

# Supplementary Material

## Contributions of Vascular Burden and Amyloid Abnormality to Cognitive Decline in Memory Clinic Patients

**Supplementary Table 1.** Associations between cortical microbleeds, amyloid abnormality, and their interaction on cognitive decline.

<b>Model</b>		<b>Cortical MB</b>	<b>A+</b>	<b>Cortical MB x A+</b>	
<b>MMSE</b> <b>(range 0-30)</b>	<i>N</i>	205	205	205	
	<i>Model 1</i>	<i>B [CI]</i>	-0.93 [-1.82--0.03]	0.19 [-1.59-1.98]	1.01 [-0.85-2.87]
	<i>p</i>	0.042	0.83	0.29	
	<i>Model 2</i>	<i>B [CI]</i>	-0.69 [-1.48-0.09]	1.12 [0.63-1.62]	
	<i>p</i>	0.08	<b>&lt;0.001</b>		
<b>Memory Delayed recall</b> <b>(Z-score)</b>	<i>N</i>	141	141	141	
	<i>Model 1</i>	<i>B [CI]</i>	-0.23 [-0.51 – 0.04]	-0.07 [-0.50-0.36]	0.21 [-0.24-0.65]
	<i>p</i>	0.10	0.74	0.36	
	<i>Model 2</i>	<i>B [CI]</i>	-0.15 [-0.37-0.06]	0.12 [0.02-0.23]	
	<i>p</i>	0.16	<b>0.02</b>		
<b>Processing speed</b> <b>(Z-score)</b>	<i>N</i>	92	92	92	
	<i>Model 1</i>	<i>B [CI]</i>	-0.10 [-0.47-0.28]	-0.11 [-0.74-0.53]	0.30 [-0.36-0.96]
	<i>p</i>	0.60	0.74	0.37	
	<i>Model 2</i>	<i>B [CI]</i>	0.00 [-0.31-0.30]	0.17 [0.02-0.33]	
	<i>p</i>	0.99	<b>0.03</b>		
<b>Executive functions</b> <b>(Z-score)</b>	<i>N</i>	74	74	74	
	<i>Model 1</i>	<i>B [CI]</i>	-0.43 [0.03-0.82]	0.29 [-0.35-0.93]	-0.16 [-0.82-0.49]
	<i>p</i>	0.03	0.38	0.62	
	<i>Model 2</i>	<i>B [CI]</i>	0.37 [0.06-0.69]	0.13 [-0.02-0.28]	
	<i>p</i>	<b>0.02</b>	0.08		
<b>Verbal fluency</b> <b>(Z-score)</b>	<i>N</i>	137	137	137	
	<i>Model 1</i>	<i>B [CI]</i>	-0.31 [-0.55--0.07]	-0.24 [-0.64-0.15]	0.35 [-0.06-0.76]
	<i>p</i>	0.01	0.23	0.09	
	<i>Model 2</i>	<i>B [CI]</i>	-0.19 [-0.39-0.00]	0.09 [-0.02-0.19]	
	<i>p</i>	0.052	0.11		

Interactions represented by B [CI], as predicted by linear mixed modelling adjusted for baseline age, education years and gender, and cohort as random factor. Model 1 includes the interaction term of the vascular marker with amyloid abnormality. Model 2, without the interaction term, was executed when the interaction in Model 1 was non-significant. MMSE, Mini-Mental State Examination; A+, amyloid abnormality.

