**Proceedings Paper:**
Menze, I., Bernal Moyano, J., Kaya, P. et al. (53 more authors) (2024) Interrelationship between perivascular spaces and white matter hyperintensities: A latent growth curve analysis. In: Alzheimer's & Dementia: The Journal of the Alzheimer's Association. Alzheimer's Association International Conference 2024 (AAIC 2024), 28 Jul - 01 Aug 2024, Philadelphia, USA. Wiley

https://doi.org/10.1002/alz.095224

DOI: 10.1002/alz.095224

BIOMARKERS

POSTER PRESENTATION

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

NEUROIMAGING

# Interrelationship between perivascular spaces and white matter hyperintensities: A latent growth curve analysis

**Inga Menze**[1,2] | Jose Bernal Moyano[1,2,3] | Pinar Kaya[1,4] | Cagla Aki[1,4] | Malte Pfister[4] | Jonas Geisendörfer[4] | Renat Yakupov[1,2] | Roberto Duarte[3] | Maria del C. Valdes Hernandez[3] | Michael T. Heneka[5] | Frederic Brosseron[6] | Matthias Schmid[6,7] | Wenzel Glanz[1,2] | Enise I Incesoy[1,2,8] | Michaela Butryn[1,2] | Ayda Rostamzadeh[9] | Dix U. Meiberth[6,9] | Oliver Peters[10,11] | Lukas Preis[10] | Dominik Lammerding[10] | Daria Gref[10] | Josef Priller[11,12,13,14] | Eike Jakob Spruth[11,14] | Slawek Altenstein[11,14] | Andrea Lohse[14] | Stefan Hetzer[15] | Anja Schneider[6,16] | Klaus Fliessbach[6,16] | Okka Kimmich[6] | Ina R Vogt[6] | Jens Wiltfang[17,18,19] | Claudia Bartels[17] | Björn H. Schott[17,18,20] | Niels Hansen[17] | Peter Dechent[21] | Katharina Buerger[22,23] | Daniel Janowitz[22] | Robert Perneczky[23,24,25,26] | Boris-Stephan Rauchmann[26,27,28] | Stefan Teipel[29,30] | Ingo Kilimann[29,30] | Doreen Goerss[29,30] | Christoph Laske[31,32] | Matthias H. J. Munk[31,33] | Carolin Sanzenbacher[31] | Petra Hinderer[31] | Klaus Scheffler[34] | Annika Spottke[6,35] | Nina Roy-Kluth[6] | Falk Lüsebrink[1] | Katja Neumann[4] | Joanna M Wardlaw[3] | Frank Jessen[6,9,36] | Stefanie Schreiber[1,4] | Emrah Düzel[1,2] | Gabriel Ziegler[1,2]

[1]German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany

[2]Institute of Cognitive Neurology and Dementia Research (IKND), Otto-von-Guericke University, Magdeburg, Germany

[3]Centre for Clinical Brain Sciences, The University of Edinburgh, Edinburgh, Scotland, United Kingdom

[4]Department of Neurology, Otto-von-Guericke University, Magdeburg, Germany

[5]Luxembourg Centre for Systems Biomedicine (LCSB), University of Luxembourg, Luxembourg, Luxembourg

[6]German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany

[7]Institute of Medical Biometry, Informatics and Epidemiology, University Hospital Bonn, Bonn, Germany

[8]Department of Psychiatry and Psychotherapy, Otto-von-Guericke University, Magdeburg, Germany

[9]Department of Psychiatry and Psychotherapy, Medical Faculty, University of Cologne, Cologne, Germany

[10]Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin – Institute of Psychiatry and Psychotherapy, Berlin, Germany

[11]German Center for Neurodegenerative Diseases (DZNE), Berlin, Germany

[12]School of Medicine, Technical University of Munich; Department of Psychiatry and Psychotherapy, Munich, Germany

[13]University of Edinburgh and UK DRI, Edinburgh, United Kingdom

[14]Department of Psychiatry and Psychotherapy, Charité, Berlin, Germany

[15]Berlin Center for Advanced Neuroimaging, Charité – Universitätsmedizin Berlin, Berlin, Germany

[16]Department of Neurodegenerative Diseases and Geriatric Psychiatry, University of Bonn Medical Center, Bonn, Germany

[17]Department of Psychiatry and Psychotherapy, University Medical Center, University of Goettingen, Goettingen, Germany

[18]German Center for Neurodegenerative Diseases (DZNE), Goettingen, Germany

[19]Neurosciences and Signaling Group, Institute of Biomedicine (iBiMED), Department of Medical Sciences, University of Aveiro, Aveiro, Portugal

[20]Leibniz Institute for Neurobiology, Magdeburg, Germany

[21]21MR-Research in Neurosciences, Department of Cognitive Neurology, Georg-August-University Goettingen, Goettingen, Germany

[22]Institute for Stroke and Dementia Research (ISD), University Hospital, LMU, Munich, Germany

