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Associations of Fibrinogen, Factor VII and PAI-1 with Baseline Findings among 10,500 Male Participants in a Prospective Study of Myocardial Infarction

The Prime Study

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Summary

The contribution of coagulation factors and fibrinolytic variables to the development of ischaemic arterial disease is still not clearly established. The PRIME study is a prospective cohort study of myocardial infarction in men aged 50-59 years and recruited from three MONICA field centers in France (Lille, Strasbourg and Toulouse) and the center in Northern Ireland (Belfast). Baseline examination included measurement of plasma fibrinogen, factor VII, and PAI-1 activity in over 10,500 participants. We investigated the associations of these haemostatic variables with cardiovascular risk factors, prevalent atherosclerotic disease and geographical area. Fibrinogen level increased with age, smoking, waist-to-hip ratio, LDL-cholesterol, and it decreased with educational level, leisure physical activity, alcohol intake and HDL-cholesterol. Factor VII activity increased with body mass index, waist-to-hip ratio, triglycerides, HDL- and LDL-cholesterol. PAI-1 activity increased with body mass index, waist-to-hip ratio, triglycerides, alcohol intake, smoking, and decreased with leisure physical activity. PAI-1 level was higher in diabetic subjects than in subjects without diabetes. Cardiovascular risk factors explained 8%, 9%, and 26% of the total variance in fibrinogen, factor VII, and PAI-1, respectively. Compared with participants without prevalent cardiovascular disease, those with previous myocardial infarction (n = 280), angina pectoris (n = 230), or peripheral vascular disease (n = 19) had significantly higher levels of fibrinogen, but those with stroke (n = 67) had not. PAI-1 activity showed a similar pattern of association. The odds ratio for cardiovascular disease associated with a rise of a one standard deviation in fibrinogen and PAI-1 was 1.31 (95% confidence interval: 1.20 to 1.42, $p < 0.001$) and 1.38 (95% confidence interval: 1.27 to 1.49, $p < 0.001$), respectively. After adjustment for cardiovascular risk factors, these associations were attenuated but remained highly significant. There was no significant association between factor VII activity and prevalent cardiovascular disease. Fibrinogen level and, to a lesser extent, factor VII and PAI-1 activity were higher in Northern Ireland than France after adjustment for the main cardiovascular risk factors. These geographical variations are consistent with the 2 to 3-fold higher incidence of myocardial infarction in Northern Ireland than France. Our results provide further epidemiological evidence for a possible role of fibrinogen and PAI-1 in the pathogenesis of coronary heart disease.

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Introduction

Evidence has accumulated that thrombosis may contribute to the onset of symptomatic coronary heart disease (CHD), not only as an acute complication of atheroma and plaque rupture, but also as an underlying cause of the chronic process of atherogenesis (1). However, the relation of haemostatic variables to the risk of cardiovascular disease is incompletely established (2, 3).

Population-based studies have consistently showed that an elevated level of plasma fibrinogen is a risk factor for CHD (4, 5) and stroke (6, 7). Factor VII activity has also been shown to be a predictor of CHD incidence (4, 8), but negative findings have been recently reported in a large cohort of healthy men (9). Associations of factor VIII, von Willebrand factor, protein C and antithrombin III with the risk of CHD have been inconsistent (9-13).

With respect to fibrinolytic function, a rise in the whole-blood clot lysis time (14) and PAI-1 activity (15, 16) have emerged as putative risk factors for CHD, and it has been suggested that metabolic risk factors belonging to insulin resistance syndrome could operate through reduced fibrinolysis (17). Although t-PA antigen has been shown to be predictive of CHD (13, 18-21), PAI-1 activity is prognostic in some studies (15, 16, 22) but not in others (18, 23). In addition, prospective evidence for a role of PAI-1 in the development of CHD among healthy subjects is lacking and whether components of the fibrinolytic system are independent CHD risk factors remains unclear (16).

As part of a prospective study of haemostatic variables and incidence of myocardial infarction in middle-aged men, we investigated the associations of fibrinogen, factor VII and PAI-1 with cardiovascular risk factors, prevalent atherosclerotic disease and geographical area.

