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Migraine and Vascular Disease Biomarkers: A population-based case-control study

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Abstract

Background—The underpinnings of the migraine-stroke association remain uncertain, but endothelial activation is a potential mechanism. We evaluated the association of migraine and vascular disease biomarkers in a community-based population.

Methods—Participants (300 women, 117 men) were recruited as a part of the Dutch CAMERA 1 (Cerebral Abnormalities in Migraine, an Epidemiologic Risk Analysis) study. Participants were: ages 30–60 (mean 48) years, 155 migraine with aura (MA), 128 migraine without aura (MO), and 134 controls with no severe headaches. Plasma concentrations of fibrinogen, Factor II, D-dimer, high sensitivity C-reactive protein (hs-CRP), and von Willebrand factor antigen were compared between groups, also stratifying by sex.

Results—Fibrinogen and hs-CRP were elevated in migraineurs compared to controls. In logistic regression analyses, MO and MA had increased likelihood of elevated fibrinogen, MA had increased likelihood of elevated Factor II and hs-CRP. Fibrinogen and Factor II were associated with MA in women but not men. In the migraine subgroup, total number of years of aura, but not headache, predicted elevated hs-CRP, and average number of aura, but not headache, attacks predicted all biomarkers but Factor II.

Conclusions—Elevated vascular biomarkers were associated with migraine, particularly MA, as well as with years of aura and number of aura attacks.

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Keywords

Migraine; Aura; Headache; Biomarker; Vascular Disease; Inflammation; Stroke; Endothelial Activation

Introduction

Migraine is associated with stroke, particularly migraine with aura (1). The migraine populations at highest stroke risk includes women, those with high attack frequency, and long duration since migraine onset (1,2). Additional factors strengthening the migraine-stroke relationship include the absence of many of the conventional cardiovascular risk factors for atherosclerotic disease (3). In the context of these epidemiological findings, the mechanisms to account for the migraine-stroke association have been of considerable interest. There is likely a link to an increased (e.g. genetic) propensity to develop cortical spreading depression (the electrophysiological correlate of migraine aura), as reported in FHM1-mice (4). Further, numerous studies suggested that there might be increased endothelial activation in migraine, characterized by a pro-coagulatory and pro-inflammatory milieu, but results were variable (5). A clinic-based case-control study of premenopausal women reported a robust relationship between biomarkers of oxidative stress, coagulation, and inflammation (6) in interictal ICHD 2-defined migraine (7). The migraine-biomarker association was influenced by migraine frequency and subtype, being stronger for migraine with aura (MA) than for migraine without aura (MO). To date, most of the studies on biomarkers in migraine have been limited by the size, age, sex of the populations, or by the methods of migraine ascertainment.

Our objective in this study was to overcome such limitations, and to determine, within a well-characterized community-based population of men and women across the spectrum of adulthood, whether plasma biomarkers related to endothelial activation and vascular disease are associated with migraine. To this end, we have evaluated biomarkers from participants in the Dutch CAMERA 1 (Cerebral Abnormalities in Migraine, an Epidemiologic Risk Analysis) study (8). In this population we were able to examine the influence of the stroke-associated clinical phenotype (including MA, female sex, and long duration and high attack frequency of aura and of headache) on the relationship of vascular disease biomarkers and migraine.

Methods

Participants and Sample Selection

The Dutch general population-based Genetic Epidemiology of Migraine (GEM) and its substudy, the CAMERA 1 Study have been described previously (8). In brief, 863 persons with migraine, diagnosed according to the ICHD 2 criteria (7), and 5628 controls were identified in the GEM study (9). Controls were people who indicated that they had no severe headaches that interfered with their daily activities. This excluded people with chronic daily headache and cluster headache, but people with possible mild migraine attacks or episodic tension-type headache may have been included. From those between the ages of 30 to 60

years, 134 MO, 161 MA, and 140 controls, who were frequency matched by sex, five-year age strata, and place of residence, were randomly selected for the MRI and vascular biomarker study. Cases and controls did not differ by age, sex, and cardiovascular risk factors (including low education, body mass index [BMI], hypertension, cholesterol, diabetes, smoking, and alcohol use). The CAMERA 1 protocol included a structured telephone interview and a clinic visit for a brain MRI, blood draw, and a standard physical and neurological examination (8). To help the participants estimate headache and aura attack frequency, the interview was structured to allow persons to recount their history of migraine using their own benchmarks for when a different pattern started and stopped. In addition to reported age at first and last migraine and aura attack, these data were used to calculate a weighted average of the number of attacks per month. All participants gave written informed consent and participated without any financial reimbursement. The study protocol was approved by the Leiden University Medical Center, Netherlands ethics committee, and exempt from the University of Toledo, USA Institutional Review Board.

