Elevated circulating vascular cell Adhesion Molecule-1 (sVCAM-1) is associated with concurrent depressive symptoms and cerebral white matter Hyperintensities in older adults

The Harvard community has made this article openly available. Please share how this access benefits you. Your story matters

Citation
Tchalla, Achille E., Gregory A. Wellenius, Farzaneh A. Sorond, Thomas G. Travison, Thierry Dantoine, and Lewis A. Lipsitz. 2015. “Elevated circulating vascular cell Adhesion Molecule-1 (sVCAM-1) is associated with concurrent depressive symptoms and cerebral white matter Hyperintensities in older adults.” BMC Geriatrics 15 [1]: 62. doi:10.1186/s12877-015-0063-7. http://dx.doi.org/10.1186/s12877-015-0063-7.

Published Version
doi:10.1186/s12877-015-0063-7

Citable link
http://nrs.harvard.edu/urn-3:HUL.InstRepos:17295653

Terms of Use
This article was downloaded from Harvard University’s DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA
Elevated circulating vascular cell Adhesion Molecule-1 (sVCAM-1) is associated with concurrent depressive symptoms and cerebral white matter Hyperintensities in older adults

Achille E. Tchalla1,2,3,4*, Gregory A. Wellenius5, Farzaneh A. Sorond6, Thomas G. Travison1, Thierry Dantoine4 and Lewis A. Lipsitz1,2,3

Abstract

Background: Circulating vascular adhesion molecule-1 (sVCAM-1) is a presumed marker of endothelial activation and dysfunction, but little is known about its association with mood. We hypothesized that elevated plasma concentrations of sVCAM-1 may be a marker of depressive symptoms due to cerebral vascular disease.

Methods: We studied 680 community-dwelling participants in the MOBILIZE Boston Study, aged 65 years and older. sICAM-1 and sVCAM-1 were measured by ELISA assay and depressive symptoms were assessed during home interviews using the Revised Center for Epidemiological Studies Depression Scale (CESD-R). Cerebral White Matter Hyperintensities (WMHs) were quantified by MRI in a subgroup of 25 participants.

Results: One hundred seventy nine (27 %) subjects had a CESD-R Score ≥ 16, indicative of depressive symptoms. The mean sVCAM-1 concentration (±SD) was 1176 ± 417 ng/mL in a group with CESD-R Scores <16 and 1239 ± 451 ng/mL in those with CESD-R Scores ≥16 (p = 0.036). CESD-R Score was positively associated with sVCAM-1 (r = 0.11, p = 0.004). The highest quintile of sVCAM-1, which is indicative of endothelial dysfunction, was significantly associated with depressive symptoms compared to the lowest quintile (OR = 1.97 (1.14-3.57) p = 0.015). In a subset of subjects, sVCAM-1 concentration was positively correlated with cerebral WMHs volume (p = 0.018).

Conclusions: The association between high levels of sVCAM-1 and depressive symptoms may be due to endothelial dysfunction from cerebral microvascular damage. Future longitudinal studies are needed to determine whether sVCAM-1 can serve as a biomarker for cerebrovascular causes of depression.

Keywords: Endothelial dysfunction, sVCAM-1, Depression symptoms, Cerebral white matter
concentrations of CAMs have also been associated with multiple organ dysfunction, disease severity, or death [11].

It has been hypothesized that late-life depression may be due in part to cerebrovascular disease [12, 13]. Ischemia has been shown to induce the expression of ICAM-1 [14]. In post-mortem studies there is an increased expression of CAMs in the dorsolateral prefrontal cortex in people with depressive symptoms [15], which is consistent with a theory of vascular depression [16, 17]. In addition, there is a correlation between sICAM-1 and depressive symptoms during treatment of melanoma with interferon [18].

We hypothesized that elevated plasma concentrations of circulating CAMs associated with aging may be a marker of depressive symptoms due to cerebral vascular disease. We therefore used plasma biomarkers and data from the MOBILIZE Boston Study (Maintenance Of Balance, Independent Living, Intellect, and Zest in the Elderly) to explore the relationships between plasma levels of CAMs and depressive symptoms in a community-based population of older adults.

