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Circulating fibrinogen but not D-dimer level is associated with vital exhaustion in school teachers

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Abstract
Meta-analyses have established elevated fibrinogen and D-dimer levels in the circulation as biological risk factors for the development and progression of coronary artery disease (CAD). Here, we investigated whether vital exhaustion (VE), a known psychosocial risk factor for CAD, is associated with fibrinogen and D-dimer levels in a sample of apparently healthy school teachers. The teaching profession has been proposed as a potentially high stressful occupation due to enhanced psychosocial stress at the workplace.

Plasma fibrinogen and D-dimer levels were measured in 150 middle-aged male and female teachers derived from the first year of the Trier-Teacher-Stress-Study. Log-transformed levels were analyzed using linear regression. Results yielded a significant association between VE and fibrinogen (p = 0.02) but not D-dimer controlling for relevant covariates. Further investigation of possible interaction effects resulted in a significant association between fibrinogen and the interaction term "VE X gender" (p = 0.05). In a secondary analysis, we reran linear regression models for males and females separately. Gender-specific results revealed that the association between fibrinogen and VE remained significant in males but not females.

In sum, the present data support the notion that fibrinogen levels are positively related to VE. Elevated fibrinogen might be one biological pathway by which chronic work stress may impact on teachers' cardiovascular health in the long run.

Keywords: *D-dimer, fibrinogen, hemostasis, teacher, Trier-Teacher-Stress-Study, vital exhaustion*

Introduction

Increased circulating levels of fibrinogen, an acute phase reactant and procoagulant molecule in the process of hemostasis (Herrick et al. 1999), has been established as an important and independent risk factor for cardiovascular morbidity (and mortality), like coronary artery disease (CAD), atherosclerotic vascular disease (AVD), myocardial infarction or (ischemic) stroke (Markovitz and Matthews 1991; Ernst and Resch 1993; Danesh et al. 1998; Maresca et al. 1999; Hackam and Anand 2003; Koenig 2003; Faxon et al. 2004; Fibrinogen Studies Collaboration 2005). The circulating glycoprotein fibrinogen is synthesized in the liver, acts at the final step in the coagulation response to vascular and tissue injury and is transformed by thrombin into fibrin that is the main component of a thrombus. Besides its role in thrombosis, other functions of fibrinogen are potentially relevant for onset and progression of cardiovascular syndromes (Hackam and Anand 2003), such as regulation of cell adhesion, chemotaxis and proliferation; vasoconstriction at sites of vessel wall injury; stimulation of platelet aggregation; and determination of blood viscosity. In the hemostastic process, enhanced fibrin turnover is indicated by high levels of D-dimer, which demonstrates activation of both

coagulation (ongoing thrombus formation) and fibrinolysis (von Kanel 2007). High circulating D-dimer levels are a marker for a hypercoagulable state and have been shown to be an independent predictor of CAD and have proved useful as an early diagnostic marker for CAD (Lip and Lowe 1995; Bayes-Genis et al. 2000; Danesh et al. 2001).

In addition to the classical cardiovascular risk factors for heart diseases (e.g. hypertension, hypercholesterolemia, impaired fasting glucose and diabetes, obesity, adverse health behaviors including smoking and a sedentary lifestyle) (Danesh et al. 1998; Hackam and Anand 2003; Faxon et al. 2004; Coban et al. 2005), psychological factors like acute and chronic stress may also contribute to the development and progression of heart diseases (Rozanski et al. 1999, 2005; von Kanel et al. 200Ib, 2007; Rosengren et al. 2004; Strike and Steptoe 2004; Bhattacharyya and Steptoe 2007; Thrall et al. 2007). A psychological state that is viewed as a potential consequence of long-term, chronic stress is vital exhaustion (VE). VE is characterized by unusual fatigue, loss of mental and physical energy, increased irritability and a feeling of demoralization (Kop 1999; Appels 2004). Epidemiological studies accumulated evidence that VE is an independent risk factor for cardiovascular disease (Kop 1999; Prescott et al. 2003; Appels 2004). Such findings led to the hypothesis that elevated fibrinogen and D-dimer levels might be possible biological links between VE and the onset and progression of heart diseases. There is a paucity of data on the relationship between fibrinogen, and especially D-dimer and VE in different populations. Van Diest et al. (2002) observed significantly higher fibrinogen levels in 29 vitally exhausted men compared to 30 controls, while Kop et al. (1998) could not observe differences in fibrinogen concentrations in a smaller sample of 15 men with VE versus 15 otherwise healthy controls. Also in an exclusively male sample of 231 subjects with and without coronary heart disease Lahlou-Laforet et al. (2006) found higher fibrinogen levels in exhausted men than in those who were not exhausted. In a large scale epidemiological study comprising 1645 men and 2623 women aged >65 years and at risk for incident cardiovascular disease, VE as measured by an abridged instrument was significantly associated with fibrinogen concentrations in both genders (Kop et al. 2002). Recently, Toker et al. (2005) investigated fibrinogen levels in 630 women and 933 men with respect to burnout, a concept closely related to VE. The authors found that, after controlling for depression, a significant association between fibrinogen and burnout emerged in women but not in men, pointing to the possibility of a gender-specific association. As regards D-dimer, von Kanel et al. (2004a) could not find a relationship with VE in a predominantly male sample of industrial workers. Though, in other studies D-dimer level was found to be increased in subjects with panic-like anxiety (von Kanel et al. 2004b) and in chronically stressed Alzheimer caregivers compared to controls (von Kanel et al. 2006).

