Fibrinogen, Viscosity, and White Blood Cell Count Are Major Risk Factors for Ischemic Heart Disease

The Caerphilly and Speedwell Collaborative Heart Disease Studies

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Background. **Recent studies have suggested that hemostatic factors and white blood cell count are predictive of ischemic heart disease (IHD). The relations of fibrinogen, viscosity, and white blood cell count to the incidence of IHD in the Caerphilly and Speedwell prospective studies are described.**

Methods and Results. **The two studies have a common core protocol and are based on a combined cohort of 4,860 middle-aged men from the general population. The first follow-up was at a nearly constant interval of 5.1 years in Caerphilly and 3.2 years in Speedwell; 251 major IHD events had occurred. Age-adjusted relative odds of IHD for men in the top 20% of the distribution compared with the bottom 20% were 4.1 (95% confidence interval, 2.6–6.5) for fibrinogen, 4.5 (95% confidence interval, 2.8–7.4) for viscosity, and 3.2 (95% confidence interval, 2.0–4.9) for white blood cell count. Associations with IHD were similar in men who had never smoked, exsmokers, and current smokers, and the results suggest that at least part of the effect of smoking on IHD is mediated through fibrinogen, viscosity, and white blood cell count. Multivariate analysis shows that white blood cell count is an independent risk factor for IHD as is either fibrinogen or viscosity, or possibly both. Jointly, these three variables significantly improve the fit of a logistic regression model containing all the main conventional risk factors. Further, a model including age, smoking habits, fibrinogen, viscosity, and white blood cell count predicts IHD as well as one in which the three hemostatic/rheological variables are replaced by total cholesterol, diastolic pressure, and body mass index.**

Conclusion. **Jointly, fibrinogen, viscosity, and white blood cell count are important risk factors for IHD. (*Circulation* 1991;83:836–844)**

Numerous epidemiological studies[1,2] have found raised blood pressure, elevated total cholesterol, and smoking to be major factors associated with an increased risk of ischemic heart disease (IHD). Nevertheless, on an individual basis, the prediction of the risk of IHD from levels of blood pressure, lipids, and smoking is poor.[3] There is evidence[4,5] that occlusive thrombi are to be found in almost all cases of acute myocardial infarction and in the majority of sudden cardiac deaths. Thus, there may be a role for hemostatic and rheological factors in the etiology of the disease. In recent years, there have been a few reports[6–9] relating hemostatic factors to incidence of IHD and other reports[10–12] showing white blood cell count to be associated with risk of the disease.

See p 1098

The Caerphilly and Speedwell studies[13] recruited their joint population of 4,860 middle-aged men between 1979 and 1983. In addition to the conventional risk factors, measurements were made of a number of hemostatic and rheological variables. In the present report of the first follow-up of the two cohorts, the roles of fibrinogen, plasma viscosity, and white blood cell count in the incidence of ischemic heart disease are described.

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Methods

Study Populations

In the Caerphilly study,[13] a 100% sample including only men was selected from within a defined area: the town of Caerphilly plus five adjacent villages. The men were chosen by date of birth so that they were aged 45–59 years when examined between 1979 and 1983. A total of 2,512 men were seen – 89% of the 2,818 who were found to be eligible. In the Speedwell study,[13] a 100% sample including only men was selected from the age/sex registers of 16 general practitioners working from two neighboring health centers in the Speedwell area of Bristol. These men were chosen so that they were between 45 and 59 years of age on September 1, 1978, immediately before the study began. The men were thus between 45 and 63 years old when examined between 1979 and 1982. A total of 2,348 men were seen in the recruitment phase – 92% of the eligible population of 2,550. The combined cohort thus numbers 4,860 men.

Survey Methods for Recruitment Phase

The two studies were conducted by two teams of investigators with a common training at the Medical Research Council Epidemiology Unit, Cardiff, UK. The two studies had a common core protocol, and the same laboratories were used for all hematological tests.

The men were invited to attend an afternoon or evening clinic. A standard medical and smoking history was obtained; the London School of Hygiene and Tropical Medicine (LSHTM) chest pain questionnaire was administered; height, weight, and blood pressure were measured; and a 12-lead electrocardiogram (ECG) was recorded. Detailed methods for these, and for the wide range of other measures made, are described elsewhere.[13,14] The subjects were then asked to return, after an overnight fast, to an early morning clinic where a blood sample was taken with minimal venous stasis. Fasting samples were obtained from 4,641 men.