Materials and Methods
Participants
The study sample consisted of 680 community-dwelling seniors living in the Boston area who participated in the MOBILIZE Boston Study (MBS). The design and methodology for this study have been previously described in detail [19, 20]. In brief, 765 persons were enrolled using door-to-door population based recruitment. To be included, individuals had to be > 65 years, able to understand and communicate in English, able to walk 20 feet without personal assistance (walking aids permitted), and expected to live in the area for at least 2 years. Exclusion criteria included terminal disease, severe vision or hearing deficits, and Mini-Mental State Examination score < 18 [21, 22]. All subjects underwent a complete home and laboratory assessment of demographic characteristics, medical conditions, medications, functional status, gait speed, smoking status, alcohol use, blood pressure, and cerebral hemodynamics at baseline.

Depressive Symptoms Assessment
Depressive symptoms were assessed at study enrollment using the Revised Center for Epidemiologic Studies Depression scale (CESD-R) [23]. The CESD-R is a 20-item self-administered instrument designed to measure the presence of depressive symptoms over the previous two weeks in community studies. Note that the CESD-R does not capture information on a patient’s clinical or treatment history and is not useful as a diagnostic tool for depression. The CESD-R has been validated [24, 25]. As in previous work [26], we chose a priori to use scores of < 16 to indicate no or minimal depressive symptoms and ≥ 16 to indicate the presence of moderate or severe symptoms.

Biomarker measures
Plasma concentrations of sICAM-1, sVCAM-1, and interleukin-6 (IL-6) were measured by ELISA assay (R&D Systems, Minneapolis, MN). For sICAM-1 this assay has a sensitivity of 0.35 ng/mL, and the day-to-day variability of the assay at concentrations of 64.2, 117, 290 and 453 ng/mL are 10.1, 7.4, 6.0 and 6.1 %, respectively. For sVCAM-1 the assay has a sensitivity of 2.0 ng/mL and the day-to-day variability of the assay at concentrations of 9.8, 24.9 and 49.6 ng/mL is 10.2, 8.5 and 8.9 %, respectively. For IL-6, the assay has a sensitivity of 0.094 pg/mL, and the day-to-day variability of the assay at concentrations of 0.49, 2.78 and 5.65 pg/mL are 9.6, 7.2 and 6.5 %, respectively. In addition, the concentration of high sensitivity C-reactive protein (hsCRP) was determined using an immunoturbidimetric assay on a Hitachi 917 analyzer (Roche Diagnostics - Indianapolis, IN), using reagents and calibrators from DiaSorin (Stillwater, MN). This high-sensitivity assay has a limit of detection of 0.03 mg/L. The day-to-day variability of the assay at concentrations of 0.91, 3.07 and 13.38 mg/L are 2.81, 1.61 and 1.1 %, respectively. All assays were performed by Dr. Nader Rifai’s group at Boston Children’s Hospital.

Magnetic Resonance Image data
Volumes of cerebral white matter hyperintensities (WMH) normalized by intracranial volume were estimated from the MRI data in a subset of 25 MBS participants who completed MRI substudy. Eligible and willing participants were imaged using a Siemens Trio 3 Tesla system (Erlangen, Germany) employing a 12-channel phased-array head coil for reception and body coil for transmission. Cerebral WMH were measured with Free Surfer (http://surfer.nmr.mgh.harvard.edu) using a multispectral procedure that classifies white matter as normal or abnormal from signal intensities from the T1, PD, and T2 images at each voxel. The Free Surfer procedure for lesion segmentation combines the initial standard segmentation with an extension of the subcortical segmentation procedure that incorporates information from a co registered T2 and PD image for the segmentation of signal abnormalities within the white matter. Although the procedure with T1-weighted images alone tends to underestimate white matter lesion volumes, the incorporation of information from T2/PD provides more robust estimation of the lesion volumes. The multiple image modalities were registered to the T1 with boundary-based registration (BBR) and the segmentation of WMH from healthy WM was accomplished with a multispectral Gaussian classifier for each subject based on the atlas values.