[23]German Center for Neurodegenerative Diseases (DZNE), Munich, Germany

[24]Imperial College London, London, United Kingdom

[25]Munich Cluster for Systems Neurology (SyNergy), Munich, Germany

[26]Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Munich, Germany

[27]Sheffield Institute for Translational Neuroscience, University of Sheffield, Sheffield, United Kingdom

[28]Department of Neuroradiology, LMU University Hospital, Munich, Germany, Munich, Germany

[29]Department of Psychosomatic Medicine, Rostock University Medical Center, Rostock, Germany

[30]German Center for Neurodegenerative Diseases (DZNE), Rostock, Germany

[31]German Center for Neurodegenerative Diseases (DZNE), Tuebingen, Germany

[32]Section for Dementia Research, Hertie Institute for Clinical Brain Research and Department of Psychiatry and Psychotherapy, University of Tuebingen, Tuebingen, Germany

[33]Department of Psychiatry and Psychotherapy, University of Tuebingen, Tuebingen, Germany

[34]Department of Biomedical Magnetic Resonance, Tuebingen, Germany

[35]Department of Neurology, University of Bonn, Bonn, Germany

[36]Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Cologne, Germany

**Correspondence**
Inga Menze, German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany.
Email: Inga.Menze@dzne.de

## Abstract

**Background:** Inadequate glymphatic clearance through perivascular spaces (PVS) is hypothesized to contribute to the formation of white matter hyperintensities (WMH). However, longitudinal evidence for such a mechanistic link in aging remains limited. Using multivariate modelling, we investigated the interrelationship between PVS and WMH over time to elucidate potential cascades of early cerebrovascular alterations and tested whether AD-biomarkers and inflammatory markers associated with vascular disease can explain individual variability in their occurrence and progression.

**Methods:** We quantified PVS and WMH using T1w MPRAGE and T2w FLAIR imaging of 439 cognitively unimpaired participants from the DELCODE study (52.85% females; $mean_{age}$ = 69.88±5.72), who underwent annual scans over a four-year period and attended at least three visits ($n_{observations}$ = 1790; $mean_{number\ of\ visits}$ = 4.08±0.79). We employed latent growth curve modelling to assess reciprocal connections between PVS and WMH, focusing on their initial volumes (latent intercepts) and their rates of change over four years (latent slopes). We used log10-transformed total PVS and WMH volumes, and controlled for age, sex, years of education, total cardiovascular risk score, and total intracranial volume. We then derived interindividual latent factor scores and tested their relation to CSF-derived AD-biomarkers (Aβ42/40, pTau181; available for $n$ = 195; z-scored) and inflammatory markers (CRP, IL-6; available for $n$ = 125; Box-Cox-transformed) via Spearman's correlation (FDR-corrected).

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION



**Results:** The model showed good model fit (*CFI* = 0.997; *RMSEA* = 0.021; *SRMR* = 0.017; **Fig. 1A**). WMH and PVS volumes increased over time ($intercept_{WMH\text{-}slope}$ = 0.068, *SE* = 0.004, *Z* = 16.490, $p<0.001$; $intercept_{PVS\text{-}slope}$ = 0.036, *SE* = 0.007, *Z* = 4.927, $p<0.001$; **Fig. 1B**). Participants with higher baseline PVS volumes not only had higher baseline WMH volumes ($covariance_{PVS\text{-}intercept\&WMH\text{-}intercept}$ = 0.120, *SE* = 0.040, *Z* = 2.936, $p$ = 0.003; **Fig. 1C**) but also tended to exhibit faster WMH volume increase over time ($covariance_{PVS\text{-}intercept\&WMH\text{-}slope}$ = 0.007, *SE* = 0.004, *Z* = 1.796, $p = 0.072$; **Fig. 1C**). In this sample of cognitively unimpaired participants, biomarkers of AD and inflammation did neither relate to individual baseline differences nor progression rates (**Table 1**).

**Conclusion:** Our findings are consistent with the notion that PVS dysfunction might contribute to and precede WMH progression (**Fig. 1D**). However, the individual variability requires further investigation to elucidate mechanisms driving PVS dysfunction in the first place. Unraveling the interrelationships and further factors contributing to cerebrovascular alterations will be crucial to understand pathological cascades in aging that could inform targeted treatment strategies.