The present sample is composed of male and female school teachers. This population was selected since there appears to be an increased risk of emotional exhaustion in the teaching profession (Guglielmi and Tatrow 1998). With this report, we aimed to contribute to the question whether VE is related to circulating fibrinogen and D-dimer levels in chronically stressed but otherwise healthy individuals. Such an association could help explain the recently reported increase in the cardiovascular disease risk in individuals suffering from burnout syndrome (Honkonen et al. 2006; Melamed et al. 2006).

Methods

Sample recruitment and study protocol

Teachers of all major school types were approached by personal visits in local schools and by newspaper announcements in the region of Trier (Germany) and Luxembourg. Volunteers with psychiatric disorders, medicated with corticosteroids or psychotropic drugs, a history of cancer, artery disease or heart failure, serious endocrine diseases (including diabetes, polycystic ovarian syndrome), or pregnant women were not included. Demographics (gender, age, years of employment, type of school) and current health status (acute and chronic diseases, medication intake) were assessed during a telephone screening in eligible subjects.

After the telephone screening, participants received questionnaires via postal mail for the psychometric assessment of VE and depressive symptoms (see below). After an overnight fast, they were invited to an early morning laboratory visit (i.e. before school), which included the assessment of health behaviors (smoking status, alcohol consumption, physical activity), anthropometric measures (body-mass-index BMI, resting blood pressure) and a venous blood draw for the measurement of fibrinogen, D-dimer, total cholesterol and glucose levels. At the end of the laboratory appointment, participants received saliva sampling materials for ambulatory assessment of cortisol day profiles (to be reported by Bellingrath et al. in press). The ethics committees of the State Medical Association of Rheinland Pfalz and the University of Trier approved the study protocol. All participants provided written informed consent and were paid 50 Euros as an incentive after completion of the study.

Psychological assessment

VE was measured using a German version of the 9-item short form of the original Maastricht VE

Questionnaire (Appels et al. 1987) as used in previous studies (Kudielka et al. 2006, 2007). Items ask about unusual fatigue, a disturbed sleeping pattern, general malaise, irritability, a loss of mental and physical energy and feelings of demoralization. Possible answers are "no", which results in a score of 0, indeterminate, which is marked as "?" and scored as 1; and "yes", scored as 2. This answering format gives rise to a range of a total VE score between 0 and 18. Scores from 0 to 3 indicate "no exhaustion", scores from 4 to 10 are equivalent to "mild to moderate exhaustion" and scores from 11 to 14 reflect "substantial exhaustion", whereas scores > 14 are consistent with "severe exhaustion". Cronbach's alpha was 0.87, reflecting good reliability.

Depressive symptoms were assessed by the German version of the depression subscale of the Hospital Anxiety and Depression Scale (HADS) (Herrmann 1997) consisting of seven items. Answers are coded on a 4-point Likert scale ranging from 0 = not at all to 3 = mostly, giving rise to a range of a total depression score between 0 and 21. In the German normative sample *(N* = 6200) Cronbach's alpha is 0.81.

With respect to the interrelationship between VE and depressive symptomatology, we recently showed in a sample of 822 employees (using the same questionnaires as in the present study) that both concepts are significantly interrelated but constitute distinct psychological constructs (Kudielka et al. 2004).