Other covariates
Covariates included sociodemographic characteristics, health status, and amount of physical activity. Sociodemographic
characteristics assessed in the home interview included age, sex, race (self-identified), and years of education. We used the validated Physical Activity Scale for the Elderly (PASE) to measure physical activity in the previous week [27]. Participants were asked about physician-diagnosed major medical conditions. Details of the study variables have been published previously [19, 20]. Diabetes was defined using an algorithm based on self-reported diabetes, use of antidiabetic medications, and laboratory measures from the baseline clinic visit, including random glucose ($\geq 200 \text{ mg/dL}$) and hemoglobin A$_1c$ ($\geq 7\%$).

Body mass index (calculated as weight in kilograms divided by height in meters squared) was calculated from measured height and weight. Comorbidity index was the number of comorbidities or medical conditions. Medication use (antihypertensive, antidepressant, and benzodiazepine) was also assessed.

### Ethics Statement
The MOBILIZE Boston Study was reviewed and approved by the Hebrew SeniorLife Institutional Review Board (IRB). Written informed consent was obtained from each participant. The study was conducted according to the principles of the Helsinki Declaration.

### Data Analysis
Concentrations of sVCAM-1 and sICAM-1 were natural log-transformed to approximate a normal distribution prior to modeling as continuous variables. We also divided the distributions of sVCAM-1 and sICAM-1 into quintiles according to the distribution in the entire study population for categorical analyses. We compared baseline characteristics of different groups of study participants by using t tests, $\chi^2$ tests, or Wilcoxon rank-sum tests, as appropriate.

We used multivariate logistic regression to estimate the odds ratio and 95% confidence intervals (CIs) for quintiles of sVCAM-1 and sICAM-1 and depressive symptoms.

### Table 1 Characteristics of participants according to CESD-R score status (<16 vs. ≥16), N = 668*

| Baseline Characteristics | CESD-R scorea | P Valueb |
|-------------------------|---------------|----------|
|                         | <16 (n = 489, 73 %) | ≥16 (n = 179, 26 %) |
| **Demographics**        |               |          |
| Age, mean (SD), y       | 77.9 ± 5.3    | 78.4 ± 5.5 | 0.44   |
| Gender                  |               | 0.071    |
| Men                     | 193 (39.5)    | 57 (31.8) |        |
| Women                   | 296 (60.5)    | 122 (68.2) |       |
| White Race              | 397 (81.2)    | 138 (77.0) | 0.58   |
| Educational level, mean (SD), y | 14.98 ± 5.1 | 14.97 ± 8.1 | 0.11   |
| **Health behaviors**    |               |          |
| Body mass index, kg/m², b |            | 0.31     |
| <25                     | 148 (30.3)    | 62 (34.6) |        |
| 25-29.9                 | 208 (42.5)    | 78 (43.6) |        |
| ≥30                     | 133 (27.2)    | 39 (21.8) |        |
| Current smoker          | 283 (57.9)    | 102 (57.1) | 0.84   |
| Alcohol use (Endorsing ≥2 drinks per week) | 136 (27.8) | 35 (19.6) | 0.03   |
| Physical activity scorec |            | 0.024    |
| 0-66                    | 139 (28.4)    | 68 (38.0) |        |
| 6601-124                | 164 (33.5)    | 59 (33.0) |        |
| 12401-559              | 181 (37.0)    | 49 (27.4) |        |
| **Health conditions**   |               |          |
| Comorbidity index       | 2.8 ± 1.4     | 3.8 ± 1.8 | <.0001 |
| Hypertension            | 374 (76.5)    | 147 (82.1) | 0.075  |
| Hyperlipidemia          | 285 (58.3)    | 103 (57.5) | 0.54   |
| Diabetes                | 84 (17.2)     | 42 (23.5) | 0.066  |
| Previous Stroke         | 39 (8.0)      | 27 (15.1) | 0.007  |
| Coronary artery disease | 67 (13.7)     | 40 (22.4) | 0.0044 |
| Congestive Heart failure| 16 (3.3)      | 18 (10.1) | 0.0004 |
| Cognitive impairment (MMSE < 24)d | 42 (8.6) | 30 (16.8) | 0.0026 |
| **Medications**         |               |          |
| Any cardiovascular medication | 320 (65.4) | 134 (74.86) | 0.024  |
| Psychotropic Medication | 30 (6.1)      | 16 (8.94) | 0.21   |
| **Biomarkers measures** |               |          |
| C-Reactive Protein, mean (SD), mg/L | 3.8 ± 12.3 | 5.3 ± 14.8 | 0.19   |
| Interleukin-6, mean (SD), pg/mL | 3.8 ± 7.5 | 4.2 ± 5.7 | 0.046  |

