Supplementary Methods:

Demographic and Cognitive data

Data analyzed included demographic features; age at the first visit, age at MCI, dementia, and death; clinical conditions at baseline and cognitive, behavioral, or motor symptoms that developed throughout the disease; and neurological examination findings. Symptoms and findings were determined as absent/present at first and last evaluation. We performed a crosstab with Chi2 test to analyze frequencies on categorical variables and a frequencies analysis with Chi2 statistics to describe the motor and cognitive changes reported by the clinician at baseline and the end of follow-up. We analyzed medical conditions and lifestyle features at baseline. Sleep, drug abuse, cardio metabolic, and presence/type of migraine were assessed clinically by a neurologist. A battery of tests was performed in Spanish, the primary language of participants. The cognitive battery was made of memory, language, visuospatial ability, executive function, reasoning, and global functioning. All tests were validated according to age and education for the Colombian population14 and conducted by trained psychologists/neuropsychologists.

PVS quantification. We quantified perivascular space dilatation for 15 CAA and non-CAA vessels in the occipital cortex of each case. Sections stained with Aβ were used for *PSEN1* FAD cases while HE stained sections were used for CADASIL, since latter were not stained for Aβ. Images at 5X magnification were exported from the whole-image scan file, using the NDP.view2 software (Hamamatsu Photonics, Hamamatsu, Japan). ImageJ Software (version 1.52p, NIH, Bethesda, MA, USA) was used to measure the longest distance between the parenchyma and the vessel to determine the exact size of the perivascular spaces. PVS ratio was calculated by dividing this distance by the diameter of the measured vessel. To exclude vessel size as the determinant for larger perivascular spaces, the caliber of the vessels was measured in the same manner as the perivascular space dilatation.

Fibrinogen Immunoreactivity. To determine the extent of BBB leakage whole stained sections were used to quantify fibrinogen immunoreactivity around 100 cortical vessels per case. A vessel was counted as leaking once there was fibrinogen staining around the vessel. For *PSEN1* FAD this quantification was additionally performed taking the PVS into account. A vessel was defined as dilated when the ratio was PVS $\geq$ 1.

PDGFRβ Immunohistochemistry. PDGFRβ immunoreactivity was determined to assess perivascular pericyte coverage for assessing mural cell integrity. Using ImageJ Software (version 1.52p, NIH, Bethesda, MA, USA), we determined periarteriolar PDGFRβ reactivity in 100 cortical vessels per case. The plugin Colour deconvolution[29] using the H&E vectors was used to separate the channels. After applying the automatic threshold, particles analysis was used to measure PDGFRβ signal, particles defined as any continuous signal positive object as identified by the software. Measurements included the area, standard deviation, min and max grey value, mean grey value, shape descriptions and integrated density. Particles smaller than 100 µm were excluded from this analysis. To account for measurements of particles bigger than the biological norm, the top 1% of each dataset was subtracted. In addition, PDGFRβ total signal restricted to vessels was also assessed, discriminating between those with thickened walls and PVS dilation.

Ultrastructural analysis. Three *PSEN1* FAD formalin-fixed temporal cortices were fixed in glutaraldehyde and chrome-osmium, dehydrated in ethanol and embedded in Epon 812 (Serva Electrophoresis GmbH, Heidelberg, Germany). After polymerization, 1-mm-thick sections were cut, stained with toluidine blue and checked for presence of arterioles. Relevant specimens were further processed for electron microscopy by cutting 100 nm-thick sections which were contrasted with uranyl replacement stain (22405, Electron Microscopy Sciences, Hatfield, PA, USA) and lead citrate solution. Sections were viewed and representative pictures taken using a LEO EM 912AB electron microscope (Zeiss, Oberkochen, Germany).

Aquaporin-4 (AQP4) Immunoreactivity. AQP4 immunoreactivity was determined to study the status of astrocytic responses, particularly the end-feet localised perivascularly. The positive signal was measured using ImageJ Software. Here, we assessed 15 vessels in dilated perivascular spaces and 15 vessels in within parenchyma without any dilated spaces per case. Immunostained vessel profiles were exported at 80X magnification from the whole-image scan. Again, colour deconvolution was used to obtain separated channels. The automated threshold was applied and measured, resulting in total AQP4 signal.

