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Younger, premenopausal women with major depressive disorder have more abdominal fat and increased serum levels of prothrombotic factors: implications for greater cardiovascular risk☆
The POWER Study

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For the POWER (*P*remenopausal, *O*steopenia/Osteoporosis, *W*omen, Alendronat*e*, Dep*r*ession) Study Group

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Abstract

Major depressive disorder (MDD) is one of the most common psychiatric illnesses in the adult population. It is often associated with an increased risk of cardiovascular disease.

We measured body fat distribution as well as plasminogen activator inhibitor-1 (PAI-1) concentration and factor VIII (fVIII) activity at 8:00 AM and 8:00 PM in 45 premenopausal women with MDD vs 28 healthy controls (age, 37 ± 6.8 vs 35 ± 6.5; weight [kg], 75.3 ± 17.2 vs 67.9 ± 10.2; mean ± SD] participating in a prospective study of bone turnover, the POWER Study. At the time of evaluation, women with MDD were mildly depressed and mostly in clinical remission on antidepressants.

After adjusting for body weight, women with MDD had greater waist circumference and abdominal fat as well as significantly higher evening (8:00 PM) PAI-1 and fVIII levels than controls. Even when age-, race-, and body mass index–matched subsets were compared, the MDD group continued to exhibit statistically higher PAI-1 and fVIII levels.

The observed alterations in body fat distribution (increased abdominal fat) and prothrombotic factors (increased PAI-1 and fVIII) may be in part responsible for the increased risk of cardiovascular disease reported in association with major depression.
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1. Introduction

Major depressive disorder (MDD) is one of the most common psychiatric illnesses in the adult population. This condition is associated with an approximately 2-fold increase in nonsuicidal mortality in women [1]. Cardiovascular diseases, followed by neoplasms, are the leading causes of death in this population [1,2]. Both central adiposity [3,4] and increased plasminogen activator inhibitor-1 (PAI-1) concentration [5,6] are associated with increased risk of cardiovascular diseases. PAI-1 is an important pathophysiological link between visceral obesity, insulin resistance, and cardiovascular diseases [7,8].

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Subjects with MDD are prone to increased central fat distribution [9,10]. Although the exact mechanisms are not known, alterations of the hypothalamic-pituitary-adrenal axis secondary to depression, such as increased 24-hour plasma cortisol concentration [11,12], could contribute to central obesity [13,14]. Augmented coagulability due to increased concentration or activity of coagulation factors [15,16] and PAI-1 [17,18] has in fact been reported in other hypercortisolemic states, such as Cushing's syndrome, and in patients treated with glucocorticoids. The potential association between depression and prothrombotic factors has seldom been addressed. In the Cardiovascular Health Study, a large, epidemiological study of subjects 65 years of age and older, a positive correlation was found between depressive symptoms and factor VII and fibrinogen, but not with factor VIII (fVIII) [19].

In this study, we tested whether MDD is associated with changes in the prothrombotic factors, PAI-1 and fVIII, as well as with altered body fat distribution, which may lead to hypercoagulability and subsequent cardiovascular diseases. We also assessed whether these factors correlate with the severity of depression and cortisol concentration.

2. Subjects and methods

2.1. Study design

This study was done as part of the POWER project (*P*remenopause, *O*steopenia/Osteoporosis, *W*omen, Alendronat*e*, Dep*r*ession), a prospective study of bone turnover in premenopausal women, aged 21 to 45 years, with MDD. We report data on 45 women with MDD and 28 controls, who had at least one inpatient visit during which specimens for prothrombotic factors were collected between April 1, 2001, and July 31, 2004. The Scientific Review Board and the Institutional Review Board of the National Institute of Mental Health approved this study. A written informed consent was obtained from all participants.

2.2. Study subjects

Participants were recruited from the Washington, DC, metropolitan area by advertising in newspapers, on radio, and internet, and by flyers posted in the Clinical Center of the National Institutes of Health (NIH-CC).