Laboratory Methods

For measurements of fibrinogen, plasma viscosity, and white blood cell count, the sample was immediately distributed into a specimen tube containing EDTA. Fibrinogen was estimated by a nephelometric method after heat precipitation in buffered saline.[15] Plasma viscosity was measured on a Harkness viscometer.[16] White blood cells were counted on a Coulter model S-plus (Coulter Corp., Hialeah, Fla.). In both studies, at least 5% of the samples sent to the laboratory were unidentifiable split-sample duplicates. Coefficients of variation for these blind duplicates were 7% for fibrinogen, 1–2% for viscosity, and 2–3% for white blood cell count.

Follow-up Procedure

The records of all men at the National Health Service Central Registry are flagged so that notification of death is automatic and a copy of the death certificate is received. Notifications of all admissions to local hospitals with a diagnosis coded International Classification of Diseases (ICD) 410–414 (ischemic heart disease) are received from the hospital activity analysis (HAA).

Men who were still alive and resided in, or close to, the original area were invited again to a follow-up clinic, where the LSHTM chest pain questionnaire, in particular, was applied again and a second ECG was recorded. The few men who had moved out of the respective areas were sent a self-administered version of the chest pain questionnaire. This last was used in the follow-up simply to identify events that might have been myocardial infarctions (see below).

The results reported in the present study refer to the first follow-up in each area. Considerable efforts were made to keep the length of follow-up constant within each area. In the Caerphilly study, the time to first follow-up was 61±5 (mean±SD) months. In the Speedwell study, the follow-up interval was 38±3 months. In the Caerphilly study, 90% of the men were seen between 56 and 67 months after entry into the study; in the Speedwell study, 90% were seen between 34 and 41 months.

Definition of Major Incident IHD Events

Three types of major incident IHD events have been defined: 1) death due to IHD, 2) Clinical myocardial infarction, and 3) ECG myocardial infarction.

Death due to IHD. All death certificates were coded by one of us (J.W.G.Y.) according to the ninth revision of the ICD. Deaths due to IHD are those coded ICD 410–414. Deaths attributed to other causes have been treated as non-IHD events.

Clinical myocardial infarction. The LSHTM chest pain questionnaire was extended to include questions about hospitalization for severe chest pain. This, together with HAA notification of admissions coded ICD 410–414, was used as the basis for a detailed search of hospital notes to identify events that satisfied the World Health Organization (WHO) criteria for definite acute myocardial infarction. In the Caerphilly study, this procedure was followed exactly. In the Speedwell study, the hospital notes were not available to us at the first follow-up. Instead, we defined clinical myocardial infarction as either an HAA-notified admission to hospital that was coded ICD 410 (acute myocardial infarction) or as any event for which the general practitioner had a hospital discharge letter that clearly described an episode satisfying the WHO criteria. Any misclassification introduced by this alternative procedure in the Speedwell study is likely to be very small indeed.

ECG myocardial infarction. The WHO criteria for acute myocardial infarction include a series of categories based purely on sequential ECGs. We have included only the first of these WHO categories as an ECG-defined myocardial infarction: no Q-QS wave (Minnesota codes 1-1, 1-2, or 1-3) on the recruitment phase ECG but major or moderate Q-QS waves

(Minnesota codes in the range 1-1-1 through 1-2-5 plus 1-2-7) on the follow-up ECG.

Statistical Methods

Adjusted mean differences in the hemostatic/rheological variables between various groups (Tables 2 and 4) have been obtained by analysis of covariance, using standard multiple regression techniques.

The remainder of the analysis has been performed using multiple logistic regression analysis with the occurrence, or not, of a major-incident IHD event as the dependent variable. Logistic regression takes no account of the timing of events as is required by other models, such as that of Cox. However, any model involving time would face the problem that "time to event" cannot be known for ECG-defined myocardial infarction. Men with evidence of IHD when first examined have not been excluded from the analysis. Instead, for reasons we give later, we have allowed for preexistent IHD by including it as a covariate in the analysis.

The difference in incidence between the two study areas, Caerphilly and Speedwell, arising from their different lengths of follow-up has been accommodated by including area as a two-level factor in all analyses. The assumption that the relations between incidence of IHD and the independent variables in the two areas are parallel on the logit scale was tested, and no statistically significant interactions were found.