*Missing values = 12 from 680; ‡ Global test: $\chi^2$ or Fisher’s exact test for binary variables; analysis of variance for continuous variables.

a CESD-R, Center for Epidemiological Studies Depression Scale Revised
b Body mass index is calculated as weight in kilograms divided by height in meters squared
c Physical activity tertiles measured using the Physical Activity Scale for the Elderly
d Mini-Mental State Examination (MMSE) cut off point for cognitive impairment
(CESD-R Score ≥16). Analyses were adjust for the following groups of confounders: 1) other biomarkers (IL6, C-Reactive Protein); 2) socio-demographic conditions (age, gender, white race, education level, BMI, current smoker, alcohol use); 3) Health conditions (diabetes, hypertension, congestive heart failure, hyperlipidemia, cognitive status, any cardiovascular medications, coronary disease, previous stroke), and 4) physical activity level.

Subjects with missing data for depressive symptoms, sVCAM-1 and sICAM-1 were excluded. All analyses were performed using SAS software, version 9.3 (SAS Institute Inc, Cary, North Carolina). A two-sided P value of less than 0.05 was considered indicative of statistical significance.

### Results

#### 1. Subject Characteristics

As shown in Table 1, 489 (73.2 %) participants had no depression symptoms and 179 (26.8 %) had depressive symptoms. The mean IL6 was significantly higher in those with depression symptoms. 605 (90.6 %) had a least one cardiovascular disease, those with depression had significantly more co-morbidities (p < 0.0001) and performed less physical activity (p = 0.007) than those without.

Although IL6 was higher in the group with depressive symptoms, it was not linearly correlated with CESD-R score (r = 0.03 p = 0.32).

#### 2. Soluble VCAM-1 and Depression symptoms (CESD-R ≥16)

The mean sVCAM-1 concentration was 1177. ± 417 in the group without depressive symptoms (CESD-R < 16) and 1239 ± 451 in the group with depressive symptoms (CESD-R ≥ 16) (p = 0.036). Univariate logistic regression analyses showed associations between sVCAM-1 and many cardiovascular diseases, comorbidity index, and less physical activity (Table 2). The unadjusted model (Model 1) showed that the highest quintile of sVCAM-1 was associated with depression symptoms (CESD-R ≥16) (OR = 2.28 (1.24 – 3.84) p = 0.0066). After adjustment, the final multivariate logistic regression model (Model 4) showed that the highest quintile of sVCAM-1 compared to lowest quintile was significantly associated with depressive symptoms (CESD-R ≥16) (OR = 1.97 (1.14 – 3.57) p = 0.015) (Table 3).

#### 3. Soluble ICAM-1 and other biomarkers

sICAM-1 and hs-CRP concentrations were both weakly correlated with CESD-R score (respectively, r = 0.12 p = 0.0028 and r = 0.08 p = 0.046). After adjustment for sVCAM-1, age, gender, white race health condition and physical activity score, the final model showed no significant relationships between depressive symptoms and these biomarkers.

#### 4. Cerebral WMHs, sVCAM-1, and Depression symptoms

Table 4 summarizes the characteristics of the 25 participants with brain MRI data.

We observed that cerebral WMH volume was correlated with sVCAM-1 concentration (r = 0.47 p = 0.018) and the association still significant when adjusted for co-morbidity index (Fig 1). WMHs volumes were also higher among participants with CESD-R ≥16; 22.43 mL vs. 10.78 mL (p = 0.039)
but not reach statistical significance when adjusted for comorbidity index (p = 0.056).

**Discussion**

The results of this study showed cross-sectional associations between elevated plasma levels of sVCAM-1 and 1) depressive symptoms, and 2) cerebral white matter damage among older community-dwelling adults.