Biochemical analysis

All biological data were determined by a commercial laboratory (Synlab, Trier, Germany). Venous blood was collected either into citrate tubes for fibrinogen and D-dimer or into serum tubes not containing anticoagulants for total cholesterol and fasting glucose (Sarstedt, Niimbrecht, Germany). After blood withdrawal, citrate tubes were instantaneously stored on ice; all samples were centrifuged immediately at 4°C for 15 min at 2000g in an adjacent room and pipetted into aliquots. Within 60 min, aliquots were transferred to the core lab (Synlab) and processed immediately. Plasma fibrinogen levels were determined by a routine clotting assay following the Clauss method (Clauss 1957). Precision was between 2.1 and 4.3% (intra assay variability) and 3.7-6.1% (inter assay variability); the upper limit of detection was 10 g/1. D-dimer levels were analyzed by an enzyme-linked immuno-fluorescence assay (VIDAS® D-Dimer Exclusion™). Precision was between 3.9 and 5.3% (intra assay variability) and 5.8-7.1% (inter assay variability); lower and upper limits of detection were 0.05 and 10|jig/ml, respectively. Total cholesterol and glucose (hexokinase method) concentrations were analyzed by a kinetic enzymatic UV-assay using an autoanalyzer (Olympus AU 640 + AU 2700, Olympus). For total cholesterol, precision was between 0.8 and 0.9% (intra assay variability) and 1.0-2.0% (inter assay variability); for glucose, precision was between 1.1 and 1.2% (intra assay variability) and 0.8-1.3% (inter assay variability). Lower and upper limits of detection for total cholesterol were 25 and 700 mg/dl, respectively and 10 and 800 mg/dl for glucose.

Statistical analysis

Statistical analyses were performed using SPSS 13.0 for Windows (Chicago, IL, USA). The significance level was set at£ < 0.05 and all testing was two-tailed. Data are presented as means ± SD. Body-mass-index (BMI) was defined as kg/m^2; mean arterial blood pressure (MAP) was ((2 X *diastolic blood pressure) + systolic blood pressure)*/3. Medical data (MAP, total cholesterol, glucose, fibrinogen and D-dimer levels) were logarithmically transformed to obtain a normal distribution. In a first step, univariate analyses were carried out using Spearman correlation and Student's t-test. In a second step, linear regression was used to analyze the association between fibrinogen levels (dependent variable) and VE (predictor) after adjustment for covariates. D-dimer levels were analyzed accordingly. We controlled for gender, age, BMI, seasonality (month of laboratory visit), tobacco smoking status (yes/no), alcohol consumption (number of days alcohol was consumed in a typical week), physical activity (physical exercise per week in hours), MAP, total serum cholesterol, fasting serum glucose and depressive symptomatology (HADS-depression scale) (Folsom et al. 1991). In subsequent linear regression models, the interaction terms "VE X gender" and "VE X age" were additionally included to investigate possible interaction effects. Finally, we reran linear regression models separately in males and females for fibrinogen levels. Here, we first controlled for the full set of covariates. Then we controlled (a) for the five covariates that rendered significant associations with fibrinogen level in univariate analysis, namely age, BMI, smoking status, MAP and total cholesterol (Table II) and (b) for the five covariates that showed significant associations with fibrinogen level in the linear regression analysis in the total sample (Table III), namely age, BMI, seasonality (trend), total cholesterol (trend) and fasting serum glucose level to prevent model overfitting by inclusion of too many covariates given our sample size of 101 females and 49 males (Babyak 2004). The test power (1 - /3), which reflects the probability of finding an effect in the data when the effect actually exists in the "real world", was calculated using the software GPower3 by Paul et al. (2007) which can be downloaded from http://www.psycho.uni-duesseldorf.de/abteilungen/aap/gpower3.

Table I. Demographic and medical data of 150 teachers studied (mean ± SD).

