n=4043)	Yes (n=563)	Mean	95% confidence interval
Fibrinogen ($g.l^{-1}$)	3·64 (0·81)	3·98 (0·89)	0·30	0·23–0·37
Viscosity (cp)	1·685 (0·095)	1·724 (0·098)	0·037	0·029–0·046

*Values are given as mean (standard deviation). Numbers of men are slightly higher for viscosity at 4045 and 564.

Table 2 Mean levels of fibrinogen and viscosity by time to first incident ischaemic heart disease event*

	Number of men	Mean (SD)	Age-standardized difference from men with no incident event	
			Mean	95% confidence interval
Fibrinogen ($g.l^{-1}$)				
No incident event	4043	3·64 (0·81)	—	—
Interval to first incident event.				
0–39 months	163	4·07 (0·86)	0·38	0·26–0·51
40–79 months	147	4·06 (0·96)	0·37	0·24–0·51
≥80 months	161	3·87 (0·80)	0·20	0·07–0·33
Viscosity (cp)				
No incident event	4045	1·685 (0·095)	—	—
Interval to first incident event.				
0–39 months	164	1·735 (0·096)	0·047	0·032–0·061
40–79 months	147	1·731 (0·103)	0·043	0·028–0·059
≥80 months	161	1·719 (0·089)	0·032	0·017–0·047

*Incident events defined purely from sequential ECGs have been excluded as the time to the event is unknown.

adjusting for the presence of pre-existent disease is almost certainly a conservative procedure. In fact, the associations are slightly stronger for men without any evidence of pre-existent disease when again the adjustment is likely to be conservative.

Results

A total of 603 incident ischaemic heart disease events occurred during the follow-up; 312 in Caerphilly and 291 in Speedwell. The average annual incidence was 1·2% in Caerphilly and 1·3% in Speedwell. The formal analysis is based on the 4641 men who gave a fasting blood sample, among whom there were 571 incident events. Information was missing on fibrinogen for 35 men, viscosity for 32, total cholesterol for 79 and low density lipoprotein cholesterol for 301.

Table 1 shows mean levels of fibrinogen and viscosity according to whether or not the man developed ischaemic heart disease over the 10-year follow-up period, together with age-adjusted mean differences, with 95% confidence intervals. For fibrinogen the mean difference is 0·30 $g\,l^{-1}$, with 95% confidence interval 0·23 to 0·37 $g\,l^{-1}$. For viscosity, the mean difference is 0·037 cp (centipoise), with 95% confidence interval 0·029 to 0·046. For both variables, the test of statistical significance to compare the adjusted mean values yields a t-test in excess of 8. Table 2 shows mean levels of fibrinogen and viscosity according to the time interval between recruitment and first incident event. Mean levels of both fibrinogen and viscosity are very similar for events occurring within 40 months of recruitment and for events occurring between 40 and 80 months after recruitment. There is a decrease, particularly for fibrinogen, in these mean levels for events occurring more than 80 months after recruitment. However, even in this latter group, age-standardized fibrinogen is higher by 0·20 $g\,l^{-1}$ than among the men with no incident disease (P=0·002) and age-standardized viscosity is higher by 0·032 cp (P<0·0001).

Figure 1 shows relative odds of incident ischaemic heart disease by 5ths of both fibrinogen and viscosity with successive adjustments for possible confounders. All relative odds are based on the 4463 men with a complete set of data for all the variables, among whom there were 544 incident ischaemic heart disease events. Age-adjusted relative odds of disease increase steadily to 3·3 and 3·4 in the 20% of men with the highest levels of fibrinogen and viscosity, respectively. Adjusting

