Title

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Authors

Camacho, Álvaro
Larsen, Britta
McClelland, Robyn L
et al.

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Association of Subsyndromal and Depressive Symptoms with Inflammatory Markers among different Ethnic groups: The Multi-Ethnic Study of Atherosclerosis (MESA)

Álvaro Camacho, MD, MPH[1], **Britta Larsen, PhD**[1], **Robyn L. McClelland, PhD**[2], **Cindy Morgan, MSc**[1], **Michael Criqui, MD, MPH**[1], **Mary Cushman, MD, MSc**[3], and **Matthew A. Allison, MD, MPH**[1]

[1]Department of Family, Preventive Medicine. University of California, San Diego

[2]Department of Biostatistics. University of Washington. Seattle, WA

[3]Department of Medicine. University of Vermont. Burlington, VT

Abstract

Objective—Depressive symptoms are associated with inflammation yet the association between inflammation and different levels of depression remains unclear. Therefore, we studied the association of subsyndromal and depressive symptoms with inflammatory markers in a large multi-ethnic cohort.

Methods—C-reactive protein (CRP) (n=6,269), interleukin-6 (IL-6) (n=6,135) and tumor necrosis factor-alpha (TNF-α) (n=1,830) were measured in selected participants from the Multi-Ethnic Study of Atherosclerosis (MESA). Subsyndromal depressive symptoms were defined as a CES-D value from 8 to 15, depressive symptoms as a CES-D≥16 and normal as a CES-D≤7. Depressive states (subsyndromal and depressed) were entered into multivariable linear regression models incrementally adjusting for demographic, behavioral, biologic and comorbidities.

Results—Among 6,289 participants not taking antidepressants and free from CVD, the mean age was 62.2, while 52% were women, 36.4% were Caucasian, 28.9% African-American, 22.3% Hispanics and 12.4% Chinese-American. Of the total, 24.2% had subsyndromal depression and 11.8% had depressive symptoms. Compared to the non-depressed group and after controlling for demographics, there was no association between both subsyndromal and depressive symptoms with logCRP(β=−0.01, *p=0.80* and β=−0.05, *p=0.25;* respectively), logIL-6(β=0.01, *p=0.71* and β=−0.04, *p=0.07;* respectively) and logTNF-α(β=−0.03, *p=0.29* and β=0.06, *p=0.18;*

Correspondence Information: Author: Álvaro Camacho, MD, MPH, Address: 2417 Marshall Ave. Ste 1. Imperial CA. 92251, acamacho@ucsd.edu.

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Conflict of Interest:
None

respectively). Moreover, fully adjusted models showed no significant associations for logIL-6 and logTNF-α and the different depressive categories. However, with full adjustment, we found a significant inverse association between depressive symptoms and lnCRP(β=−0.10; *p=0.01*) that was not present for subsyndromal depression (β=−0.05; *p=0.11*).

Conclusion—Among participants not taking anti-depressants, subsyndromal depression is not associated with inflammation. However, depressive symptoms measured by CES-D≥16 are associated with a lower inflammation (CRP).

Keywords

subsyndromal depression; inflammation; cardiovascular disease; depressive states

INTRODUCTION

For more than 5 decades, research has identified that inflammation and negative emotional states are recognized risk factors for the development of cardiovascular disease (CVD) (Amyre Morris A et al. 2011, Libby P and Ridker PM 1999, Dinan TG 2009, Musselman D et al. 1998). Notably, depression is associated with inflammation among patients without CVD and studies have postulated that depression could be an inflammatory condition (Whooley MA et al. 2007, Dinan TG 2009, Tiemeier H et al. 2003, Kop WJ et al. 2002, Maes M et al. 2009, Camacho A 2013). For instance, in the Third National Health and Nutrition Examination Survey (NHANES), men with a history of major depression had a 2.77 higher adjusted odds (95%CI; 1.43–5.26) of elevated C-reactive protein compared to controls (Danner et al. 2003a).

