Author’s response to reviews

Title: Elevated Circulating Vascular Cell Adhesion Molecule-1 (sVCAM-1) Is Associated With Concurrent Depressive Symptoms and Cerebral White Matter Hyperintensities in Older Adults.

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Author’s response to reviews: see over
Dear Editor;

We greatly appreciate your interest in publishing our manuscript, referenced above, and have responded to the reviewers’ helpful suggestions in the attached revised version. We believe the paper is much improved as a result. Our responses to each of the reviewer’s comments are itemized below.

As you requested the revised manuscript conforms to the *BMC Geriatrics* journal style. The added text to the manuscript is highlighted in yellow.

We look forward to seeing our work published in *BMC Geriatrics*. Thank you for your consideration.

Sincerely,

Achille Tchalla MD PhD

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**RESPONSE TO REVIEWERS – BMC GERIATRICS - MS: 1509127810157825**

Elevated Circulating Vascular Cell Adhesion Molecule-1 (sVCAM-1) Is Associated with Concurrent Depressive Symptoms and Cerebral White Matter Hyperintensities in Older Adults.
Older Adults.

Achille E Tchalla, Gregory A Wellenius, Farzaneh A Sorond, Thomas G Travison, Thierry Dantoine and Lewis A Lipsitz

Reviewer 1: Aurel Popa-Wagner report:

Comments: Aging is associated with depressive symptoms. In human studies, increased concentrations of circulating Vascular Cell Adhesion molecule-1 (sVCAM-1) and Intercellular Adhesion Molecule-1 (sICAM-1) are associated with systemic inflammatory and cardiovascular diseases and therefore with an increased risk of hypertension and atherosclerosis. In this study the authors hypothesized that elevated plasma concentrations of circulating CAMs associated with aging may be a marker of depressive symptoms due to cerebral vascular disease. 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. This is a well done study.

Thank you for this comment.

However, the inclusion criteria were not very stringent; for example, the inflammatory status should have been evaluated prior to enrollment. The authors should justify this omission.

The inflammatory status of all participants was assessed using the inflammatory biomarkers Il-6 and CRP. These are included in Table 1 showing baseline subject characteristics and are used as covariates in our analyses.
Nevertheless, the percent of patients with depressive behaviour is reasonable.

*Thank you for this comment.*


*Thank you for this comment. We have added these two relevant references on pages 16, 17.*

**Reviewer: Jukka Jolkkonen report**

This is a short paper describing possible association between blood VCAM-1 and depressive symptoms in the elderly people. White matter changes were studied in a subgroup of participants. The results suggest that endothelial dysfunction is indeed related to depressive symptoms.

I have the following minor comments and concerns:

1. The Authors shortly present the hypothesis that late-life depression might be due to cerebrovascular disease. The examples given, however, show just causal relationships.

*Thank you for pointing this out. Previous work by Alexopoulos and a recent study by Popa-Wagner et al. 2014 suggest a vascular cause of depression in some patients, as well as complex relationships between depression, aging,
inflammation and perfusion deficits. This work supports our hypothesis that late-life depression might be due to cerebrovascular disease. We have added these references in the manuscript on page 17.

2. Please explain how the participants were selected for MRI study. Eligible and willing participants were imaged for a substudy of the MOBILIZE Boston that examined the relationships between white matter hyperintensities, cerebral blood flow regulations, and gait abnormalities (Sorond F et al 2011; Purkayastha S et al 2014):


- Purkayastha S, Fadar O, Mehregan A, Salat DH, Moscufo N, Meier DS, Guttmann CR, Fisher ND, Lipsitz LA, Sorond FA. Impaired cerebrovascular hemodynamics are associated with cerebral white matter damage. Journal of Cerebral Blood Flow & Metabolism. 2014 Feb; 34(2); 228-134. PMID: 24129749. PMC3915198].

We studied the 25 participants who completed the MRI study. We added this to the manuscript text on page 7 and the references on pages 16, 17.

3. The correlation between VCAM (and ICAM) and depressive score was weak. Did the Authors measure any other markers?
Yes, we measured inflammatory markers as IL6 and CRP as indicated in the table below.

<table>
<thead>
<tr>
<th>Inflammatory markers</th>
<th>CESD-R Score</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 16 (n=489, 73%)</td>
<td>≥ 16 (n=179, 26%)</td>
<td>P Value</td>
<td></td>
</tr>
<tr>
<td>C-Reactive Protein, mean (SD), mg/L</td>
<td>3.8±12.3</td>
<td>5.3±14.8</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>Interleukin-6, mean (SD), pg/mL</td>
<td>3.8±7.5</td>
<td>4.2±5.7</td>
<td>0.046</td>
<td></td>
</tr>
</tbody>
</table>

4. The sentence in the line 244 is incomplete.

Thank you for pointing this out. We completed this in the manuscript text on page 12.