Depressive symptoms are related with hemostatic factors in middle-aged women: A report from the Study of Women Health Across the Nation (SWAN)

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Abstract

Objective: Depression may be a risk factor for coronary heart disease (CHD) morbidity and mortality, but the mechanism(s) for the association are not established. The present study examined the relationship between one possible mechanism, hemostatic factors, and depressive symptoms in middle-aged women. **Method:** We measured levels of fibrinogen, Factor VIIc, plasminogen activator inhibitor antigen-1 (PAI-1), and tissue plasminogen activator antigen (TPA-ag) in 3,016 women aged 42-52 years enrolled in the Study of Women's Health Across the Nation (SWAN). Depressive symptoms were measured by the Center for Epidemiological Studies Depression Scale (CES-D), with scores ≥ 16 suggestive of depression. **Results:** Depressed women had high levels of all four hemostatic factors (all p <0 .01). After controlling for age, smoking, ethnicity, prevalent cardiovascular disease, osteoarthritis, and diabetes, and use of medications (including psychotropics), depressed women still had elevated levels of fibrinogen (mean, 95% confidence intervals 299, 304 – 295 mg/dl vs. 291, 294 – 288mg/dl, p= 0.003) and Factor VIIc (124, 127 – 121 ng/dl vs. 119, 121 – 117 ng/dl, p= 0.01) levels, compared to nondepressed women. **Conclusions:** These findings suggest that hemostatic factors may be a key mechanism accounting for the relationship between depression and CHD. *[Castilla RC, Bromberger JT, Zhang Y, Perel JM, Matthews KA. Depressive symptoms are related with hemostatic factors in middle-aged women: A report from the Study of Women Health Across the Nation (SWAN). MedUNAB 2004; 7:57-64]*

Key words: Hemostatic factors, depression, mid-life, women

Introduction

Depression may be a risk factor for coronary heart disease (CHD) morbidity and mortality, particularly in coronary patients.[1-3] Among the possible mechanisms offered to account for the association are poor adherence to medical regimens, unhealthy life style, parasympathetic nervous system abnormalities, endothelial dysfunction, platelet reactivity and coagulation factors.[4-7] Previous studies identified an increased rate of perimenopausal depression, mostly in women who had had a history of depression. These studies lend support to a vulnerability theory-women who have previously had affective disorders may be at increased risk of mood disturbance during the menopausal transition. [1]

Little data are available about the relationship between depression and hemostatic factors. In healthy adults, higher circulating levels of inteleukin-6, C-reactive protein, and tumor necrosis factor-alpha, are associated with depression, in part because of obesity.[4] Some antidepressant medications (e.g. selective serotonin reuptake inhibitors) are associated with reduced cardiovascular mortality among patients with major depression.[8, 9] Also supporting the hypothesized relationship between depression and hemostatic factors are data regarding platelet activation because of the interrelationship between the platelet and coagulation cascade. Patients with major depression exhibit greater platelet activation and higher procoagulant properties than do healthy controls.[10] They also exhibit more binding sites relevant to platelet physiology, including imipramine, paroxetine, and inositol on the platelet surface. Platelet monoamine oxidase activity is elevated in depressed patients, especially in women.[11]

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In the present study, we evaluated the association of depressive symptoms and fibrinogen, Factor VIIc, plasminogen activator inhibitor (PAI-1), and tissue plasminogen activator antigen (tPA-ag) levels in a multiethnic cohort of middle-aged women. We hypothesized that women with elevated depressive symptoms would have high levels of hemostatic factors. Further, we expected that these differences would be maintained after controlling for other factors that affects hemostasis (i.e., age, ethnicity, BMI, smoking status; history of diabetes mellitus, CHD and hypertension; and use of medications for cardiovascular diseases and diabetes and for psychiatric illness).

Methods

Participants. 3304 participants were enrolled in the Study of Women's Health across the Nation (SWAN), a multi-site, longitudinal cohort study of the perimenopausal transition. Eligibility criteria were ages 42 to 52 years; intact uterus and at least 1 ovary; no current use of reproductive hormones or other medications known to affect ovarian function; at least one menstrual period in the 3 months before screening, and self-identification as a member of one of the five eligible ethnic groups: Black or African American, non-Hispanic White, Chinese or Chinese American, Japanese or Japanese American, or Hispanic (Cuban American, Dominican, Puerto Rican, South American or Spanish). Women were enrolled at 7 clinical sites in the following geographic areas: Boston, MA, Chicago, IL, Detroit area in Michigan, Los Angeles, CA, Hudson County, NJ, Oakland, CA, and Pittsburgh, PA. Recruitment techniques were designed to generate a representative sample of Caucasian and one minority group at each site. The appropriate institutional review boards approved this study, and all subjects provided written informed consent. Details of recruitment strategies and participant characteristics are described elsewhere.[12] Of the 3304 participants, 3202 supplied blood for further assay; 3016 met minimal criteria for inclusion in the analysis, i.e. had complete data for age, ethnicity, smoking status, body mass index, and at least one of the hemostatic variables that are the focus of this report.