Subsyndromal depression is a condition where depressive symptoms are present, yet the full criteria for a major depressive episode have not been met. Subsyndromal depression affects 15 to 20% of patients older than 65 years, is under treated and frequently associated with functional disability and chronic medical conditions comparable to major depressive disorder (Judd LL et al. 2002, Vahia IV et al. 2010, VanItallie 2005, Bruce ML 2010). Subsyndromal depressive symptoms are measured categorically by lowering the established cut-off point from validated scales that screen for depression, such as the Center for Epidemiologic Scale for Depression (CES-D)(Vahia IV et al. 2010). For example, subsyndromal depressive states have scores between 8 and 16 in the CES-D scale (Vahia IV et al. 2010). Other studies report that subsyndromal depression could also be defined by the presence of only one or two symptoms of depression (Vahia IV et al. 2010, Judd LL et al. 2002). Furthermore, the core symptoms required to diagnose a major depressive episode, which are depressed mood and anhedonia, are not required to define subsyndromal depression (Vahia IV et al. 2010, American Psychiatric Association 2000).

To understand the association of different depressive states with chronic medical conditions such as cardiovascular disease, studies have examined the role of inflammation as a possible common pathway (Ranjit N et al. 2007, Ross R 1999). Proinflamatory cytokines and acute phase proteins, such as CRP, interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), are higher among individuals with depressive states and cardiovascular disease (Liukkonen et al. 2006, Amyre Morris A et al. 2011, Matthews et al. 2007), although results are

inconsistent. Even though the literature has frequently reported an association between depression and inflammation (Dinan TG 2009, Amyre Morris A et al. 2011, Miller AH et al. 2009), several studies found no associations between depression and inflammation (Whooley MA et al. 2007, Janszky I et al. 2005, Schins A et al. 2005). Different methodological approaches for defining depression (depressive symptoms/states vs. major depressive disorder) might account for the different results (Steptoe A et al. 2003, Amyre Morris A et al. 2011, Matthews et al. 2007, Whooley MA et al. 2007).

In the current study, we tested the hypothesis that compared to individuals with no depressive symptoms, depressive states (subsyndromal and depressive symptoms) are associated with selected inflammatory markers among individuals from different ethnic groups participating in a large epidemiologic study. To our knowledge, this is the first study that looks at the association of subsyndromal depression with inflammatory markers in a large ethnically diverse cohort.

METHODS AND MATERIALS

Study Population

This study utilized data from the Multi-Ethnic Study of Atherosclerosis (MESA). Briefly, MESA is a multi-site cohort study with the objective of identifying risk factors for the presence and progression of subclinical atherosclerosis. The cohort includes men and women ages 45–84 years recruited from 6 field centers between 2000 and 2002. All participants were free from known CVD, chronic infections or psychiatric disorders at baseline (Ranjit N et al. 2007, Bild et al. 2002). Details of the study design are published elsewhere (Bild et al. 2002) and are also available at www.mesa-nhlbi.org.

To avoid the potential for misclassification of depressive symptoms, and since we classified individuals solely based on their CES-D results, we excluded individuals who reported taking anti-depressants (n=497). This resulted in a total sample size of 6,269 participants in which CRP was measured, 6,135 participants in which IL-6 was measured and 1,830 participants in which TNF-α was measured.

Data Collection

Standardized questionnaires and laboratory testing were used to collect sociodemographic, ethnicity and health information. All information was collected during the same visit. Biologic variables included systolic blood pressure, body mass index (kg/m^2), total cholesterol, HDL cholesterol, triglycerides and glucose. Behavioral variables included smoking status (never, former, current); alcohol use (never, former, current); and physical activity defined as total number of minutes walked per week for exercise, to get places or leisure. Additional covariates included presence of diabetes, lipid-lowering medication use and antihypertensive medication use. Diabetes was defined by the 2003 American Diabetes Association's criteria of fasting plasma glucose >126 mg/dl or taking medication for diabetes (Roy B et al. 2010, 'Position statement: diagnosis and classification of diabetes mellitus.' 2008). Baseline medication use was collected through questionnaires, medical

history and a validated medication inventory (Roy B et al. 2010, Delaney JA et al. 2009, Psaty BM et al. 1992)

Measure of Depressive Symptoms

Depressive symptoms/states were assessed using the CES-D and categorized as normal (CES-D ≤ 7), subsyndromal (CES-D: 8–15) and depressive symptoms (CES-D ≥16). This scale assesses depressive symptoms over the past week. Respondents are asked to indicate on a scale from 0 (rarely or none of the time) to 3 (all of the time) how often they experience symptoms related to depression (e.g., I felt everything I did was an effort). The scale has been validated for population studies, showing a Cronbach's alpha of 0.85(Radloff LS 1977). The different depressive categories selected for this study were based on published studies emphasizing the importance of identifying patients with subsyndromal symptoms of depression (Ranjit N et al. 2007, Lekander M et al. 2004, Hamer M 2012, VanItallie 2005, Greden JF 2001, Wassertheil-Smoller S et al. 2004).