**Supplementary Table 2.** Cognitive performance per AVrisk group.

		A-V-	A-V+	A+V-	A+V+	<i>p</i>
<b>MMSE</b> <b>(range 0-30)</b>	<i>N</i>	35	54	50	94	
	<i>Baseline</i>	28.05 [27.08-29.02] <sup>c,d</sup>	27.71 [26.97-28.44] <sup>c,d</sup>	25.92 [25.17-26.67] <sup>a,b</sup>	25.80 [25.10-26.29] <sup>a,b</sup>	<b>&lt;0.001</b>
	<i>Slope (per year)</i>	0.06 [-0.50-0.63] <sup>c,d</sup>	-0.43 [-0.90-0.04] <sup>c,d</sup>	<b>-1.58 [-2.10--1.06]<sup>a,b</sup></b>	<b>-1.30 [-1.68--0.92]<sup>a,b</sup></b>	<b>&lt;0.001</b>
<b>Memory</b> <b>Delayed recall</b> <b>(Z-score)</b>	<i>N</i>	31	43	31	47	
	<i>Baseline</i>	-0.80 [-1.34--0.25] <sup>c,d</sup>	-0.60 [-1.03--0.17] <sup>c,d</sup>	-1.65 [-2.15--1.16] <sup>a,b</sup>	-1.77 [-2.21--1.34] <sup>a,b</sup>	<b>&lt;0.001</b>
	<i>Slope (per year)</i>	0.02 [-0.10-0.13]	-0.04 [-0.14-0.06]	-0.09 [-0.21-0.04]	<b>-0.13 [-0.24--0.02]</b>	0.31
<b>Processing</b> <b>speed</b> <b>(Z-score)</b>	<i>N</i>	26	30	18	24	
	<i>Baseline</i>	-0.72 [-1.23--0.21]	-0.52 [-0.97--0.08]	-0.68 [-1.23--0.13]	-0.07 [-0.59-0.45]	0.32
	<i>Slope (per year)</i>	<b>0.18 [0.05-0.32]</b>	<b>0.13 [0.00-0.25]</b>	0.04 [-0.12-0.21]	-0.08 [-0.24-0.08]	0.08
<b>Executive</b> <b>functions</b> <b>(Z-score)</b>	<i>N</i>	24	27	13	16	
	<i>Baseline</i>	-0.81 [-1.37--0.26]	-0.21 [-0.69-0.28]	0.09 [-0.57-0.76]	-0.06 [-0.69-0.58]	0.17
	<i>Slope (per year)</i>	<b>0.20 [0.08-0.32]<sup>b,c</sup></b>	0.00 [-0.11-0.12] <sup>a</sup>	-0.11 [-0.27-0.05] <sup>a</sup>	0.00 [-0.17-0.17]	<b>0.02</b>
<b>Verbal fluency</b> <b>(Z-score)</b>	<i>N</i>	28	43	31	45	
	<i>Baseline</i>	-0.15 [-0.54-0.24] <sup>c,d</sup>	-0.41 [-0.72--0.11] <sup>c,d</sup>	-1.07 [-1.42--0.72] <sup>a,b</sup>	-0.90 [-1.21--0.59] <sup>a,b</sup>	<b>0.002</b>
	<i>Slope (per year)</i>	-0.01 [-0.12-0.11]	-0.02 [-0.11-0.07]	-0.07 [-0.18-0.05]	<b>-0.11 [-0.21--0.01]</b>	0.48

Numbers represent in B [CI] as predicted by linear mixed modelling adjusted for baseline age, education years and gender, and cohort as random factor. Significance  $p < 0.05$ : <sup>a</sup> compared to A-V-, <sup>b</sup> compared to A-V+, <sup>c</sup> compared to A+V-, <sup>d</sup> compared to A+V+. A is defined by amyloid abnormality; V is defined by vascular risk factors. Bold text indicates a significant increase or decrease compared to 0. MMSE, Mini-Mental State Examination.