The variables of interest, fibrinogen, viscosity, and white cell count, have been treated in two ways. First, their distributions have been divided, within each area separately, into equal fifths, and results are presented as the odds of major incident IHD in each fifth, relative to the odds in the lowest fifth; 95% confidence intervals (CIs) for these relative odds have been estimated from the logistic regression analyses. Second, they have been treated as continuous variables, and the results are presented as logistic regression coefficients, with standard errors and significance levels.

Results

Follow-up Status

A total of 132 (5.3%) Caerphilly men and 106 (4.5%) Speedwell men died before the first follow-up. Eight (0.3%) men in each area could not be contacted, but 12 of these 16 were known to be alive. Of the 4,606 men available for examination, 4,399 (96%) completed a chest pain questionnaire, and 4,296 (93%) had a repeat ECG.

Incidence of Major IHD

Incidence of the three types of major IHD event are shown in Table 1. In total, 251 major events occurred. The distribution of the three types of IHD event was very similar in the two areas; 50% were fatal, 39% were clinical nonfatal myocardial infarction, and 11% were ECG-defined myocardial infarction.

TABLE 1. Incidence of Major Ischemic Heart Disease in Two Study Areas

Type	Caerphilly (n=2,512)	Speedwell (n=2,348)
Fatal IHD	75 (3.0%)	51 (2.2%)
Clinical nonfatal MI	63 (2.5%)	34 (1.4%)
ECG MI	15 (0.6%)	13 (0.6%)
Total	153 (6.1%)	98 (4.2%)
Average annual incidence*	1.2%	1.3%

IHD, ischemic heart disease; MI, myocardial infarction; ECG MI, MI defined by findings on electrocardiogram (see "Methods").
*Average length of follow-up was 61 months in Caerphilly and 38 months in Speedwell.

Missing Data

The remainder of the analysis is based on the 4,641 men who provided a fasting blood sample. Of these 4,641 men, 233 had a major incident IHD event. Information was missing on smoking habits for 13 men, fibrinogen for 35, viscosity for 32, and white blood cell count for 26. A total of 4,589 men (among whom there were 230 major IHD events) had a complete set of these data.

Fibrinogen, Viscosity, and White Blood Cell Count Univariate Analyses

Mean levels of fibrinogen, viscosity, and white blood cell count were all higher in the men who developed major IHD (Table 2). The mean differences, standardized for age and area, are both large and highly statistically significant, with t values in excess of six.

Figure 1 shows relative odds of major incident IHD by fifths of the distribution of the three variables. The solid lines show the relative odds adjusted for age and area. The odds rise steadily as fibrinogen increases so that in the top 20%, relative odds are 4.1 (95% CI, 2.6–6.5). For viscosity, the corresponding relative odds are 4.5 (95% CI, 2.8–7.4), and for white blood cell count, they rise steadily to a value of 3.2 (95% CI, 2.0–4.9).

Multivariate Analysis

In assessing the importance of fibrinogen, viscosity, and white blood cell count as risk factors for IHD, other risk factors have to be taken into account, and

TABLE 2. Mean Levels of Fibrinogen, Viscosity, and White Blood Cell Count and Incidence of Major Ischemic Heart Disease

	Incidence*		Age- and area-standardized difference	
	No major IHD (n=4,408)	Major IHD (n=233)	Mean	95% CI
Fibrinogen (g/l)	3.66±0.82	4.09±0.92	0.38	0.28–0.49
Viscosity (cp)	1.688±0.096	1.735±0.099	0.045	0.032–0.057
WBCs (10^9/l)	7.02±2.01	7.86±2.22	0.84	0.57–1.10

IHD, ischemic heart disease; CI, confidence interval; WBCs, white blood cells.
*Values are area-standardized and given as mean±SD.