Laboratory & Inflammatory Markers

Laboratory assays were measured using venous blood obtained after a 12-hour fast. CRP was measured using the BNII nephelometer (N High Sensitivity CRP; Dade Behring Inc., Deerfield, IL). IL-6 was measured by ultra-sensitive ELISA (Quantikine HS Human IL-6 Immunoassay; R&D Systems, Minneapolis, MN). TNF-α was measured using Bio-Rad Luminex flow cytometry (Millpore, Billerica, MA). Average analytical coefficients of variation across several control samples for these analytes ranged from 2.0–13.0%.

Statistical Analyses

Continuous variables were described by means/standard deviations (SD) and categorical variables as frequencies/percentages. Log-transformation of the biomarkers was performed to reduce skewness. A series of multivariable linear models were used to analyze the association of depressive symptoms (subsyndromal and syndromal) with each biomarker (CRP, IL-6, TNF-α) and different covariates. Model 1 was unadjusted while model 2 controlled for age, gender and ethnicity. Model 3 additionally controlled for behaviors; smoking status (never, former current), alcohol use (never, former, current) and physical activity. Model 4 additionally controlled for body mass index (BMI), systolic blood pressure, lipids, glucose, and presence of diabetes (yes/no) as well as use of antihypertensive and lipid lowering medication use. Stratified analyses were performed to assess the association of different ethnic groups with inflammatory markers by depressive symptoms/states adjusting for age, gender and BMI. For the stratified analyses we only adjusted for gender and BMI since these variables have been described to have a strong relationship with the progression of depressive symptoms (Sullivan MD et al. 2013).

RESULTS

Among the 6,289 subjects not taking antidepressants, 4,021 (64%) had a normal CES-D score, 1,519 (24.2%) were classified as subsyndromal and 744 (11.8%) had depressive symptoms. Table 1 summarizes the characteristics of the participants within the different categories of depressive symptoms. The mean age was 61.9 (10.4) among subsyndromal

depressed participants, 61.3 (10.8) among depressed and 62.6 (10.1) among normals. Women comprised 47% of non-depressed, 55.2% of the subsyndromal group and 68.3% of the depressed group. Among participants classified with subsyndromal depression 34.3% were Caucasian, 29.6% African-American, 24.1% Hispanics and 12% Chinese. Depressed participants were 27% Caucasian, 27.3% African-American, 37.1% Hispanics and 8.6% Chinese. Among non-depressed, 38.9% were Caucasian, 28.6% African-American, 19% Hispanics and 13.4% Chinese.

Table 2 describes the different CES-D mean scores by gender and ethnic group. In summary, mean CES-D scores were higher in the depressed category for Hispanic (24; SD=7.7) and African-American females (23.3; SD=6.9). In the subsyndromal category, Hispanic females also had a higher mean CES-D score (11; SD=2.2) compared to the other ethnic groups. Pair wise comparisons showed that all of the CES-D scores were significantly different from Caucasians (*p<0.001).*

In table 3, compared to non-depressed, unadjusted analyses showed a non-significant association between subsyndromal depression and logCRP (β=0.05; *p=0.14)*, while depressive symptoms were significantly associated with logCRP (β=0.12; *p*=0.009). After adjusting for demographics, these associations were attenuated to the null. However, with full adjustment, there was a significant inverse association of depressive symptoms with logCRP (β=−0.10; *p=0.02)* and a marginal association for subsyndromal depression (β= −0.05; *p=0.11).* There was no significant interaction between ethnicity and depression group for logCRP after controlling for age, gender and BMI (*p_interaction 0.60).*

For logIL-6, unadjusted analyses showed a significant association with depressive symptoms (β=0.09; *p=0.001*) but not for subsyndromal depression (β=0.02; *p=0.35*). There was no significant association of the different depression categories in the fully adjusted model. After controlling for age, gender and BMI, there was a borderline significant interaction between ethnicity and depression group for logIL-6 (*p_interaction=0.06).* More specifically, and compared to Caucasians, stratified analyses showed a significant association of logIL-6 with Hispanics (β=0.15; *p<0.05)* and African-Americans (β=0.06; *p<0.05)* but not Chinese Americans (β= −0.03; *p*=0.32).

