Peer Community In Registered Reports

White matter lessions are associated with increases in blood pressure and global cognitive decline

A recommendation by ***Chris Chambers*** *based on peer reviews by* ***Isabel Garcia Garcia*** *of the STAGE 2 REPORT:*

Frauke Beyer, Laurenz Lammer, Markus Loeffler, Steffi Riedel-Heller, Stéphanie Debette, Arno Villringer, A. Veronica Witte (2024) Progression of white matter hyperintensities is related to blood pressure increases and global cognitive decline – a registered report. OSF, ver. 2, peer-reviewed and recommended by Peer Community in Registered Reports.
https://doi.org/10.17605/OSF.IO/REA4W

Submitted: 21 February 2024, Recommended: 22 April 2024

Cite this recommendation as:
Chambers, C. (2024) White matter lessions are associated with increases in blood pressure and global cognitive decline. *Peer Community in Registered Reports*, 100717. 10.24072/pci.rr.100717

Published: 22 April 2024

Cerebral small vessel disease (CSVD) is a common and multi-faceted set of pathologies that affect the small arteries, arterioles, venules and capillaries of the brain. The disease manifests through a range of symptoms and conditions, including psychiatric disorders, abnormal gait, and urinary incontinence, while accounting for 25% of strokes and nearly 50% of dementia. The presence of CSVD is associated with white matter lesions detected as white matter hyperintensities (WMH) using neuroimaging, which have in turn been shown to predict future stroke, cognitive decline and dementia. While vascular risk factors of CSVD (such as hypertension and obesity) are also associated with CSVD, a complete picture of the predictive relationship between WMH, cognitive decline, and blood pressure remains to be determined, as does the role of sex/gender. These inter-relationships are important to determine for improving the diagnosis and treatment of CSVD. In the current study, Beyer et al. analysed a large emerging dataset from the LIFE-Adult project – a longitudinal, two-wave, population-based study – to ask whether higher blood pressure predicts a greater increase in WMH, and whether progression of WMH is associated with measures of memory and executive function. In addition, the authors explored the relationship between abdominal obesity and WMH progression, and the extent to which WMH progression, and its interaction with vascular risk factors, depends on sex/gender. Results revealed no reliable association between baseline blood pressure with WMH progression. WMH progression significantly predicted global cognitive decline but not decline in executive function specifically. Exploratory analyses revealed that increases in diastolic blood pressure as well as baseline and systolic blood

pressure were associated with WMH progression, specifically in frontal periventricular regions, but there was no association of waist-to-hip ratio (a proxy of abdominal fat deposits) with WMH progression nor any gender-specific associations. The authors conclude that strict control of blood pressure might confer a protective effect, limiting WMH progression and negative effects on global cognitive function in the middle-aged to older population. The Stage 2 manuscript was evaluated over one round of in-depth review. Based on responses to the reviewer's comments, the recommender judged that the manuscript met the Stage 2 criteria and awarded a positive recommendation. **URL to the preregistered Stage 1 protocol:** https://osf.io/qkbgj **Level of bias control achieved:** Level 2. *At least some data/evidence that was used to answer the research question had been accessed and partially observed by the authors prior to Stage 1 in-principle acceptance, but the authors certify that they had not yet observed the key variables within the data that were used to answer the research question.*
List of eligible PCI RR-friendly journals:

- Brain and Neuroscience Advances
- Cortex
- F1000Research
- Imaging Neuroscience
- In&Vertebrates
- NeuroImage: Reports
- Peer Community Journal
- PeerJ
- Royal Society Open Science

References:

1. Beyer, F., Lammer, L., Loeffler, M., Riedel-Heller, S., Debette, S., Villringer, A. & Witte, A. V. (2023). Progression of white matter hyperintensities is related to blood pressure increases and global cognitive decline – a registered report [Stage 2]. Acceptance of Version 2 by Peer Community in Registered Reports. https://osf.io/k24pm

Reviews

Evaluation round #1

DOI or URL of the preprint: **https://osf.io/gmn6q**
Version of the preprint: 1

Authors' reply, 12 April 2024

Dear Dr. García-García and dear Dr. Chambers,
thank you very much for your reviews and comments on the stage 2 manuscript.
Please find below my replies to your comments:

Comment 1: I highlighted the interpretation supported by the data in Table 7 in bold.