Menopause, defined as the absence of menstrual periods during the preceding 6 months, was an exclusion criterion. In addition, we excluded those subjects whose last menstrual period occurred 3 to 6 months before the start of the study if their serum estradiol was lower than 20 pg/mL (73 pmol/L), and their serum FSH was above 20 IU/L. We excluded subjects with serious medical conditions, including endocrine disorders such as uncontrolled hypo- or hyperthyroidism, or any condition or treatment that might have influenced bone turnover.

All potential subjects were evaluated by experienced personnel with the structured clinical interview for *DSM-IV* Axis I disorders (SCID). Patients were enrolled if they met *DSM-IV* criteria for MDD and, in addition, had an episode of major depression in the past 3 years. A time limit of 3 years was arbitrarily chosen in an effort to minimize the bias associated with recollection of more remote events. Patients judged by the study psychiatrist (PEM) to be at potential suicidal risk were also excluded. Subjects with a current or past history of eating disorders, bipolar disorders, schizophrenia, or schizoaffective disorder were excluded. In contrast, subjects with a current or past history of anxiety disorders or a past history of alcohol or drug dependence in remission for 5 years were included. At the time of evaluation, the majority of women with MDD were in clinical remission on long-term treatment with antidepressants. Study participants were allowed to continue any current pharmacological or nonpharmacological antidepressant treatments and were followed in the community by a health care professional for the management of their depression during the study. Controls were enrolled if they had no history of any *DSM-IV* diagnoses, with the exception of past alcohol abuse.

From the initial total of 120 candidate patients screened for this study, 31 were excluded: 12 because of other psychiatric diagnoses, 10 because of no depressive episode within the past 3 years, 5 because of incomplete screening, 2 because of use of exclusionary medications, 1 because of vitamin D deficiency, and 1 because of being postmenopausal. From the initial total of 63 controls, 19 were excluded: 11 because of other psychiatric diagnoses, 1 because of use of exclusionary medications, 2 because of vitamin D deficiency, 4 because of other medical conditions, and 1 because of consent withdrawal. Therefore, a total of 89 patients with MDD and 44 controls participated in the POWER Study.

Subjects were evaluated at baseline, month 6, and month 12. Such evaluations were preferably conducted during inpatient visits. If a subject was not available for an inpatient visit, the evaluation was conducted on an outpatient basis, in which case, prothrombotic factors were not measured. Determinations of prothrombotic factors were therefore conducted on a total of 45 women with MDD and 28 healthy controls who had at least one inpatient visit.

2.3. Procedures

Participants in the inpatient visit were admitted to the NIH-CC in the afternoon, and blood specimens were collected for measurement of prothrombotic factors at 8:00 PM. Participants were on an ad libitum diet, and lights were turned off at 11:00 PM. Fasting blood was collected at 8:00 AM, and then blood was collected every hour until 8:00 AM of the following morning for a total of 25 samples, via an intravenous access line. During the

night, blood was collected via a long intravenous catheter to avoid disturbing the subjects' sleep. The total amount of blood drawn during the inpatient visit was approximately 0.3 L. Twenty-four-hour urine was also collected from 8:00 AM until 8:00 AM of the following morning.

2.3.1. Psychiatric assessment

The severity of depression was assessed by the Hamilton Depression Scale (HAM-D, 24 questions) and the severity of anxiety by the Hamilton Anxiety Scale (HAM-A, 14 questions). We also inquired about the age of onset and the number, clinical characteristics, and duration of the depressive episodes.

2.3.2. Anthropometric measurements

Body weight was measured to the nearest 0.1 kg using a platform digital scale; height was measured 3 times to the nearest 0.1 cm using a stadiometer, and the mean of the 3 measurements was calculated. Anthropometric measurements were obtained using standardized techniques [20]. Waist circumference (WC) was measured with a nonstretch tape to the nearest 0.1 cm at the level of the uppermost lateral border of the right iliac crest, which usually is at the level of the umbilicus. The mean of 3 measurements was used for analysis.