Research suggests that mood can become impaired when one or more of the brain’s frontal-subcortical circuits are damaged [28, 29]. Three of these circuits (dorsolateral prefrontal, lateral orbitofrontal, and medial frontal/anterior cingulate) play an important role in mood regulation, and damage in these areas produces a neurobehavioral syndrome. Previous studies suggested that a relationship between white matter hyperintensities, cerebral blood flow regulations [30, 31]. Brain endothelial dysfunction indicated by higher levels of sVCAM-1 may be a key pathogenic mechanism. Elevated levels of plasma sVCAM-1 concentration (>1200 ng/mL) may signal vascular damage in the cerebral white matter that carries axons from frontal-subcortical circuits involved in mood regulation. Furthermore, endothelial dysfunction may impair cerebral blood flow regulation, resulting in ischemic damage to these circuits [32, 33].

Previous work by our group and others [34] has shown that elevations in sVCAM-1 are associated with abnormal CO₂ vasoreactivity in the brain. Those with depressive

| Table 3 | Odds ratio from logistic regression relationship between levels of soluble VCAM-1 and depression symptoms (CESD-R score ≥16), No. = 668† |
|---------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Quintiles of sVCAM-1‡, Median (IQR), ng/mL                                                                 | P for trend |
| 736 (660–810)  | 937 (899–970)  | 1115 (1071–1169)  | 1332 (1277–1389)  | 1711 (1567–2011)  |
| No.          | 1.32  | 1.35  | 1.35  | 1.32  | 1.34  |
| Model 1 Odds ratio (95 % CI) | 1.00  | 1.58 (0.88-2.82)  | 1.68 (0.94-2.97)  | 1.59 (0.89-2.83)  | 2.18 (1.24-3.84)  |
| P value      | Reference  | 0.13  | 0.08  | 0.12  | 0.0066  | 0.011  |
| Model 2 Odds ratio (95 % CI) | 1.00  | 1.59 (0.89-2.86)  | 1.61 (0.90-2.87)  | 1.53 (0.85-2.74)  | 1.96 (1.09-3.51)  |
| P value      | Reference  | 0.12  | 0.10  | 0.15  | 0.024  | 0.025  |
| Model 3 Odds ratio (95 % CI) | 1.00  | 1.69 (0.93-3.08)  | 1.62 (0.90-2.92)  | 1.55 (0.85-2.82)  | 2.10 (1.17-3.78)  |
| P value      | Reference  | 0.12  | 0.11  | 0.15  | 0.024  | 0.026  |
| Model 4 Odds ratio (95 % CI) | 1.00  | 1.79 (0.95-3.39)  | 1.65 (0.88-3.07)  | 1.68 (0.89-3.17)  | 1.97 (1.14-3.57)  |
| P value      | Reference  | 0.07  | 0.12  | 0.11  | 0.015  | 0.030  |

†sVCAM-1: Soluble Vascular Cell Adhesion Molecule-1; CI, confidence interval; IQR, interquartile range.
‡Missing values = 12 from 680; Model 1: non adjusted; Model 2: adjusted for Biomarkers (IL6, C-Reactive Protein); Model 3: additionally adjusted for Socio-demographic condition (Age, gender, White race, Body Mass Index, Current Smoker, Alcohol use, physical activity); Model 4: additionally adjusted for Health conditions (Diabetes, Hypertension, Congestive Heart failure, Cognitive status, Any cardiovascular medications, Coronary disease, Previous stroke, any cardiovascular medication and psychotropic medication)

| Table 4 | Demographics and clinical characteristics of participants with MRIs at baseline, No =25 |
|----------|------------------------------------------------------------------------------------------------|
| Baseline Characteristics | MRI data |
| **Demographics** | |
| Age, mean (SD), y | 77.6 ± 6.3 |
| Women | 17 (68.0) |
| White Race | 23 (92.0) |
| Educational level, median (IQR), y | 16 [14–17] |
| **Medical condition** | |
| Comorbidity index, mean (SD) | 2.7 ± 1.9 |
| Cardiovascular disease | 24 (96.0) |
| **Medication** | |
| Any psychotropic medication | 3 (12.0) |
| Any cardiovascular medication | 16 (64.0) |
| **Brain imaging** | |
| White matter hyperintensities volume, mean (SD), mL | 15.84 ± 12.61 |
| White matter hyperintensities % ICC, mean (SD) | 1.08 ± 0.86 |
| **Biomarkers measures** | |
| C-Reactive Protein, Mean (SEM),mg/L | 1.6 ± 0.5 |
| Interleukin-6, Mean (SEM),pg/mL | 2.7 ± 0.6 |
| Soluble ICAM-1, Mean (SEM), ng/mL | 268 ± 19 |
| Soluble VCAM-1, Mean (SEM), ng/mL | 1172 ± 96 |