Women/men (A/)	101/49	
Age in years (range)	45.5 ± 9.9 (23-63)	
Years of employment	18.2 ± 11.2	
Type of school (A/)		
Primary/elementary school ("Grundschule")	36	
Basic-level secondary school ("Hauptschule")	20	
Secondary school ("Realschule") Grammar	15	
school ("Gymnasium") Comprehensive	27	
school ("Gesamtschule") Vocational school	7	
("Berufsbildende Schule") Not further	20	
specified Missing	24	
BMI	1	
Smoking yes/no (A?)	25.2 ± 4.4	
Mean arterial blood pressure (MAP; mmHg)	12/138	
Total serum cholesterol (mg/dl)	97.2 ± 13.0	
Fasting serum glucose (mg/dl)	208.3 ± 40.3	Normal range*: < 200
Plasma fibrinogen (g/1)	95.2 ± 11.8	Normal range*: 74-106
Plasma D-dimer (|j,g/ml) *(N*— 149)	3.9 ± 0.7	Normal range*: 1.80-3.50
HADS-depression score (range)	0.27 ± 0.2	Normal range*: 0.00-0.50
VE score (range)	4.6 ±3.9 (0-19)	
	8.6 ± 5.5 (0-18)	

Normal range as provided by the laboratory (Synlab, Trier, Germany).

Results

Data were complete in *N*= 150 apparently healthy employed teachers, except for one missing data point for D-dimer levels. Demographics, medical data and questionnaire scores of the 101 women and 49 men are shown in Table I.

First, we tested bivariate associations between fibrinogen level and VE score as well as traditional risk factors and covariates using Student's r-test and Spearman correlation. Results are shown in Table II. Linear regression with the dependent variable fibrinogen level and the VE score as predictor revealed a significant association *(p* = 0.02) after controlling for covariates, explaining 3% of the observed variance by VE score. R^2 for the full model was 0.29. Results of the full linear regression model are shown in Table III. Subsequent linear regression models additionally including the interaction terms VE X gender or VE X age revealed a significant relationship for VE X gender *(p = 0.05;* see Table III) but not for VE X age *(p* > 0.59). In a final step, we computed separate linear regression models for males and females. In the female subsample, the association between the VE score and fibrinogen level was not significant when controlling for the full set of covariates *(p* > 0.3), as well as for the models with reduced sets of covariates (both *p* > 0.6). In the male subsample, however, the association between the VE score and fibrinogen level rendered significance controlling for the reduced sets of covariates (both *Std.fi* > 0.38 both *t* > 3.2 both

Table II. Bivariate associations between plasma fibrinogen level and traditional risk factors or covariates.

	Plasma fibrinogen	(g/1)	Student's £-test
VE	VE score < 10:	2.9 ± 0.6	£(148) = 3.54, *p* = 0.001
	VE score > 10:	3.3 ± 0.8	
Women/men	Women:	3.1 ± 0.8	£(148) = 2.78, *p* = 0.006
	Men:	2.8 ± 0.6	
Smoking	Yes:	3.2 ± 1.0	£(148) = -0.99,p> 0.3
	No:	3.0 ± 0.7	
	Fibrinogen (g/1)		Spearman correlation
Age (years)			*r*= 0.26, *p* = 0.002
BMI			r = 0.33, *p* = 0.001
Seasonality (month of lab visit)			ns
Alcohol consumption (days consumed alcohol in typical week)			ns
Physical activity (physical exercise per week in hours)			ns
Mean arterial blood pressure (MAP; mmHg)			r = 0.17, *p* = 0.03
Total serum cholesterol (mg/dl)			*r* = 0.24, *p* = 0.003
Fasting serum glucose (mg/dl)			ns
HADS-depression score			ns
VE score			r = 0.24, *p* = 0.003

Statistics are based on log-transformed levels for fibrinogen, MAP, total serum cholesterol and fasting serum glucose levels.

Table III. Linear regression analyses in the total study sample *(N* — 150) with the dependent variable plasma fibrinogen level, the predictor VE score and covariates.

	Linear regression		
Dependent variable	Plasma fibrinogen (g/l)		
Variables entered	Std.β	t	p
Gender	−0.24	−3.3	0.001
Age	0.19	1.9	0.04
BMI	0.35	4.2	0.001
Seasonality	−0.13	−1.8	0.07
Smoking			ns
Alcohol consumption			ns
Physical activity			ns
MAP			ns
Total cholesterol (mg/dl)	0.12	1.5	0.12
Fasting glucose (mg/dl)	−0.21	−2.6	0.01
HADS-depression score			ns
VE score	0.23	2.4	0.02
		$R^2 = 0.29$	
Interaction VE × gender	0.44	1.9	0.05
		$R^2 = 0.31$	

A secondary regression model additionally included the interaction term VE X gender; only significant results are shown; statistics are based on log-transformed levels for plasma fibrinogen level, MAP, total serum cholesterol and fasting serum glucose level.