Measurement of Confounders and Covariates

Sociodemographic and medical characteristics were assessed by interview. Education was categorized into low (primary school or lower vocational education) and high. Smoking history was defined as never, former, and current and, for ever smokers, pack-years of exposure. The average alcohol intake in the past year was based on responses to questions on frequency and quantity of drinks per occasion and categorized into none, moderate (1–3 drinks per day), and high (≥3 drinks per day). Women reported the number of years they used oral contraceptives (OC). Measured weight and height were used to calculate body mass index (BMI: weight in kilograms divided by the square of height in meters). Blood pressure (BP) was the mean of 3 measurements obtained at 1- minute intervals in the upper arm with an electronic oscillometric BP monitor. Hypertension was defined as a systolic BP of 160 mmHg and higher or a diastolic BP of 95 mmHg and higher or current use of antihypertensive drugs. A measure of total cholesterol was available from the baseline GEM examination (8).

Laboratory Testing

The samples were collected ≥ 3 days after and >3 day before a migraine attack during 1999 and 2000. Samples were taken in a non-fasting state from an ante-cubital vein, labeled, processed within one hour after venipuncture, and frozen at −70 degree Celsius. Assays were performed in the University of Toledo Laboratory Services blinded to the participants' health and laboratory information. Von Willebrand factor (vWF) antigen (Ag), a well-established plasma marker of endothelial activation and dysfunction, was analyzed by immuno-turbidimetric method, using 0.5 ml of plasma using an automated instrument (STA-R Evolution® (Diagnostica Stago) (10), with limits of detection being 3%–420%. High sensitivity C-reactive protein (hs-CRP) was measured by Near Infrared Particle Immunoassay rate methodology using 0.5 ml serum using instrument IMMAGE® Immunochemistry Systems (Beckman Coulter) (11), with limits of detection being 0.2 mg/L- 1440 mg/L. Fibrinogen was analyzed by clot based method using 0.5 ml of plasma analyzed by STA-R Evolution® (Diagnostica-Stago) (12), with limits of detection being 60 mg/dL – 1800 mg/dL. D-dimer is measured by immuno-turbidimetric method using 0.5 ml

of Plasma analyzed by STA-R Evolution® (Diagnostica-Stago) (13), with limits of detection being 0.27mcg/mL FEU – 20.0 mcg/mL FEU. Factor II activity is measured by mechanical clot methodology, an automated method using 0.5 ml plasma analyzed by STA-R Evolution® (Diagnostica-Stago) (14), with limits of detection being 2%–1200%.

Statistical Analysis

Based on previous studies of migraine and stroke, and of migraine and biomarkers, the focus of our analysis was primarily on the association of biomarker levels with migraine, and its subtypes, MA and MO. Initially the relationship was examined at the cohort level, then repeated after stratifying by sex. The analysis was extended to explore the biomarker association with migraine variables such as headache attack frequency and duration since onset of headache. Within the MA cohort, we assessed biomarker association with aura frequency and duration since onset of aura. Data were analyzed using the Statistics Package for Social Sciences (SPSS) version 21.0. Level of significance was set a priori at $p < 0.05$ to reduce the type I error rate. Descriptive statistics were reported as means and standard deviations for continuous and frequencies and percentages for categorical variables. The differences in mean vascular biomarker levels between migraine and control groups were obtained by computing independent samples t- tests. For a secondary approach, biomarkers were divided based on population medians, and values corresponding to greater than or lower than the median values, were used to define elevated or lower levels of biomarkers for all study participants. Risk of having elevated levels of biomarkers was derived by computing the odds ratios with logistic regression analyses. Adjustments for demographic and cardiovascular risk factor variables (BMI, smoking, hypertension, cholesterol, use of oral contraceptives) were included in the estimation of risk for elevated biomarker levels. Odds ratios were computed through logistic regression analysis and used to examine the association of elevated biomarkers with migraine and migraine type (MA, MO) compared with controls. The adjusted regression model fits were verified using Hosmer Lemeshow test. All models except that involved stratified analysis had permissible number of terms not exceeding 10% of the sample size of the smaller group in the model. In the migraine cohort the relationship between different biomarkers and average headache frequency, average aura frequency, total number of years since headache onset and since aura onset was examined using multivariate linear regression analyses. For data with deviations from normality, log transformation was performed.

