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Biomarkers of Vascular Risk, Systemic Inflammation and Microvascular Pathology and Neuropsychiatric Symptoms in Alzheimer's Disease

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Abstract

Numerous serum and plasma based biomarkers of systemic inflammation have been linked to both neuropsychiatric disorders and Alzheimer's disease. The present study investigated the relationship of clinical biomarkers of cardiovascular risk (cholesterol, triglycerides and homocysteine) and a panel of markers of systemic inflammation (CRP, TNF-α, IL1-ra, IL-7, IL-10, IL-15, IL18) and microvascular pathology (ICAM-1, VCAM-1) to neuropsychiatric symptoms in a sample with mild Alzheimer's disease. Biomarker data was analyzed on a sample of 194 diagnosed with mild to moderate probable Alzheimer's disease. The sample was composed of 127 females and 67 males. The presence of neuropsychiatric symptoms was gathered from interview with caretakers/family members using the Neuropsychiatric Inventory. For total sample IL15, VCAM (Vascular Adhesion Molecule) and triglycerides were significantly and negatively related to number of neuropsychiatric symptoms and total cholesterol and homocysteine were positively related and as a group accounted for 16.1% of the variance. When stratified by gender different patterns of significant biomarkers were found with relationships more robust for males for both total symptoms and symptom clusters. A combination of biomarkers of systemic inflammation, microvascular pathology and clinical biomarkers of cardiovascular risk can account for a significant portion of the variance in the occurrence of neuropsychiatric symptoms in Alzheimer's disease supporting a vascular and inflammatory component of psychiatric disorders found in Alzheimer's disease. Gender differences suggest distinct impact of specific risks with total cholesterol a measure of cardiovascular risk being the strongest marker for males and IL-15 a marker of inflammation being the strongest for females.

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Keywords

Alzheimer's Disease; neuropsychiatric symptoms; biomarkers; gender

Introduction

In addition to the cognitive impairments of Alzheimer's disease, the neuropsychiatric symptoms that frequently accompany dementia [1, 2, 3, 4] have a significant impact on patients and care givers alike and are a major factor in caregiver stress [5, 6, 7], decline in cognition and quality of life [8, 9] and nursing home placement [10]. Although apathy and depression are the most frequently occurring neuropsychiatric symptoms [11], psychosis [12], agitation [2] and disturbances of sleep [13] are prevalent. The Neuropsychiatric Inventory (NPI) [14] has been extensively used in the study of behavioral and psychological symptoms in Alzheimer's disease. Aalten et al. [15] factor analyzed the NPI and identified four frequently occurring neuropsychiatric subsyndromes in dementia: hyperactivity, psychosis, affective symptoms, and apathy.

Various neurobiological mechanisms have been proposed to account for the high rate of occurrence of these neuropsychiatric symptoms. Among the explanations put forth are those that emphasize the relationship of vascular risks to neuropsychiatric symptoms (NPS) in dementia [16, 17]. A number of biomarkers of vascular risks, systemic inflammation, and microvascular pathology have been related to Alzheimer's disease and neuropsychiatric disorders in Alzheimer's disease or neuropsychiatric symptoms (NPS) in other CNS disorders.

Cholesterol, triglycerides and homocysteine are widely used clinically as biomarkers of vascular risk and have been related to neuropsychiatric symptoms in Alzheimer's. Cholesterol [18] has been shown to be a factor both in amyloid production and the development of NPS in Alzheimer's disease. Although there is little literature directly relating triglycerides to neuropsychiatric symptoms in Alzheimer's, there is evidence of a relationship between depression and level of triglycerides in the elderly [19, 20]. The research on homocysteine and NPS has produced mixed result. A positive relationship has been found between homocysteine and mental illness in the elderly [21]. Elevated levels of homocysteine have been linked to depression and cognitive functioning in older women [22] and a relationship between homocysteine and apathy in Alzheimer's disease has been reported for women but not men [23]. Tabet et al [24] on the other hand found no relationship between plasma homocysteine concentrations and NPS in Alzheimer's. C-reactive protein (CRP) is a widely used marker of acute phase and chronic inflammation and has been related to risk for stroke, heart disease and cognitive decline [25]. CRP has also been associated with apathy in a sample of community dwelling elderly [26]. Prior studies by our group [27, 28] have shown a relationship between CRP and symptoms of depression in Alzheimer's disease.