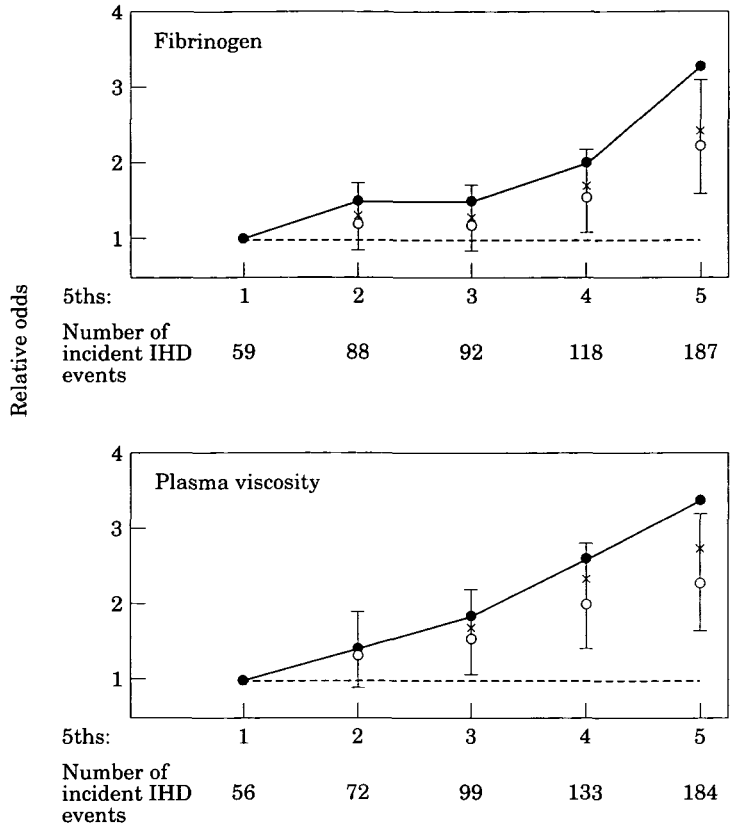

Figure 1 **Relative odds of incident ischaemic heart disease (IHD) by 5ths of fibrinogen and plasma viscosity. ■=base group for calculation of relative odds; ●=odds adjusted for age; ✖=odds adjusted for age, smoking habit and pre-existent disease status; ǂ=odds adjusted for age, smoking habit, pre-existent disease status, diastolic blood pressure, body mass index and plasma cholesterol, with 95% confidence interval.**

for smoking habit and pre-existing disease reduces the relative odds in the top 20% to 2·4 (95% confidence interval 1·8 to 3·4) for fibrinogen and 2·8 (95% confidence interval 2·0 to 3·8) for viscosity. Further adjustment for diastolic blood pressure, body mass index and total cholesterol produces further small reductions to 2·2 (95% confidence interval 1·6 to 3·1) for fibrinogen and 2·3 (95% confidence interval 1·7 to 3·2) for viscosity. Even after adjusting for all these standard cardiovascular risk factors, the trend for incident disease to increase with both fibrinogen and viscosity is highly statistically significant ($P<0·000001$). The corresponding, fully adjusted, standardized relative odds are 1·27 (95% confidence interval 1·16 to 1·39) for fibrinogen and 1·28 (95% confidence interval 1·16 to 1·40) for viscosity.

Incidence of ischaemic heart disease in relation to fibrinogen and viscosity jointly is shown in Fig. 2. At each of the three levels of viscosity, incidence increases with increasing fibrinogen. Equally, however, at each of the three levels of fibrinogen, incidence increases with increasing viscosity. There is no suggestion of any interaction between fibrinogen and viscosity, a formal test for interaction yielding χ^2 (4 d.f.)=1·12, $P>0·80$. When both variables are entered together into a multiple logistic regression, the age-adjusted standardized relative odds are 1·22 and 1·29 for fibrinogen and viscosity, respectively. Further adjusting for the same complete set of standard risk factors used in the earlier analysis reduces the standardized relative odds to 1·16 (95% confidence interval 1·04 to 1·30) for fibrinogen ($P=0·008$) and to 1·17 (95% confidence interval 1·04 to 1·31) for viscosity ($P=0·007$).