Results

The characteristics of the study participants have been previously published (8). In brief, patients with migraine with aura and without aura were randomly selected from the GEM cases aged 30 to 60 years. The control group was randomly selected from the cohort to frequency match the cases by sex, municipality, and age (Table 1). Blood samples for 18 subjects were not available (due to failed venipuncture in five, insufficient plasma in six, hemolysis during initial processing of plasma in one, and damage to sample during transport in six), leaving 155 subjects with MA, 128 with MO, and 134 controls. Over 70% of the participants were women and the mean age was 48 years. There were no significant differences across the groups in education, BMI, hypertension, diabetes mellitus, tobacco

use, serum cholesterol, and alcohol consumption. In a comparison of the women in the control and migraine groups, there was no difference between the proportions of long duration (>15 years) contraceptive use (24.0% v. 24.4%, p=0.94). There were no differences between the frequency of migraine in days per year within the MA and MO subtypes.

The biomarkers we selected are related to vascular disease. With the exception of the pairing of d-dimer and factor II, there were significant positive correlations between each biomarker pairing (data not shown). Adjusting for age, the strongest correlations were between fibrinogen and hs-CRP (0.547, p<.001), fibrinogen and factor II (0.356, p<.001), and hs-CRP and factor II (0.307, p<0.001). In the controls these three correlations, but no others, were significant. In the migraine group, and in the MA subgroup, all biomarker correlations were significant, except for between D-dimer and each of the following: factor II, vWF Ag, and fibrinogen.

In the primary approach, we examined the mean levels of biomarkers between control and migraine groups (all migraine, MA and MO) (Table 1). Levels of fibrinogen and hs-CRP were elevated in those with migraine as compared to controls, and levels of fibrinogen were elevated in the MA subgroup compared to controls. Biomarker levels did not significantly differ between MA and MO. Adjustment for age, sex, and level of education did not alter the results.

In the secondary approach, we made an unadjusted comparison between control and migraine, MA and MO groups based on the proportion of persons with biomarker levels above the population median. We demonstrated that compared to controls elevated levels of fibrinogen, factor II and hs-CRP were more likely to occur in those with migraine and with MA, and elevated levels of fibrinogen in those with MO (Table 2, Model 1). When adjusted for factors predictive of some or all of the examined biomarkers (age, sex, BMI, smoking status, hypertension, and cholesterol), elevated OR remained for fibrinogen in the migraine group and in the MA and MO subgroups and for Factor II in the migraine group and in the MA subgroup (Table 2, Model 2). For hs-CRP the association with migraine and with MA did not remain significant.

When stratifying by sex, and controlling for age, BMI, smoking status, hypertension, cholesterol, and OC use (>15 years), we found in women that elevated levels of fibrinogen and factor II were more likely in the migraine group and in the MA subgroup compared to controls (Table 3). By contrast, in men vascular biomarkers were not associated with migraine and with MA (Table 3).

In the migraine group we assessed the relationship between biomarkers with total years since onset and attack frequency for both headache (in MA and MO) and aura (in MA) by conducting a multivariate linear regression. Headache and aura frequencies were log transformed and age, gender, BMI, and smoking status were included as covariates. Total number of years of headache attacks and average number of headache attacks were not associated with biomarkers. However, total number of years of aura attacks was a significant predictor of hs-CRP (β=0.32, p<0.001). In addition, the average number of aura attacks was

a significant predictor of hs-CRP (β=0.39, p<0.001), vWF Ag (β=0.22, p=0.007), D-dimer (β=0.26, p=0.001), and fibrinogen (β=0.16, p=0.036).

Discussion

Our results show that in a population-based cohort selected vascular disease biomarkers are elevated in migraine, particularly in the subgroups most strongly linked to ischemic stroke risk– those with aura, and women. We also demonstrated that within the MA subgroup, it was aura, not headache, attack frequency and duration since onset that strengthened the association with the biomarkers of fibrinogen, hs-CRP, vWF Ag, and D-dimer.

