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

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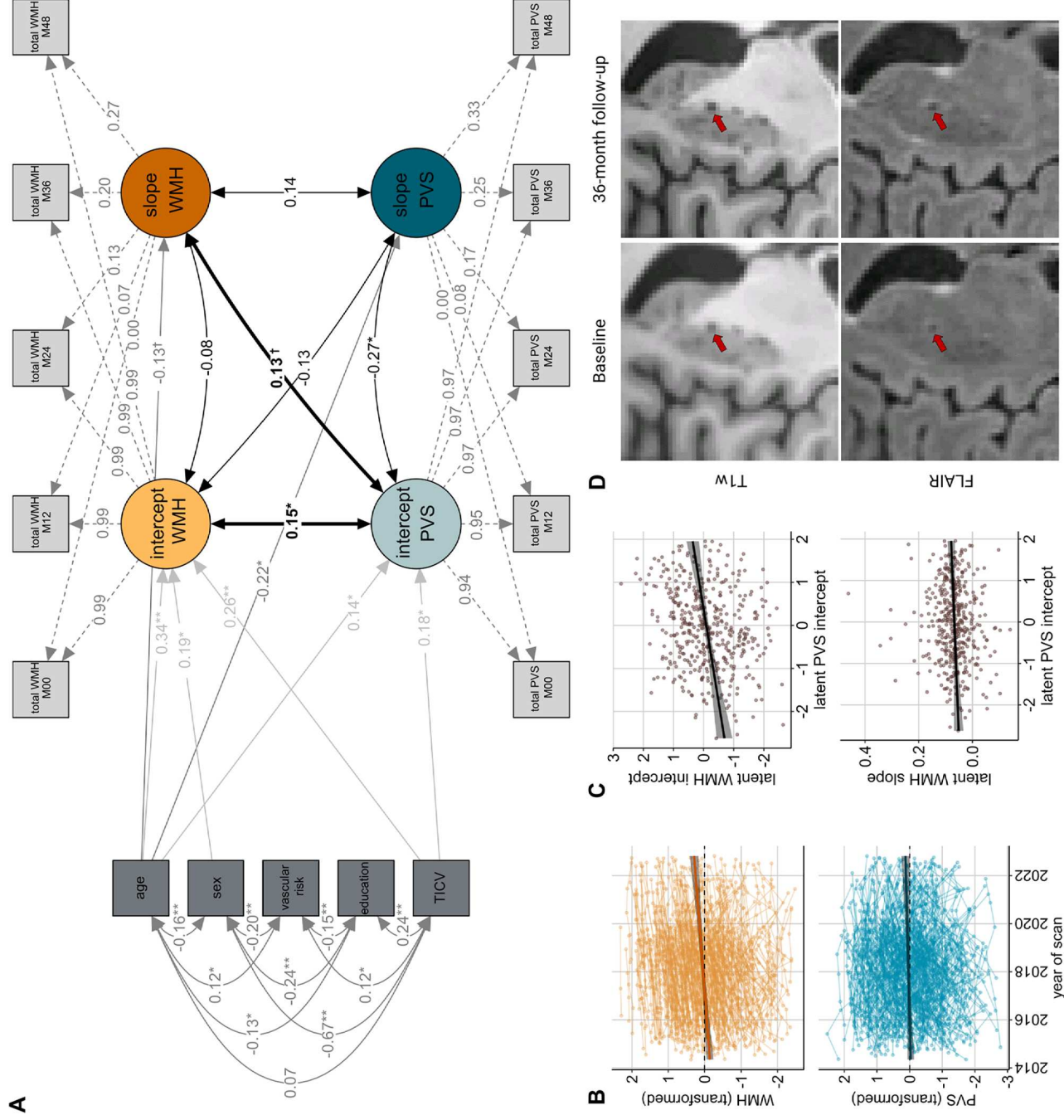
#### Abstract

**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<sub>age</sub> = 69.88±5.72), who underwent annual scans over a four-year period and attended at least three visits ( $n_{\text{observations}} = 1790$ ; mean<sub>number of visits</sub> = 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 log<sub>10</sub>-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 (A $\beta$ <sub>42</sub>/40, pTau<sub>181</sub>; 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).

**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 ( $intercept_{WMH-slope} = 0.068$ ,  $SE = 0.004$ ,  $Z = 16.490$ ,  $p < 0.001$ ;  $intercept_{PVS-slope} = 0.036$ ,  $SE = 0.007$ ,  $Z = 4.927$ ,  $p < 0.001$ ; **Fig. 1B**). Participants with higher baseline PVS volumes not only had higher baseline WMH volumes ( $covariance_{PVS-intercept\&WMH-intercept} = 0.120$ ,  $SE = 0.040$ ,  $Z = 2.936$ ,  $p = 0.003$ ; **Fig. 1C**) but also tended to exhibit faster WMH volume increase over time ( $covariance_{PVS-intercept\&WMH-slope} = 0.007$ ,  $SE = 0.004$ ,  $Z = 1.796$ ,  $p = 0.072$ ; **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.

**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.

Latent factors	CSF derived biomarkers			
	A $\beta$ 42/40	pTau181	IL-6	CRP
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