Subjects and Methods

Study Design and Cohort

The PRIME Study (Prospective Epidemiological Study of Myocardial Infarction) is a prospective study of myocardial infarction based in three World Health Organization MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) field centers in France (Lille, Strasbourg and Toulouse)

and the center in Northern Ireland (Belfast). Each center recruited approximately equal numbers of participants (nearly 2500), for a total of 10,592. Sample sizes were such that the number of incident cases of myocardial infarction expected was about 200 over five years of follow-up. All participants gave informed consent and local ethical committees approved the study. The initial examination was conducted from 1991 to 1993. All the participants were men aged 50-59 years and were recruited from both industrial and community settings.

Clinical Measurements

Baseline self-administered questionnaires were completed at home by participants and included assessment of health behaviors, sociodemographic factors, and history of cardiovascular disease and diabetes mellitus. The questionnaires were checked at the clinic by an interviewer who sought information on missing items. Clinical examination included measures of anthropometry, blood pressure and a 12-lead electrocardiogram.

Educational level was categorized in low (none or primary school), middle (secondary school), or high (tertiary or university). Physical activity during leisure time was coded as 1 (low level) to 4 (high level corresponding to intense physical activity for at least 20 min a week). The body mass index was computed as weight (kg) divided by height squared (m^2). Circumferences of the waist (umbilical level) and hip (maximum buttocks) were measured to the centimeter. The ratio of waist and hip circumferences was calculated as a measure of fat distribution. Blood pressure was measured after a 5-min rest in the sitting position using an automated device (Spengler SP9). Prevalent hypertension was defined as systolic pressure > 150 mm Hg, diastolic pressure > 95 mm Hg, or use of antihypertensive agents. Prevalent diabetes mellitus was defined as a self-reported history of physician-diagnosed diabetes and/or use of antidiabetic agents. Prevalent coronary heart disease was defined as a self-reported history of physician-diagnosed myocardial infarction or angina pectoris. Prevalent cardiovascular disease was defined as prevalent coronary heart disease or a self-reported history of a stroke or intermittent claudication.

Blood Sampling and Assay Procedures

Subjects were asked to fast for at least 10 h before blood collection. Venous blood (9 volumes) was collected between 9 and 10 A.M. into siliconised vacutainer tubes (Vacutainer, Becton Dickinson) containing 0.11 M trisodium citrate (1 volume). Platelet-poor plasma was obtained by centrifugation at 4,500 × g and 4°C (PAI-1 measurement) or 20°C (fibrinogen and factor VII assay) for 15 mn. Without delay, aliquots of plasma were transferred into plastic tubes and frozen on-site to -80° C, and then they were shipped in batch to the central laboratory in Lille.

Haemostatic variables were measured in the central haemostasis laboratory of La Timone Hospital at Marseille, France. Fibrinogen was measured according to the method of Clauss (24) with reagents (Fibriprest automate) and reference material obtained from Diagnostica Stago (Asnières, France). Factor VIIc was assayed in a regular one-stage system using rabbit brain thromboplastin obtained from Diagnostic Reagents Limited (Oxon, England). Factor VII-deficient substrate plasma was prepared from absorbed bovine plasma and concentrate of human factors IX, X, and II as described (25). Factor international standard was obtained from NIBSC (National Institute for Biological Standard and Control, Hertfordshire, England). Results were expressed as a percentage of reference plasma. PAI-1 activity was measured by a two-stage amidolytic method using a commercially available kit (Spectrolyse/TM/Fibrin, Biopool, Umeå, Sweden).

All the haemostatic tests were performed in duplicate between January 1991 and January 1994 and over 600 runs were needed for each haemostatic variable. Accuracy and precision of haemostatic assays were assured by a strict internal quality control program. A single batch of normal plasma pool prepared from 50 healthy subjects was used as a control material. For each assay, 2-4 controls were included in each run of PRIME study samples. Analysis of internal quality control data showed that laboratory coefficient of variation was ranged from 4.3% (fibrinogen) to 9.5% (PAI-1).

Plasma prepared with EDTA was used for analysis of lipids. Plasma total cholesterol and triglycerides were measured by enzymatic methods using reagents obtained from Boerhinger Mannhein (Mannhein, FRG). High density lipoprotein (HDL)-cholesterol was measured after sodium phosphotungstate-magnesium chloride precipitation. LDL-cholesterol was calculated according to Friedewald, Levy and Fredrickson (26).