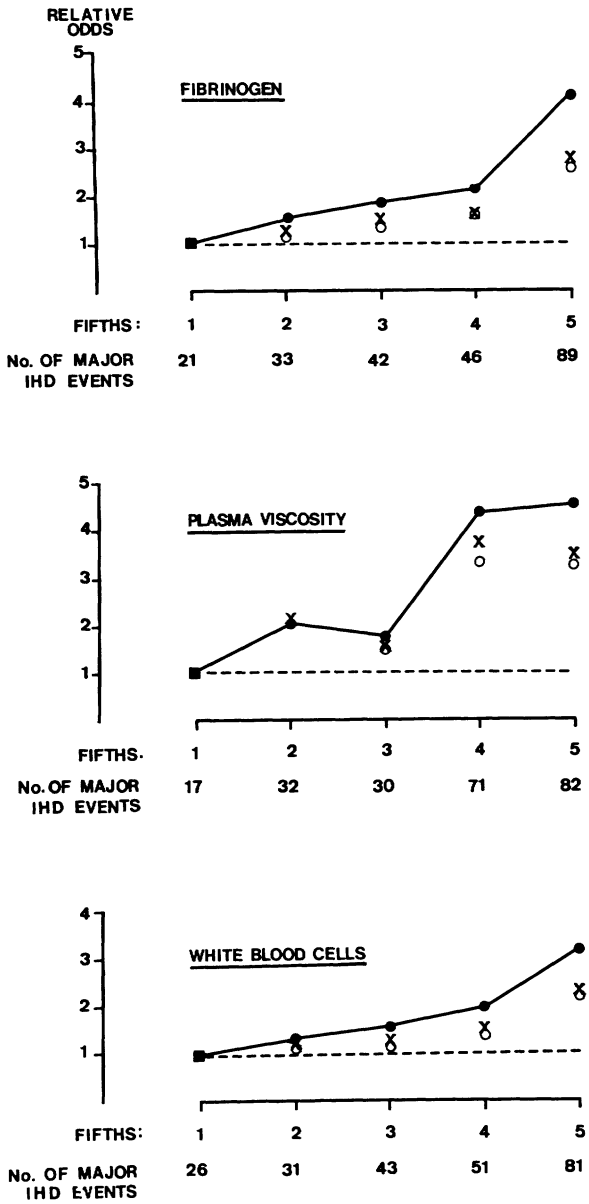

FIGURE 1. *Plots showing relative odds of a major incident ischemic heart disease (IHD) event by fifths of fibrinogen, plasma viscosity, and white blood cell count.* ■, *Base group for calculation of relative odds;* ●, *odds adjusted for age and area;* ×, *odds adjusted for age, area, smoking habit, and preexistent IHD;* ○, *odds adjusted for age, area, smoking habit, preexistent IHD, diastolic blood pressure, body mass index, and total cholesterol.*

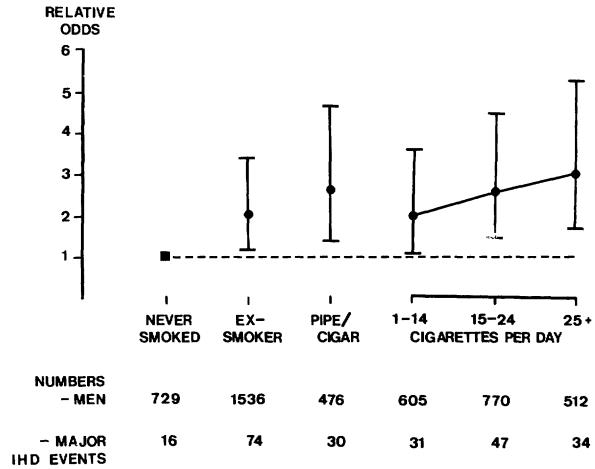

FIGURE 2. *Age- and area-standardized relative odds of a major incident ischemic heart disease (IHD) event and smoking habit.* ■, *Base group for calculation of relative odds;* ●, *relative odds (bars indicate 95% confidence interval).*

the roles of smoking and of preexistent disease are crucial.

Smoking habits. Incidence of major IHD was lowest (2.2%) among men who had never smoked. Figure 2 shows that all categories of smokers are at least twice as likely to develop major IHD as the men who have never smoked. Relative odds are smallest, at 2.0, for the exsmokers and the lightest cigarette smokers and greatest, at 3.0, for the heaviest smokers. They are significantly greater than 1.0 for all five categories of smokers.