Inflammatory processes have been linked to the pathogenesis of Alzheimer's disease and neuropsychiatric symptoms [29, 30]. A number of pro- and anti-inflammatory markers have been related to neuropsychiatric symptoms and functional level in aging and Alzheimer's disease including TNFα [31], IL-1 [32, 33], IL-6 [30, 34, 35], IL-7 [36], IL-10 [37], IL-15 [38] and IL-18 [39].

Another set of biomarkers associated with vascular disease and inflammation that have been related to Alzheimer's disease are the soluble adhesion molecules [40, 41]. These markers of microvascular pathology within the brain have been related to the development of degeneration in Alzheimer's disease [42] and late life depression [28, 43. 44].

While there are reported relationships between inflammatory markers and NPS, inflammatory processes and AD, and NPS and AD, this study addressed whether a collection of biomarkers of neuroinflammation, microvascular disease and cardiovascular disease would predict the expression of NPS in mild to moderate Alzheimer's disease. Our previous research on biomarkers of depression [27, 28] and functional impairment [36] in Alzheimer's disease has shown the importance of studying gender effects directly; therefore the current study also evaluated the impact of gender on the biomarker/neuropsychiatric symptom relationship.

Materials and Methods

Participants

The sample was drawn from the individuals enrolled in the Longitudinal Research Cohort of the Texas Alzheimer's Research Care Consortium (TARCC) that had complete serum biomarker panel and a completed NPI interview. TARCC is a longitudinal multi-site study of a cohort of Alzheimer's disease patients and normal controls where each participant undergoes an annual evaluation that includes a medical examination, interview, neuropsychological testing, and blood draw. Individuals with a history of significant psychiatric disorders or the presence of neuropsychiatric symptoms such as depression as assessed by history, interview and score on the Geriatric Depression Scale at the time of initial evaluation are excluded from the cohort. Alzheimer's disease patients meet consensus-based diagnosis for probable AD based on NINCDS-ADRDA criteria [45]. The final sample of 194 consisted of 127 females and 67 males meeting the diagnostic criteria for Alzheimer's disease. The mean age of the sample was 75.53 (SD=8.30) with an average education of 14.08 years (SD= 3.31), a mean MMSE of 19.30 (SD= 6.20) and a mean CDR Sum of Boxes of 7.75 (SD= 4.33). The total years of education was determined from the patient's self-report of completed years of education. Institutional Review Board approval was obtained at each TARCC site and written informed consent was obtained from all participant and/or caregivers.

Methods

As part of the TARCC evaluation the NPI was administered to family members or caregivers with direct knowledge of participant's behavior. The NPI is a brief informant-based assessment of neuropsychiatric symptoms (NPS) that has been shown to be valid and reliable [46]. The informant reports the presence of twelve NPS and rates their severity on a 1–3 scale from mild to severe. Factor analyses [15] of the NPI has revealed four factors; hyperactivity, psychosis, affective symptoms and apathy. Following Aalten et al [15], the hyperactivity factor included the NPI items of agitation, disinhibition, irritability, aberrant motor behavior and euphoria; the psychosis factor included delusions, hallucinations and night-time behavior disturbances; the affective symptoms included depression and anxiety items; and the apathy factor included the apathy and the appetite and eating abnormalities item. Although this factor structure was based on a total NPI score (sum of each item multiplied by its severity score), we choose to utilize only the total number of neuropsychiatric symptoms to reflect the occurrence of these symptoms not their severity. T he severity ratings include both severity and level of change from the previous month and may be a more subjective rating than simple occurrence. Data were recorded for the presence of each of the 12 NPS and these items were summed to produce a score for the total number of symptoms. The number of symptoms reported for each factor were summed and made up the score for each factor. The total number of symptoms reported and the number of symptoms reported for each of the factors served as the primary outcomes. Symptom severity which is also assessed by the NPI was not included in the total score as our focus was on the occurrence of the symptoms not the perceived severity.