**Supplementary Table 3.** Cognitive performance per AVdisease group.

		A-V-	A-V+	A+V-	A+V+	<i>p</i>
<b>MMSE</b> <b>(range 0-30)</b>	<i>N</i>	65	24	85	59	
	<i>Baseline</i>	28.07 [27.36-28.78] <sup>c,d</sup>	27.25 [26.17-28.32] <sup>c,d</sup>	26.00 [25.43-26.56] <sup>a,b</sup>	25.39 [24.64-26.14] <sup>a,b</sup>	<b>&lt;0.001</b>
	<i>Slope (per year)</i>	-0.13 [-0.55-0.28] <sup>c,d</sup>	-0.51 [-1.24-0.22] <sup>c</sup>	<b>-1.42 [-1.81--1.04]<sup>a,b</sup></b>	<b>-1.33 [-1.83--0.83]<sup>a</sup></b>	<b>&lt;0.001</b>
<b>Memory</b> <b>Delayed recall</b> <b>(Z-score)</b>	<i>N</i>	55	19	55	23	
	<i>Baseline</i>	-0.66 [-1.07--0.25] <sup>c,d</sup>	-0.77 [-1.41--0.12] <sup>c,d</sup>	-1.69 [-2.07--1.32] <sup>a,b</sup>	-1.83 [-2.44--1.22] <sup>a,b</sup>	<b>&lt;0.001</b>
	<i>Slope (per year)</i>	-0.04 [-0.12-0.05]	0.05 [-0.10-0.21]	<b>-0.13 [-0.22--0.03]</b>	-0.07 [-0.23-0.09]	0.24
<b>Processing</b> <b>speed</b> <b>(Z-score)</b>	<i>N</i>	45	11	34	8	
	<i>Baseline</i>	-0.63 [-1.02--0.23]	-0.49 [-1.18-0.20]	-0.30 [-0.71-0.12]	-0.84 [-1.73-0.06]	0.59
	<i>Slope (per year)</i>	<b>0.16 [0.06-0.26]</b>	0.10 [-0.10-0.30]	0.01 [-0.12-0.14]	-0.13 [-0.38-0.12]	0.08
<b>Executive</b> <b>functions</b> <b>(Z-score)</b>	<i>N</i>	42	9	25	4	
	<i>Baseline</i>	-0.50 [-0.94--0.07]	-0.41 [-1.20-0.38]	-0.02 [-0.53-0.49]	-0.02 [-1.19-1.16]	0.56
	<i>Slope (per year)</i>	<b>0.10 [0.01-0.19]</b>	0.08 [-0.14-0.30]	-0.03 [-0.16-0.10]	-0.18 [-0.45-0.10]	0.15
<b>Verbal fluency</b> <b>(Z-score)</b>	<i>N</i>	52	19	53	23	
	<i>Baseline</i>	-0.33 [-0.62--0.04] <sup>c</sup>	-0.23 [-0.69-0.23] <sup>c</sup>	-1.05 [-1.32--0.78] <sup>a,b</sup>	-0.73 [-1.16--0.29]	<b>0.002</b>
	<i>Slope (per year)</i>	0.01 [-0.06-0.09] <sup>d</sup>	-0.11 [-0.25-0.03]	-0.04 [-0.13-0.04] <sup>d</sup>	<b>-0.22 [-0.37--0.08]<sup>a,c</sup></b>	<b>0.03</b>

Numbers represented in B [CI] predicted by linear mixed modelling adjusted for baseline age, education years and gender, and cohort as random factor. Significance  $p < 0.05$ : <sup>a</sup> compared to A-V-, <sup>b</sup> compared to A-V+, <sup>c</sup> compared to A+V-, <sup>d</sup> compared to A+V+. A is defined by amyloid abnormality; V is defined by vascular disease. Bold text indicates a significant increase or decrease compared to 0.

MMSE, Mini-Mental State Examination.

**Supplementary Table 4.** Cognitive performance per AVMRI group, excluding dementia patients.

		A-V-	A-V+	A+V-	A+V+	<i>p</i>
<b>MMSE</b> <b>(range 0-30)</b>	<i>N</i>	65	16	66	29	
	<i>Baseline</i>	28.09 [27.50-28.68] <sup>c,d</sup>	27.63 [26.56-28.70]	26.96 [26.41-27.52] <sup>a</sup>	26.82 [25.95-27.69] <sup>a</sup>	<b>0.04</b>
	<i>Slope (per year)</i>	-0.14 [-0.50-0.21] <sup>c,d</sup>	0.10 [-0.58-0.78] <sup>c,d</sup>	<b>-1.01 [-1.37--0.64]<sup>a,b</sup></b>	<b>-1.15 [-1.74--0.56]<sup>a,b</sup></b>	<b>&lt;0.001</b>
<b>Memory</b> <b>Delayed recall</b> <b>(Z-score)</b>	<i>N</i>	54	17	43	18	
	<i>Baseline</i>	-0.47 [-0.89—0.06] <sup>c,d</sup>	-0.74 [-1.41—0.06] <sup>c,d</sup>	-1.57 [-2.00—1.14] <sup>a,b</sup>	-1.86 [-2.54—1.18] <sup>a,b</sup>	<b>0.00</b>
	<i>Slope (per year)</i>	-0.03 [-0.12-0.06]	0.06 [-0.09-0.21]	-0.10 [-0.21-0.00]	-0.04 [-0.22-0.14]	0.39
<b>Processing</b> <b>speed</b> <b>(Z-score)</b>	<i>N</i>	44	12	25	12	
	<i>Baseline</i>	-0.53 [-0.91--0.15]	-0.77 [-1.40--0.14]	-0.24 [-0.70-0.22]	-0.56 [-1.24-0.12]	0.56
	<i>Slope (per year)</i>	<b>0.16 [0.05-0.26]</b>	0.14 [-0.05-0.33]	0.01 [-0.13-0.16]	-0.03 [-0.24-0.18]	0.24
<b>Executive</b> <b>functions</b> <b>(Z-score)</b>	<i>N</i>	41	10	20	8	
	<i>Baseline</i>	-0.50 [-0.94--0.06]	-0.41 [-1.16-0.33]	0.01 [-0.55-0.58]	-0.01 [-0.83-0.82]	0.52
	<i>Slope (per year)</i>	0.08 [-0.02-0.17]	0.18 [0.00-0.37]	0.01 [-0.13-0.15]	-0.18 [-0.39-0.03]	0.07
<b>Verbal fluency</b> <b>(Z-score)</b>	<i>N</i>	51	17	43	18	
	<i>Baseline</i>	-0.25 [-0.54-0.04] <sup>c,d</sup>	-0.41 [-0.87-0.06] <sup>d</sup>	-0.73 [-1.03--0.44] <sup>a</sup>	-1.23 [-1.70--0.76] <sup>a,b</sup>	<b>0.01</b>
	<i>Slope (per year)</i>	0.00 [-0.08-0.08]	-0.01 [-0.14-0.13]	-0.09 [-0.19-0.00]	0.09 [-0.07-0.25]	0.25