Supplementary tables

Table 1 Demographics of *PSEN1* FAD and SAD subjects

Group	Genotype	GeNAer	AoO	AoD	PM (h)	Brain Weight (g)	Braak	CERAD score	ApoE	HTN	Diabetes	BMI	Smoking	Dyslipidaemia	IHD	Stroke	# CVA
FAD	Glu280Ala	F	55	64	13	800	6	3	NA	1	0	NA	1	0	0	0	0
FAD	Glu280Ala	F	51	54	12	1260	6	3	3/3	0	0	NA	1	0	0	0	0
FAD	Glu280Ala	F	45	50	7,5	987,6	6	3	3/3	0	1	NA	1	0	0	0	0
FAD	Glu280Ala	M	46	52	4,8	1061,3	6	3	3/3	0	0	NA	1	0	0	0	0
FAD	Glu280Ala	M	47	55	3,3	941,6	6	3	3/3	0	0	NA	1	0	0	0	0
FAD	Glu280Ala	F	57	62	4	968,7	6	3	3/3	0	0	NA	0	0	0	0	0
FAD	Glu280Ala	F	45	48	4	886,5	6	3	3/3	1	0	NA	0	0	0	0	0
FAD	Glu280Ala	F	52	60	2,8	768,1	6	3	3/3	0	0	NA	0	0	0	0	0
FAD	Glu280Ala	F	48	52	2,5	960,8	6	3	2/3	0	0	18,96	1	0	0	0	0
FAD	Glu280Ala	F	47	52	8,5	1026,1	6	3	3/3	1	0	23,00	1	1	0	0	0
FAD	Glu280Ala	F	58	64	3,5	909,2	6	3	3/4	0	0	30,82	0	0	0	0	0
FAD	Glu280Ala	F	49	61	3,5	695,4	6	3	3/3	1	0	NA	0	1	0	0	0
FAD	Glu280Ala	M	45	53	7,2	953,1	6	3	NA	0	0	23,70	0	0	0	0	0
FAD	Glu280Ala	M	55	61	7,3	1034,2	6	3	NA	0	0	21,00	1	0	0	0	0
FAD	Glu280Ala	F	49	57	7,8	1008,2	6	3	NA	1	0	22,30	1	1	0	0	0
FAD	Glu280Ala	M	50	57	9,2	874,2	6	3	3/4	1	0	24,20	0	1	0	0	0
FAD	Glu280Ala	M	52	61	4	846	6	3	3/4	0	0	25,80	0	0	0	0	0
FAD	Glu280Ala	M	47	54	8,2	1089,8	6	3	NA	0	0	20,80	1	0	0	0	0
FAD	Glu280Ala	F	45	51	4,4	964,3	6	3	3/3	0	0	23,70	0	0	0	0	0
FAD	Glu280Ala	F	52	60	5	665,3	6	3	3/3	1	0	20,30	0	0	0	0	0
FAD	Glu280Ala	M	51	62	4,15	1141,1	6	3	3/3	0	0	19,40	1	0	0	0	0
SAD	NA	M	NA	67	10	1225	5	3	3/3	NA	NA	NA	NA	NA	0	NA	NA
SAD	NA	M	80	86	6,3	1200	4	3	NA	NA	NA	NA	NA	NA	0	NA	NA
SAD	NA	F	55	70	11,3	890	4	2	3/4	NA	NA	NA	NA	NA	0	NA	NA
SAD	NA	F	79	87	2,8	842,8	5	3	3/4	NA	NA	NA	NA	NA	0	NA	NA
SAD	NA	F	82	91	4,5	956	6	3	3/3	NA	NA	NA	NA	NA	0	NA	NA
SAD	NA	F	65	74	2,5	846,0	4	3	3/3	NA	NA	NA	NA	NA	0	NA	NA
SAD	NA	F	65	76	4,3	NA	5	3	4/4	NA	NA	NA	NA	NA	0	NA	NA
SAD	NA	F	69	76	8	NA	6	3	3/4	NA	NA	NA	NA	NA	0	NA	NA
SAD	NA	M	70	83	4,3	981,1	6	3	3/2	NA	NA	NA	NA	NA	0	NA	NA
SAD	NA	F	50	61	4,1	NA	6	3	3/3	NA	NA	NA	NA	NA	0	NA	NA
SAD	NA	M	80	84	24	NA	6	3	3/4	0	NA	NA	1	NA	NA	0	0
SAD	NA	M	81	87	15	NA	6	3	3/4	0	NA	NA	NA	NA	NA	0	0
SAD	NA	F	NA	91	20	NA	5	3	NA	NA	NA	NA	NA	NA	NA	0	0
SAD	NA	F	80	87	35	NA	5	3	3/4	0	NA	NA	NA	NA	NA	0	0
SAD	NA	F	NA	83	24	870	5	3	NA	1	NA	NA	NA	NA	NA	0	0
SAD	NA	M	77	88	36	1180	6	3	NA	0	NA	NA	NA	NA	NA	0	0
SAD	NA	F	84	92	24	940	6	2	NA	1	NA	NA	NA	NA	NA	0	0
SAD	NA	M	65	76	6	1247	6	3	3/3	1	1	NA	NA	NA	1	0	1
SAD	NA	F	90	94	58	1660	6	3	3/4	1	NA	NA	NA	NA	1	0	1
SAD	NA	M	81	91	24	1250	5	3	3/4	1	NA	NA	1	NA	NA	0	0
SAD	NA	F	79	85	36	934	5	3	3/4	1	NA	NA	NA	NA	NA	0	0
SAD	NA	M	76	82	24	1430	5	3	?	1	NA	NA	1	NA	NA	0	0
SAD	NA	M	84	91	24	1310	5	3	3/4	0	NA	NA	1	NA	NA	0	0
SAD	NA	F	75	NA	36	1087	6	3	3/4	0	NA	NA	NA	NA	NA	0	0
SAD	NA	M	80	90	24	1096	6	3	4/4	1	NA	NA	NA	NA	NA	0	0
SAD	NA	M	76	87	24	1192	6	3	3/4	1	1	NA	1	NA	NA	0	0
SAD	NA	F	73	88	36	1034	6	3	3/4	0	1	NA	NA	NA	NA	0	0
SAD	NA	F	95	96	34	1124	6	3	3/4	NA	NA	NA	NA	NA	NA	0	0

AoO: Age of Onset, AoD: Age of Death, CADASIL: Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy, FAD: FAD, HTN: Hypertension, IHD: Ischemic Heart Disease, NA: Not Available, PM: post-mortem, SAD: Sporadic Alzheimer's Disease