Biomarkers

The TARCC research platform use the Rules Based Medicine multiplexed immunoassay Multi-Analyte Profile (humanMAP) which is able to assay over 152 serum- based biomarkers. Based on the literature and our prior work on biomarkers of depression [27, 28] and biomarkers of functional behavior in Alzheimer's [36], the serum-based clinical biomarkers of vascular risk selected for analysis were Total Cholesterol, Homocysteine and Triglycerides and the biomarkers of inflammation related to Alzheimer's disease were IL-1ra1, IL-7, IL-10, IL-15, IL-18, TNFα (Tumor Necrosis Factor) and CRP. IL-6, which has been related to a number of neuropsychiatric disorders, was measured but fell below the detectable range and was not included in the panel of biomarkers. The levels of VCAM -1(Vascular Cell Adhesion Molecule 1) and ICAM-1 (Intracellular Adhesion Molecule) were selected as biomarkers of microvascular pathology.

Assays

The majority of the blood draws were conducted at the time of the annual evaluation. When that was not possible the evaluation and the blood draw were carried out no more that 30 days apart. Non-fasting samples were collected with 10mL serum-separating (tiger-top) vacutainers tubes at the time of interview. Samples were allowed to clot at room temperature for 30 minutes in a vertical position before being centrifuged at 1300 x g for 10 minutes. Next, 1mL aliquots were pipetted into polypropylene cryovial tubes and placed in −20° C (non-frost free) or −80° C freezers until shipment to TARCC Biobank. Total processing time (stick to freezer) was two hours or less. All samples from the current project were shipped in to Myriad Rules Based Medicine (Myriad RBM) for assay on the luminex-based HumanMAP 1.0 platform. Over 100 proteins were quantified utilizing fluorescent microspheres with protein-specific antibodies. Information regarding the least detectable dose (LDD), inter-run coefficient of variation, dynamic range, overall spiked standard recovery, and cross-reactivity with other humanMAP analytes can be obtained from Myriad Rules Based Medicine.

Data Analysis

Gender differences on demographic variables (Table 1), NPI scores and biomarkers were analyzed by t tests. Analyses were conducted using stepwise forward regression modeling with the biomarker panel serving as the predictor variables and total number of NPI symptoms and NPI factor scores as dependent measures for the complete sample. Initial analysis co-varied gender, age and education. Subsequently participants were stratified by gender for stepwise regression modeling with age and education co-varied.

Results

Table 1 presents the characteristics of the sample with the data for Males and Females. There was no difference between males and females on education, MMSE or CDR-Sum of Boxes although the female sample was significantly older ($t= 2.56$, $df= 192$, $p= .011$). Table 2 presents the means and standard deviations for each of the biomarkers for the entire sample of 194 participants as well as by gender. Females had significantly higher levels of cholesterol ($t= −4.92$, $df= 192$, $p<.000$) and ICAM ($t= 2.05$, $df= 192$, $p=.022$) than males. There was no difference between the genders on any of the other biomarkers. Table 3 shows that there was no significant difference between males and females on total number of NPI symptoms or any of the 4 NPI factors.

Stepwise regression modeling for the total sample (N=194) with the biomarkers as predictors and NPI variables as outcomes (Table 4) revealed that IL15, VCAM and triglycerides were significantly and negatively related to total NPI symptoms and total

Cholesterol and Homocysteine were positively related. As a group these biomarkers accounted for 16.1% of the variance in total number of neuropsychiatric symptoms. The biomarkers of IL-15 and VCAM-1 were significantly and negatively related to hyperactivity while homocysteine levels were positively related to the number of hyperactive symptoms. A model containing these biomarkers accounted for 8.9% of the total variance. IL-7, IL-18 and VCAM 1 were significantly and negatively related to symptoms of psychosis and accounted for 10% of the total variance. ICAM-1 and VCAM-1 were negatively related to affective symptoms while homocysteine was positively related. When combined, however, they accounted for less than 7% of the variance. None of the biomarkers were significantly related to apathy. For the total sample the significant biomarkers accounted for between 6.6 % and 10% of the variance in NPI Factors.