The major strengths of this study include its population-based design, a standardized diagnosis of migraine following ICHD 2 criteria,[7] and the detailed description of the cohort that allowed us to control for possibly confounding factors due to other cardiovascular diseases. All specimens were collected within one year and randomly relative to migraine status. Limitations include the fact that the blood samples were analyzed nearly a decade after collection. The lower values in this study of the biomarkers fibrinogen and hs-CRP compared to some other studies (5,15) indicate that the samples may have lost some of their biological activity. It is however unlikely that there was any differential loss between the migraine and control samples, leading to false associations. Another limitation is the possibility of unaccounted factors influencing the biomarkers, such as the effect of insulin and glucose on fibrinogen. Our samples were non-fasting, although with examinations of both cases and controls equally distributed over the day, a “fasting” effect in one or the other group is unlikely. The small sample size may have resulted in lack of power to detect associations between migraine and biomarkers that may potentially exist in larger samples, and also to evaluate potential differences in subgroups, such as pre-and postmenopausal woman. Given the cross-sectional nature of the study, cause and effect relationships cannot be established for the association between migraine, and elevated biomarkers. This study also includes exploratory analyses and adjustment of p-values for multiple hypotheses testing was not performed and certain findings may be due to chance.

Novel discoveries from this study are the finding that elevated fibrinogen and Factor II levels were closely associated with migraine, particularly in women with MA. These associations were robust even when controlling for traditional stroke risk factors. Fibrinogen is involved in primary hemostasis, platelet aggregation, and leukocyte– endothelial cell interaction, and it is the major determinant of whole blood and plasma viscosity (16). Inflammation, from any cause, triggers hepatic fibrinogen production. Elevated fibrinogen levels, in turn, induce a state of hypercoagulability, cause inflammation and endothelial injury, and aggravate cerebral hypoperfusion (17). Fibrinogen may also damage blood vessel walls by causing smooth muscle proliferation and migration (18). Thus, elevated fibrinogen may be either the cause or consequence of endothelial injury. In some, but not all, epidemiological studies fibrinogen has been linked to heart disease and stroke, including in young and middle-aged adults (19). Plasma fibrinogen levels have also been associated with the risk of silent cerebrovascular lesions (20). A recent systematic review revealed only a few studies of fibrinogen in migraine (5). One small study reported an increase of plasma fibrinogen in migraineurs compared to controls (21), whereas another small study reported slightly lower

plasma levels in persons with migraine (22). The large Women's Health Study, which included women >45 years of age, found no differences in fibrinogen levels between migraine and control groups (16).

Coagulation factor II, also known as plasma prothrombin, is a vitamin K– dependent pro-enzyme that functions in the blood coagulation cascade and is required in the formation of fibrin. Increased levels of factor II, as occurs with the inherited prothrombin G20210a mutation, has been associated with 2 to 3 fold increased risk for the development of thrombosis, but usually in the venous system (23). The mutation has been associated with cryptogenic stroke, hypothesized to be related to paradoxical embolism with patent foramen ovale (24). Studies of the prothrombin G20210a mutation in migraine revealed no difference in the prevalence in persons with migraine compared to controls, including in migraineurs who have coexisting ischemic cerebrovascular disease (25). In our study, coagulation factor II was associated with migraine, especially migraine with aura, but unlike all the other markers, in linear regression analysis factor II was not associated with aura frequency or duration since aura onset in the MA subgroup.

We found that hs-CRP, a marker of inflammation and vascular disease, was elevated in migraine. The association of hs-CRP with migraine had been previously demonstrated in four case-control studies (6,26–28), including one with MO (26) and two with MA (6,27). Large population-based studies have also demonstrated that hs-CRP is elevated in persons with headache in children and adolescents (29) and in older individuals (15). In the population-based Reykjavik Study, however, hs-CRP levels were not increased among migraine sufferers compared with non-migraineurs (30). In analysis of the subgroup of young adult women (19–34 years), those with MO had borderline higher hs-CRP levels than non-migraineurs and those with MA (1.01mg/l vs. 0.81 and 0.75mg/l, p=0.08 and p=0.08).

Plasma levels of vWF antigen, a well-established marker of endothelial activation, correlated positively with all the other biomarkers, as well as with aura frequency and duration since onset in the MA cohort. Von Willebrand factor antigen levels were not, however, elevated in migraine compared to controls. This is in contrast to our clinic-based study where premenopausal women with migraine had higher adjusted odds ratios for elevated von Willebrand factor activity (OR 6.51; 95% CI, 1.94 to 21.83) (6). There are substantial differences in the populations of these two studies, including population type (clinic vs. general), proportion of females (100% vs. <75%), mean age (38 years vs. 48 years) and headache frequency (12 days per month vs. 1.4 days per month). Further study is needed to clarify the reasons for the discrepant results.