Supplementary Table 2 Demographics of CADASIL and Control subjects

Group	Genotype	GeNAer	AoO	AoD	PM (h)	Brain Weight (g)	Braak	CERAD score	ApoE	HTN	Diabetes	BMI	Smoking	Dyslipidaemia	IHD	Stroke	# CVA
CADASIL	Notch3 R1031C	F	54	60	3	925	NA	NA	NA	1	1	NA	1	1	NA	1	10
CADASIL	Notch3 R1031C	F	52	58	3,5	1021,1	NA	NA	NA	1	0	NA	0	0	NA	0	0
CADASIL	Notch3 C455R	F	65	70	10,5	931,8	NA	NA	NA	1	1	NA	1	1	NA	1	4
CADASIL	Notch3 R1031C	F	62	65	2,4	904,6	NA	NA	NA	1	0	NA	0	0	NA	1	5
CADASIL	Notch3 R1031C	F	52	76	9,8	939	NA	NA	NA	1	0	30,90	0	1	NA	1	4
CADASIL	Notch3 R1031C	M	61	65	4	252,2	NA	NA	NA	1	1	NA	1	0	NA	1	5
CADASIL	Notch3 R1031C	F	45	47	2,2	917	NA	NA	NA	0	0	NA	0	0	NA	1	2
CADASIL	Notch3 C455R	F	45	45	3,7	917	NA	NA	NA	0	0	28,80	1	0	NA	1	1
CADASIL	Notch3 R1031C	F	NA	NA	5,75	1177,4	NA	NA	NA	1	1	26,10	0	0	NA	0	0
CADASIL	Notch3 R1031C	M	58	59	5,8	948	NA	NA	NA	0	0	19,40	1	0	NA	1	4
CADASIL	Arg153Cys	F	36	44	24	1100	NA	NA	NA	NA	1	1	NA	NA	NA	1	>1
CADASIL	Arg133Cys	F	47	53	24	1250	NA	NA	NA	NA	NA	NA	NA	NA	NA	1	>1
CADASIL	Arg558Cys	M	44	55	24	1050	NA	NA	NA	NA	NA	NA	NA	NA	NA	1	>1
CADASIL	Arg985Cys	M	45	58	36	1220	NA	NA	NA	NA	NA	NA	NA	NA	NA	1	>1
CADASIL	Arg169Cys	M	47	59	42	1292	NA	NA	NA	NA	NA	NA	NA	NA	NA	1	>1
CADASIL	Arg169Cys	M	51	61	33	1200	NA	NA	NA	NA	1	1	NA	NA	NA	1	>1
CADASIL	D239_D253del	F	43	66	36	NA	NA	NA	NA	NA	1	1	NA	NA	NA	1	>1
CADASIL	Arg133Cys	F	50	68	25	1110	NA	NA	NA	NA	NA	NA	1	NA	NA	1	>1
CADASIL	Arg153Cys	M	40	68	72	1219	NA	NA	NA	NA	NA	NA	1	NA	NA	1	>1
CADASIL	Arg141Cys	M	53	63	24	1250	NA	NA	NA	NA	NA	NA	NA	NA	NA	1	>1
CADASIL	Arg141Cys	M	52	65	24	1200	NA	NA	NA	NA	NA	NA	NA	NA	NA	1	>1
CADASIL	Arg141Cys	M	42	52	12	1100	NA	NA	NA	NA	NA	NA	NA	NA	NA	1	>1
Ycontrol	NA	M	NA	53	24	NA	0	0	3/4	NA	0	NA	NA	NA	1	NA	NA
Ycontrol	NA	F	NA	54	24	1150	0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA
Ycontrol	NA	F	NA	69	24	NA	0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA
Ycontrol	NA	F	NA	58	39	1180	0	0	2/3	NA	NA	NA	NA	NA	NA	NA	NA
Ycontrol	NA	F	NA	59	19	1153	NA	0	3/3	NA	NA	NA	NA	NA	NA	NA	NA
Ycontrol	NA	F	NA	69	19	1190	0	0	3/3	NA	NA	NA	NA	NA	NA	NA	NA
Ycontrol	NA	M	NA	68	54	1280	0	0	3/3	NA	NA	NA	NA	NA	NA	NA	NA
Ycontrol	NA	M	NA	74	54	1420	0	0	3/3	NA	NA	NA	NA	NA	NA	NA	NA
Ycontrol	NA	F	NA	52	24	NA	0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA
Ycontrol	NA	F	NA	53	24	NA	0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA
Control	NA	M	NA	72	24	NA	1	1	3/4	NA	NA	NA	NA	NA	NA	NA	NA
Control	NA	F	NA	78	23	1140	2	1	2/3	NA	NA	NA	NA	NA	NA	NA	NA
Control	NA	F	NA	72	24	NA	1	1	NA	NA	NA	NA	NA	NA	NA	NA	NA
Control	NA	M	NA	99	24	1322	0	0	3/3	NA	NA	NA	NA	NA	NA	NA	NA
Control	NA	F	NA	74	24	1235	1	0	3/3	NA	NA	NA	NA	NA	NA	NA	NA
Control	NA	F	NA	74	36	1280	3	0	3/3	0	NA	NA	NA	NA	NA	NA	NA
Control	NA	F	NA	94	36	1171	2	0	2/3	0	NA	NA	NA	NA	1	1	NA
Control	NA	F	NA	98	24	1137	3	0	3/3	NA	NA	NA	NA	NA	NA	NA	NA
Control	NA	F	NA	78	24	1179	0	0	2/3	0	NA	NA	NA	NA	NA	NA	NA
Control	NA	F	NA	95	24	1230	3	0	3/3	0	NA	NA	NA	NA	NA	NA	NA
Control	NA	M	NA	89	24	1187	3	0	3/3	NA	NA	NA	NA	NA	NA	NA	NA
Control	NA	M	NA	73	24	1244	0	0	3/3	0	NA	NA	NA	NA	NA	NA	NA
Control	NA	F	NA	96	24	1124	3	0	3/3	NA	NA	NA	NA	NA	NA	NA	NA
Control	NA	F	NA	97	24	1062	2	1	3/4	0	NA	NA	NA	NA	NA	NA	NA
Control	NA	NA	NA	NA	24	1515	NA	NA	3/3	NA	NA	NA	NA	NA	NA	NA	NA
Control	NA	F	NA	89	24	1168	2	2	3/3	NA	NA	NA	NA	NA	NA	NA	NA
Control	NA	F	NA	99	24	1106	4	2	3/3	NA	NA	NA	NA	NA	NA	NA	NA