$p < 0.003$) and approached significance for the full set of covariates (Std./3 = 0.29, $t > 1.7$, £ = 0.10). Figure 1 illustrates the bivariate correlation between the VE score and fibrinogen level separately in females *(r* = ns) and males *(r* = 0.45, $p = 0.001$).

For D-dimer level, significant bivariate associations emerged for age (r=0.27, $p< 0.001$), BMI (r=0.30, $p< 0.001$), MAP (r=0.17, $p < 0.05$) and fasting serum glucose *(r* = 0.20, $p < 0.02$). No significant differences in D-dimer level emerged between males and females, neither between smokers and non-smokers nor between subjects with a VE score < 10 and > 10 (all $p > 0.28$). Linear regression with the dependent variable D-dimer level and VE score as predictor revealed no significant association for VE score *(p* > 0.40) after controlling for covariates. In the full regression model, only gender (£ = 0.03), age (£ = 0.02) and BMI (£ = 0.01) reached significance. Inclusion of interaction terms did not reveal any significant interaction effects (both £ > 0.65). Finally, post-hoc analyses of the test power (1 — /3) showed that the probability of revealing a significant association between the VE score and D-dimer level in the full linear regression was >99% given big or medium sized effects of interest (effect sizes $/^2$ = 0.35 and $/^2$ = 0.15 according to Cohen's criteria) but 41% for small effect sizes ($/^2$ = 0.02), respectively. This shows that the given /3-error was satisfactorily low for medium to big but not small effect sizes. A sensitivity power analysis showed that an effect size *off* = 0.09 (or/ = 0.05) could have been detected if the /3-error was fixed to 95% (or 80%).

Discussion

This study further elucidated whether heightened circulating fibrinogen and D-dimer levels might be plausible biological links between chronic stress and CAD. We assessed chronic stress in terms of VE in 150 male and female school teachers since the teaching profession has been proposed as a potentially highly stressful occupation (Guglielmi and Tatrow 1998). In sum, we confirmed findings of a modest association between VE score and the level of the procoagulant molecule fibrinogen but not D-dimer. These findings are consistent with earlier reports from predominantly male samples (Kop et al. 2002; van Diest et al. 2002; von Kanel et al. 2004a; Lahlou-Laforet et al. 2006). We also showed that the association between the VE score and fibrinogen level was retained independently of a set of traditional cardiovascular risk factors. In accordance with Toker et al. (2005) who strongly

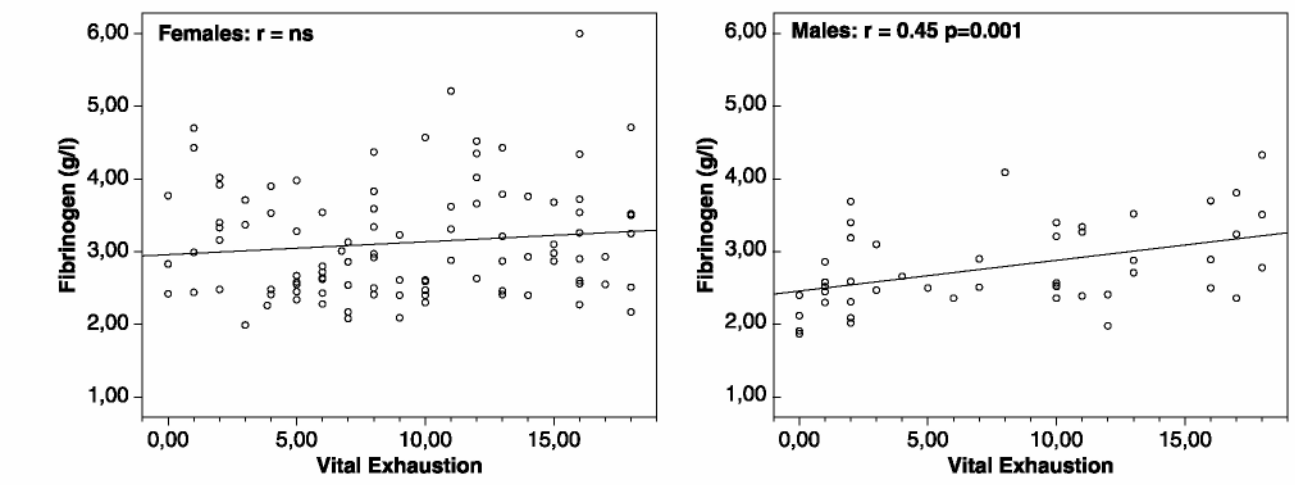

Figure 1. Scatterplots illustrating the association between plasma fibrinogen levels (g/1) and VE score separately in females *(N* — 101) and males *(N* — 49); statistics are based on log-transformed fibrinogen levels.