2.3.3. Body composition

Dual-energy x-ray absorptiometry (DXA) measurements of body composition were performed by Hologic DXA QDR 4500 (Bedford, Mass). One radiologist (JR) reviewed the DXA films and reported percent fat in the whole body as well as in the abdominal area defined as T12/L1 interface to the L4/L5 interface; such measurement included both visceral and subcutaneous abdominal fat.

2.3.4. Cooper test (12-minute walk/run test)

We used the Cooper test, a widely used test that measures the distance a subject is able to cover during 12 minutes by running or walking as fast as possible, as an indirect index of the level of physical fitness [21]. The Cooper test was done on the morning of the third admission day.

2.3.5. Blood tests

All tests were performed at the NIH-CC Department of Laboratory Medicine and had intra-/interassay coefficients of variation of up to 15%. Specimens were assayed blindly to the diagnosis of the study subject. As a diurnal variation for PAI-1 [22] and fVIII [23] has been reported, we measured it at the time of the day of the expected largest diurnal variation, 8:00 AM and 8:00 PM. PAI-1 antigen was measured by enzyme-linked immunosorbent assay, and fVIII activity was assayed using the STA Hemostasis System by Diagnostica Stago (Parsippany, NJ). Plasma adrenocorticotropic hormone (ACTH) and urinary free cortisol (UFC) concentrations were measured with chemiluminescent immunoassay using the Nichols Advantage analyzer (San Juan Capistrano, Calif). Serum cortisol was measured by chemiluminescent immunoassay using the DPC Immulite-2000 analyzer (Los Angeles, Calif).

2.4. Statistical analyses

Data resided in a central, password-protected, electronic database. All data are reported as mean ± SD. Because PAI-1 (Fig. 1) exhibited a non-Gaussian (exponential) distribution, we used its natural logarithmic transformation values for statistical analysis. We used the unpaired *t* test and Fisher exact test to assess differences between controls and subjects with MDD, and the paired *t* test to assess differences between matched pairs of subjects. Analysis of covariance was used to assess the effect of depression on body fat distribution and prothrombotic factors, adjusting for weight as a covariate. We used Pearson correlation to assess the association of the clinical parameters of depression and anxiety and cortisol with body fat distribution, PAI-1, and fVIII in the MDD group. For all