AoO: Age of Onset, AoD: Age of Death, CADASIL: Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy, FAD: FAD, HTN: Hypertension, IHD: Ischemic Heart Disease, NA: Not Available, PM: post-mortem, SAD: Sporadic Alzheimer's Disease

Supplementary Table 3 Variability of cognitive domains during follow-up between *PSEN1* FAD and CADASIL

	MMSE				Attention				Memory				Executive Function			
	***PSEN1* FAD**		**CADASIL**		***PSEN1* FAD**		**CADASIL**		***PSEN1* FAD**		**CADASIL**		***PSEN1* FAD**		**CADASIL**	
Timepoints	**MEDIA**	**SE**	**MEDIA**	**SE**	**MEDIA**	**SE**	**MEDIA**	**SE**	**MEDIA**	**SE**	**MEDIA**	**SE**	**MEDIA**	**DE**	**MEDIA**	**DE**
1	-6,87	1,77	-1,82	2,54	-2,37	1,19	-1,70	1,72	-2,93	0,45	-0,82	0,66	-1,36	0,26	-0,37	0,37
2	-8,19	1,81	-2,29	2,54	-2,25	1,21	-2,08	1,72	-3,19	0,46	-0,72	0,66	-1,48	0,26	-0,91	0,37
3	-9,94	1,80	-3,20	2,60	-4,38	1,23	-4,82	1,78	-3,55	0,46	-1,15	0,67	-1,58	0,27	-0,94	0,39
4	-10,79	1,84	-6,19	2,76	-3,93	1,28	-4,33	1,86	-4,06	0,47	-1,48	0,69	-1,58	0,28	-1,08	0,40
5	-11,81	1,93	-8,24	2,86	-3,91	1,36	-4,14	2,05	-4,03	0,49	-2,08	0,73	-1,77	0,30	-1,26	0,44
6	-15,08	2,05	-16,81	3,49	-7,79	1,49	-8,11	2,67	-4,45	0,52	-3,27	0,88	-2,20	0,32	-2,30	0,58
7	-18,62	2,16	-17,13	4,01	-8,37	1,60	-7,77	3,17	-5,91	0,55	-3,80	1,00	-2,67	0,35	-2,15	0,68
8	-19,42	2,44	NA	NA	-7,86	1,87	NA	NA	-5,89	0,61	NA	NA	-2,54	0,40	NA	NA
9	-19,46	2,59	NA	NA	-12,05	2,02	NA	NA	-6,09	0,65	NA	NA	-2,67	0,44	NA	NA
10	-23,96	3,12	NA	NA	-12,46	2,51	NA	NA	-6,73	0,77	NA	NA	-2,77	0,54	NA	NA
11	-25,67	3,66	NA	NA	-9,93	3,01	NA	NA	-7,87	0,90	NA	NA	-3,78	0,65	NA	NA
12	-25,35	4,94	NA	NA	-15,40	4,15	NA	NA	-7,61	1,21	NA	NA	-4,45	0,90	NA	NA
13	-29,75	4,94	NA	NA	-15,40	4,15	NA	NA	-7,61	1,21	NA	NA	-4,45	0,90	NA	NA
14	-32,09	4,94	NA	NA	-15,40	4,15	NA	NA	-7,61	1,21	NA	NA	-4,45	0,90	NA	NA

MMSE: F test (11,7) P value (0,000) *. Atention: F test (64,1) P value (0,000) *. Memory: F test (9,62) P value (0,000) *. Executive Function: F test (4,91) P value (0,000). *P<0,05

Supplementary Table 3 (Continuation) Variability of cognitive domains during follow-up between *PSEN1* FAD and CADASIL

	Language				Praxis				Reasoning			
	***PSEN1* FAD**		**CADASIL**		***PSEN1* FAD**		**CADASIL**		***PSEN1* FAD**		**CADASIL**	
Timepoints	**MEDIA**	**SE**	**MEDIA**	**SE**	**MEDIA**	**SE**	**MEDIA**	**SE**	**MEDIA**	**SE**	**MEDIA**	**SE**
1	-1,61	0,47	-0,74	0,68	-2,26	0,47	-1,40	0,68	-2,48	0,40	-0,91	0,57
2	-1,96	0,48	-1,17	0,68	-2,51	0,47	-2,10	0,68	-2,78	0,40	-0,93	0,57
3	-2,88	0,48	-1,59	0,70	-3,50	0,48	-2,78	0,69	-3,04	0,41	-1,49	0,59
4	-3,19	0,49	-2,21	0,72	-3,70	0,49	-2,45	0,71	-3,14	0,42	-1,68	0,61
5	-3,63	0,52	-2,77	0,77	-4,23	0,51	-3,53	0,76	-3,69	0,45	-3,09	0,67
6	-3,80	0,55	-4,63	0,94	-4,65	0,54	-4,13	0,91	-4,35	0,48	-3,73	0,85
7	-4,76	0,58	-4,43	1,09	-5,96	0,57	-4,23	1,04	-4,91	0,52	-4,07	1,00
8	-4,88	0,66	NA	NA	-6,37	0,64	NA	NA	-5,48	0,60	NA	NA
9	-5,54	0,70	NA	NA	-5,95	0,67	NA	NA	-5,56	0,64	NA	NA
10	-6,32	0,84	NA	NA	-6,29	0,81	NA	NA	-5,80	0,79	NA	NA
11	-7,91	0,99	NA	NA	-7,99	0,94	NA	NA	-6,72	0,94	NA	NA
12	-8,53	1,35	NA	NA	-9,02	1,27	NA	NA	-8,12	1,29	NA	NA
13	-8,53	1,35	NA	NA	-9,02	1,27	NA	NA	-8,12	1,29	NA	NA
14	-8,53	1,35	NA	NA	-9,02	1,27	NA	NA	-8,12	1,29	NA	NA