sVCAM-1: Soluble Vascular Cell Adhesion Molecule-1; sICAM-1: Soluble Inter Cellular Adhesion Molecule-1. *Missing values = 12 from 680 but not reach statistical significance when adjusted for comorbidity index (p = 0.056).
symptoms seem to have higher WMHs volumes, but in our small subsample with MRI data, this association did not reach statistical significance after adjustment for co-morbidities index.

This current study had some limitations: first, its cross-sectional design precludes investigating the temporal relation between CAMs and depressive symptoms. The second is that our population may not be representative of all older adults. We could only examine the relationship between sVCAM-1 and WMHs in a small subsample that was willing and able to undergo MRI studies, which may be not representative of the general population. The third is that we did not examine other mechanisms of depressive symptoms. The link between depressive symptoms and sVCAM-1 may be attributable, in part, to a common genetic vulnerability or to pathophysiologic factors, including increased platelet reactivity, an underlying inflammatory state, or situational stresses that may be associated with elevated sVCAM-1 plasma levels [35, 36]. We tried to address this in part, by controlling for the inflammatory biomarkers CRP and IL6 in the multivariable analysis and our results suggest that plasma levels of sVCAM-1 was independently associated with depression symptoms.

Conclusion
In summary, our study suggests that elevated plasma levels of sVCAM-1 may be a biomarker for the presence of cerebral microvascular disease in community-dwelling elderly people with symptoms of depression. It may be important to identify elderly people with high levels of sVCAM-1 as having a high risk of late life depression, and to treat their atherosclerotic and cardiovascular disease rigorously for secondary prevention. Additional prospective studies are needed to confirm our findings and determine whether sVCAM-1 can serve as a biomarker for cerebrovascular causes of depression.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
AET, GAW, and LAL were involved in the original study conception and design. AET, FAS and LAL designed the cohort study. GAW, FAS and LAL acquired the data for analysis. AET, GAW, TGT and LAL performed statistical analysis. AET, GAW, FAS, TGT, TD and LAL were responsible for interpretation of data. AET, GAW, FAS, TGT, TD and LAL drafted and wrote the paper. All authors read and approved the final manuscript.

Acknowledgements
This research was supported by grants NS085002, P01 AG04390 and R37 AG25037 from the National Institute on Aging and by grants R01-ES020871 and R00-ES015774 from the National Institute for Environmental Health Sciences. Dr. Wellenius has received consulting fees from Environmental Health and Engineering, Inc., for work unrelated to this manuscript. The authors declare no competing financial interests. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Dr. Tchalla was supported by the Limoges University, University Hospital Center of Limoges (CHU de Limoges) and Regional Council of Limousin from France. Dr. Lipsitz holds the Irving and Edyth S. Usen and Family Chair in Geriatric Medicine at Hebrew SeniorLife. We thank the MOBILIZE Boston research team and study participants for their time, effort, and dedication.

Author details
1Institute for Aging Research, Hebrew SeniorLife, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA; 2Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA; 3Harvard...
Medical School, Boston, Massachusetts, USA. 4Geriatric Medicine Department, IFR 145 GEIST, EA 6310 HAVAE (Disability, Activity, Aging, Autonomy and Environment), Limoges University, CHU Limoges, Limoges F-87025, France. 5Brown University School of Public Health, Providence, Massachusetts, USA. 6Department of Neurology, Stroke Division, Brigham and Women’s Hospital, 45 Francis St, Boston, MA 02115, USA.