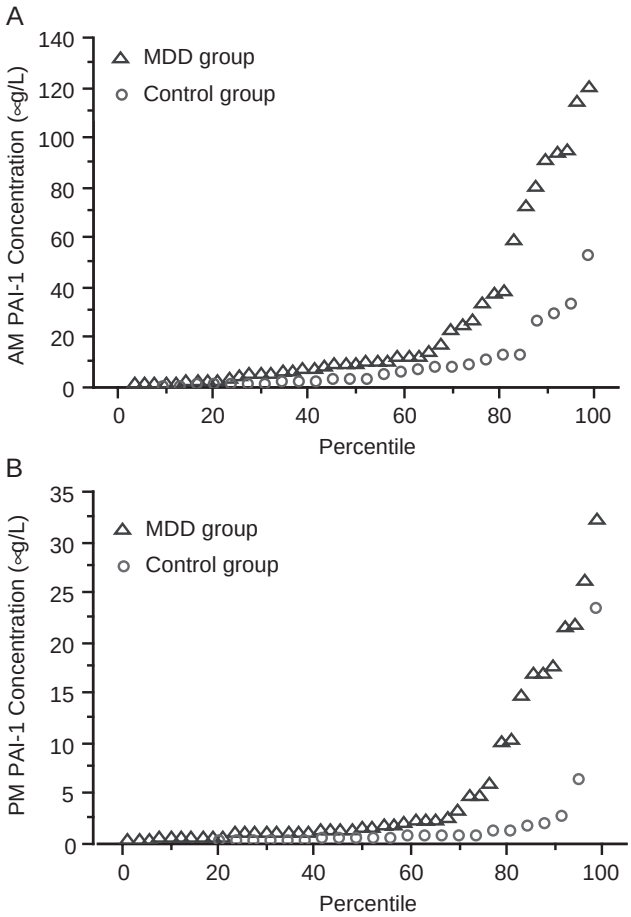

Fig. 1. Plasminogen activator-1 (PAI-1) concentrations exhibit an exponential distribution both in subjects with MDD and controls. Panel A, 8:00 AM PAI-1 concentration. Panel B, 8:00 PM PAI-1 concentration.

Table 1
Demographic characteristics and clinical features of the study subjects

Characteristics	Control group (n = 28)*	MDD Group (n = 45)*	95% CI of the difference	P
Age (y)	35 ± 6.5	37 ± 6.8	−0.9, 5.5	.15
Race (white)	96% (27/28)	97% (43/45)	N/A	1.0
Weight (kg)	67.9 ± 10.2	75.3 ± 17.2	0.15, 14.5	.05
BMI (kg/cm^2)	24.1± 3.4	27.5 ± 6.3	0.8, 5.9	.004
Smoking (pack year)	2.2 ± 5.4	2.8 ± 5.6	−2.1, 3.3	.65
Use of oral contraceptive	32% (9/28)	24% (11/45)	N/A	.6
Physical fitness (Cooper test)	1411 ± 272 (n = 21)	1312 ± 346 (n = 32)	−279, 80	.3
Current depression	0	20% (9/45)	N/A	N/A
GAF	80 ± 5.0	61 ± 9.2	N/A	N/A
HAM-D score	1.5 ± 2.1	9 ± 7.6	N/A	N/A
HAM-A score	1 ± 1.6	6 ± 5.0	N/A	N/A
Age of onset of depression	N/A	19 ± 9.2 (n = 34)	N/A	N/A
Number of depressive episodes	N/A	4 ± 3 (n = 34)	N/A	N/A
Cumulative duration of depression (mo)	N/A	67 ± 73 (n = 34)	N/A	N/A
Antidepressant medications	0	91% (41/45)	N/A	N/A
Anxiolytic medications	0	11% (5/45)	N/A	N/A

Data reported as mean ± SD. *P* values based on unpaired *t* test and Fisher exact test. N/A indicates not applicable.

* Sample sizes unless otherwise stated.

of these analyses we used the SAS program (SAS Institute, Cary, NC) with 2-sided level of significance set at .05. In addition, we performed cosinor analysis, using the Chronolab 3.0.3 program (available from Universidad de Vigo, Spain, Bioengineering and Chronobiology Laboratory, http://www.tsc.uvigo.es/BIO/) to assess 24-hour plasma ACTH and serum cortisol rhythmicity.

3. Results

3.1. MDD vs control group

3.1.1. Demographic characteristics and clinical features of depression

The clinical characteristics of women with MDD and controls are shown in Table 1. There were no significant differences in age, racial distribution, smoking, use of oral contraceptives, and level of physical fitness between the MDD group and healthy controls.

Nine of 45 (20%) women with MDD met the criteria for current major depression (defined as depression over the preceding 4 weeks) at baseline. On average, patients with MDD were mildly depressed (8.9 ± 7.6, HAM-D score) and mildly anxious (6.0 ± 5.0, HAM-A score). Ninety-one percent of patients with MDD (41/45) were taking at least one antidepressant medication.

3.1.2. Body composition and anthropometric measurements

Patients with MDD on average had significantly higher weight and body mass index (BMI) than controls (Table 1). After adjusting for weight, subjects with MDD still had significantly greater WC and percent abdominal fat (Table 2). There was no significant interaction between weight and study group for either of these parameters, indicating that the relationship between weight and WC or percent abdominal fat was independent of the study group (MDD vs controls). Whole-body percent fat was similar in the 2 groups.