In unadjusted and fully adjusted models there were no associations between subsyndromal and depressive symptoms with logTNF-α. After adjusting for age, gender and BMI, there was no significant interaction between ethnicity and depression group (*p_interaction=0.23)*.

DISCUSSION

In this cross-sectional analysis, we found that after adjustment for demographic, behavior, biologic and comorbid covariates there was a significant inverse association of depressive symptoms (CES-D≥16) with logCRP but the association with subsyndromal symptoms was non-significant. Conversely, there was no association of subsyndromal and depressive symptoms with logTNF-α or logIL-6 in the unadjusted and fully adjusted models. However, there was a significant interaction between ethnicity and depression group for IL-6 such that

the association was significantly stronger in Hispanics ($p<0.05$) and African-Americans ($p<0.05$).

Our study confirms the findings of Whooley et al., whom also found an inverse association between depressive symptoms and inflammation as measured by CRP and IL-6, although in Whooley study the participants had a history of coronary heart disease (Whooley MA et al. 2007). Our sample represents participants without a history of CVD, raising the hypothesis that levels of depressive symptoms alone could have an important role in the complex inflammatory process that needs to be further studied. Studies have reported that states of depression are associated with high levels of cortisol and cortisol/dehydroepiandrosterone ratio (Whooley MA et al. 2007, Otte C et al. 2004, Fagundes et al. 2012). High levels of cortisol and dehydroepiandrosterone have been found to decrease levels of some inflammatory cytokines such as TNF-α and IL-6 in animal models (Kipper-Galperin M et al. 1999). This could be a possible explanation of the inverse association between depressive symptoms and inflammation; although how this association applies to high depressive symptoms and low levels of CRP is still unclear.

Contrary to our hypothesis, subsyndromal symptoms of depression were not associated with inflammation. Even though subsyndromal symptoms of depression have been associated with considerable social impairment in adults and adolescents (González-Tejera G et al. 2005, Judd LL et al. 2002), our data shows that subsyndromal depressive symptoms are not be associated with the measured inflammatory markers. Another factor is that participants could have had a previous episode of major depression that could account for the current inverse association with inflammation, illustrating a case of selective survival. Furthermore, in order to avoid misclassification, we excluded participants taking antidepressants who have been shown to have some potential anti-inflammatory effect (Häuser W et al. 2013).

Different methodological approaches could explain the inconsistent associations among prior studies of depression with inflammation (Capuron L et al. 2008). For example, studies reporting a non-significant association used structured interviews to diagnose major depression and use this as predictor of inflammation (Danese A et al. 2008, Whooley MA et al. 2007). Conversely, studies showing a significant association of depression with inflammation measured depressive symptoms using a screening scale (Gegenava T et al. 2011, Fagundes et al. 2012). Structured interviews are considered the gold standard for psychiatric diagnosis. For depression, structured interviews take into account that the individual has at least 5 of nine symptoms, being depressed and anhedonia the cardinal ones and that the symptoms have been present daily for at least 2 weeks and cause considerable impairment in functioning (American Psychiatric Association 2000). The interview also inquires about present and past episodes of major depression.

Depression scales focus mainly on symptoms endorsed over the last week, are screening tools and do not provide diagnosis or measure level of impairment (Spitzer RL et al. 1992). Other methodological approaches used in studies that reported a significant association of inflammation with depression tested changes of depressive symptoms over time and studied participants older than 65 years of age (Vaccarino V et al. 2008, Liukkonen et al. 2006, Penninx BW et al. 2003, Danner et al. 2003b). In the MESA, the CES-D scale was used to

measure depressive symptoms over the last week without inquiring for functional impairment and without an attempt to make a diagnosis of depression. In our study, we chose to lower the screening cut-point on the CES-D scale due to the clinical significance of subsyndromal depression. Further longitudinal studies are needed to discern the association of clinically relevant levels of affective states with inflammatory markers.