Data Analysis

The PRIME cohort totalled 10,592 participants. We excluded from this analysis participants with cancer (n = 32), and those who reported currently taking anticoagulants (n = 37). Statistical analysis used procedures available in the Statistical Analysis System (SAS) software (SAS Institute, INC., CARY, NC). Distributions of fibrinogen and PAI-1 were positively skewed and log transformed values were used. Mean levels of fibrinogen and PAI-1 are given in arithmetic form. Baseline characteristics of participants were described as field center-specific means and standard deviations or prevalence estimates. Geographical variations in levels of haemostatic factors were studied by t tests. Covariance analysis was used to adjust for age, body mass index, waist-to-hip ratio, hypertension, smoking, HDL- and LDL-cholesterol, triglycerides, and diabetes. Associations of haemostatic variables with cardiovascular risk factors at baseline were examined in participants without prevalent cardiovascular disease by correlation analysis. Pearson correlation coefficients were adjusted for field centers. Stepwise multiple linear regressions were used to assess the relative contribution of CHD risk factors to the prediction of haemostatic variables. A forward stepping procedure was used including only CHD risk factors which had been found significantly related to haemostatic variables in the univariate analysis. Haemostatic factor levels of those with and without prevalent cardiovascular disease were compared by analysis of variance after adjustment for field centers. Odds ratios for prevalent cardiovascular disease per one standard deviation differences in haemostatic variable levels were computed from multiple logistic regression models. A first model was adjusted only for field centers, and a second one was adjusted for field centers, age, body mass index, waist-to-hip ratio, hypertension, smoking, HDL- and LDL-cholesterol, triglycerides, and diabetes. All the baseline data from the different centers were pooled after testing for consistency.

Results

Geographical Variations

Table 1 shows the center-specific baseline characteristics among participants in the PRIME Study. There was a striking geographical variation in fibrinogen concentration. Mean levels of fibrinogen were 42 to 49 mg/dl higher in Belfast than France. The level of some CHD risk factors, including current smoking, HDL- and LDL-cholesterol, also differed between Northern Ireland and France. The highest mean values of body mass index, waist-to-hip ratio, and PAI-1 activity were seen in Strasbourg.

Table 2 shows the mean levels of haemostatic variables in Northern Ireland and France before and after adjustment for age, smoking, body mass index, waist-to-hip ratio, hypertension, HDL- and LDL-cholesterol, triglycerides, and diabetes. The difference in fibrinogen levels between countries was similar and remained highly significant. Factor VII and PAI-1 activities were also higher in Northern Ireland than France but the differences were small.

Cardiovascular Risk Factors

Table 3 shows the correlation coefficients between haemostatic variables and baseline characteristics after exlusion of participants with prevalent cardiovascular disease. Fibrinogen was positively associated with age, smoking status, body mass index, waist-to-hip ratio, and

Table 1 Center-specific baseline characteristics of participants in the PRIME Study

Characteristic	Belfast n=2718	Strasbourg n=2578	Toulouse n=2598	Lille n=2604
Age, y	55 (2)	55 (2)	55 (2)	55 (2)
BMI, Kg/m2	26.2 (3.4)	27.4 (3.6)	26.3 (3.1)	26.6 (3.6)
Waist-to-hip ratio	0.94 (0.05)	0.99 (0.06)	0.96 (0.05)	0.95 (0.05)
Cholesterol, mg/dl	228 (39)	224 (40)	213 (34)	222 (38)
HDL Cholesterol, mg/dl	46 (13)	49 (13)	48 (12)	52 (13)
LDL Cholesterol, mg/dl	147 (38)	145 (36)	139 (32)	142 (35)
Triglycerides, mg/dl	176 (108)	153 (109)	131 (87)	139 (90)
Current smoking, %	32	25	25	25
Alcohol intake (g/day)	28 (43)	42 (36)	37 (34)	44 (38)
Diabetes mellitus, %	2	9	9	13
Hypertension, %	24	33	19	36
Fibrinogen, mg/dl	363 (98)	318 (86)	314 (91)	321 (99)
Factor VII, %	135 (37)	132 (39)	128 (42)	132 (49)
PAI, IU/ml	14.6 (11.9)	15.2 (11.0)	12.2 (9.7)	13.3 (11.2)

Values are mean (SD) or percent
All the between-center comparisons are significant at p<0.001, exept for age

