
Depressive Symptoms are Associated with Subclinical Neurovascular Disease among Healthy Older Women, not Men

S. Carrington Rice, M.A.¹

Megan M. Hosey, B.S.¹

David M. Lefkowitz, M.D.²

Leslie I. Katzel, M.D., Ph.D.^{3,4}

Eliot L. Siegel, M.D.^{2,4}

William F. Rosenberger, Ph.D.⁵

Shari R. Waldstein, Ph.D.¹

¹Department of Psychology, University of Maryland, Baltimore County

²Department of Diagnostic Radiology, University of Maryland, Baltimore County

³Division of Gerontology, Department of Medicine, University of Maryland School of Medicine

⁴Geriatric Research Education and Clinical Center, Baltimore VA Medical Center

⁵Department of Statistics, George Mason University

Background: Depression, Neurovascular Disease, and Brain Atrophy

- Both depression and neurovascular disease are common and compromise the health of our aging population (Beyer, 2007; de Leeuw et al., 2001).
 - Associations between unipolar depression and neurovascular disease among older adults are well recognized (Kales et al., 2005)
 - Clinical: Stroke, vascular dementia
 - Subclinical: White matter hyperintensities, silent infarcts
 - These associations are likely bidirectional:
 - Depression → Neurovascular disease
 - Neurovascular disease → “Vascular depression” (Alexopoulos, 1997)
 - Prior research does not support an association between depression and measures of generalized cerebral atrophy (Soares & Mann, 1997), although regional volumetric differences have been identified (Beyer & Krishnan, 2002).
-

Background: Sex Differences in Depression and Subclinical Neurovascular Disease

- Epidemiologic studies consistently replicate a higher prevalence of depression in adult women compared to adult men (Kessler et al., 1993)
 - Sex differences in later life depression have been less well characterized, but at a minimum, the higher prevalence rates among women appear to persist. (Mulsant & Ganguli, 1999)
 - Sex differences in subclinical neurovascular disease have also been identified:
 - Higher prevalence of white matter lesions among elderly women in the population-based Rotterdam Scan Study (de Leeuw et al., 2001)
 - Little research has examined effect modification by sex in associations between depressive symptoms and neurovascular disease among healthy older adults
 - To our knowledge, previous studies have examined only patients with clinical depression, clinical neurovascular disease, or both, with inconsistent findings (Alexopoulos et al., 1997; Lavretsky et al., 1998; Paradiso & Robinson, 1998)
-

Study Objective

- To identify whether depressive symptoms were differentially associated with indices of a) subclinical neurovascular disease and b) global brain atrophy in men versus women among a sample of healthy older adults.
-

Sample

- 103 healthy, community-dwelling older adults
 - Aged 54 to 81 years (M=67, SD=7)
 - 59% male, 88% white
 - Enrolled in an ongoing investigation of cardiovascular risk factors, brain, and cognitive function
-

Sample (continued)

- Exclusionary criteria:
 - History or clinical evidence of cardiovascular disease (other than mild-to-moderate hypertension)
 - Diabetes
 - Other major medical disease (e.g., renal, hepatic, pulmonary)
 - Neurologic disease
 - Stroke
 - Known or suspected dementia (MMSE<22)
 - Psychiatric disorder
 - Heavy alcohol use (>14 drinks/wk)
 - Severe head injury (LOC>30 min)
 - Medications affecting central nervous system function

Method: Depressive Symptoms

- Beck Depression Inventory
 - 21-item measure assessing current level of depressive symptoms
 - Participants rate a variety of symptoms of depression on a 0 to 3 scale.
 - Scores range from 0 to 63, with higher values signifying higher levels of depressive symptoms.
-

Method: Magnetic Resonance Imaging (MRI)

- 1.5 Tesla scanner
 - Images rated blindly for:
 - Periventricular white matter hyperintensities (WMH): 0=absent, 1=cap, 2=band, 3=irregular hyperintensity extending into the deep white matter
 - Deep WMH: 0=absent, 1=punctuate, limited, 2=beginning confluent, 3=confluent.
 - Number of silent infarctions ($\geq 3\text{mm}$)
 - Ventricular enlargement: 0=absent, 1=mild, 2=moderate, 3=severe
 - Sulcal widening: 0=absent, 1=mild, 2=moderate, 3=severe
-