It is well known that smokers have substantially higher levels of fibrinogen, viscosity, and white blood cell count than men who have never smoked, whereas exsmokers have intermediate levels that are related to the length of time after quitting.[17] It is clearly possible that the univariate associations between IHD and the three hemostatic/rheological variables arise solely because both are related to smoking habit. In fact, this is not so. Table 3 shows that when logistic regression models are fitted separately, the coefficients for each of the hemostatic/rheological factors are similar in current smokers, exsmokers, and men who have never smoked. The coefficients are not statistically significant for the men who have never smoked, but there are only a small number (16) of IHD events in this subgroup. Multiple logistic regression models that included a term for the interaction between smoking and each hemostatic factor were also fitted. In no case did that interaction term approach statistical significance. Thus, there is no evidence that the relations are different in the different smoking groups.

TABLE 3. Logistic Regression Coefficients for Fibrinogen, Viscosity, and White Blood Cell Count in Relation to Incidence of Ischemic Heart Disease Within Smoking Groups

	Logistic regression coefficient±SE		
Smoking group	Fibrinogen	Viscosity	White blood cell count
Nonsmoker	0.44±0.26	2.74±2.63	0.21±0.20
Exsmoker	0.42±0.13	4.56±1.15	0.10±0.06
Current smoker	0.48±0.10	3.80±0.76	0.16±0.03

Values are mean±SEM.

Each logistic regression model includes age, area, and one of fibrinogen, viscosity, or white blood cell count as independent variables.

TABLE 4. Mean Levels of Fibrinogen, Viscosity, and White Blood Cell Count in Men With and Without Major Incident Ischemic Heart Disease According to Preexistent Ischemic Heart Disease Status

	Incidence*		Age- and area-standardized mean difference	
Preexistent IHD	No major IHD	Major IHD	Mean	95% CI
Absent	(n=3,427)	(n=110)		
Fibrinogen (g/l)	3.61±0.79	4.01±1.01	0.36	0.21–0.51
Viscosity (cp)	1.681±0.092	1.731±0.094	0.048	0.031–0.066
WBCs (10^9/l)	6.96±2.03	7.86±2.34	0.90	0.51–1.29
Present	(n=981)	(n=123)		
Fibrinogen (g/l)	3.82±0.90	4.15±0.83	0.31	0.14–0.47
Viscosity (cp)	1.709±0.104	1.738±0.105	0.027	0.008–0.047
WBCs (10^9/l)	7.24±1.93	7.86±2.11	0.63	0.25–0.99

IHD, ischemic heart disease; CI, confidence interval; WBCs, white blood cells.
Preexistent IHD includes angina, severe chest pain lasting more than half an hour, and possible and probable ischemia according to findings on electrocardiogram.
*Values are area-standardized and given as mean±SD.

In all subsequent analyses, smoking habit is treated as a three-level factor; nonsmoker, exsmoker, and current smoker. It was found that subdivision of current smokers by dose had no material effect on the relations between the incidence of IHD and hemostatic factors.

Preexistent ischemic heart disease. We have previously shown[18] that men with preexistent IHD (angina, history of severe chest pain lasting more than half an hour, and ECG ischemia)[19] have raised levels of fibrinogen, viscosity, and white blood cell count. Odds of major IHD in these men relative to the odds in men with no evidence of preexistent IHD range from 3.0 for possible ECG ischemia to 5.1 for probable ECG ischemia, with angina and history of severe chest pain in the intermediate range. It is possible, therefore, that the associations of fibrinogen, viscosity, and white blood cell count with incidence of major IHD are simply a consequence of preexisting disease. In fact, this is not so. Mean levels of the three hemostatic/rheological variables in men who developed major-incident IHD and those who did not are shown in Table 4, subdivided by whether any manifestation of existent disease was present on first examination. For all three variables, the age- and area-standardized mean differences are slightly larger for men with no evidence of preexistent IHD, and all six mean differences are significantly greater than zero ($p<0.0001$ for all three variables for men without preexistent IHD; $p<0.01$ for men with preexistent IHD).

Other risk factors. As already described, the solid lines in Figure 1 show the relative odds of IHD by fifths of the level of fibrinogen, viscosity, and white blood cell count adjusted for age and area. The crosses show the odds further adjusted for both smoking habit and three separate indicators of preexistent disease (angina, severe chest pain, and ECG ischemia). For all three variables, this adjustment reduces the relative odds. Nevertheless, the effects are still large; the odds of major IHD in the top 20% of the distributions are still 2.8, 3.5, and 2.3 times the odds in the lowest 20% for fibrinogen, viscosity, and white blood cell count, respectively.