Table 2 Haemostatic variables by countries in the PRIME Study

	Univariate		Multivariate §	
Variable	Northern Ireland	France	Northern Ireland	France
Fibrinogen, mg/dl	363 (2)	318 (1)*	361 (2)	318 (1)*
Factor VII, %	135 (1)	131 (1)*	134 (1)	131 (1)*
PAI-1, IU/ml	14.6 (0.2)	13.6 (0.1)*	15.0 (0.2)	13.4 (0.1)*

Values are mean (SEM)
§ adjusted for age, body mass index, waist-to-hip ratio, hypertension, smoking, diabetes, HDL-cholesterol, LDL-cholesterol, and triglycerides
* p<0.001

LDL-cholesterol. Fibrinogen was negatively associated with educational level, leisure physical activity score, alcohol intake, and HDL cholesterol. Factor VII activity increased with body mass index, waist-to-hip ratio, triglycerides, alcohol intake, HDL- and LDL-cholesterol. PAI-1 activity increased with body mass index, waist-to-hip ratio, triglycerides, alcohol intake, smoking and decreased with leisure physical activity score, and HDL-cholesterol. PAI-1 level was higher in diabetic subjects than in subjects without diabetes.

Tables 4-6 show the relative contribution of cardiovascular risk factors to haemostatic variables from multiple regression analysis. Age, smoking status, leisure physical activity, educational level, alcohol intake, waist-to-hip, LDL- and HDL-cholesterol were independent predictors of fibrinogen concentration. However, only 8% of total variance in fibrinogen was explained by these variables. Smoking was the most striking correlate of fibrinogen, whereas each of other cardiovascular risk factors explained less than 1 % of total variance in this variable. Body mass index was not independently associated with fibrinogen after adjustment for waist-to-hip ratio. Body mass index, waist-to-hip ratio, triglycerides, HDL- and LDL-cholesterol were the only independent predictors of factor VII. Alcohol intake was no longer associated with factor VII after adjustment for plasma lipids. Cardiovascular risk factors explained only 9% of the variance in factor VII. Body mass index and triglycerides were the most important predictors of PAI-1 activity and explained up to 24 % of variance in PAI-1. Alcohol intake, waist-to-hip ratio, diabetes smoking status, and leisure physical activity improved further the prediction of PAI-1, but these characteristics explained less than 1 % of variance in PAI-1. HDL- and LDL-cholesterol were no longer associated with PAI-1 activity in multivariate analysis.

Prevalent Cardiovascular Disease

Table 7 shows the center-adjusted mean values of haemostatic variables at baseline according to category of prevalent cardiovascular disease. Coronary heart disease comprised most of prevalent cardiovascular disease (86%). Compared with participants without cardiovascular disease, those with previous myocardial infarction (n = 280), angina pectoris (n = 230), or peripheral vascular disease (n = 19) had significantly higher levels of fibrinogen, but those with stroke (n = 67) had not. PAI-1 activity showed a similar pattern of association with prevalent cardiovascular disease, although the relation to intermittent claudication was not significant. Participants with intermittent claudication

Table 3 Pearson correlation coefficients between haemostatic variables and cardiovascular risk factors in the PRIME Study

	Fibrinogen	Factor VII	PAI-1
Age	+0.08**	+0.01	+0.01
BMI	+0.05**	+0.10**	+0.39**
Waist/hip	+0.09**	+0.11**	+0.28**
Smoking (n/y)	+0.12**	+0.02	+0.04*
Alcohol intake (n/y)	-0.04**	+0.09**	+0.06**
Educational level	-0.06**	+0.01	-0.01
Leisure activity	-0.05**	+0.01	-0.06**
Diabetes (n/y)	+0.01	-0.01	+0.10**
HDL-cholesterol	-0.09**	+0.05**	-0.18**
LDL-cholesterol	+0.05**	+0.06**	-0.03*
Triglycerides	-0.01	+0.21**	+0.36**

Educational level is coded from 1 (low) to 3 (high).
Leisure activity is coded from 1 (low) to 4 (high)
Correlation coefficients are adjusted for field center.
** p<0.001, *p<0.01

Table 4 Stepwise multiple regression with baseline fibrinogen as the dependent variable in the PRIME Study

Variable	Regression coefficient (SD)	Partial P	Improved R2
Smoking (n/y)	0.26 (0.02)	<0.0001	0.053
Waist/hip	1.18 (0.17)	<0.0001	0.061
Age	0.03 (0.01)	<0.0001	0.066
HDL-cholesterol	-0.58 (0.08)	<0.0001	0.071
LDL-cholesterol	0.13 (0.03)	<0.0001	0.076
Alcohol intake (n/y)	-0.10 (0.03)	<0.0001	0.077
Educational level	-0.05 (0.02)	<0.001	0.078
Physical activity	-0.03 (0.01)	<0.001	0.079

Educational level is coded from 1 (low) to 3 (high).
Physical activity is coded from 1 (low) to 4 (high)
Field centers were forced into the model and explained 0.039 of the variance.
No other variables met the .05 level to enter into the model.