The association of depressive states with inflammation may also be explained not only by the severity of symptoms but also by type of symptoms (somatic vs. cognitive-emotional) measured by the different scales. In this regard, the majority of scales used to measure depressive symptoms cluster in two main factors: cognitive/emotional vs. somatic. Similarly, previous studies have shown that the association between depressive states and inflammation vary according to the type of depressive symptoms endorsed. That is, somatic or neurovegetative symptoms of depression (fatigue, sleep disturbances, poor appetite, weight loss) are associated with inflammation while emotional/cognitive symptoms (depressed mood, worthlessness, anhedonia, poor concentration) are not (Cho et al. 2009, Capuron L et al. 2008). This could potentially explain the inverse association found with depressive symptoms as well as the lack of association with subsyndromal depression. Different from emotional symptoms, most inflammatory states present clinically with somatic symptoms of depression (Maes M et al. 2009). The importance of differentiating the association of somatic vs. emotional symptoms of depression with inflammation has been previously addressed in other studies (Matthews et al. 2007, Cho et al. 2009).

Strengths of our study include a large sample size and adjustment for multiple confounders. Limitations include a cross-sectional study design and that we studied only a few markers of inflammation. For example, we did not have the possibility to measure newer markers such as IL-1β which have recently shown a stronger association with depressive states (Zhang K et al. 2012). Another limitation is the one time measurement of inflammatory markers. Even though we adjusted for a comprehensive number of biologic and behavioral covariates, residual confounding should be considered in the inverse association observed between depressive symptoms and CRP. For example adjusting for smoking as a categorical variable only could result in residual confounding due to the strong association of smoking with depressive symptoms (Patton et al. 1998). Another factor is that symptoms of depression were only measured during the last week and level of impairment was not addressed.

In conclusion, our cross-sectional study suggests that among participants not taking anti-depressants, depressive symptoms measured by CES-D≥16 are associated with less inflammation as measured by CRP, but not other markers such as IL-6 and TNF-α. The association of subsyndromal depression with the different types of depressive symptoms (cognitive vs. somatic) remains to be further tested, especially among different ethnic groups. Additionally, future studies are needed to examine the association of depression and anxiety symptoms with inflammation among different ethnic groups, especially Hispanics. This ethnic group is the fastest growing minority group with the highest prevalence of chronic inflammatory conditions such as diabetes and metabolic syndrome and high levels of anxiety and depression compared to other ethnic groups (Yaffe K et al. 2007, Familiar et al. 2011, Breslau J et al. 2011).

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Abbreviations

CVD	Cardiovascular disease
CES-D	Center for Epidemiologic Studies-Depression Scale
BMI	Body Mass Index
CRP	C-reactive protein
IL-6	Interleukin 6
TNF-α	Tumor necrosis factor-alpha

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Table 1

Characteristics of MESA participants with and without subsyndromal depression.

Variables	CES-D Normal n=4,021	CES-D SubSyndromal n=1,519	CES-D Depressed n=744	*p-value*
Demographics				
Age *M* (SD)	62.6 (10.0)	61.9 (10.4)	61.3 (10.7)	*<0.05**
Females, n (%)	1,891 (47)	839 (55.2)	508 (68.3)	*<0.001**
Ethnicity, n (%)				
Caucasian	1,566 (38.9)	521 (34.3)	200 (27.0)	
Chinese	538 (13.4)	182 (12.0)	64 (8.6)	*<0.001**
African-American	1,152 (28.6)	449 (29.6)	203 (27.3)	
Hispanic/Latinos	765 (19.1)	367 (24.1)	276 (37.1)	
Behaviors, M (SD)				
Smoking Status, n (%)				
Never	2,135 (50.6)	775 (51.1)	395 (53.1)	*<0.001**
Former	1,532 (38.1)	513 (33.8)	225 (30.2)	
Current	454 (11.3)	229 (15.1)	125 (16.7)	
Alcohol Use, n (%)				
Never	772 (19.3)	359 (23.7)	178 (24.1)	*<0.001**
Former	913 (22.8)	365 (24.1)	193 (26.1)	
Current	2,316 (57.9)	788 (52.1)	369 (49.9)	
Total Walking, min/per week	502.6 (614.9)	500.3 (631.4)	506.7 (660.7)	0.97
Biologic, M (SD)				
BMI	28.0 (5.2)	28.6 (5.6)	28.8 (5.8)	*<0.001**
Systolic Blood Pressure, mm Hg	127(21.2)	126(21.3)	127(23.5)	0.44
Glucose, mg/dl	97 (28.9)	98 (31.3)	100 (35.4)	*0.02**
Total Cholesterol, mg/dl	193 (34.7)	195 (37.1)	195 (37.5)	0.21
HDL Cholesterol, mg/dl	51 (14.9)	51 (14.2)	52 (15.0)	*0.01**
Triglycerides, mg/dl	130 (88.3)	131 (93.1)	137 (90.8)	*0.18*
Comorbidities and Medications				
Diabetes, n (%)	476 (11.9)	197 (13.0)	120 (16.2)	*0.03**
Lipid-Lowering Medications, n (%)	639 (15.9)	245 (16.1)	92 (12.4)	*0.03**