3.1.3. Prothrombotic parameters

PAI-1 concentration and fVIII activity were significantly higher at 8:00 AM than at 8:00 PM in both the MDD and control groups, confirming the existence of circadian rhythmicity (Table 2). Both PAI-1 and fVIII were significantly higher at 8:00 PM in women with MDD than in controls, even after adjusting for weight as a covariate. There was no significant interaction between weight and group for either of these parameters.

Table 2
Body fat distribution, prothrombotic factors, and adrenocortical parameters

		Control group (n = 28)	MDD Group (n = 45)	95% CI of the difference	P
WC (cm)		86.1 ± 7.5	94.6 ± 14.2	0.4, 6.5[a]	.03*
Whole-body fat (fraction)		31.4 ± 5.1	35.5 ± 7.4	−0.5, 4.1[a]	.1*
Abdominal (L1-L4) fat (fraction)		23.2 ± 7.4	29.8 ± 9.9	0.39, 6.07[a]	.03*
8:00 AM PAI-1 (μg/L)		9.5 ± 12.4	24.3 ± 33.4	−0.21, 1.04[a]	.2*
8:00 PM PAI-1 (μg/L)		1.9 ± 4.4	5.3 ± 7.9	0.12, 1.14[a]	.02*
8:00 AM fVIII (fraction)		1.23 ± 0.38	1.46 ± 0.45	−0.03, 0.38[a]	.09*
8:00 PM fVIII (fraction)		1.09 ± 0.33	1.40 ± 0.50	0.04, 0.47[a]	.02*
UFC	μg/day	66 ± 18	63 ± 27	−15, 8.5	.6
	(nmol/d)	(182 ± 50)	(174 ± 75)	(−41, 23)	
8:00 AM serum cortisol	μg/dL	20.2 ± 8.2	20.7 ± 5.7	−2.8, 3.8	.8
	(nmol/L)	(558 ± 226)	(571 ± 157)	(−77, 105)	

Data reported as mean ± SD. *P* values based on *t* test.

[a] Confidence interval of the difference adjusted for weight.

* *P* values based on analysis of covariance after accounting for weight as a covariate.

Table 3
Correlation analyses of prothrombotic factors with body fat distribution and UFC in women with MDD

	8:00 AM PAI-1		8:00 PM PAI-1		8:00 AM fVIII		8:00 PM fVIII	
	r	*P*	r	*P*	r	*P*	r	*P*
WC	0.54	<.001	0.67	<.001	0.29	.01	0.30	.01
Whole-body % fat	0.32	.03	0.63	<.001	0.18	.2	0.17	.3
Abdominal % fat	0.36	.02	0.71	<.001	0.30	.04	0.3	.08
UFC (per day)	0.15	.3	0.18	.3	0.35	.02	0.32	.03

r and *P* values based on Pearson correlation analysis.

3.2. MDD group

To assess the potential impact of clinical and hormonal factors on the prothrombotic variables, we performed the following analyses.

3.2.1. Relationship of the severity of depression/anxiety with body fat distribution and prothrombotic factors

We found no association between the duration and severity of depression and anxiety (indicated by the scores on HAM-D, global assessment of functioning (GAF) or HAM-A, the age of onset of depression, the number of depressive episodes, and the cumulative months of depression), and levels of prothrombotic factors or body fat distribution. Furthermore, the women (N = 8) with more severe clinical depression, defined by using the clinically accepted cutoff of 18 on the HAM-D, had similar prothrombotic factors and body fat distribution to the women with less severe depression (N = 37).

3.2.2. Correlation of body fat distribution with prothrombotic factors

Waist circumference correlated positively with both morning and evening PAI-1 and fVIII levels. Whole-body percent fat correlated positively with both morning and evening PAI-1, but not with fVIII. Abdominal percent fat correlated positively with both morning and evening PAI-1 and AM fVIII, but not with evening fVIII (Table 3).