Received: 22 January 2015 Accepted: 26 May 2015
Published online: 04 June 2015

References
1. Thielke SM, Diehr P, Unutzer J. Prevalence, incidence, and persistence of major depressive symptoms in the Cardiovascular Health Study. Aging Ment Health. 2010;14:168–76.
2. Gonzalez HM, Tarraf W. Comorbid cardiovascular disease and major depression among ethnic and racial groups in the United States. Int Psychogeriatr. 2013;25:833–41.
3. Arbelaez JJ, Ariyo AA, Crum RM, Fried LP, Ford DE. Depressive symptoms, inflammation, and ischemic stroke in older adults: a prospective analysis in the cardiovascular health study. J Am Geriatr Soc. 2007;55:1825–30.
4. Gilmour MM, Maseklo J, Gilman SE, Patton RK, Arvidsson M. Depressive symptoms predict incident stroke independently of memory impairments. Neuropsychology. 2010;24:363–70.
5. Ruo B, Rumsfeld JS, Hlatky MA, Liu H, Browner WS, Whooley MA. Depressive symptoms and health-related quality of life: the Heart and Soul Study. JAMA. 2003;290:215–21.
6. Mulvihill NT, Foley JB, Crean P, Walsh M. Prediction of cardiovascular risk using soluble cell adhesion molecules. Eur Heart J. 2002;23:1569–74.
7. Muller WA, Wiegl SA, Deng X, Phillips DM, PECAM-1 is required for transendothelial migration of leukocytes. J Exp Med. 1993;178:449–60.
8. Gearing AJ, Hemingway J, Pigott R, Hughes J, Rees AJ, Cashman SJ. Soluble forms of vascular adhesion molecules, E-selectin, ICAM-1, and VCAM-1: pathological significance. Ann N Y Acad Sci. 1992;667:324–31.
9. Gearing AJ, Newman W. Circulating adhesion molecules in disease. Immunol Today. 1993;14:506–12.
10. Hackman A, Abe Y, Insull Jr W, Pownall H, Smith L, Dunn K, et al. Levels of soluble cell adhesion molecules in patients with dyslipidemia. Circulation. 1996;93:1334–8.
11. Pigott R, Dillon LP, Hemingway JH, Gearing AJ. Soluble forms of E-selectin, ICAM-1 and VCAM-1 are present in the supernatants of cytokine activated cultured endothelial cells. Biochem Biophys Res Commun. 1992;187:384–9.
12. Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson M. Vascular depression hypothesis. Arch Gen Psychiatry. 1997;54:915–21.
13. Krishnan KR, Hays JC, Blazer DG. MRI-defined vascular depression. J Neurol Sci. 1996;137:69–76.
14. Kim JS. Cytokines and adhesion molecules in stroke and related diseases. J Neurol Sci. 1996;137:69–78.
15. Bench CJ, Friston KJ, Brown RG, Scott LC, Frackowiak RS, Dolan RJ. The anatomy of melancholia–focal abnormalities of cerebral blood flow in major depression. Psychol Med. 1992;22:2607–15.
16. Thomas AJ, Ferrier IN, Kalaria RN, Woodward SA, Ballard C, Oakley A, et al. Elevation in late-life depression of intercellular adhesion molecule-1 expression in the dorsolateral prefrontal cortex. Am J Psychiatry. 2000;157:1682–4.
17. Davis S, Thomas A, Perry R, Oakley A, Kalaria RN, O’Brien JT. Glial fibrillary acidic protein in late life major depressive disorder: an immunocytochemical study. J Neurol Neurosurg Psychiatry. 2002;73:556–60.
18. Schaefer M, Horn M, Schmidt F, Schmid-Wendtner MH, Volkenandt M, Ackennehl M, et al. Correlation between sICAM-1 and depressive symptoms during adjuvant treatment of melanoma with interferon-alpha. Brain Behav Immun. 2004;18:555–62.
19. Levelle SG, Kiel DP, Jones RN, Roman A, Hannan MT, Sorond FA, et al. The MOBILIZE Boston Study: design and methods of a prospective cohort study of novel risk factors for falls in an older population. BMC Geriatr. 2008;8:16.