argued for the control for depression, our set of control variables also included depressive symptomatology as an important psychosocial risk factor of CAD (Rozanski et al. 1999; von Kanel et al. 200la; Rosengren et al. 2004; Strike and Steptoe 2004; Bhattacharyya and Steptoe 2007). In contrast to these previous studies, our sample of potentially stressed school teachers was composed of males *(N* = 49) as well as females *(N* = 101). This meets the claim by Vorster (1999) to also include women in studies on fibrinogen and health because women have largely been neglected in earlier studies.

Interestingly, we found a significant interaction between the VE score and gender for the association between the VE score and fibrinogen level. A secondary analysis stratified by gender revealed that the association was significant in the male but not in the female subsample. Earlier studies on a relationship between fibrinogen levels and burnout (Toker et al. 2005) and job conditions in terms of Karasek's job-demand-control model (Tsutsumi et al. 1999; Kittel et al. 2002) already raised the idea of gender-specific associations. However, findings are not uniform. Toker et al. (2005) found a significant association between burnout and fibrinogen levels in women but not in men (after controlling for depression). In the SHEEP study, Tsutsumi et al. (1999) concluded that the relation between adverse job characteristics and plasma fibrinogen concentrations might be more relevant in female workers. Using multiple logistic regression, they found that men in the job strain group had an increased risk of falling into the increased plasma fibrinogen concentration group while in women, low self-reported control, high demand and job strain were significantly associated with increased plasma fibrinogen concentrations. More in line with the present results, Kittel et al. (2002) found a significant association between higher levels of job strain and plasma fibrinogen in males but not in females in the BELSTRESS study. Only after stratification for educational level, was there a positive association observed between psychological job demands or job strain and plasma fibrinogen levels in males (in the lowest educational level) and job strain and plasma fibrinogen in females (in the middle educational level). Notably, the educational level as well as socioeconomic status was relatively high and homogeneous in our sample of school teachers. Finally, our finding of a significant association between fibrinogen and VE in men but not women could partially explain recent observations by Honkonen et al. (2006). In a representative nationwide population health survey, they examined the relationship between burnout and physical illness in Finland and found that burnout is associated with musculoskeletal diseases among women and with cardiovascular diseases among men. Our results could point to one potential biological pathway underlying their findings. One might speculate that such gender differences might be related to differences in the importance of life roles in men and women (Cinamon and Rich 2002). For example, in the Stockholm Female Coronary Risk Study (Orth-Gomer 2007), it was found that marital stress and stressful conditions in family life were stronger predictors of heart disease in women than stress at work, though work stress had also been established as an important risk factor for cardiovascular disease in women as well as in men.

Our findings are in line with reports on biological links between VE and CAD focusing on other parameters of the hemostasis process. For example, several studies report on positive associations between VE and plasminogen activator inhibitor 1 (PAI-1) (Raikkonen et al. 1996; Kop et al. 1998; van Diest et al. 2002; von Kanel et al. 2004a; Lahlou-Laforet et al. 2006). Elevated PAI-1 levels under chronic stress point to a reduced fibrinolytic capacity, which may facilitate atherothrombotic conditions. Since we did not observe a relationship between VE and D-dimer levels, which concurs with a finding by von Kanel et al. (2004a), it might be speculated that unchanged D-Dimer levels indicate that VE does not necessarily result in enhanced fibrin turnover. From this, one could further hypothesize that VE is associated with the increase in an individual clotting factor (i.e. fibrinogen), yet this increase might not be sufficient to lead to overall coagulation activation as reflected by the lack of an association between VE and D-dimer levels.