Figure 3 shows how the incidence of ischaemic heart disease varies jointly with fibrinogen and plasma low density lipoprotein cholesterol. Again, incidence increases with increasing fibrinogen at each level of cholesterol and it increases with increasing cholesterol at each level of fibrinogen. A formal test for an interaction between fibrinogen and cholesterol gives χ^2 (4 d.f.)= 5·71, $P>0·20$. Thus there is no evidence of any interaction, and no suggestion that low-density lipoprotein cholesterol is unrelated to the incidence of disease when the fibrinogen level is low. An exactly similar result is obtained when this analysis is repeated with total cholesterol in place of low density lipoprotein cholesterol.

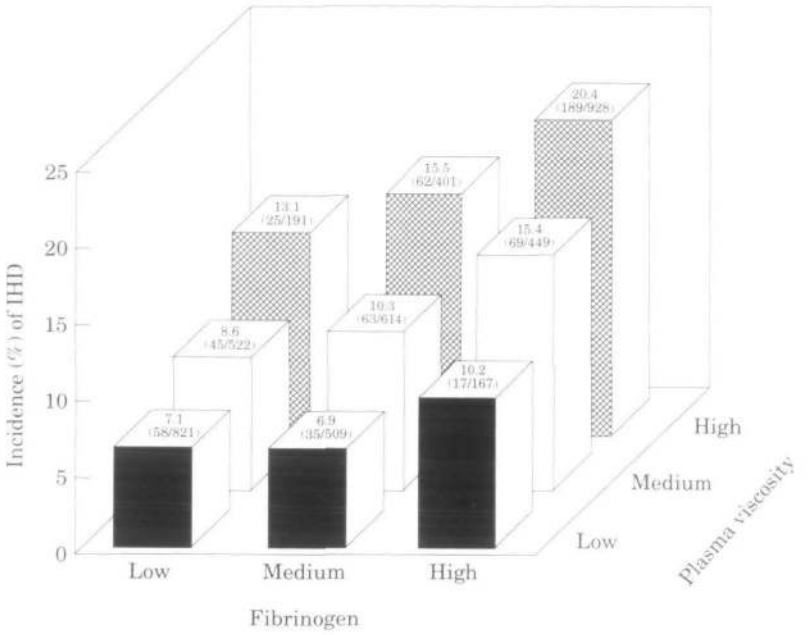

Figure 2 10-year incidence of ischaemic heart disease (IHD) jointly in relation to both fibrinogen and plasma viscosity.

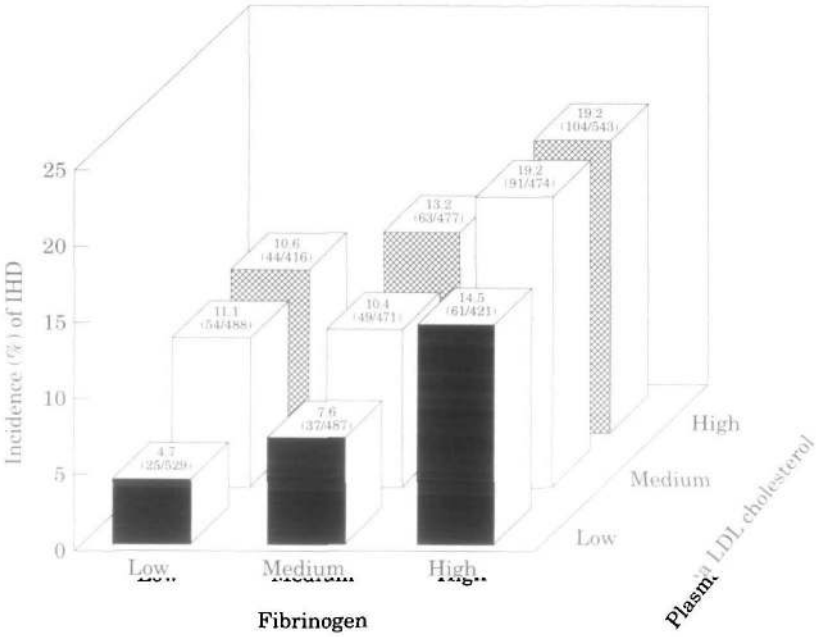

***Figure 3* 10-year incidence of ischaemic heart disease (IHD) jointly in relation to both fibrinogen and plasma low density lipoprotein (LDL) cholesterol.**