Conclusions

This study suggests that endothelial activation, as manifested by elevated biomarkers of hypercoagulability and inflammation, is associated with migraine, particularly in women. The correlation of biomarker levels with aura frequency and total number of aura-years suggests the possibility that aura is causally related to endothelial activation. If true, treatments that prevent aura, protect and repair the vasculature, or inhibit platelet aggregation and inflammation might prevent stroke in this at-risk subgroup of migraineurs.

Whether elevated levels of these biomarkers are associated with subclinical MRI findings or with increased prevalence of PFO in this population remains to be determined.

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Clinical implications

- Case-control population-based data in a well-characterized sample demonstrate that migraine is associated with biomarkers of hypercoagulability and inflammation, two components of endothelial activation.
- The presence of aura, as well as its frequency and years since onset, predict vascular biomarker levels, which may contribute to the link between migraine with aura and stroke.
- Treatments that prevent aura, protect and repair the vasculature, or decrease coagulation and inflammation may prevent stroke in this subgroup of migraineurs.

Table 1

Levels of unadjusted biomarkers for migraine compared to controls and migraine with aura compared to migraine without aura

	Control n=134	Migraine n=283	Migraine with aura n=155	Migraine without aura n=128
Age, mean (SE) years	48.18 (0.66)	48.52 (0.46)	48.17 (0.64)	48.95 (0.69)
Females, N (%)	94 (70)	206 (73)	111 (72)	95 (74)
Low Education, N (%)	67 (50)	145 (51)	82 (53)	63 (49)
Body Mass Index, mean (SE)	24.41 (0.32)	25.23 (0.25)	25.56 (0.37)	24.84 (0.35)
Hypertension, N (%)	44 (33)	115 (41)	64 (41)	51 (40)
Diabetes Mellitus, N (%)	5 (4)	4 (1)	1 (0.5)	3 (2.3)
Total Cholesterol, mean (SE), mmol/L	5.23 (0.08)	5.35 (0.05)	5.36 (0.07)	5.34 (0.08)
Smoking Current, N (%) Ever, N (%)	50 (37) 94 (70)	87 (31) 183 (65)	46 (30) 102 (66)	41 (32) 81 (63)
High (≥ 3 units/day) Alcohol Consumption, N (%)	21 (16)	21 (7)	14 (9)	7 (6)
Migraine frequency, mean (SE) days/yr	–	16.33(1.05)	15.96(1.54)	16.77(1.39)
Fibrinogen, mean (SE) mg/dL	298.87(5.18)	316.12(3.63)¶	318(4.95) ¶	313.70(5.34)
D-dimer, mean (SE) mcg/mL FEU	0.35(0.02)	0.32(0.01)	0.33(0.02)	0.32(0.01)
Factor II activity, mean (SE) % lab norm	108.14(1.23)	110.21(0.96)	111.07(1.29)	109.17(1.45)
vWF antigen, mean (SE) % lab norm	109.51(1.97)	109.69(2.32)	106.55(3.05)	113.48(3.54)
hs-CRP, mean (SE) mg/L	2.56(0.28)	3.43(0.27) ¶	3.52(0.38)	3.30(0.39)

Values reported in the table are means ± standard error (SE) of biomarker levels. vWF: von Willebrand factor, hs-CRP: high sensitivity C-reactive protein. Blood samples available for 134 controls and 283 migraineurs (Migraine with aura [MA]=155 and Migraine without aura [MO]=128)

¶= migraine vs. controls, $p < 0.05$. Fibrinogen: Migraine vs. control, p=0.007, MA vs. control, p=0.02; hs-CRP: Migraine vs. control, p=0.03 Adjustment for age, gender, and education did not alter the comparison results between MA, MO, and controls.

Table 2

Unadjusted and adjusted logistic regression analyses for biomarkers in migraineurs compared to controls (median split)