Comment 2: I was surprised by the lack of results regarding waist-to-hip ratio. In my experience, measuring waist-to-hip ratio can be prone to errors, specially in population datasets where multiple evaluators are involved. Have the authors checked if this variable correlates well with other indicators of obesity (such as visceral fat, if available in the dataset)? Was there any standardized operational procedure to ensure consistency across evaluators?

Answer: We agree that waist-to-hip ratio could be prone to errors where multiple raters might perfom the measurement differently. Standard operating procedures have been in place in the LIFE-Adult center to ensure that raters chose the same anatomical locations for waist and hip measurement, yet, there might be considerable variability. In a subset of 251 individuals from our cohort, we could check the association of WHR and visceral (VAT) and subcutaneous fat (SCAT) measured via abdominal MRI. There was a robust correlation of VAT and WHR (r=0.75), and a slightly smaller correlation of VAT divided by SCAT and WHR (r=0.62). We therefore believe that even though WHR might have been a slightly flawed measure, it still captured abdominal obesity fairly well in this sample. Also, higher WHR was related to higher WMH volume, although not nominally significant (e.g. Figure 2). A lack of power might therefore be the reason we did not detect a significant effect here. We edited the discussion accordingly.

Comment 3: When reporting the list of assessments related to executive functions, a description of semantic fluency is missing, while this variable appears right after in the calculation of the index.

Answer: We added a sentence describing the tests used from the CERAD battery, including the Animals-Test for semantic fluency.

Comment 4: The authors were clear and transparent regarding how missing data has been handled and inputed. Perhaps in Table 1 they could include the percentage of data that was missing for each variable.

Answer: We agree that this has not been clearly reported, and also realized that numbers of imputed data points depended on baseline and followup assessments. We therefore expanded Table 1 to include the number of available datapoints (N) per measure and timepoint. CESD was the variable with highest amount of missing, and antihypertensive medication had more missings at followup than baseline.

Looking forward to your response and with best wishes,
Frauke Beyer

Download tracked changes file

Decision by Chris Chambers, posted 18 March 2024, validated 18 March 2024

Minor Revision

One of the reviewers from Stage 1 was available to assess your completed Stage 2 submission, and I have decided based on this evaluation and my own reading that we can proceed with an interim Stage 2 decision. As you will see from the enclosed comments, the reviewer is broadly satisified with your submission – I concur and feel that it is already very close to meeting the Stage 2 criteria. The reviewer offers some useful remarks for consideration in a revision/response.

In addition to addressing these points, I would also recommend adding a column to the right of the study design table (Table 7) that reports the outcome in each case (i.e. whether the hypothesis was confirmed or disconfirmed).

I look forward to receiving your revised submission and response.

Reviewed by Isabel Garcia Garcia, 14 March 2024

This longitudinal study examines the associations between blood pressure, abdominal obesity, and progression of white matter hyperintensities progression after 6 years in a community-dwelling population with a

mean age of 63 years, and with a relatively low burden of white matter hyperintensities at baseline (1.88 cm3). The power analyses was extensively described, and I appreciated that the authors presented results from both linear models using change scores and linerar mixed models, and discussed the small differences of results obtained with each analysis.

Overall, this is an excellent study and I only have a few minor comments:

- I was surprised by the lack of results regarding waist-to-hip ratio. In my experience, measuring waist-to-hip ratio can be prone to errors, specially in population datasets where multiple evaluators are involved. Have the authors checked if this variable correlates well with other indicators of obesity (such as visceral fat, if available in the dataset)? Was there any standardized operational procedure to ensure consistency across evaluators?

- When reporting the list of assessments related to executive functions, a description of semantic fluency is missing, while this variable appears right after in the calculation of the index.

- The authors were clear and transparent regarding how missing data has been handled and inputed. Perhaps in Table 1 they could include the percentage of data that was missing for each variable.