Discussion

We have shown, as have others[1,2,22], that fibrinogen is a long-term predictor of ischaemic heart disease. We have also shown that plasma viscosity is a long-term predictor. Age-adjusted baseline fibrinogen and viscosity levels were, respectively, 0·30 g . l^{-1} and 0·037 cp higher among the 563 men who developed incident disease over the 10 years of the follow-up. For fibrinogen this difference is similar to, but rather larger than, that found by either the Northwick Park Heart Study[1] or the Gothenburg Study[2]. In the Northwick Park Study, the age-adjusted mean difference was approximately 0·2 g . l^{-1} among 179 men who developed disease[1], while in the Gothenburg Study it was higher, by 0·26 g . l^{-1} among 92 men who developed myocardial

infarction[2]. The third cohort study[22], which had reported a follow-up in excess of 10 years, did not present data from which a comparable figure could be calculated. There seem to be no comparable figures for plasma viscosity.

At our first follow-up, which occurred at 5·1 years in Caerphilly and at 3·2 years in Speedwell, the age-adjusted mean differences in fibrinogen and viscosity were 0·38 g . l^{-1} and 0·045 cp[5] respectively. Thus, the predictive powers are less good over the longer than the shorter period. This is to be expected, as a single measurement will be a better estimate of the subjects' usual fibrinogen or viscosity over the shorter period. In other words, the regression dilution effect can be expected to be greater over the longer periods. Nevertheless, as we have shown, even those events occurring more than 80 months after the baseline measurements still have age-adjusted fibrinogen and viscosity levels that are higher, by 0·20 g . l^{-1} (P=0·002) and 0·032 cp (P=0·00002) respectively, than those among men not developing ischaemic heart disease. The interval to the event in this group averages nearly 8·5 years and the fact that both fibrinogen and viscosity predict such long-term events increases the likelihood that the associations may be causal.

Age-adjusted standardized relative odds of ischaemic heart disease were 1·42 for fibrinogen and 1·45 for viscosity. These standardized relative odds are very high, so that fibrinogen and viscosity are not only long-term predictors, but also powerful predictors. For fibrinogen, adjusting the standardized relative odds for the main cardiovascular risk factors reduces it from 1·42 to 1·27 (95% confidence interval 1·16 to 1·39). This value of 1·27 is similar to that reported by Kannel *et al.*[22] from the Framingham Study, after adjusting for similar risk factors. Thus the association between fibrinogen and incident disease is largely independent of the standard cardiovascular risk factors. However, the association is partially dependent on the association of both fibrinogen and ischaemic heart disease with plasma viscosity. Fibrinogen is one of the major contributors to the viscosity of plasma, and in our studies the correlation between fibrinogen and viscosity is high, at 0·56. Koenig *et al.*[23] concluded that geographical differences in plasma viscosity might partly explain the differences in ischaemic heart disease event rates between Glasgow and Augsburg and that one mechanism by which fibrinogen might promote disease was by increasing plasma viscosity. Meade[6], considers that increasing plasma viscosity might be the most important pathway by which fibrinogen predisposes to ischaemic heart disease. Our results show that when plasma viscosity is added to the model which already includes the main cardiovascular risk factors, the standardized relative odds for fibrinogen are reduced from 1·27 to 1·16. This value is still statistically significant (P=0·008) as is the value of 1·17 for viscosity itself (P=0·007). This finding strongly supports the proposition that viscosity is an important, independent, predictor of risk and that it may be one of the important pathways by which fibrinogen promotes ischaemic heart disease.

We find that fibrinogen remains a predictor of risk at every level of viscosity. Equally we have found both that fibrinogen is a predictor of risk at every level of low-density lipoprotein cholesterol and, conversely, that cholesterol is a predictor of risk at every level of fibrinogen. This much larger study provides no support for the assertion[7,8], later withdrawn by one of the two studies[9], that low fibrinogen levels characterize patients at low risk for coronary events despite increased cholesterol levels. Our results suggest that the increased risk associated with increased low density lipoprotein or total cholesterol applies whatever the level of fibrinogen.

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