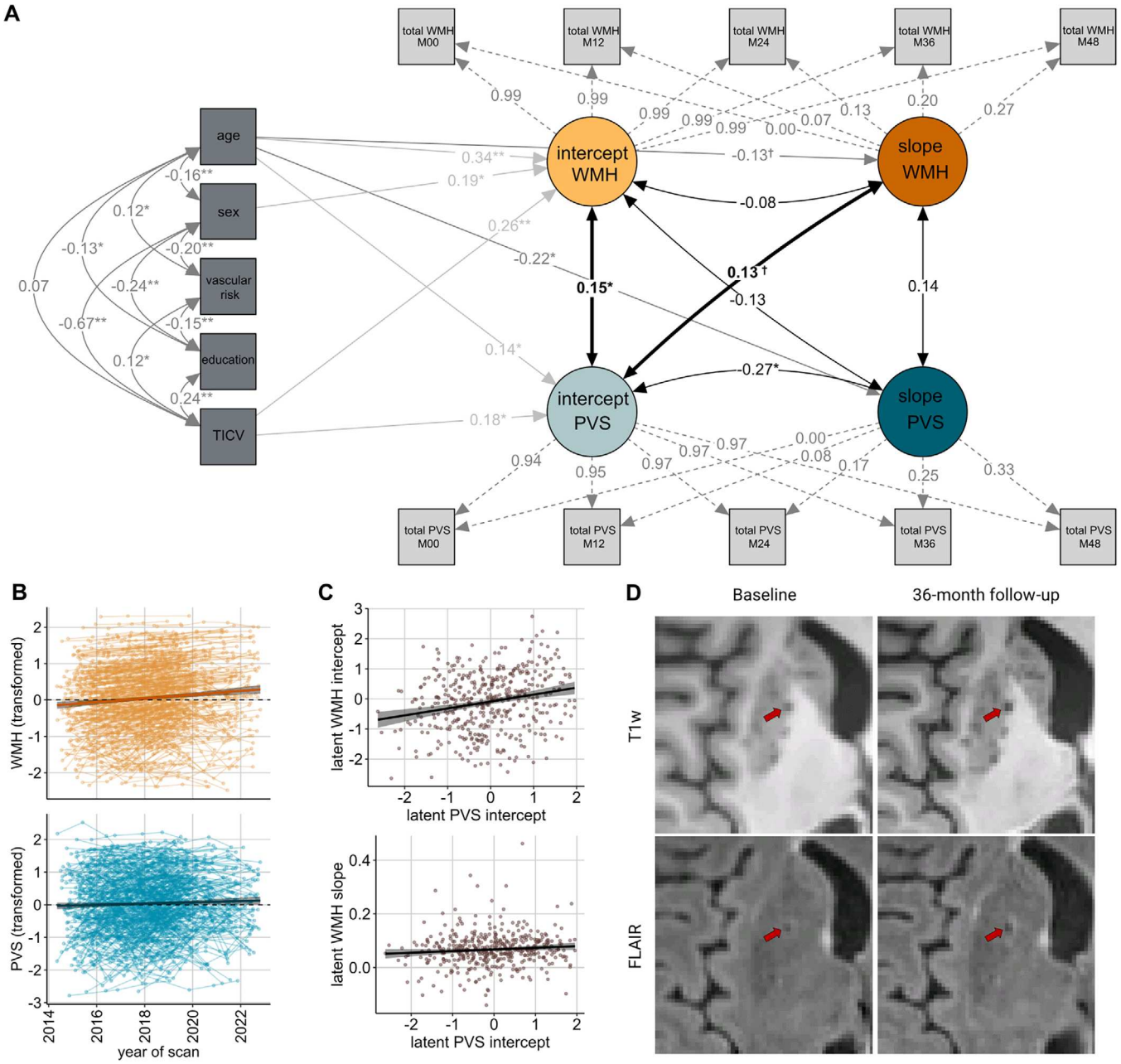


**Figure 1.** Four-year interrelation between perivascular spaces (PVS) and white matter hyperintensities (WMH). **(A)** Latent growth curve model on the 4-year interrelation between PVS and WMH. For reasons of readability, only significant paths of covariates onto latent intercepts and latent slopes are plotted. Standardized solutions are shown. Relations between latent variables were the main interest of this work. Baseline estimates of PVS and WMH are related to another. Moreover, there is a trend of an association between baseline PVS volumes and WMH progression. **p<0.001, *p<0.05, †p<0.10. **(B)** Interindividual trajectories of WMH (upper panel) and PVS (lower panel) over four years. PVS and WMH volumes were log-10 transformed and z-scored. **(C)** Associations of baseline PVS with WMH at baseline (upper panel) as well as with WMH progression (lower panel). For visualisation we extracted interindividual estimated values for the latent intercepts and latent slopes. **(D)** Example images of a subject, showing that within three years, WMH can form around a PVS.

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION



**Table 1.** Spearman's correlation between CSF-derived biomarkers and latent intercepts and slopes of the latent growth curve model. We used model derived interindividual latent factor scores, and CSF derived AD-biomarkers (z-scored) as well as inflammation markers associated with cerebrovascular disease (boxcox-transformed). All correlations were non-significant.

| | | CSF derived biomarkers | | | |
|---|---|---|---|---|---|
| | | Aβ42/40 | pTau181 | IL-6 | CRP |
| Latent factors | Latent PVS intercept | 0.041 | -0.048 | 0.014 | -0.054 |
| | Latent PVS slope | -0.046 | -0.011 | 0.071 | 0.052 |
| | Latent WMH intercept | 0.022 | -0.142 | -0.102 | -0.174 |
| | Latent WMH slope | -0.090 | 0.030 | 0.092 | -0.015 |