

## **Supplementary Material**

**Title:** Combined neuropathological pathways account for age-related risk of dementia

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**Table s1.** Results of Confirmatory Factor Analysis of Four Brain Structure Latent Constructs

Observed Variable	Latent Variable Factor Loadings:				Unique variance
	Standardized Parameter (Standard Error)				
	Vessels	Infarcts	Neocortical Tangles	Mesiotemporal Tangles	
Arteriosclerosis	.56 (.04)				.69 (.04)
Atherosclerosis	.59 (.04)				.66 (.05)
Gross infarcts		.82 (.09)			.32 (.14)
Microinfarcts		.33 (.04)			.89 (.03)
Tangles-IP			.86 (.01)		.26 (.02)
Tangles-MF			.80 (.01)		.37 (.02)
Tangles-MT			.77 (.02)	.21 (.02)	.21 (.02)
Tangles-EC				.79 (.02)	.38 (.03)
Tangles-Hip				.78 (.02)	.39 (.03)
Latent Variable Inter-correlations					
Vessels	1.00 (.)				
Infarcts	.53 (.07)	1.00 (.)			
Neocortical Tangles	.00 (.04)	-.02 (.04)	1.00 (.)		
Mesiotemporal Tangles	.10 (.04)	.03 (.04)	.50 (.03)	1.00 (.)	

Note:  $N = 1362$ . Fit statistics for final confirmatory factor analysis model were  $\chi^2(20) = 29.57$ ,  $p = .08$ ; RMSEA = .019, CI = [.000, .032]; CFI = .997; TLI = .995; and SRMR = .017.

Abbreviations: Tangles-EC: neurofibrillary tangles in the entorhinal cortex, Tangles-Hip: neurofibrillary tangles in the hippocampus, Tangles-IP: neurofibrillary tangles in the inferior parietal cortex, Tangles-MF: neurofibrillary tangles in the midfrontal cortex, Tangles-MT: neurofibrillary tangles in the midtemporal cortex.

**Table s2:** Standardized Regression Coefficient (Standard Errors) for Structural Model 5 and Model 5a, Including All Four Pathways to Dementia

Predictor	Criterion									
	Vessels	Neuritic plaques	Infarcts	Neocort Tangles	Mesio Tangles	CAA	Lewy Bodies	TDP-43	HS	Dementia
Model 5: Full model										
Age	.24 (.04)	.08 (.03)	.07 (.04)	-.04 (.03)	.22 (.03)	.13 (.03)	-.01 (.05)	.18 (.04)	.14 (.04)	.01 (.04)
Vessels		-.01 (.05)	.55 (.06)							.17 (.07)
Neuritic plaques				.55 (.01)	.55 (.02)	.27 (.02)	.20 (.05)	.27 (.03)		
Infarcts										.18 (.07)
Neocort Tangles										.32 (.03)
Mesio Tangles										.14 (.05)
CAA										.08 (.03)
Lewy bodies										.30 (.05)
TDP-43									.57 (.04)	.03 (.06)
HS										.37 (.08)
Model 5a: Constrain non-significant paths to be absent										
Age	.27 (.04)	.05 (.03)	--- <sup>a</sup>	--- <sup>a</sup>	.23 (.03)	.14 (.03)	--- <sup>a</sup>	.18 (.04)	.14 (.05)	.00 (.04)
Vessels		--- <sup>a</sup>	.59 (.06)							.17 (.08)
Neuritic plaques				.55 (.01)	.55 (.02)	.26 (.02)	.20 (.05)	.27 (.03)		
Infarcts										.17 (.07)
Neocort Tangles										.33 (.03)
Mesio Tangles										.13 (.04)
CAA										.08 (.03)
Lewy bodies										.30 (.04)
TDP-43									.58 (.04)	--- <sup>a</sup>
HS										.40 (.05)

Note: N=1362, Abbreviations: CAA: cerebral amyloid angiopathy; HS: hippocampal sclerosis; Mesio tangles: mesiotemporal neurofibrillary tangles; Neocort tangles: neocortical neurofibrillary tangles, TDP-43: TAR DNA-binding protein 43.

<sup>a</sup> Constrained non-significant path to zero