Method: Data Reduction

- All data analyses performed with SAS v9.1 (Cary, NC).
 - Principal components analysis of the 5 brain measures yielded 2 components with eigenvalues >1 :
 - Subclinical neurovascular disease
 - Periventricular WMH
 - Deep WMH
 - Silent infarcts
 - Brain atrophy
 - Ventricular enlargement
 - Sulcal widening
 - Based on these components, we created 2 rank-sum variables that served as outcome variables.
-

Method: Data Analyses

- T-tests used to identify any group differences between the men and women
 - Ordinary least squares (OLS) general linear model (GLM) multiple regression analyses used to examine relations of depressive symptoms with the rank-sum indices of subclinical neurovascular disease and brain atrophy
 - Covariates:
 - Age
 - Education
 - Systolic blood pressure (SBP)
 - Fasting glucose
 - Maximal oxygen consumption (VO_2max)
 - Body mass index (BMI)
 - Alcohol use (average number of drinks/week over past month)
 - Mini-Mental State Examination (MMSE)
-

Results: Characteristics of Study Sample

Variable	Total sample (n=103)		Men (n=61)		Women (n=42)	
	Mean (SD) or Percent	Range	Mean (SD) or Percent	Range	Mean (SD) or Percent	Range
Age (years)	66.7 (6.8)	54-81	67.7 (6.51)	54-81	65.4 (7.06)	
Sex (% male)	59.2	--	--	--	--	--
Race (% white)	88.4	--	91.8	--	83.3	--
Education (years)	16.4 (2.7)	9-23	16.5 (2.81)	9-22	16.4 (2.67)	12-23
SBP (mm Hg)*	129 (18.2)	95-178	134 (17.5)	95-178	122 (16.8)	99-169
VO ₂ max (ml/kg/min)*	24.9 (6.98)	11.7-48.7	27.0 (6.69)	15.3-48.7	21.9 (6.34)	11.7-44.8
BMI (kg/m ²)	27.2 (4.97)	18.0-42.5	27.8 (4.46)	18.0-38.0	26.4 (5.59)	18.6-42.5
Fasting glucose (mg/dL)	94.0 (12.2)	54-166	96.6 (12.8)	79-166	90.3 (10.1)	54-112
Alcohol use†	2.55 (3.25)	0-14	2.84 (3.64)	0-14	2.14 (2.56)	0-10.5
MMSE (total correct)	29.2 (1.01)	26-30	29.2 (1.02)	26-30	29.2 (1.00)	26-30
BDI (total score)	3.79 (3.58)	0-17	3.48 (3.62)	0-17	4.26 (3.51)	0-14
SND (rank sum score)	225 (90.7)	63-445	215 (90.5)	63-440	239 (90.1)	63-445
Brain atrophy (rank sum score)*	151 (68.6)	36-266	173 (66.8)	36-266	120 (58.6)	36-266

* Means differ between men and women, $p < .05$; † average # of drinks per week over past month; SD=standard deviation; SBP=systolic blood pressure; VO₂max=maximal oxygen consumption; BMI=body mass index; MMSE=Mini Mental State Examination; BDI=Beck Depression Inventory; WMH=white matter hyperintensities; SND=subclinical neurovascular disease