		Model 1: unadjusted			Model 2: adjusted		
Markers	**Control**	**Migraine**	**Migraine with aura**	**Migraine without aura**	**Migraine**	**Migraine with aura**	**Migraine without aura**
	Ref	**OR (95%CI)**	**OR (95% CI)**	**OR (95% CI)**	**AOR (95%CI)**	**AOR (95% CI)**	**AOR (95% CI)**
Fibrinogen	1	1.88 (1.24–2.87) p=0.003	1.97 (1.23–3.16) p=0.005	1.79 (1.09–2.92) p=0.02	1.76 (1.13–2.73) p=0.01	1.92 (1.16–3.19) p=0.01	1.78(1.05–3.00) p=0.03
D-dimer	1	1.03 (0.68–1.55)	1.22 (0.70–1.78)	0.91 (0.56–1.49)	0.96 (0.63–1.46)	1.07 (0.67–1.73)	0.85(0.51–1.40)
Factor II	1	1.76 (1.15–2.68) p=0.008	2.03 (1.26–3.25) p=0.003	1.48 (0.90–2.42)	1.63 (1.08–2.53) p=0.02	1.86 (1.14–3.05) p=0.01	1.41(0.84–2.36)
vWF Ag	1	0.77 (0.51–1.16)	0.69 (0.43–1.10)	0.86 (0.53–1.39)	0.69 (0.45–1.07)	0.62 (0.38–1.01)	0.78(0.47–1.29)
hs-CRP	1	1.60 (1.08–2.42) p=0.02	1.74 (1.09–2.78) p=0 02	1.43 (0.88–2.34)	1.47 (0.94–2.28)	1 60 (0.97–2.64) p=0.07	1.35(0.80–2.27)

Model 1 is unadjusted

Model 2 is adjusted for age + gender + BMI + smoking status + hypertension + cholesterol

Table 3

Adjusted logistic regression analyses for biomarkers in migraineurs compared to controls (Median split)

	Females Adjusted for age + BMI+ smoking+ hypertension + cholesterol + OCP				Males Adjusted for age + BMI+ smoking+ hypertension + cholesterol			
Markers	**Control n=94**	**Migraine n=206**	**Migraine with Aura n=111**	**Migraine without Aura n=95**	**Control n=40**	**Migraine n=77**	**Migraine with Aura n=44**	**Migraine without Aura n=33**
	Ref	**AOR (95% CI)**	**AOR (95% CI)**	**AOR (95% CI)**	**Ref**	**AOR (95% CI)**	**AOR (95% CI)**	**AOR (95% CI)**
Fibrinogen	1	1.84 (1.12–3.17) p=0.02	2.26 (1.24–4.13) p=0.008	1.61 (0.87–2.98)	1	1.49 (0.63–3.51)	1.18 (0.44–3.16)	2.32 (0.83–6.50)
D-dimer	1	0.87 (0.53–1.42)	1.05 (0.60–1.83)	0.70 (0.40–1.25)	1	1.18 (0.48–2.93)	1.05 (0.38–2.93)	1.57 (0.55–4.55)
Factor II	1	1.87 (1.08–3.09) p=0.02	2.00 (1.11–3.64) p=0.02	1.66 (0 90–3.07)	1	1.30 (0.56–3.01)	1.75 (0.67–4.58)	0.99 (0.36–2.70)
vWF Ag	1	0.72 (0.43–1.21)	0.61 (0.34–1.08)	0.86 (0.48–1.56)	1	0.64 (0.28–1.47)	0.66 (0.26–1.68)	0.81 (0.31–2.09)
hs-CRP	1	1.27 (0.75–2.13)	1.50 (0.81–2.80)	1.03 (0.55–1.94)	1	2.03 (0.84–4.90)	1.79 (0.64–4.99)	3.48(1.17–10.24) p=0.02

Data Not Shown

Marker correlations adjusted for age (full population)

Control Variables			Fibrinogen	D-dimer	Factor II	vWFAg	hs-CRP
age	Fibrinogen	Correlation	1.000	0.046	**0.239**	**0.267**	**0.507**
		Significance (2-tailed)	.	0.346	**0.000**	**0.000**	**0.000**
		df	0	414	414	414	414
	D-dimer	Correlation	0.046	1.000	−0.020	**0.231**	**0.228**
		Significance (2-tailed)	0.346	.	0.683	**0.000**	**0.000**
		df	414	0	414	414	414
	Factor II	Correlation	0.239	−0.020	1.000	0.087	0.068
		Significance (2-tailed)	0.000	0.683	.	0.076	0.164
		df	414	414	0	414	414
	vWF Ag	Correlation	**0.267**	**0.231**	0.087	1.000	**0.319**
		Significance (2-tailed)	**0.000**	**0.000**	0.076	.	**0.000**
		df	414	414	414	0	414
	hs-CRP	Correlation	**0.507**	**0.228**	0.068	**0.319**	1.000
		Significance (2-tailed)	**0.000**	**0.000**	0.164	**0.000**	.
		df	414	414	414	414	0