Table 5 Stepwise multiple regression with baseline factor VII as the dependent variable in the PRIME Study

Variable	Regression coefficient (SD)	Partial P	Improved R2
Triglycerides	10.8 (0.5)	<0.0001	0.048
HDL-cholesterol	55.5 (3.7)	<0.0001	0.066
LDL-cholesterol	11.7 (1.2)	<0.0001	0.076
BMI	0.79 (0.15)	<0.0001	0.082
Waist/hip	38.5 (8.6)	<0.0001	0.084

Field centers were forced into the model and explained 0.003 of the variance.
No other variables met the .05 level to enter into the model.

Table 6 Stepwise multpile regression with baseline PAI-1 as the dependent variable in the PRIME Study

Variable	Regression coefficient (SD)	Partial P	Improved R2
BMI	0.93 (0.03)	<0.0001	0.164
Triglycerides	2.8 (0.1)	<0.0001	0.239
Alcohol intake	2.3 (0.3)	<0.0001	0.245
Waist/hip	14.6 (2.0)	<0.0001	0.249
Diabetes	1.9 (0.4)	<0.0001	0.252
Smoking	0.9 (0.2)	<0.0001	0.253
Physical activity	-0.3 (0.1)	<0.001	0.254

Physical activity is coded from 1 (low) to 4 (high)
Field centers were forced into the model and explained 0.010 of the variance.
No other variables met the .05 level to enter into the model.

Table 7 Baseline haemostatic variables of PRIME Study particpants according to prevalence of cardiovascular diesease

	Fibrinogen (mg/dl)	Factor VII (%)	PAI-1 (AU/ml)
No CVD (n=9879)	327 (1)	132 (1)	13.6 (1)
CHD			
Myocardial infarction (n=280)	363 (6)*	134 (3)	18.7 (1)*
Angina pectoris (230)	350 (6)*	133 (3)	17.4 (1)*
All CHD (n=510)	356 (4)*	133 (2)	18.1 (1)*
Claudication (n=19)	362 (28)§	144 (8)	17.6 (2.6)
Stroke (n=67)	345 (17)	132 (5)	12.4 (1.5)

Values are center-adjusted mean (SEM)
CHD, coronary heart disease; CVD, cardiovascular disease
* p<0.001, § p<0.05 for CVD versus no CVD

Table 8 Odds ratios for prevalent cardiovascular disease associated with each 1 SD haemostatic variable difference, PRIME Study

	Model 1	Model 2
Variable	OR (95% CI)	OR (95% CI)
Fibrinogen	1.31 (1.20, 1.42)*	1.26 (1.17, 1.36)*
Factor VII	1.06 (0.97, 1.15)	1.00 (0.91, 1.09)
PAI-1	1.38 (1.27, 1.49)*	1.28 (1.16, 1.41)*

OR, odds ratio; CI, confidence interval
Model 1, odds ratio adjusted for field center.
Model 2, odds ratio adjusted for field center, age, smoking, BMI, waist-to-hip, hypertension, HDL-cholesterol, LDL-cholesterol, triglycerides, and diabetes
* p<0.001

had high levels of factor VII, but the association was not significant. There was no striking association of factor VII with other categories of cardiovascular disease.

Table 8 shows the odds ratios of prevalent cardiovascular disease for each one SD increase in haemostatic variables. Thus, the center-adjusted risk of cardiovascular disease was 31% and 38% higher per one standard deviation increment of fibrinogen and PAI-1, respectively. After adjustment for body mass index, waist-to-hip ratio, smoking status, blood pressure, HDL-cholesterol, LDL-cholesterol, triglycerides and diabetes, the odds ratios of prevalent atherosclerotic disease were attenuated but remained significantly different from 1. Odds ratio per one standard deviation higher factor VII was close to 1.