When stratified by gender a different picture emerged with very distinct patterns of significant biomarkers for males (Table 5) and females (Table 6). For males, cholesterol was a significant positive marker for total neuropsychiatric symptoms and all four NPI factors. Cholesterol was not significantly related to any of the dependent measures for females. Cholesterol alone accounted for 21.8% of the variance in total symptom. With the addition of IL-18 over 28% of the variance was accounted for. Cholesterol was positively associated with symptoms of hyperactivity ($R^2 = .145$, $p < .001$) whereas TNFα was significantly and negatively related. A regression model including both biomarkers accounted for 23.1% of the variance in hyperactive symptoms. Likewise with symptoms of psychosis, cholesterol was a primary predictor being positively and significantly related to the frequency of symptoms of hallucinations and delusions. The addition of negatively related IL-18 and positively related homocysteine accounted for 30% of the variance. Cholesterol was the only biomarker significantly associated with the affective and the apathy factors.

IL-15, IL-1ra and homocysteine were the most frequent contributors to significant regression models for females with IL-15 and IL-1ra negatively associated with neuropsychiatric symptoms and homocysteine positively associated. A regression model composed of IL-15, IL-1ra, homocysteine, VCAM-1 and triglycerides accounted for 21% of the variance in total number of neuropsychiatric symptoms in females. Interestingly the level of triglycerides was negatively related to total neuropsychiatric symptoms. The total variance accounted for by the biomarkers for the NPI factors of hyperactivity, psychosis and apathy was relatively small ranging from 6.8% for hyperactive and apathy symptoms to 8.5% for psychosis. As with triglycerides, when CRP entered into a significant model for apathy it was negatively related. Positively related homocysteine and negatively associated IL-18 and VCAM-1 combined accounted for 13.7% of the variance in the affective factor.

Discussion

The findings support a relationship between biomarkers of clinically relevant cardiovascular risks, biomarkers of inflammation, biomarkers of microvascular pathology and the presence of frequently occurring neuropsychiatric symptoms in Alzheimer's disease. The effect size is relatively small when analyzing a mixed gender sample of Alzheimer's patients. Although there was no difference between males and females on total number of reported symptoms, when the sample was stratified by gender it becomes apparent that the biomarkers under study are more robust predictors of neuropsychiatric symptoms for males. For males higher cholesterol is predictive of neuropsychiatric symptoms. This is interesting given that females had significantly higher total cholesterol and yet cholesterol was not a significant biomarker for females.

The strength of the relationship between cholesterol and neuropsychiatric symptoms for males is likely affected by the level of cholesterol. Post hoc exploratory analysis found that

those males with a total cholesterol of 200 or above (N=33) had significantly higher total number of symptoms (p= .006); symptoms of psychosis (p= .002) and symptoms of affective disturbance (p= .023) than those with cholesterol below 200 (N= 34). This relationship did not hold for females where there was no difference on any of the neuropsychiatric symptom variables for those with a total cholesterol above 200 (N=88) and those females with lower cholesterol (N= 39). A recent study found that total cholesterol was the significant biomarker in a model predicting progression [47] of Alzheimer's Disease although the impact of gender was not directly assessed.

Stage-specific gender differences in the occurrence of neuropsychiatric symptoms have been found in vascular dementia [48] and it is very possible that similar differences may be present in Alzheimer's disease. The gender differences found in the current study indicate the distinct impact of specific vascular risks with total cholesterol being the strongest marker for males and inflammatory dysregulation being stronger for females. The nature of the pathway(s) relating cholesterol and inflammation to specific neuropsychiatric symptoms and gender determinants is unclear and warrants further research.

The neuropsychiatric symptoms under study are complex behaviors whose occurrence is likely affected by multiple factors such as genetic predisposition, past psychiatric history, chronic and acute psychiatric and medical conditions, past and present treatments and current environmental and psychosocial stressors. The current research attempted to eliminate the impact of some of these factors by studying a cohort that excluded individuals with a history of psychiatric disorders. However, data was not available on medications such as statins and antidepressants or current psychosocial stressors and the affect of these and other possibly confounding variables such as smoking history can not be ruled out.

It could be argued that the amount of variance accounted for is relatively small and limits the inferences that can be drawn regarding these biomarkers. As discussed the determinants of the presence of neuropsychiatric symptoms in Alzheimer's are likely multifactorial and no one factor may be explanatory. The ability of blood based biomarkers to account for 1/6th of the variance in total NPI symptoms for the complete sample and over 20% of the variance for the sample by gender suggests a possible role in NPS that requires further inquiry.