Protocol. After an initial survey for eligibility criteria and general health status, eligible women were invited to join SWAN and a baseline evaluation was scheduled. The baseline evaluation included a fasting blood draw targeted to occur within days 2 – 7 of the menstrual cycle and prior to 10 a.m.; measurement of height, weight, waist circumference, and blood pressure; interviews regarding medical history and lifestyle; and self-report questionnaires. Instruments used in this study were translated into Cantonese, Japanese, and Spanish. Study design included annual follow-up evaluations thereafter.

Measures. Depressive symptoms were assessed by the Center for Epidemiologic Studies Depression Scale (CES-D), a 20-item scale that asks about the frequency of being bothered by depressive symptoms during the previous week.[13] We categorized women into those with scores ≥ 16 vs < 16, a classification that has been used to identify potential clinical depression in community samples.[14,15] The CES-D is a valid and reliable instrument in diverse ethnic populations, including African American, Chinese, Japanese, and Hispanics. Internal reliability in SWAN was 0.90, ranging from 0.88 – 0.90 in each ethnic group taken separately.[16-20]

Blood was anticoagulated with 3.8 percent trisodium citrate (9:1 vol/vol) and cooled on ice until centrifugation. Plasma was separated by centrifugation for 20 minutes at 2000 g and stored at -80°C for later analysis. Fibrinogen and Factor VIIc were measured using a clot-based turbidometric detection system, with Factor VIIc assay using Factor VII deficient plasma in preparing the standard curve. tPA-ag was measured in plasma using a double antibody in an enzyme-linked immunosorbant assay (American Diagnostica, Greenwich, CT), with a single chain tPA as a standard calibrated against an international standard (Hertfordshire, England). PAI-1 was measured using a solid phased monoclonal antibody and an enzyme labeled goal second antiserum for detection (American Diagnostica, Greenwich, CT).

Weight was measured in light indoor clothing with shoes removed using a balance beam scale, and height was measured using a stadiometer. Body mass index (BMI) was calculated as weight in kilograms divided height in meters squared; participants were classified as underweight, normal weight, and overweight by the National Heart, Lung and Blood Institute (NHLBI) criteria. Trained technicians measured blood pressure three times for each woman after she was seated for at least 5 minutes and the last two readings were averaged. Participants were classified as having high blood pressure if they had systolic blood pressure ≥ 140 mmHg or a diastolic blood pressure ≥ 90 mmHg or were taking anti-hypertensive medication currently. Participants were asked if they had been told by a health care professional that they had any of 23 illnesses or conditions and about their current medication use.

Statistical methods. Chi-square or t-tests were used to assess univariate association between depression and age, ethnicity, BMI, and smoking status. Included as potential covariates, were those illnesses and conditions commonly associated with heart and inflammatory diseases. Covariates included report of history of heart disease or using medications to treat heart disease (n=95); hypertension (n=578); osteoarthritis (n=592); and diabetes mellitus or use of insulin (n=150); use of anti-coagulant medications in the last 24 hours (n=20); use of pain medications (n=379); and use of psychotropics (n=296), i. e., tricyclic antidepressant, selective serotonin reuptake inhibitors (SSRIs), a selective noradrenergic reuptake inhibitor (SNRIs), lithium, anticonvulsivants,

benzodiazepines, barbiturates, sleeping pills or other sedative/hypnotic.

Those covariates that were significant in the univariate analyses were included in the multivariate analyses. Final multivariate models were conducted in a backward step-wise fashion, such that the covariates were removed that were nonsignificant, with CES-D scores remaining in the model. Statistical tests for two-way interactions between CES-D score and use of psychotropic medications were also included but none was significant and they are not discussed further. Two-sided p-values ≤ 0.05 were considered statistically significant. There were 3011, 2964, 2968, and 2945 women in the analyses of fibrinogen, Factor VIIc, tPA-ag, and PAI-1, respectively.