Discussion

Baseline data of the PRIME Study show that increased levels of both fibrinogen and PAI-1 activity, but not factor VII, are independent risk factors for prevalent CHD. Our results also provide further information on population correlates of haemostatic variables. Cross-sectional studies may not be adequate to detect any associations between haemostatic factors and CHD. Acute thrombosis and CHD management may result in haemostatic changes which are not relevant to the pathogenesis of CHD. Furthermore, it is not possible to distinguish whether the observed relation of haemostatic variables with prevalent cardiovascular disease is causal or whether it represents a marker of active and progressive disease. Another drawback of prevalence studies is the exlusion of fatal events, which may lead to underestimate the strenght of associations. The PRIME study is based on a large sample of middle-aged men and baseline clinical data were collected in a well standardized way. Prevalent cardiovascular disease was assessed under non-acute cicumstances and participants who were taking anticoagulants were carefully excluded. Quality control data showed that haemostatic measurements were reliable throughout the assay period.

Fibrinogen

The finding of a positive association between fibrinogen and prevalent cardiovascular disease is consistent with previous studies using cross-sectional (27-32) or prospective (4-10, 13) design. The nature of this association remains unclear. Plasma fibrinogen is an acute phase protein and therefore, high levels may reflect ongoing tissue damage associated with atherothrombosis. However, high fibrinogen levels may also be relevant to the pathogenesis of CHD through effects on blood viscosity, platelet aggregation, fibrin formation, and atheroma itself (33). There was no significant association between fibrinogen and prevalent stroke in the PRIME Study. However, the number of participants who reported history of stroke was relatively small and no attempt was made to separate ischaemic and haemorragic stroke. A lack of statistical power may explain this negative finding.

Fibrinogen levels were higher in Northern Ireland than France. The difference was substantial and remained highly significant after adjustment for the main CHD risk factors. This geograghical variation in fibrinogen levels could explain in part the higher CHD incidence in Northern Ireland than in France (34). This finding is consistent with a previous report (30). Another study investigated the differences in fibrinogen level between populations at contrasting risk for CHD. Japanese of the Akita Study have significantly lower fibrinogen levels than either European or African Americans and this difference is consistent with the higher rate of CHD mortality in the United States than Japan (35).

Smoking status was the most striking correlate of fibrinogen concentration at baseline in the PRIME Study, and a dose-response with the number of cigarettes was observed. There is much evidence that fibrinogen is related to smoking (36-38), and much of the association between smoking and CHD risk may be mediated through fibrinogen levels (4, 5, 7). Two studies provided evidence for a positive interaction of smoking and a HaeIII polymorphism at the β-fibrinogen locus in determining plasma fibrinogen levels (39, 40). In these studies, associations of polymorphisms of the β fibrinogen gene with plasma fibrinogen were restricted to smokers and this finding may be relevant to the hypothesis that the effect of smoking on fibrinogen is mediated through cytokines (39, 40).

Rates of CHD mortality are higher in the lower social classes, which cannot be explained by the main determinants of coronary risk (41, 42). Few population-based studies have investigated the associations of fibrinogen with socioeconomic status. Lower educational level was associated with higher fibrinogen level among participants in the PRIME Study, and this effect was independent of other correlates of fibrinogen. These results and those of other studies (38, 43) suggest that fibrinogen may be a marker of the biological pathways that mediate the inverse socioeconomic gradient in CHD.

Our data show an inverse association between leisure physical activity and fibrinogen level after adjustment for CHD risk factors. A similar finding has been reported in a cross-sectionnal study, but the association was no longer significant after adjustment for smoking and social class (37). Our results are consistent with baseline data of two other prospective cohort studies (38, 44).

Plasma fibrinogen was associated with the degree of obesity among participants in the PRIME Study. However, the relation of fibrinogen with body mass index was less strong than that with waist-to-hip ratio in univariate analysis. Furthermore, multivariate analysis showed that waist-to-hip ratio, but not body mass index, was an independent predictor of fibrinogen. These results suggest that central body fat distribution is more relevant than general adiposity to population correlates of fibrinogen. Our data are consistent with results of two other cross-sectional studies (45, 46).

Age and alcohol consumption were significant correlates of fibrinogen among participants in the PRIME Study. These associations are consistent with baseline findings of other prospective studies (4-7, 36-38). Multivariate analysis also showed that LDL-cholesterol was positively correlated with fibrinogen, whereas HDL-cholesterol was negatively associated. Associations of fibrinogen with plasma lipids have been reported in another large population sample (38) and they are consistent with the hypothesis that fibrinogen plays a role in the development of CHD.