The circles on Figure 1 show the effect when the relative odds are further adjusted for total cholesterol, diastolic blood pressure, and body mass index. The changes are small. In the top 20% of the distributions, relative odds are 2.6 (95% CI, 1.6–4.3), 3.2 (95% CI, 1.8–5.6), and 2.2 (95% CI, 1.3–3.5) for fibrinogen, viscosity, and white blood cell count, respectively. In three multiple logistic regression models with the identical sets of variables (except that fibrinogen, viscosity and white blood cell count are entered as continuous variables), the regression coefficients for all three are highly significant ($p<0.0001$).

Correlations between the hemostatic/rheological variables and cholesterol, blood pressure, and body mass index are small. Viscosity is positively correlated (r=0.2) with total cholesterol and shows small positive associations (r=0.1) with both diastolic blood pressure and body mass index. Fibrinogen has a small positive correlation only with total cholesterol; white blood cell count shows no association with any of the three.

Fibrinogen, Viscosity, and White Blood Cell Count Considered Jointly

The three hemostatic/rheological variables are interrelated; the correlation coefficient between fibrinogen and viscosity is 0.57 in both the Caerphilly and Speedwell studies, and the coefficients for fibrinogen and white blood cell count and for viscosity and white blood cell count in the two areas are between 0.24 and 0.32. Table 5 shows the results of two multiple logistic regression models when all three, treated as continuous variables, are entered jointly into models together with age, area, smoking habit, and preexistent IHD. The second model in Table 5 also includes diastolic blood pressure, body mass index, and total cholesterol.

Model 1 in Table 5 shows that the levels of significance are substantially lower than when the

TABLE 5. Logistic Regression Coefficients When Fibrinogen, Viscosity, and White Blood Cell Count Are Included Together in Two Models Relating Risk Factors to Major Incident Ischemic Heart Disease

	Model 1			Model 2		
Variable	Coefficient	*t*	*p*	Coefficient	*t*	*p*
Age	0.047	2.8	0.005	0.052	3.1	0.002
Exsmoker	0.390	1.5	0.15	0.400	1.4	0.16
Current smoker	0.534	2.0	0.04	0.585	2.1	0.04
Fibrinogen	0.174	1.8	0.08	0.210	2.1	0.03
Plasma viscosity	1.970	2.4	0.02	1.419	1.7	0.10
White blood cell count	0.096	2.9	0.004	0.102	3.0	0.002
Total cholesterol	...	...	...	0.120	2.1	0.03
Diastolic BP	...	...	...	0.017	3.1	0.002
Body mass index	...	...	...	0.019	1.0	0.34

BP, blood pressure.
Both models also include area and the three indicators (angina, history of severe chest pain, and ischemia according to findings on electrocardiogram) of preexistent ischemic heart disease.

three variables are considered individually, particularly for fibrinogen and viscosity, but that those for white blood cell count and viscosity are still statistically significant. However, if only two of the variables, white blood cell count together with one of either fibrinogen or viscosity, are entered into the model, then both are significant at $p<0.001$.

The addition of total cholesterol (mmol/l), diastolic blood pressure (mm Hg), and body mass index (kg/m^2) (shown as model 2 in Table 5) marginally increases the coefficients for fibrinogen and white blood cell count but decreases the coefficient for viscosity by nearly 30%. Again, however, if only white blood cell count together with either one of fibrinogen or viscosity is entered into model 2, both are significant at $p<0.001$.

To further evaluate the predictive power of these hemostatic/rheological factors, a third model was fitted that included only the conventional risk factors: total cholesterol, diastolic blood pressure, and body mass index (together with age, area, smoking habit, and preexistent IHD). Comparison of this third model with the one in which the hemostatic/rheological tests were also included (model 2 in Table 5) provides an overall significance test for the effect of adding fibrinogen, viscosity, and white blood cell count to a model containing all the conventional risk factors. The improvement in fit is highly significant: $\chi^2(3df)=33, p<0.00001$.

Fit and Predictive Power of the Logistic Models

From model 1 with fibrinogen, viscosity, and white blood cell count, a predicted risk for each individual was calculated. If that distribution of predicted risk is divided into five equal groups, then the sum of the individual predicted risks within each fifth is the number of major IHD events expected under the logistic model. There was close agreement between observed and expected events, showing that the model fitted the data well. Further, the model had considerable predictive power. Only 10% of observed events occurred in the bottom 40% of the distribution of predictive risk, whereas nearly 80% occurred in the top 40%. There were more than 12 times as many events in the top 20% as in the bottom 20% of the distribution.