Language: F test (12,6) P value (0,000) *. Praxis: F test (12,7) P value (0,000) *. Reasoning: F test (9,19) P value (0,000) *P<0,05

Supplementary Table 4 Variability of cognitive domains during clinical progression between *PSEN1* FAD and CADASIL

	CADASIL						*PSEN1* FAD							
	Healthy		MCI		Dementia		Healthy		MCI		Dementia			
	MEDIA	SE	MEDIA	SE	MEDIA	SE	MEDIA	SE	MEDIA	SE	MEDIA	SE	F-test	P-value
MMSE	0,03	1,97	-1,01	2,59	-10,85	1,72	-2,15	1,73	-3,88	1,42	-13,36	0,91	35,5	,000*
Attention	0,53	1,56	-4,36	2,01	-6,70	1,38	0,97	1,33	-0,74	1,11	-6,03	0,73	20,1	,000*
Memory	-0,05	0,48	-0,64	0,59	-2,66	0,43	-1,14	0,39	-2,60	0,33	-4,44	0,24	42,6	,000*
Language	-0,14	0,44	-1,35	0,63	-3,45	0,38	-0,16	0,41	-0,78	0,34	-3,64	0,19	53,0	,000*
Praxis	-0,16	0,42	-2,09	0,54	-4,33	0,38	-0,91	0,36	-1,23	0,30	-4,43	0,20	88,2	,000*
Reasoning	-0,01	0,36	-0,72	0,50	-3,40	0,31	-0,83	0,32	-1,38	0,27	-4,12	0,16	85,9	,000*
Executive function	-0,09	0,27	-0,47	0,36	-1,91	0,24	-0,39	0,24	-0,63	0,20	-2,15	0,12	46,1	,000*

*P<0,05

	CADASIL		*PSEN1* FAD	
	MEAN	SE	MEAN	SE
MMSE	-7,96	2,29	-18,36	1,70
Attention	-4,71	1,41	-8,68	1,12
Memory	-1,90	0,60	-5,54	0,44
Language	-2,50	0,61	-5,54	0,44
Praxis	-2,95	0,62	-5,75	0,46
Reasoning	-2,27	0,49	-5,16	0,38
Executive Function	-1,29	0,31	-2,69	0,24

Supplementary Table 5 Neuroimaging patterns

Neuroimaging pattern		GROUP		
		PSEN1 FAD	CADASIL	p-value
Normal	No	69,6%	17,4%	0,547
	Yes	13,0%	0,0%	
MT	No	43,5%	13,0%	0,404
	Yes	39,1%	4,3%	
TP	No	73,9%	17,4%	0,676
	Yes	8,7%	0,0%	
PC	No	78,3%	17,4%	0,826
	Yes	4,3%	0,0%	
FL	No	78,3%	17,4%	0,826
	Yes	4,3%	0,0%	
WMH	No	73,9%	4,3%	0,021*
	Yes	8,7%	13,0%	
SI	No	78,3%	8,7%	0,067
	Yes	4,3%	8,7%	
CM	No	82,6%	8,7%	0,024*
	Yes	0,0%	8,7%	

Chi2 statistics; $p \leq 0,05$. MEANl Temporal (MT). Temporoparietal Cortex (TP). Parieta Cortex (PC). Frontal lobe (FL) White Matter Hyperintensities (WMH). Subcortical Infarcts (SI). Cerebral Microbleeds (CM)

Supplementary Table 6 Neuroimaging Evaluation of *PSEN1* FAD cases MRI

#	Age of Death	Sex	Fazekas	ERICA	MTA (Scheltens)	Sulcal – GCA (Pasquier)			Ventricular – GCA (Pasquier)				Koedam
						F	PO	T	F	PO	T	3º	
1	59	F	1	1	2	0-1	1-2	1-2	0-1	1-2	1-2	1	1-2
2	54	F	0	1	1	1-1	2-2	1-1	2-2	2-2	2-2	1	2-2
3	66	F	0	1	2	1-1	2-2	1-1	1-1	2-2	1-1	2	2-2
4	44	M	1	1	1	0-1	1-2	1-1	0-1	1-1	1-1	1	1-2
5	59	F	1	1	2	1-1	1-1	1-1	1-1	2-2	1-1	1	2-2
6	46	F	0	2	3	1-1	2-2	2-2	2-2	2-2	2-2	2	2-2
7	53	F	0	1	2	1-1	2-2	1-1	1-1	2-2	1-1	2	2-2
8	48	F	1	1	2	1-1	2-2	2-2	1-1	2-2	1-1	1	2-2
9	46	F	1	0	1	1-1	1-1	1-1	1-1	1-1	1-1	1	1-1
10	60	F	1	2	2	1-1	2-2	1-1	2-2	3-2	2-2	2	3-3
11	53	F	1	2	2	1-1	2-2	2-2	2-2	3-3	1-1	3	2-2
12	57	M	0	2	1	1-1	2-2	2-2	0-0	1-1	0-0	0	1-1
13	55	M	1	2	2	1-1	2-2	1-1	1-1	2-2	1-1	0	2-2
14	49	F	0	1	1	0-0	1-1	1-1	1-1	1-1	1-1	1	1-1
15	50	F	0	1	1	0-0	2-2	1-1	0-0	0-0	0-0	0	1-1
16	52	M	1	0	1	1-1	1-1	1-1	0-0	1-1	0-0	0	1-1
17	47	M	0	1	1	1-1	1-1	1-1	0-1	0-1	0-1	0	1-1
18	43	F	0	0	0	0-0	0-0	0-0	0-0	0-0	0-0	0	0-0
19	52	F	0	1	1	0-0	1-1	0-0	0-0	1-1	0-0	0	0-0
20	52	M	0	0	1	0-0	1-1	0-0	0-0	0-0	0-0	0	0-0
Mean (SD)	56.67 (4.95)		0.45 (0.51)	1.05 (0.69)	1.45 (0.69)	0.70 (0.47)	1.50 (0.60)	1.08 (0.62)	0.80 (0.77)	1.38 (0.88)	0.85 (0.71)	0.90 (0.91)	1.40 (0.82)