20. Samelson EJ, Kelsey JL, Kiel DP, Roman AM, Cupples LA, Freeman MB, et al. Issues in conducting epidemiologic research among elders: lessons from the MOBILIZE Boston Study. Am J Epidemiol. 2008;168:1444–51.
21. Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”: a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12:189–98.
22. Escobar JI, Brinton A, Kamo M, Forsythe A, Landers VJ, Golding JM. Use of the Mini-Mental State Examination (MMSE) in a community population of mixed ethnicity. Cultural and linguistic artifacts. J Neurol Ment Dis. 1986;174:607–14.
23. Kohout FJ, Berkman LF, Evans DA, Corrinn-Huntley J. Two shorter forms of the CES-D (Center for Epidemiological Studies Depression) depression symptoms index. J Aging Health. 1993;5:179–93.
24. Farmer WE, Locke EZ, Moscicki EK, Dannenberg AL, Larson DB, Radloff LS. Physical activity and depressive symptoms: the NHANES I Epidemiologic Follow-up Study. Am J Epidemiol. 1988;128:1340–51.
25. Weissman MM, Sholomskas D, Potteiger M, Prussoff BA, Locke BZ. Assessing depressive symptoms in five psychiatric populations: a validation study. Am J Epidemiol. 1979;106:203–14.
26. Wang W, Albert CM, Sears Jr SF, Lamport R, Conti JR, Wang PJ, et al. Depression as a predictor for appropriate shocks among patients with implantable cardioverter-defibrillators: results from the Triggers of Ventricular Arhythmias (TOVA) study. J Am Coll Cardiol. 2005;45:1090–5.
27. Washburn RA, Smith KW, Jette AM, Janney CA, The Physical Activity Scale for the Elderly (PASE): development and evaluation. J Clin Epidemiol. 1993;46:153–62.
28. Trimble MR, Mendez MF, Cummings JL. Neuropsychiatric symptoms from the temporopolar lobes. J Neuropsychiatr Clin Neurosci. 1997;9:429–38.
29. Ferret T, Gaudreau P, Schumann-Bard P, Billard JM, et Papwa-Wagner A. « Mechanisms Underlying the Neuroprotective Effect of Brain Reserve against Late Life Depression ». Journal of Neural Transmission (Vienna, Austria:1996), 5 janvier 2014. doi:10.1007/s00702-013-1154-2.
30. Ungvari Z, Kaley G, de Cabo R, Sonntag WE, Csizas A. Mechanisms of vascular aging: new perspectives. J Gerontol A Biol Sci Med Sci. 2010;65:1038–41.
31. Sorond F, Ikely DK, Galica A, Moscufo N, Serrador JM, Iloputaife I, et al. Neurovascular Coupling is Impaired in Slow Walkers: The MOBILIZE Boston Study. Ann Neurol. 2011;70(2):213–20.
32. Parkayastha S, Fadar O, Mehregan A, Salat DH, Moscufo N, Meier DS, et al. Impaired cerebrovascular hemodynamics are associated with cerebral white matter damage. J Cereb Blood Flow Metab. 2013;34(2):228–134.
33. Seals DR, Jablonski KL, Donato AJ. Aging and vascular endothelial function in humans. Clin Sci (Lond). 2011;120:357–75.
34. Novak V, Zhao P, Manor B, Sejdic E, Alipio D, Abduljalil A, et al. Adhesion molecules, altered vasoreactivity, and brain atrophy in type 2 diabetes. Diabetes Care. 2011;34:2438–41.
35. Muelle JG, Vaccarino V. Cardiovascular Disease, Psychosocial Factors, and Genetics: The Case of Depression. Prog Cardiovasc Dis. 2013;55:557–62.
36. Popa-Wagner A, Buga AM, Tica AA, Albu CV. Perfusion Deficits, Inflammation and Aging Precipitate Depressive Behaviour. Biogerontology. 2014;15(5):439–48.

Submit your manuscript at: www.biomedcentral.com/submit

Submit your next manuscript to BioMed Central and take full advantage of: • Convenient online submission • Thorough peer review • No space constraints or color figure charges • Immediate publication on acceptance • Inclusion in PubMed, CAS, Scopus and Google Scholar • Research which is freely available for redistribution