Table 6 compares the predictive power of two models, both based on the 4,463 men with complete data (models 1 and 3). The predictive power of the model with fibrinogen, viscosity, and white blood cell count is at least as good as that for the model with total cholesterol, diastolic blood pressure, and body mass index.

Discussion

When analyzing cohort studies for the association between risk factors and incidence of disease, it is common but not universal[2] practice to exclude subjects with evidence of IHD on entry. The exclusions are usually either a very small[8] group of men with previous myocardial infarction or a rather ill-defined group with clinical symptoms of IHD.[20] We have

TABLE 6. Comparison of Predictive Power of Two Multiple Logistic Regression Models

Fifth of predicted risk	No. of men	Observed major IHD events	
		Model 1	Model 3
1	892	10	10
2	893	12	13
3	893	26	35
4	892	53	49
5	893	123	117
Total	4,463	224	224

IHD, ischemic heart disease; model 1, variables included age, area, smoking, preexistent IHD, fibrinogen, viscosity, and white blood cell count; model 3, variables included age, area, smoking, preexistent IHD, total cholesterol, diastolic blood pressure, and body mass index.

shown,[19] as did the British Regional Heart Study,[2] that about 25% of middle-aged British men have some evidence of IHD and that just over half the major incident IHD events occurred in this group. Neither exclusion of a small subgroup nor exclusion of the whole group containing over half of the events of interest seems to be satisfactory, and like the Regional Heart Study, we have included all men in the analysis.

It could be argued that this inclusion of men with preexistent IHD increases the possibility that any relations found are a consequence of the disease already existing rather than a contribution to its development. However, this argument only holds true if the inclusion of men with preexistent disease is ignored in the analysis. We have allowed for their presence by including standardized measures of angina, severe chest pain, and ECG ischemia on entry to the study as covariates in all analyses. Further, we have shown that the relations between the hemostatic variables and incidence of IHD are similar in men with and without any evidence of preexistent disease. In this circumstance, inclusion of all men and the use of preexistent IHD as a covariate will result in more accurate estimates of the relations between possible risk factors and the incidence of IHD than the alternative of excluding relatively small groups of men with clinical symptoms and assuming, incorrectly, that the remainder are disease free. Whether such relations are causal can, of course, never be completely answered by any observational study.

Univariate analyses show that white blood cell count, fibrinogen, and plasma viscosity are all strongly associated with the incidence of major IHD. Adjusting only for age and area, the odds of IHD in the top 20% of the white blood cell count distribution are more than three times the odds in the lowest 20%; for fibrinogen and viscosity, the corresponding relative odds are in excess of four. These relative odds are larger than those commonly reported[1,2] for the more conventional risk factors such as blood pressure, total cholesterol, high-density lipoprotein cholesterol, and body mass index. The important question is to what extent these associations are independent of smoking habit, preexistent disease, and the other conventional risk factors.

White Blood Cell Count

There are a number of studies[10–12] in the literature showing that white blood cell count is associated with the incidence of disease, but there is disagreement as to whether this association arises solely because both are dependent on smoking habit. Zalokar et al[11] find the association only in smokers who inhale and conclude that white blood cell count is simply an excellent indicator of exposure to cigarette smoke. Friedman et al[10] and Grimm et al[12] both conclude that part of the association is independent of smoking habit. Our data support this latter conclusion. Figure 1 shows the relative odds of IHD in the top 20% of the white blood cell count distribution reduced from 3.2 to 2.4 on standardizing for both smoking habit and preexistent disease. Further adjustment for total cholesterol, diastolic pressure, and body mass index only reduced the odds to 2.2. This is a stronger association than that found in the "usual care" group of the Multiple Risk Factor Intervention Trial,[12] in which similarly adjusted relative odds of IHD of 1.53 were found in the top third of the white blood cell count distribution.

It is possible that the association between white blood cell count and the incidence of IHD is a consequence of the disease. However, this explanation is rendered less likely by the finding of a highly significant difference in count between men who develop the disease and those who do not, among the men with no evidence of preexistent disease.