Numbers represent in B [CI] as predicted by linear mixed modelling adjusted for baseline age, education years and gender, and cohort as random factor. Significance  $p < 0.05$ : <sup>a</sup> compared to A-V-, <sup>b</sup> compared to A-V+, <sup>c</sup> compared to A+V, <sup>d</sup> compared to A+V+. A is defined by amyloid abnormality; V is defined by MRI vascular burden. Bold text indicates a significant increase or decrease compared to 0. MMSE, Mini-Mental State Examination.

**Supplementary Table 5.** Memory recognition at baseline and decline per AVMRI group.

		A-V-	A-V+	A+V-	A+V+	<i>p</i>
<b>Memory</b>	<i>N</i>	55	18	51	26	
<b>Recognition</b>	<i>Baseline</i>	-0.45 [-0.84 – -0.06] <sup>c,d</sup>	-0.89 [-1.51 – -0.27]	-1.30 [-1.68 – -0.93] <sup>a</sup>	-1.36 [-1.91- -0.93] <sup>a</sup>	<b>0.02</b>
<b>(Z-score)</b>	<i>Slope (per year)</i>	-0.01 [-0.09 – 0.07] <sup>d</sup>	0.10 [-0.04 – 0.24] <sup>c,d</sup>	<b>-0.10 [-0.19 – -0.01]<sup>b</sup></b>	<b>-0.20 [-0.35 – -0.05]<sup>a,b</sup></b>	<b>0.02</b>

Numbers represent in B [CI] as predicted by linear mixed modelling adjusted for baseline age, education years and gender, and cohort as random factor. Significance  $p < 0.05$ : <sup>a</sup> compared to A-V-, <sup>b</sup> compared to A-V+, <sup>c</sup> compared to A+V-, <sup>d</sup> compared to A+V+. A is defined by amyloid abnormality; V is defined based on MRI vascular burden. Bold text indicates a significant increase or decrease compared to 0.

**Supplementary Table 6.** Associations between individual vascular MRI markers, amyloid abnormality, and their interaction on decline in memory recognition.

	<b>Model</b>		<b>Microbleeds</b>	<b>A+</b>	<b>Microbleeds x A+</b>	<b>WMH</b>	<b>A+</b>	<b>WMH x A+</b>
<b>Memory</b>		<i>N</i>	141	141	141	150	150	150
<b>Recognition (Z-score)</b>	<i>Model 1</i>	<i>B [CI]</i>	0.04 [-0.23 – 0.30]	-0.22 [-0.60 – 0.17]	0.08 [-0.31 – 0.49]	-0.10 [-0.29 – 0.10]	-0.29 [-0.56 – -0.02]	0.17 [-0.12 – 0.47]
		<i>p</i>	0.79	0.27	0.69	0.33	<b>0.04</b>	0.25
	<i>Model 2</i>	<i>B [CI]</i>	0.00 [-0.20 – 0.20]	-0.14 [-0.25 – -0.03]		-0.02 [-0.17 – 0.13]	-0.14 [-0.25 – -0.03]	
		<i>p</i>	1.00	<b>0.01</b>		0.80	<b>0.01</b>	

Interaction effects are represented by B [CI], as predicted by linear mixed modelling adjusted for baseline age, education years and gender, and cohort as random factor. Significant p-values are shown in bold text. Model 1 includes the interaction term of the vascular marker (dichotomous) with amyloid abnormality. Model 2, without the interaction term, was executed when the interaction in Model 1 was non-significant. Prevalence of infarcts and microhemorrhages was too low to perform reliable analyses. A+, A $\beta$ <sub>42</sub> abnormality; WMH, white matter hyperintensities.