There are a number of limitations to the current research that may affect the generalizability of the findings. The size of the sample was relatively small although the cohort is well characterized as an Alzheimer's disease cohort. The study is cross-sectional and assesses the relationship in mild to moderate cases of Alzheimer's at one point in time. A possible confound that may affect the interpretation of the findings is that many of these biomarkers can be viewed as non-specific measures of disease rather than specifically As a number of studies have shown the levels of inflammatory processes change as the disease progresses [49] and the impact may be different at different points in the disease. This may be reflected by the fact that the prevalence of the various neuropsychiatric symptoms changes over the course of the disease [50].

An additional limitation relates to the use of informant data. The data on the presence of the neuropsychiatric symptoms was dependent on caregiver reports and although gathered by trained interviewers the interpretation of the symptoms may vary from informant to informant. The analytic approach involved a large number of regression analyses which may increase the likelihood of Type I error. The biomarker samples were non-fasting and as such may not be representative of the actual level of circulating biomarkers such as cholesterol. The present study investigated the link between a range of biomarkers and neuropsychiatric symptoms; it is possible that other biomarkers not included in our analysis may be involved. This is especially true in the inability to assess the role of IL-6 in this relationship.

A combination of biomarkers of inflammation, microvascular pathology and clinical biomarkers of cardiovascular risk account for a significant portion of the variance in the occurrence of neuropsychiatric symptoms in Alzheimer's disease supporting a vascular and inflammatory component of neuropsychiatric psychiatric disturbances in Alzheimer's disease. The findings of distinct biomarker profiles for males and females underscores the importance of studying gender differences in relationship of biomarkers to neuropsychiatric symptoms. The current study provides a foundation for further studies that address the value of biomarkers in predicting different facets of Alzheimer's disease in larger populations of patients with dementia. The findings represent a first step in developing a blood based biomarker profile that may allow the identification of those AD patients, especially males, with increased likelihood of developing these troublesome behaviors and as such may provide an opportunity for early intervention.

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Appendix

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Table 1

Characteristics of Sample

	Total Sample	Males	Females	*p*
	***N*=194**	***N*=67**	***N*=127**	
Age	*M*= 75.53	*M*= 75.17	*M*= 78.31	.011
	SD= 8.30	*SD*= 7.99	*SD*= 8.21	
Education	*M*= 14.08	*M*= 14.24	*M*= 14.00	.632
	SD= 3.31	*SD*= 3.48	*SD*= 3.22	
MMSE	*M*= 19.21	*M*= 19.29	*M*= 19.17	.774
	SD= 6.24	*SD*= 7.44	*SD*=5.54	
CDRSOB	*M*= 7.86	*M*= 7.42	*M*= 8.09	.247
	SD= 4.44	*SD*= 4.87	*SD*= 4.20	

CDRSOB = Clinical Dementia Rating Sum of Boxes

Table 2

Biomarkers of Cardiovascular Risk, Systemic Inflammation and Vascular Pathology

Biomarker	Total Sample	Males	Females	*p*
	***N*= 194**	***N*=67**	***N*= 127**	
Cholesterol	*M*= 210.53	*M*= 188.55	*M*= 221.96	.000
	SD= 50.34	*SD*=41.62	*SD*=50.82	
Triglyceride	*M*= 184.18	*M*= 189.89	*M*= 181.21	.749
	SD=87.88	*SD*=82.29	*SD*=90.82	
Homocysteine	*M*= 16.18	*M*= 16.84	*M*= 15.839	.788
	SD=9.03	*SD*=7.64	*SD*=9.68	
C Reactive Protein	*M*= 3.27	*M*= 2.92	*M*= 3.46	.229
	SD=4.91	*SD*=4.49	*SD*=5.13	
IL-1ra	*M*= 110.03	*M*= 103.68	*M*= 113.33	.169
	SD=61.27	*SD*=71.3	*SD*=55.31	
IL-7	*M*= 111.29	*M*= 103.04	*M*= 115.61	.214
	SD=66.81	*SD*=66.89	*SD*=66.63	
IL-10	*M*= 9.18	*M*= 9.08	*M*= 9.24	.838
	SD=5.33	*SD*=4.87	*SD*=5.57	
IL-15	*M*= .835	*M*= .775	*M*= .866	.075
	SD=.407	*SD*=.426	*SD*= .395	
IL-18	*M*= 280.88	*M*=265.18	*M*=289.10	.257
	SD=139.54	*SD*=102.49	*SD*=155.19	
TNF-α	*M*= 9.88	*M*= 9.50	*M*= 7.98	.869
	SD=11.14	*SD*= 12.41	*SD*= 9.83	
ICAM-1	*M*= 132.30	*M*= 124.61	*M*= 136.30	.022
	SD= 35.84	*SD*= 40.29	*SD*= 32.75	
VCAM-1	*M*= 831.95	*M*= 805.47	*M*= 845.71	.102
	SD= 212.89	*SD*= 203.73	*SD*= 217.01	