Results

The mean age of the group was 45.9 $\pm$ 2.7 years, with 11% older than 50. By study design almost half the women were Caucasian (47.1%), with approximately one-quarter African-American, and equal numbers of Hispanic, Japanese, and Chinese. The prevalence of elevated depressive symptoms was 24.4% in the analytic sample.

Compared with women with low CES-D scores, women with elevated scores were younger and were more likely to smoke and to be overweight or underweight. Depressed women were more likely to report having heart disease and hypertension, or using medications for these conditions, and having osteoarthritis and using psychotropic or pain medications (table 1).

Depressed women had elevated coagulation factors compared with non-depressed women (figure 1), all $p<0.01$ in univariate analyses. After statistical adjustment for the relevant covariates of age, ethnicity, BMI, smoking status, high blood pressure, diabetes, arthritis, and medication use, depressed women, compared to nondepressed women, still had elevated fibrinogen levels, mean (95% confidence intervals) 299 (304–295) vs. 291 (294–289), p=0.003, and Factor VIIc levels, mean (95% confidence intervals) 124 (127–121) vs. 119 (121–118), p=0.01. However, depression was no longer associated with tPA-ag, p=0.85, and PAI-1, p=0.39, after covariate adjustment. Use of psychotropic medications was significant in the multivariate analyses of PAI-1, p=0.006 (table 2).

Depressed women who were currently using any psychotropic medication (n=151) did not have a higher level of fibrinogen, 307 vs. 303 mg/dl p=0.59, compared with non-users who were depressed.

Levels of all coagulation factors were higher in older women, heavier women, and current smokers (table 2). As reported elsewhere (Matthews et al., submitted, 2003), fibrinogen levels were highest in African-American women ($p < 0.005$ vs all other groups), and the other levels were higher in Hispanics than in Caucasians. Japanese and Chinese women exhibited the lowest levels of coagulation factors. Women with elevated fasting glucose levels had elevated levels of hemostatic factors.

Discussion

This study is the first to report that elevated fibrinogen and Factor VIIc levels are associated with depressive symptoms, after adjustment for many covariates, in women with diverse ethnic backgrounds. Inflammatory and coagulation processes are thought to play a key role in coronary artery disease and its sequalae, although there is discussion whether they are markers of disease or play a causal role. Epidemiological studies show associations between risk for CHD and fibrinogen,[21,22] FVII clotting activity,[22,23] FVIII clotting activity,[24] vWF antigen,[24,25] t-PA antigen,[25,26] PAI-1 antigen,[27] D-dimer,[28-30] and plasmin-[alpha]2-antiplasmin complex.[29,30] In turn, altered fibrinolytic capacity reflected by t-PA activity[22,23,30] and prolonged euglobulin clot lysis time[22] as well as low antithrombin III consumed in anticoagulant processes with severe atherosclerosis[22,23] may all prospectively be associated with CHD. Epidemiological studies show that patients with depressive symptoms are at increased risk for developing CHD,[31-35] and cerebrovascular disease,[36] although several recent reports differ.[37,38] Indeed, of patients with CHD, 16% to 23% exhibit symptoms of major depression[2,39,40] with the presence of depression predictive of future cardiac complications[32,33,39] and diminishing survival time.[2,41]

Depressive symptoms may contribute to the onset and the maintenance of a chronic inflammatory response to injuries to the endothelium through maladaptive health practices such as cigarette smoking.[4] However, our analyses adjusted for the effects of lifestyle factors, so this is an unlikely explanation of our results. Similarly, depression appears to increase susceptibility to infection with latent pathogens that colonize the vessel wall[42] but, as best we could, we controlled for prevalent disease and use of relevant medications through history. Stress triggers dysregulation of the neurohormonal system responsible for cortisol and catecholamine secretion.[43] Elevations in plasma catecholamines may increase platelet activity in depressed women and, in turn, lower the threshold for myocardial ischemia, and increase the risk of coronary thrombosis.[10,44,49] Each of these processes could damage the endothelium, thereby triggering inflammatory/coagulation processes that contribute to the progression of atherosclerosis.[44,45,48]

Several limitations deserve comment. First, the analysis presented here is cross-sectional. Thus, cause and effect relationships cannot be proven. Second, the hemostatic variable levels were determined at only one point in time

Table 1. Sample of women according to depression (CES-D) scores.