3.2.3. Correlation of pituitary-adrenocortical axis parameters with body fat distribution and prothrombotic factors

There were no significant differences in circadian rhythmicity, peak, nadir, and average of 24-hour plasma ACTH and serum cortisol concentration between subjects with MDD and controls (data not shown). Urinary free cortisol and morning (8:00 AM) serum cortisol concentrations were also within the reference ranges and similar between the 2 groups as well (Table 2).

The correlations of UFC with prothrombotic factors are shown in Table 3. Urinary free cortisol concentration correlated positively with fVIII.

3.3. Subset of matched pairs

To control for demographic differences, a subset of women with MDD (N = 17) were matched individually with controls for race, age (±3 years), and BMI (±2.0 kg/m^2). The demographic characteristics were as follows: MDD: age, 36 ± 6.9; BMI, 24.2 ± 4.1; controls: age, 37 ± 6.6; BMI, 23.9 ± 3.5. All matched subjects were white, and there was no difference in smoking history, use of oral contraceptives, and physical fitness between the 2 groups.

As shown in Table 4, both the morning and evening values of PAI-1 and fVIII were significantly higher in the MDD than in the control subset, although there was no significant difference in WC, total, and abdominal fat between the 2 subsets. As with the total groups, prothrombotic factors exhibited diurnal variation with higher concentrations in the morning (PAI-1: $P < .001$; fVIII: $P = .05$).

3.4. Subset of subjects with MDD with lower- and higher evening PAI-1 concentration

To identify the factors contributing to elevated evening PAI-1 levels, we compared the subjects with MDD with the higher evening PAI-1 concentration (10-32.2 μg/L, N = 10) with the subjects with MDD with the lower concentration (0.2-0.6 μg/L, N = 10) by grossly skimming the data (Fig. 1).

Subjects with higher PAI-1 concentration were older (41 ± 5 vs 32 ± 7 years; $P = .004$; confidence interval [CI]

Table 4
Body fat distribution, prothrombotic factors, and cortisol concentrations in the age-, race-, and BMI-matched subsets

		Control group (n = 17)	MDD Group (n = 17)	95% CI of the difference	*P*
WC (cm)		85.0 ± 7.9	88.3 ± 10.9	−0.5, 7.1	.08
Whole-body % fat		30.5 ± 5.2	31.9 ± 7.7	−1.8, 4.7	.4
Abdominal (L1-L4) % fat		21.1 ± 7.1	24.4 ± 9.6	−0.7, 7.2	.1
8:00 AM PAI-1 (μg/L)		6.5 ± 8.6	15.1 ± 21.4	0.20, 1.77	.02
8:00 PM PAI-1 (μg/L)		0.9 ± 0.7	2.9 ± 7.6	0.02, 1.09	.04
8:00 AM fVIII (fraction)		1.22 ± 0.39	1.51 ± 0.35	0.07, 0.51	.01
8:00 PM fVIII (fraction)		1.07 ± 0.36	1.40 ± 0.35	0.09, 0.55	.009
UFC	μg/day	62 ± 15	65 ± 23	−14, 20	.7
	(nmol/day)	(171 ± 41)	(176 ± 63)	(−39, 55)	
8:00 AM serum cortisol	μg/dL	20.3 ± 9.8	22.1 ± 7.6	−2.6, 8.0	.5
	(nmol/L)	(560 ± 270)	(610 ± 210)	(−72, 221)	

Data reported as mean ± SD. *P* values based on paired *t* test.

3-14), had higher weight (94.2 ± 12.3 vs 59.6 ± 9.7 kg; $P < .001$; CI 24.2-45.0), BMI (35.3 ± 3.9 vs 21.9 ± 3.3 kg/cm^2; $P < .001$; CI 10.0-16.8), and more total body fat (42.2% ± 3.9% vs 29.0% ± 8.3%; $P < .001$; CI 7.1-19.2), and were less fit (Cooper test: 1116 ± 108 vs 1609 ± 441 m; $P = .02$; CI −898 to −88). The age of onset, severity and duration of depression, severity of anxiety, use of antidepressants, and UFC were not different between these 2 groups.