We acknowledge that the clinical relevance of the 3% of the variance in fibrinogen accounted for by VE remains somewhat unclear. As suggested by Kop (1999), the impact of exhaustion on fibrinogen might have been greater if participants had been more exhausted. While 94 of our subjects scored between 0 and 10 in the VE questionnaire, indicating no to moderate exhaustion, 56 subjects scored above 11, indicating substantial to severe exhaustion; no subject was on sick leave or had clinical treatment due to exhaustion. It is noteworthy, however, that the VE score correlated with fibrinogen level at least as highly as some of the cardiovascular risk factors like MAP, total serum cholesterol and even age (Table II). Only BMI showed a somewhat higher univariate association with fibrinogen levels. In accordance, in multiple regression analysis we found a higher beta weight for BMI compared to the contribution of the VE score, although comparable beta weights emerged for age and fasting serum glucose levels. A clinical significance of our findings might be assumed based on earlier reports from the PROCAM study and two meta-analyses published by Danesh and coworkers. In our study, fibrinogen levels differed by 0.4 g/1 between subjects with no to moderate VE score versus subjects with substantial to severe VE score (Table II). In the PROCAM study, the predictive power of hemostatic

variables was assessed for coronary risk in healthy men. At 6-year follow-up, the mean plasma fibrinogen level of the coronary event group (82 events in 2116 screened participants) exceeded that of the non-event groups by 0.25 g/1 (Heinrich et al. 1994); at the 8-year follow-up, the difference was 0.32 g/1 between the non-event and event group (130 events in 2781 screened participants) (Assmann et al. 1996). Danesh et al. (1998) conducted a meta-analysis of published data from 18 studies, involving approximately 4000 cases of CAD and found a relative risk of 1.8 (95% confidence interval CI 1.6-2.0) per 1 g/1 increase in plasma fibrinogen. More recently, the Fibrinogen Studies Collaboration (2005) conducted another large and comprehensive meta-analysis, which comprised 6944 first non-fatal myocardial infarction or stroke events and 13,210 deaths; cause-specific mortality information was available among 1,54,211 participants derived from 31 different studies. Interestingly, there was no evidence of a threshold within the range of usual fibrinogen levels studied at any age. The age- and sex-adjusted hazard ratio per 1 g/1 increase in usual fibrinogen levels was 2.42 (95% CI 2.24-2.60) for CAD, 2.06 (95% CI, 1.83-2.33) for stroke, 2.76 (95% CI, 2.28-3.35) for other vascular mortality and 2.03 (95% CI, 1.90-2.18) for non-vascular mortality.

An important limitation of our study is its cross-sectional design, which does not allow for any causal inferences. Furthermore, although our study sample is larger than some earlier reports on VE and fibrinogen levels (Kop et al. 1998; van Diest et al. 2002), our sample size was limited, especially with respect to men. However, it can be regarded as a strength that our study sample comprised a significant number of women (Vorster 1999). Furthermore, we did not include any clinical cases of exhaustion, but recruited working teachers with a homogeneous level of educational and socioeconomic status, which in turn can also be regarded as a strength. Unfortunately, we did not assess poor dental status which has previously been shown to be associated with increased fibrinogen levels (Beck et al. 1998). Furthermore, periodontitis was suggested as another risk factor for coronary heart disease. Finally, analyses of the test power confirmed that the probability of revealing an association between D-dimer levels and VE score was very high (1 — /3 > 99% for medium and big effects). The sensitivity analysis underlined that at least an effect with an effect size of $/^2 = 0.09$ (medium to low) could have been discovered within the present sample giving a test power of 95%.

In clinical terms, our data may suggest that a reduction in chronic stress by psychological intervention might be suitable to reduce coronary risk by decreasing fibrinogen levels. Recently, Claesson et al. (2006) conducted a stress management program designed specifically for women with CAD to test whether an improvement in psychosocial well-being is associated with an improvement in biochemical indicators of cardiovascular risk. This controlled study randomized 80 women to a 1-year cognitive-behavioral stress reduction program and 86 women to usual care. Although the program was successful in reducing self-rated stress behavior and VE, the changes in psychosocial variables were not associated with changes in any of the biological risk indicators, including fibrinogen, PAI-1 and other hemostatic factors. This challenges the proposition that the relationship between psychological well-being and biological cardiovascular risk indicators is a direct cause—effect phenomenon.

In summary, studying a sample of 150 male and female school teachers, we found that higher levels of VE were independently associated with higher circulating levels of fibrinogen but not with D-dimer levels. In gender-specific analysis, this effect remained significant in men but not women. From this, our findings corroborate the hypothesis that altered hemostasis might be one possible biological pathway by which chronic psychological stress might negatively impact on teachers' cardiovascular health in the long run.

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