MTA = Medial Temporal lobe Atrophy, GCA = Global Cortical Atrophy.

Supplementary Table 7 Neuroimaging Evaluation of CADASIL cases MRI

					Schelten's Scale														
					Cortical														
#	Age of Death	Sex	Fazekas	Periventricular	Frontal	Parietal	Occipital	Temporal - Anterior	Temporal -Posterior	Corpus Callosum	Caudate Nucleus	Putamen	Basal Ganglia	Thalamus	External Capsule	Internal Capsule	Cerebellum	Midbrain	Pons	Medulla
21	58	F	3	5	6	6	6	6	6	6	1	2	2	5	6	1	0	6	4	4
22	70	F	3	5	6	6	6	4	0	6	1	6	2	4	6	2	4	2	5	0
23	65	F	3	5	6	6	6	6	6	5	0	1	0	3	6	5	2	0	0	0
24	76	F	2	4	3	4	3	4	4	0	6	0	0	6	0	0	0	0	3	0
Mean (SD)	67.3 (7.6)		2.8 (0.5)	4.8 (0.5)	5.3 (1.5)	5.5 (1.0)	5.3 (1.5)	5.0 (1.2)	4.0 (2.8)	4.3 (2.9)	2.0 (2.7)	2.3 (2.6)	1.0 (1.2)	4.5 (1.3)	4.5 (3.0)	2.0 (2.2)	1.5 (1.9)	2.0 (2.8)	3.0 (2.2)	1.0 (2.0)

Supplementary Figure Legends

Supplementary Figure 1 Neuropsychological evaluation

Clinical and behavioural changes alongside neurological features are shown for PSEN1 FAD and CADASIL. There tended to be greater frequency of tobacco smokers in the Colombian subjects. However, of interest, a third of the patients had hypertensive disease in the PSEN1 FAD, CADASIL and SAD groups (A). The variability of cognitive domains during follow-up in PSEN1 FAD and CADASIL patients is shown with declined cognitive performance in all cognitive domains. When we compared the trajectories longitudinally between both groups, PSEN1 FAD presented with lower performances in memory and reasoning (B).

Supplementary Figure 2 Neuropsychological evaluations of *PSEN1* FAD and SAD patients

PSEN1 FAD patients presented with significantly lower Δ memory decline, Δ language decline, Δ attention decline, Δ praxis decline, Δ reasoning decline compared and Δ executive function decline compared with CADASIL patients (p-values: **** ≤ 0.0001, *** ≤ 0.001, ** ≤ 0.01) while no significant differences could be observed in Δ executive function decline (A). The speed of decline in cognitive domains did not differ significantly between the PSEN1 FAD group and CADASIL group (B).

Supplementary Figure 3 Vascular pathology grading

The vascular pathology scores by area are shown for *PSEN1* FAD, SAD and CADASIL (A). There were no significant differences in the cortical and BG score (Cx+BG CVP) (B). The SVD scores were affected by high blood pressure (HBP) with significantly higher scores in CADASIL subjects (p-values: *** ≤ 0.001, ** ≤ 0.01) (C). Relative white matter signal intensity of occipital cortices of *PSEN1* FAD, SAD and CADASIL patients (D).

Supplementary Figure 4 Enlarged PVS in *PSEN1* FAD, SAD and CADASIL

The perivascular space distance for three sizes of caliber are shown (A), with Non-CAA *PSEN1* FAD vessels being significantly more dilated for vessels <50µm and 50-90µm in size (p-value: **** ≤ 0.0001). In PSEN1 FAD the perivascular spacing of non-CAA vessel is positively correlated with Δ MMSE (B) (r = 0.535, p-value: 0.012) while this is negatively correlated in CADASIL (C) (r = -0.227, p-value: 0.528).

Supplementary Figure 5 Extended PDGFRβ measurements

The size of particles measured is significantly smaller for *PSEN1* FAD and CADASIL in comparison to SAD (p-values: *** ≤ 0.001, ** ≤ 0.01), and the signal intensity is significantly weaker for *PSEN1* FAD and CADASIL vs. SAD (p-values: *** ≤ 0.001, ** ≤ 0.01) (A). Representative images of PDGFRβ stained dilated and non-dilated vessels are shown (B), scale bar all panels = 50 µM. Non-dilated *PSEN1* FAD vessels with thickened walls showed significantly less perivascular PDGFRβ signal than dilated normal *PSEN1* FAD vessels, all types of SAD vessels, non-dilated thickened and both dilated CADASIL vessels (p-values: **** ≤ 0.0001, ** ≤ 0.01, * ≤ 0.05). Non-Dilated vessels with normal walls in *PSEN1* FAD presented with significantly less PDGFRβ signal than all types of SAD vessels and dilated CADASIL vessels (p-values: **** ≤ 0.0001, *** ≤ 0.001, ** ≤ 0.01). Dilated *PSEN1* FAD vessels with normal walls showed significantly less signal than dilated SAD vessel with normal vessels walls (p-value: ** ≤ 0.0089). Dilated *PSEN1* FAD vessels with thickened vessel walls presented with significantly less perivascular PDGFRβ expression than SAD (n=10) non dilated and dilated and CADASIL (n=10) dilated vessels (p-values: **** ≤ 0.0001, *** ≤ 0.001, ** ≤ 0.01, * ≤ 0.05) (C).