Factor VII

The Northwick Park Heart Study reported a strong positive association between factor VII activity among healthy men and the subsequent incidence of CHD (4). Further analysis showed that this association was restricted to fatal events (14). Analysis of the eight-year incidence of CHD in the Prospective Cardiovascular Münster Study showed that factor VII was a predictor of CHD, but the association was no longer significant after adjustment for the main CHD risk factors (8). In a recent report, the Atherosclerosis Risk in Communities (ARIC) Study failed to provide evidence for an important contribution of factor VII as a CHD risk factor (9). However, compared with women without CHD, women who developed CHD had significantly higher age-adjusted mean value of factor VII.

There was no significant association of factor VII with prevalent CHD in the PRIME Study and this result is consistent with other cross-sectional studies (29, 31, 47, 48). Several reasons could explain this negative finding. First, biases in selection of subjects may occur in cross-sectional design since only survivors of CHD are examined. Two prospective studies showed that association between factor VII and CHD was stronger in subjects who experienced a fatal event than in those who did a non fatal event (8, 14). Secondly, sample size may not be large enough to detect a small effect. However, the power of the present study was such that the minimum significant increased odds ratio of CHD associated with a rise of a one standard deviation in factor VII that could have been detected with 95% certainty was 1.2. Therefore, the present study was adequate with respect to the statistical power. Thirdly, some discrepancies between studies may be due in part to the ability of factor VII assays to detect activated factor VII. The Northwick Park factor VII assay (4), which utilized a FVII-deficient plasma depleted of protein C, exhibited an increased responsiveness to activated factor VII when compared with other factor VII assays, such as the Münster (8) or ARIC (9) assays, which used substrate plasma depleted of factor VII only (49). A factor VII assay similar to those of the Northwick Park Heart Study was used in the PRIME Study and an underestimate of activated factor VII can be excluded. Finally, the baseline findings of the PRIME Study may merely indicate that factor VII is not relevant to the pathogenesis of CHD. Therefore, prospective data will be of great interest to investigate further whether factor VII is a predictor of CHD.

Factor VII activity was higher in Northern Ireland than France after adjustment for the main cardiovascular risk factors. Although the difference was small, this geographical variation in factor VII may contribute to the higher rate of CHD incidence in the Northern Ireland than France (34). Another study reported consistent variations in factor VII in populations at contrasting risk for CHD (50).

Body mass index, triglycerides, HDL- and LDL-cholesterol were the main determinants of factor VII among participants in the PRIME Study and these correlates have been previously reported in other populations (25, 36, 38, 51-56). Furthermore, waist-to-hip ratio made an independent contribution to the prediction of factor VII. This finding emphazises the relevance of abdominal versus general adiposity in determining factor VII activity.

Associations of factor VII with smoking and alcohol intake have been inconsistent (25, 36, 38, 56). In the PRIME Study, factor VII increased with smoking and alcohol intake but these associations were weaker and non significant in multivariate analysis. Factor VII activation may be the mechanism underlying the relation of factor VII with cholesterol, whereas the rise in factor VII with serum triglyceride concentration appears to result from high concentrations of zymogen factor VII (56).

The impact of factor VII genotype on factor VII activity and antigen is large, but conflicting results have been reported with respect to the risk of myocardial infarction (48, 57). Prospective data are needed to clarify the genetic contribution to the development of CHD.

PAI-1

Epidemiological evidence for a role of PAI-1 in CHD is as yet limited and large ongoing prospective studies have not included fibrinolytic measurements in baseline examination. The Northwick Park Heart Study reported an inverse association between fibrinolytic activity (clot lysis time) and subsequent incidence of CHD among healthy men aged 40-54 years at the initial examination (14). In

contrast, fibrinolytic activity was not a significant predictor of CHD in older men (14). A positive association of t-PA antigen levels with the risk of myocardial infarction has been found in two large prospective studies (19-21). However, the relation was no longer significant after adjustment for CHD risk factors in the Physicians' Health Study cohort (19). A large European study showed that both t-PA antigen levels and PAI-1 activity had a prognostic value in predicting CHD among patients with angina pectoris (13, 16). After adjustment for CHD risk factors, t-PA antigen, but not PAI-1 activity, was an independent predictor of CHD (13). Further analysis suggested that several CHD risk factors, including the insulin resistance syndrome, could operate through impaired fibrinolysis (16).