Mechanisms that might explain this association include clumping of granulocytes and monocytes and subsequent leukoembolism[21] and the role of macrophages and monocytes in the development of fatty streaks.[22,23]

Fibrinogen and Viscosity

We have been unable to find any published study that describes the relation between plasma viscosity and the incidence of IHD. However, a positive association with plasma fibrinogen has been reported in four smaller studies.[6–9] In 1,511 middle-aged men, Meade et al[8] found a difference of 0.25 g/l in thrombin-clottable fibrinogen between men who developed IHD and those who did not. The same difference was found by Wilhelmsen et al[6] in a random sample of 792 men. Although results were not reported in exactly this manner, it seems that the Framingham study[9] also found similar differences in a 12-year follow-up of 554 men and 761 women. Stone and Thorpe,[7] in a study of 297 men, found a difference of 0.79 g/l using the same nephelometric method as in the present study. Thrombin-clottable fibrinogen was also measured in the present study, but its association with the incidence of IHD was less strong than that for the nephelometric fibrinogen.

The effects that we have found for fibrinogen and viscosity are large, and the age-adjusted relative odds of IHD are in excess of 4 in the top 20% of the distribution of each. Standardization for smoking habit and preexistent disease only reduced these relative odds to about 2.7 for fibrinogen and 3.5 for viscosity. This shows that the association is not explained by smoking. Furthermore, if preexistent IHD is caused, even in part, by high "levels" of the hemostatic/rheological factors, then we may have "overcontrolled" for this effect, and our estimations of relative risks will be conservative. Further standardization for total cholesterol, body mass index, and diastolic blood pressure produces little additional change in the relative odds.

However, fibrinogen and viscosity are not independent of each other; the correlation coefficient between them is 0.57. To try to determine which is the more

important, both fibrinogen and viscosity, together with white blood cell count, age, area, smoking habit, and preexistent disease, were put into a multiple logistic regression model. The results (Table 5) suggest that white blood cell count is an independent risk factor, but there is no clear differentiation between fibrinogen and viscosity. When either alone was put into the model it showed a strong ($p<0.001$) association with IHD, and when both were entered, the joint effect was attributed fairly equally to both. It will be possible to investigate this more fully as the length of follow-up increases and more cases of IHD accrue.

Smoking Habit

All categories of smokers had higher risks of developing major IHD than men who had never smoked. Relative odds of IHD compared with those who had never smoked were 2.5 for current smokers and 2.0 for exsmokers. The large excess risk among the exsmokers and, particularly, the fact that the risk is little different in those who gave up more than 10 years ago support the contention of the British Regional Heart Study[24] that part of the excess risk of IHD due to smoking remains long after quitting.

Although the association between smoking and IHD has been found by virtually all cohort studies, there is no clear understanding of the mechanisms involved. The multiple logistic regression model (Table 5) shows that, when white blood cell count, fibrinogen, and viscosity are included in the model, the relative odds of IHD decline to 1.7 for current smokers and 1.5 for exsmokers. This, together with the well-known observation[17] that levels of all three variables are raised in smokers, suggests that at least some of the relation between smoking and IHD is mediated through an effect on these aspects of hemostasis and rheology. This hypothesis could explain why the risk in exsmokers does not quickly revert to that in men who have never smoked. We have previously shown[17] that levels of white blood cell count, fibrinogen, and viscosity among exsmokers gradually decline but do not reach the levels of lifetime nonsmokers even after 10 years.

Conclusion

The joint predictive power of fibrinogen, viscosity, and white blood cell count is considerable, and when they are added to a model containing the major conventional risk factors, there is a highly significant improvement in the fit of the model. In a multiple logistic model that included the three together with age, smoking habit, and preexistent disease markers, 123 (55%) of the major IHD events occurred in the top 20% of the distribution of predicted risk; in comparison, only 10 (4%) occurred in the bottom 20% (Table 6). This prediction was at least as good as that achieved when the three hemostatic/rheological variables were replaced by the conventional risk factors of total cholesterol, diastolic pressure, and body mass index. Individually, white blood cell count is an independent risk factor as is either fibrinogen or viscosity, or possibly both.

These findings add substance to the views[12,25,26] that more work in these under-researched areas may yield rich dividends. In particular, research into the life-style determinants of fibrinogen, viscosity, and white blood cell count is required; the only life-style determinant known at present to have a substantial effect is smoking.

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