IL = Interleukin; TNF = Tumor Necrosis Factor; ICAM = Intracellular Adhesion Molecule; VCAM = Vascular Adhesion Molecule

Table 3

Neuropsychiatric Symptoms

Neuropsychiatric Symptoms	Total Sample *N* =194	Males *N*=67	Females *N* =127	*p*
NPI Total Symptoms	*M*= 3.87 *SD*= 2.60	*M*= 4.20 *SD*= 2.90	*M*=3.73 *SD*= 2.45	.305
Hyperactivity	*M*= 1.45 *SD*= 1.31	*M*= 1.63 *SD*= 1.31	*M*= 1.35 *SD*= 1.30	.474
Psychosis	*M*= .744 *SD*= .810	*M*= .776 *SD*= .902	*M*= .727 *SD*= .7604	.649
Affective	*M*= .851 *SD*=.802	*M*= .881 *SD*= .769	*M*= .836 *SD*=.803	.648
Apathy	*M*=.815 *SD*= .751	*M*= .836 *SD*= .771	*M*= .805 *SD*= .743	.606

NPI = Neuropsychiatric Inventory

Table 4

Biomarkers of Neuropsychiatric Symptoms for Sample *N*=194

NPI-Q Symptoms	Biomarker	*B*	R^2	*t*	*p*
Total	***Model 1***				
	IL-15**	−1.536	.056	−3.398	.001
	Model 2				
	IL-15**	−1.504		−3.393	.001
	VCAM***	−.002	.097	−2.946	.004
	Model 3				
	IL-15**	−1.504		−3.434	.001
	VCAM***	−.003		−3.466	.001
	HCY*	.048	.123	2.363	.019
	Model 4				
	IL-15**	−1.809		−3.931	.000
	VCAM***	−.003		−3.606	.000
	HCY*	.051		2.508	.013
	Triglycerides*	−.004	.141	−2.015	.045
	Model 5				
	IL-15**	−1.782		−3.906	.000
	VCAM***	−.003		−3.377	.001
	HCY*	.049		2.467	.015
	Triglycerides*	−.005		−2.228	.027
	Cholesterol*	.007	.161	2.119	.035
Hyperactivity	***Model 1***				
	IL-15**	−.625	.037	−2.740	.007
	Model 2				
	IL-15**	−.611		−2.717	.007
	VCAM-1***	−.001	.070	−2.587	.010

NPI-Q Symptoms	Biomarker	*B*	R^2	*t*	*p*
	Model 3				
	IL-15**	−.612		−2.738	.007
	VCAM-1***	−.001		−3.011	.003
	HCY*	.021	.089	1.986	.048
Psychosis	***Model 1***				
	IL-7**	−.003	.044	−3.243	.001
	Model 2				
	IL-7**	−.003		−3.156	.002
	IL-18**	−.001	.081	−2.494	.013
	Model 3				
	IL-7**	−.003		−3.030	.003
	IL-18**	−.001		−2.372	.019
	VCAM-1***-1	−.001	.100	−1.997	.047
Affective	***Model 1***				
	ICAM-1***	−.004	.026	−2.298	.023
	Model 2				
	ICAM-1***	−.004		−2.458	.015
	HCY*	.013	.047	2.019	.045
	Model 3				
	ICAM-1***	−.003		−1.604	.110
	HCY*	.016		2.436	.016
	VCAM-1***	−.001	.066	−1.977	.050
Apathy	None				