Characteristics	Total		CES-D < 16		CESD ≥ 16		P-value for depression
Demographic factors	N	%	N	%	N	%	
Age							0.0001
≤ 45	1443	48	1045	46	398	54	
45 – 49	1238	41	962	42	276	38	
≥ 50	335	11	274	12	61	8	
Ethnicity							<0.0001
Black	848	28	619	27	229	31	
Hispanic	248	8	138	6	110	15	
Chinese	234	8	201	9	33	5	
Japanese	264	9	224	10	40	5	
White	1422	47	1099	48	323	44	
BMI (kg/m²)							0.0003
< 18.5	48	2	38	2	10	2	
18.5 – 24.9	1161	38	923	40	238	32	
≥ 25	1807	60	1320	58	487	66	
Smoking Status							<0.0001
Current	521	17	341	15	180	25	
Past	755	25	578	25	177	24	
Never	1740	58	1362	60	378	51	
High Blood Pressure Yes	578	19	415	18	163	22	0.02
No	2438	81	1866	82	572	78	
Diabetes Yes	150	5	105	5	45	6	0.010
No	2866	95	2176	95	690	94	
Coronary Heart Disease Yes	95	3	54	3	41	6	<0.0001
No	2921	97	2227	97	694	94	
Osteoarthritis Yes	592	20	392	17	200	27	<0.0001
No	2424	80	1889	83	535	73	
Anticoagulant Medication Yes	20	1	11	1	9	1	0.03
No	2996	99	2270	99	726	99	
Psychotropics Yes	296	10	157	7	139	19	<0.001
No	2720	90.	2124	93	596	81	
Pain medication Yes	357	12	234	10	123	17	<0.001
No	2659	88	2047	90	612	83	