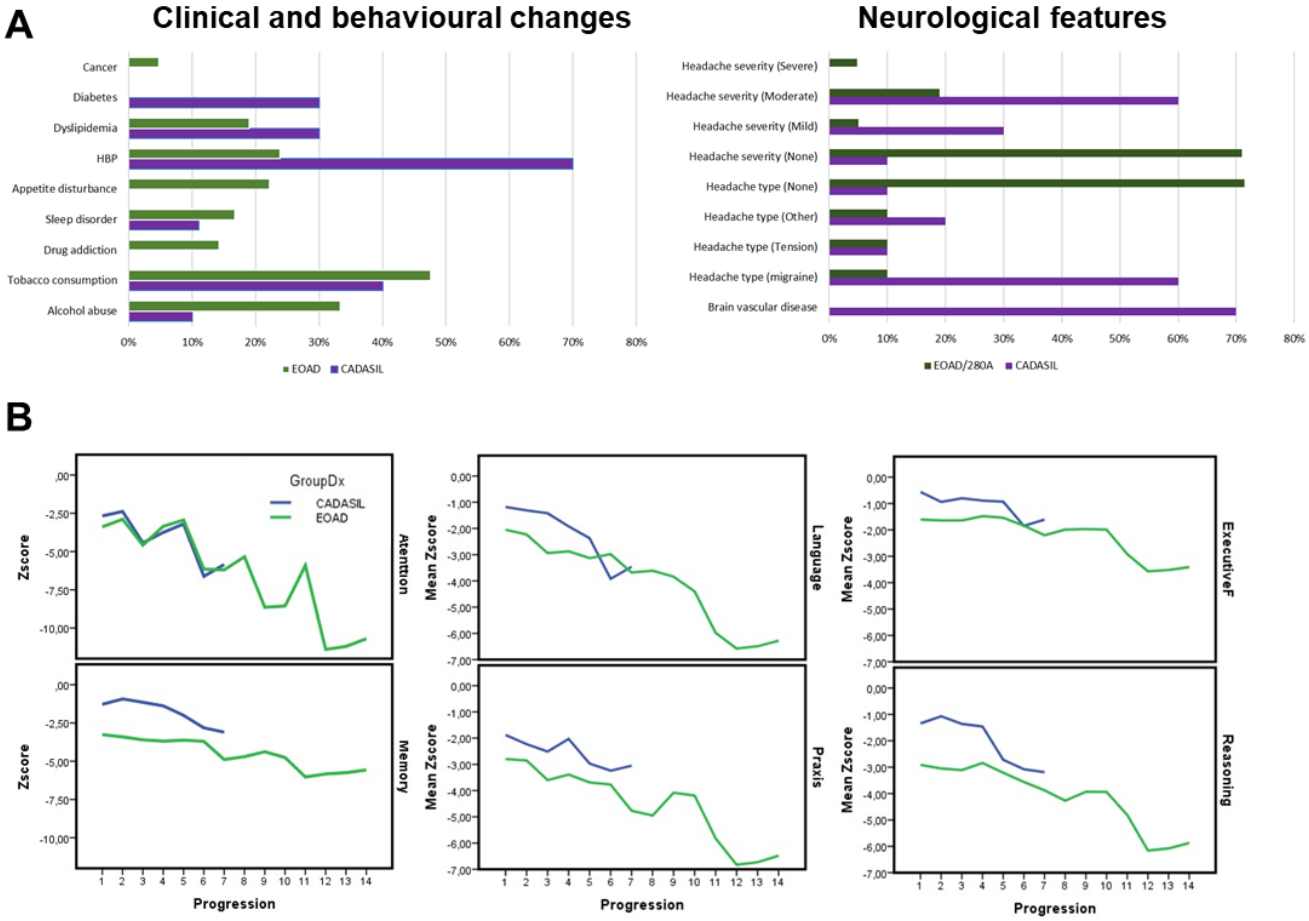
Supplementary Figure 6 Leaking Vessels and astrocytes Correlations of evaluated variables

Representative images of Aβ + GFAP co-staining are shown for *PSEN1* FAD, SAD and CADASIL, scale bar all panels = 100 µM. GFAP-positive astrocyte podocytes (empty arrow-head) can be observed in PSEN1 FAD, SAD and CADASIL, as well as no co-localisation between these and Aβ in PSEN1 FAD and SAD (A). Further, the total signal of AQP4 for all analysed vessels in PSEN1 FAD, sporadic Alzheimer's disease and CADASIL is shown, with CADASIL vessels having significantly less AQP4 signal than vessels in PSEN1 FAD and SAD (p-values: **** ≤ 0.0001) (B).