Results: Characteristics of Study Sample

Variable	Total sample (n=103)		Men (n=61)		Women (n=42)	
	Mean (SD) or Percent	Range	Mean (SD) or Percent	Range	Mean (SD) or Percent	Range
Age (years)	66.7 (6.8)	54-81	67.7 (6.51)	54-81	65.4 (7.06)	
Sex (% male)	59.2	--	--	--	--	--
Race (% white)	88.4	--	91.8	--	83.3	--
Education (years)	16.4 (2.7)	9-23	16.5 (2.81)	9-22	16.4 (2.67)	12-23
SBP (mm Hg)*	129 (18.2)	95-178	134 (17.5)	95-178	122 (16.8)	99-169
VO ₂ max (ml/kg/min)*	24.9 (6.98)	11.7-48.7	27.0 (6.69)	15.3-48.7	21.9 (6.34)	11.7-44.8
BMI (kg/m ²)	27.2 (4.97)	18.0-42.5	27.8 (4.46)	18.0-38.0	26.4 (5.59)	18.6-42.5
Fasting glucose (mg/dL)	94.0 (12.2)	54-166	96.6 (12.8)	79-166	90.3 (10.1)	54-112
Alcohol use†	2.55 (3.25)	0-14	2.84 (3.64)	0-14	2.14 (2.56)	0-10.5
MMSE (total correct)	29.2 (1.01)	26-30	29.2 (1.02)	26-30	29.2 (1.00)	26-30
BDI (total score)	3.79 (3.58)	0-17	3.48 (3.62)	0-17	4.26 (3.51)	0-14
SND (rank sum score)	225 (90.7)	63-445	215 (90.5)	63-440	239 (90.1)	63-445
Brain atrophy (rank sum score)*	151 (68.6)	36-266	173 (66.8)	36-266	120 (58.6)	36-266

* Means differ between men and women, $p < .05$; † average # of drinks per week over past month; SD=standard deviation; SBP=systolic blood pressure; VO₂max=maximal oxygen consumption; BMI=body mass index; MMSE=Mini Mental State Examination; BDI=Beck Depression Inventory; WMH=white matter hyperintensities; SND=subclinical neurovascular disease

Coefficients from Regression Models Relating Depressive Symptoms with Subclinical Neurovascular Disease & Brain Atrophy

Variable	Subclinical Neurovascular Disease <i>b</i>	Brain Atrophy <i>b</i>
Intercept	108.4	-172
Age	3.71*	5.75**
Sex	25.3	20.4
Education	-1.05	0.77
SBP	-1.09	0.26
BMI	-0.73	0.48
VO ₂ max	0.92	0.72
Glucose	0.02	0.43
Alcohol use	-1.42	-0.03
MMSE	-0.38	-6.24
BDI	11.9**	-2.89
BDI × sex	-10.8*	2.09

* $p < .05$, ** $p < .01$; SBP=systolic blood pressure; BMI=body mass index; VO₂max=maximal oxygen consumption; BDI=Beck Depression Inventory

Sex-Stratified Results

- Follow-up sex-stratified regressions showed depressive symptoms and subclinical neurovascular disease to be positively related among women ($r^2 = .17$, $b = 13.2$, $p < .01$), but not men ($r^2 = .007$, $b = 2.21$, $p > .05$).
-

Summary of Findings

- We found sex to be a significant effect modifier of the relation between depressive symptoms and subclinical neurovascular disease, such that depressive symptoms and subclinical neurovascular disease were significantly associated among women, but not men.
 - This finding does not appear to be explained by greater subclinical disease, worse physical health, or increased concurrent depressive symptoms among the women in our sample.
 - No associations between depressive symptoms and global brain atrophy were identified.
-

Conclusions

- Although beyond the scope of the present study, depressive symptoms may play a greater role in the development of subclinical neurovascular disease among women because of greater cumulative lifetime exposure to depressive symptoms and/or depression.
 - Chronic or repeated episodes of elevated depressive symptoms may predispose women to worse subclinical vascular health in older adulthood, whereas other factors drive the development of subclinical neurovascular disease among men across the lifespan.
 - In addition, women may simply be more susceptible than men to the affective consequences of subclinical neurovascular disease.
-

Strengths & Limitations

- Strengths:

- Use of a highly screened sample
- Sex differences as primary aim

- Limitations:

- Cross-sectional design
 - Reliance on a single measure of depressive symptoms
 - Unavailability of regional brain measures
-

Future Directions

- Replication in other healthy, community-dwelling samples
 - Longitudinal examinations
 - Investigations of what mechanisms account for a stronger link between depressive symptoms and subclinical neurovascular disease among healthy older women
-

Thank you!