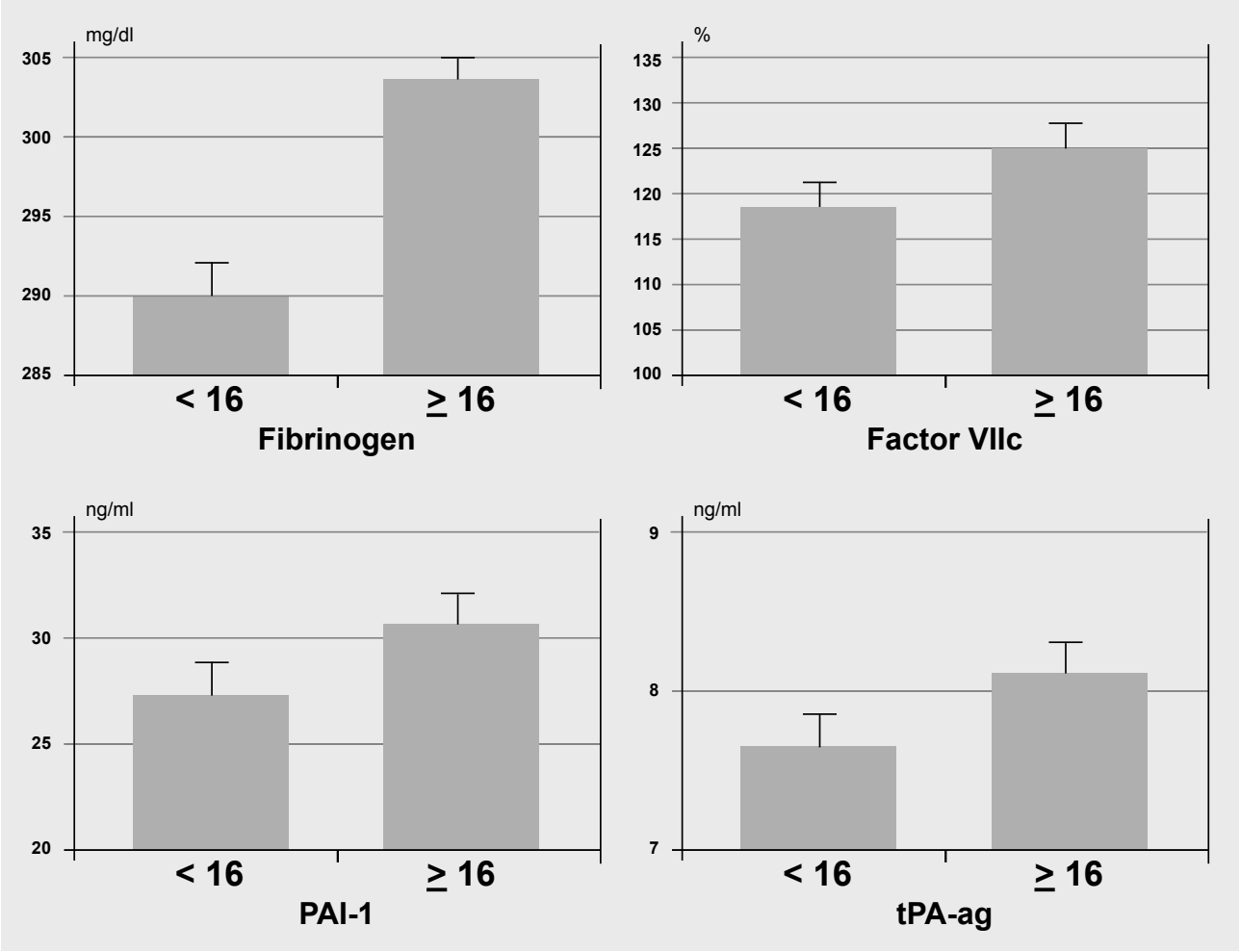

Figure 1. Mean (SEM) hemostatic factors of women according to depressive symptoms (CES-D) ≥ 16 vs. < 16

and the platelet measures were not included. Third, although we measured many potential confounding variables, the association between depressive symptoms and increase in coagulation factors concentration may be influenced by unmeasured variables. Fourth, we measured depressive symptoms rather than diagnosing clinical depression via interview. Thus, we must conclude that depressive symptoms, not the diagnosis of depression, are associated with increased hemostatic variables.

This study is the first report in a community-dwelling sample of mid-life women of an association of hemostatic variables and depressive symptoms. Although depression is common among women, most cases go unrecognized or undertreated.[46,47] If treatment for depression were effective in reducing the coagulation levels[50], then better diagnosis and treatment of depression may decrease cardiovascular morbidity and mortality associated with the hypercoagulatory state.

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Table 2. Fibrinogen, Factor VIIc, PAI-1 and TPA levels according to depressive symptoms and covariates; significance values from multivariate models.

Characteristics	Fibrinogen (mg/dl)	Factor VIIc (%)	PAI-1 (ng/ml)	TPA-ag (ng/ml)
CES-D				
≥ 16	304 (73)**	125 (54)**	31 (32)	8 (3)
<16	290(66)	119 (36)	28 (29)	8 (3)
Age				
≤ 45	291 (67)*	119 (40)**	28 (31)	8 (3)**
45 - 49	294 (69)	120 (36)	28 (28)	8 (3)
≥ 50	301 (71)	129 (60)	30 (31)	8 (3)
Ethnicity				
Black	314 (73)****	117 (36)****	31 (33)**	9 (3)**
Hispanic	290 (69)	129 (43)	36 (31)	9 (3)
Chinese	273 (46)	113 (21)	24 (22)	7 (3)
Japanese	256 (57)	119 (42)	23 (20)	7 (3)
White	292 (66)	123 (46)	27 (30)	7 (3)
BMI (kg/m²)				
< 18.5	252 (56)****	103 (23)****	16 (27)****	6 (3)****
18.5 - 25	266 (53)	112 (35)	18 (16)	6 (3)
≥ 25	312 (71)	126 (44)	35 (34)	9 (3)
Smoking status				
Current	311 (74)***	123 (45)*	32 (34)	8 (3)***
Past	293 (71)	124 (43)	29 (33)	8 (3)
Never	288 (64)	118 (39)	27 (27)	8 (3)
High blood pressure Yes	313 (74)	127 (42)**	38 (38)****	10 (3)****
No	289 (66)	119 (41)	26 (27)	7 (3)
Diabetes Yes	321 (68)**	131 (32)*	40 (45)*	10 (4)****
No	292 (68)	120 (41)	28 (29)	8 (3)
Coronary heart disease Yes	322 (86)*	124 (35)	42 (53)*	9 (4)
No	292 (68)	120 (41)	28 (29)	8 (3)
Osteo-Arthritis Yes	305 (72)	124 (42)	35 (40)**	9 (4)*
No	290 (67)	120 (41)	27 (26)	8 (3)
Anticoagulant medications Yes	318 (57)	121 (41)	39 (30)	9 (4)
No	293 (68)	120 (41)	28 (30)	8 (3)
Psychotropics Yes	307 (74)	129 (41)*	35 (43)**	8 (4)
No	292 (68)	119 (41)	27 (28)	8 (3)
Pain medications Yes	303 (76)	124 (39)	35 (40)**	8 (3)
No	292 (67)	120 (41)	27 (28)	8 (3)

Note: Unadjusted mean and standard deviation.

**p≤0.05, **p<0.01, ***p<0.001, ****p≤0.0001 from final multivariate models using backward step-wise regression.*

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