There was a strong positive association between PAI-1 activity and prevalent CHD among participants in the PRIME study. The rise in odds ratio of CHD was substantial and remained highly significant after adjustment for CHD risk factors, including markers of insulin resistance such as body mass index, waist-to-hip ratio, hypertension, triglycerides, and diabetes. Further adjustment for fibrinogen made no material change to the results. Therefore, it is unlikely that elevated PAI-1 activity reflect the inflammatory process of progressing atheroslerosis. No significant association between PAI-1 activity and risk of myocardial infarction has previously been reported in a large case-control study (58). The reasons for such a discrepancy remain unclear. The study of PAI-1 in relation to CHD incidence in the PRIME Study will provide important data to assess the relevance of fibrinolytic disturbance as an independent CHD risk factor.

There has been limited work on fibrinolytic variables in populations with differential mortality from CHD. After adjustment for CHD risk factors, PAI-1 activity was higher in Belfast than France. The difference, although not large, may be relevant to the 2 to 3-fold higher incidence of myocardial infarction in Northern Ireland than France (34). This finding has not been previously reported.

Population correlates of PAI-1 have not been extensively studied and most previous reports focused on the strong relation of fibrinolytic system with metabolic factors which belong to insulin resistance syndrome (59-63). By contrast with fibrinogen and factor VII, CHD risk factors accounted for an important part of the total variance in PAI-1 activity among participants in the PRIME Study. Body mass index and triglycerides were the most striking correlates of PAI-1. In addition, multivariate analysis showed an independent association between waist-to-hip ratio and PAI-1 activity. Another population-based study investigated the associations of both body mass index and wait-to-hip ratio with PAI-1 activity (46). Multiple regression showed that body mass index, but not waist-to-hip ratio, was an independent predictor of PAI-1 activity (46). Our results emphasize the importance of central body fat distribution as a determinant of PAI-1 activity (64).

Smoking status was a lifestyle factor slightly but significantly associated with PAI-1 activity among participants in the PRIME Study. The association remained significant in multivariate analysis. These data are consistent with previous reports (65,66) and suggest that reduced fibrinolytic potential may be relevant to increased CHD risk in smokers.

Alcohol consumption was also a correlate of PAI-1 at baseline examination of the PRIME Study. Since triglycerides levels are positively correlated with alcohol intake, a rise in PAI-1 activity with alcohol intake could reflect the effect of triglycerides on PAI-1 activity. However, alcohol consumption remained a significant determinant of PAI-1 after multivariate adjustment. This finding is consistent with experimental data showing rapid increase in PAI-1 activity with alcohol consumption in healthy volunteers (67). Two other population-based studies have reported a positive association between alcohol intake and t-PA antigen (68, 69). From these cross-sectionnal data, it is unclear, however, how these changes may be a mechanism whereby moderate alcohol consumption decreases CHD risk. An ethanol-induced cardioprotective effect could be mediated through low fibrinogen and high HDL-cholesterol levels rather than increased fibrinolytic potential. Future studies are required to clarify the possible interactions between alcohol intake, antithrombotic and fibrinolytic profiles, and CHD risk.

Leisure physical activity was inversely associated with PAI-1 activity among participants in the PRIME Study and our data are consistent with a beneficial effect of physical activity on CHD risk. Previous epidemiologic data investigating physical activity and fibrinolytic system are sparse. Elevated fibrinolytic activity after intense exercise has been reported at baseline examination in the Northwick Park Heart Study (65). However, no data on regular physical activity were available. In a recent comparison of young Indo-origin and young North European men with CHD, physical activity was also an independent predictor of PAI-1 activity and it contributed to inter-ethnic differences in fibrinolytic function (70).

The finding of an inverse association between HDL-cholesterol and PAI-1 activity is consistent with previous data (16, 60). However, HDL-cholesterol was not a significant correlate of PAI-1 after adjustment for triglycerides in the PRIME Study. This result shows the importance of triglycerides as a confounding factor in PAI-1 studies.

In conclusion, baseline data of the PRIME Study provide further epidemiological evidence for a role of fibrinogen and PAI-1 in the pathogenesis of CHD. Prospective data are needed to investigate further the relevance of factor VII in predicting CHD. Our results are consistent with the hypothesis that several cardiovascular risk factors operate through the haemostatic system.

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