4. Discussion

In this study, young women with clinically treated MDD had higher PAI-1 concentration and fVIII activity and more abdominal fat than healthy controls. Increased central body fat in association with symptoms of depression and anxiety has already been reported in large epidemiological studies of men and women [9,10]. The increase in prothrombotic factors in young women with MDD, reported here for the first time, may be of clinical importance. These differences persisted after correction for body weight and were even more evident in the subset of subjects individually matched for age and BMI, suggesting that the association between depression and these factors was specific.

PAI-1 concentrations reported here were similar to those reported in the subjects who later developed diabetes mellitus in a large prospective study [24]. Similarly, increased risk of diabetes mellitus has been reported in subjects with increased fVIII activity [25]. This sample of women with MDD was mostly in clinical remission on long-term treatment with antidepressants and was only mildly affected at time of evaluation, although some subjects carried a substantial past history of depression. It should be noted, however, that subjects with higher depression scores did not have higher PAI-1 levels. We found no association between severity of depression and fVIII activity, which was consistent with findings from the Cardiovascular Health Study [19]. Whether more pronounced changes in clinical severity of depression would have affected prothrombotic factors remains to be determined.

Consistent with the literature, women with MDD and higher PAI-1 concentration were older [26], had higher weight [27], body percent fat [28], and insulin resistance [28], and were physically less fit compared with women with lower PAI-1 concentration. Prothrombotic factors, albeit higher in women with MDD, exhibited the same diurnal variability reported in the literature, with higher levels in the morning compared to the evening [22,23].

The increases in prothrombotic factors and abdominal fat observed in women with MDD did not seem to be related to the use of antidepressants or to lifestyle factors. To our knowledge, no direct effects of antidepressants on prothrombotic factors have been reported in the literature. Similarly, amount of smoking and levels of physical fitness were similar between women with MDD and controls. There was, however, a trend toward higher use of oral contraceptives in the lower PAI-1 group, which is in accord with the literature [29].

In this sample, women with MDD had normal ACTH and cortisol levels around the clock probably because they were clinically treated for depression. Changes in hypothalamic-pituitary-adrenal axis activity in MDD are mainly reported in currently depressed subjects, and successful antidepressant treatment usually normalizes hormonal levels [30]. These findings suggest that changes in prothrombotic factors in women with MDD take place even in the absence of frank hypercortisolism. Even within the normal levels of cortisol observed in these subjects, there was, however, a correlation between UFC and fVIII activity consistent with the changes reported in fVIII in patients with Cushing's syndrome [16]. Future studies should investigate which biological factors may be responsible for the increase in prothrombotic factors in this population.

This study had several strengths: we established the diagnosis of MDD by an optimal method, a semistructured clinical interview [31], and, to decrease the chances of recall bias, we enrolled exclusively subjects with recent history of major depression. In addition, we assessed many of the factors known to affect body fat distribution and prothrombotic factors, including smoking, use of oral contraceptives, and level of fitness. Finally, our sample of premenopausal women was homogeneous and relatively free of comorbid factors, which are potential confounders. The following limitations should, however, be noted: our sample was mainly constituted by mildly depressed, clinically treated subjects, and the sample size was relatively small.

In conclusion, young women with clinically treated MDD had significantly higher PAI-1 and fVIII levels than controls, independent of their body weight. These changes were independent of the severity of depression, which indicates that they were more closely related to a potential trait associated with MDD than with the status of depression. The finding of increased levels of prothrombotic factors may explain some of the mechanisms leading to increased risk of cardiovascular disease in women with depression. The clinical significance of our observations remains to be further validated in large prospective studies.

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