IL = Interleukin; VCAM = Vascular Adhesion Molecule; HCY = Homocysteine; ICAM = Intracellular Adhesion Molecule;

*Markers of Cardiovascular Risk;

**Inflammatory Markers;

*** Markers of Microvascular Pathology

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Table 5

Biomarkers of Neuropsychiatric Symptoms for Males N=67

NPI-Q Symptoms	Biomarker	*B*	R^2	*t*	*p*
Total	***Model 1***				
	Cholesterol*	.033	.218	4.256	.000
	Model 2				
	Cholesterol*	.035		4.664	.000
	IL-18**	−.007	.282	−2.393	.020
Hyperactive	***Model 1***				
	Cholesterol*	.012	.145	3.325	.001
	Model 2				
	Cholesterol*	.013		3.842	.000
	TNF-α	−.139	.231	−3.059	.003
Psychosis	***Model 1***				
	Cholesterol*	.009	.181	3.784	.000
	Model 2				
	Cholesterol*	.010		4.217	.000
	IL-18**	−.002	.256	−2.543	.013
	Model 3				
	Cholesterol*	.010		4.333	.000
	IL-18**	−.003		−2.757	.008
	HCY*	.025	.302	2.042	.045
Affective	Cholesterol*	.005	.074	2.285	.026
Apathy	Cholesterol*	.006	.107	2.790	.007

IL = Interleukin; TNF = Tumor Necrosis Factor; HCY = Homocysteine;

*Markers of Cardiovascular Risk;

**Inflammatory Markers;

*** Markers of Microvascular Pathology

Table 6

Biomarkers of Neuropsychiatric Symptoms for Females N= 127

NPI-Q Symptoms	Biomarker	*B*	R^2	*t*	*p*
Total	***Model 1***				
	IL-15**	−1.591	.065	−2.962	.004
	Model 2				
	IL-15**	−1.699		−3.223	.002
	IL-1ra**	−.010	.112	−2.570	.011
	Model 3				
	IL-15**	−1.669		−3.215	.002
	IL1-ra**	−.010		−2.623	.010
	HCY*	.047	.146	2.214	.029
	Model 4				
	IL-15**	−1.715		−3.364	.001
	IL1-ra**	−.008		−2.128	.035
	HCY*	.055		2.635	.009
	VCAM-1***	−.002	.184	−2.410	.017
	Model 5				
	IL-15**	−2.077		−3.877	.000
	IL1-ra**	−.008		−2.067	.041
	HCY*	.057		2.732	.007
	VCAM-1***	−.002		−2.514	.013
	Triglycerides*	−.005	.210	−1.986	.049
Hyperactive	***Model 1***				
	IL-1ra**	−.005	.044	−2.422	.017
	Model 2				
	IL-1ra**	−.005		−2.480	.014
	HCY*	.026	.068	2.270	.025

NPI-Q Symptoms	Biomarker	*B*	R^2	*t*	*p*
Psychosis	***Model 1***				
	IL-15 **	−.420	.047	−2.501	.014
	Model 2				
	IL-15 **	−.442		−2.666	.009
	VCAM-1 ***	−.001	.085	−2.263	.025
Affective	***Model 1***				
	HCY *	.021	.063	2.910	.004
	Model 2				
	HCY *	.021		2.981	.003
	IL-18 **	−.001	.104	−2.400	.018
	Model 3				
	HCY *	.024		3.347	.001
	IL-18 **	−.001		−2.469	.015
	VCAM-1 ***	−.001	.137	−2.159	.033
Apathy	***Model 1***				
	IL-15 **	−.353	.035	−2.136	.035
	Model 2				
	IL-15 **	−.348		−2.131	.035
	CRP *	−.027	.068	−2.110	.037

IL = Interleukin; HCY = Homocysteine; VCAM = Vascular Adhesion Molecule; CRP = C-Reactive Protein;

*Markers of Cardiovascular Risk;

**Inflammatory Markers;

***Markers of Microvascular Pathology