Variables	**CES-D Normal n=4,021**	**CES-D SubSyndromal n=1,519**	**CES-D Depressed n=744**	***p-value***
Hypertension Medication, n (%)	1,448 (36.0)	577 (38.0)	290 (39.0)	0.17
Inflammatory Markers (SD)				
[a] C-reactive protein (CRP)	1.83 (5.7)	1.93 (5.2)	2.0 (7.0)	*0.02**
[a] Interleukin-6 (IL-6)	1.20 (1.2)	1.24(0.65)	1.32 (1.32)	*0.02**
[a] Tumor Necrosis Factor (TNF)	4.69 (8.4)	4.54 (3.7)	4.88(20.8)	*0.01**

CES-D Symptoms: Normal (scores 0–7), Sub-Syndromal (scores 8–15), Depressed (scores ≥ 16). Mean (SD) reported unless otherwise specified.

* $p<0.05$;

[a] Geometrical Means.

Table 2

Depressive Scores by Gender and Ethnic group

	CES-D Normal		CES-D Subsyndromal		CES-D Depressed	
	Male	**Female**	**Male**	**Female**	**Male**	**Female**
Caucasians	2.9(2.1)	3.3(2.2)	10.7(2.1)	10.9(2.2)	22.7(6.7)	23(6.9)
African-Americans	2.8(2.3)	3.2(2.3)	10.4(2.1)	10.9(2.2)	21.9(6.1)	23.3(6.9)
Hispanic/Latinos	3.1(2.3)	3.2(2.3)	10.8(2.1)	11(2.2)	23.4(6.5)	24(7.7)
Chinese	2.8(2.3)	2.8(2.2)	10.6(2.2)	10.9(2.2)	22.1(5.3)	22.3(7.5)

Values presented as Means (SD)

Table 3

Association of subsyndromal and depressive symptoms with inflammation.

		[a] CRP			[a] IL-6			[a] TNF		
		β	**Adj Mean**	***p***	**β**	**Adj Mean**	***p***	**β**	**Adj Mean**	***p***
Unadjusted	Normal	Ref			Ref			Ref		
	Subsyndromal	0.05	0.66	0.14	0.02	0.21	0.35	−0.04	1.51	0.19
	Depressed	0.12	0.73	*0.009**	0.09	0.28	*0.001**	0.03	1.59	0.38
Model 2	Normal	Ref			Ref			Ref		
	Subsyndromal	−0.01	0.55	0.80	0.01	0.17	0.71	−0.03	1.50	0.29
	Depressed	−0.05	0.51	0.25	0.05	0.21	0.07	0.06	1.59	0.18
Model 3	Normal	Ref			Ref			Ref		
	Subsyndromal	−0.02	0.61	0.57	−0.00	0.23	0.87	−0.03	1.53	0.25
	Depressed	−0.22	0.56	0.10	0.03	0.26	0.27	0.05	1.62	0.16
Model 4	Normal	Ref			Ref			Ref		
	Subsyndromal	−0.05	0.53	0.11	−0.02	0.21	0.34	−0.03	1.55	0.33
	Depressed	−0.10	0.48	*0.02**	0.02	0.24	0.42	0.07	1.65	0.09

[a]Log transformed values.

Model 2: Age, Gender, Ethnic group

Model 3: + Smoking, Alcohol Use, Physical Activity.

Model 4: + BMI, lipids, systolic blood pressure, glucose, diabetes, antihypertensives and lipid-lowering medications.