Supplementary Figure 7 Correlations of evaluated variables

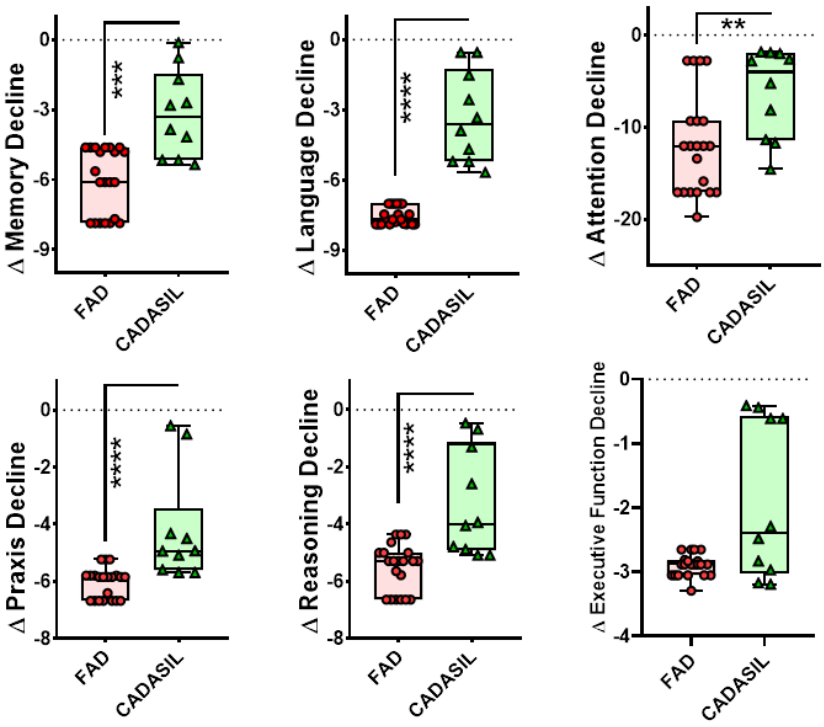
Heatmap depicting positive (red hues) and negative (blue hues) correlations for evaluated variables in *PSEN1* FAD are shown. Only statistically significant correlations ($p < 0.05$) and over or under critical values (0.436, -0.436, respectively) are shown.

Supplementary Figure 1



Supplementary Figure 2

A



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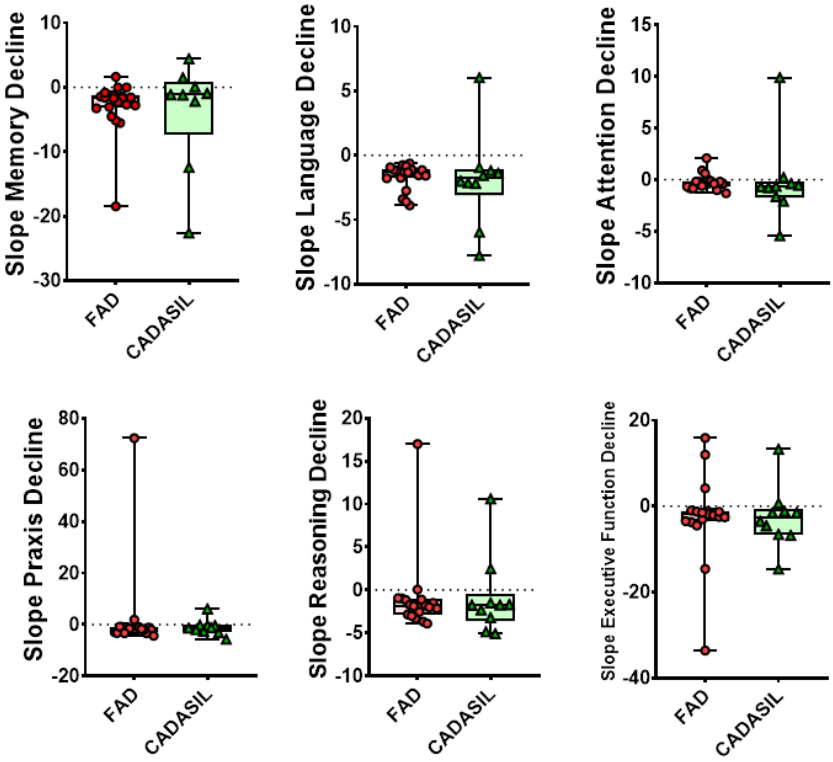

Supplementary Figure 3

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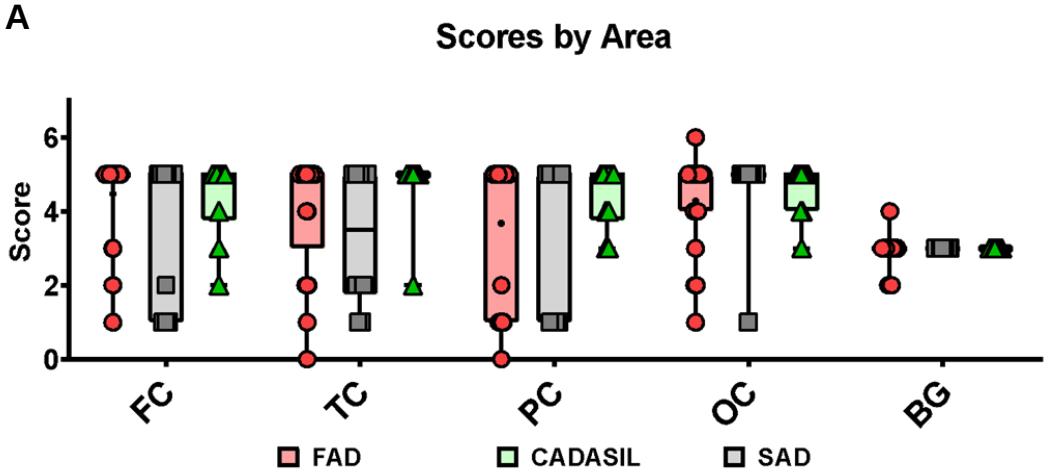

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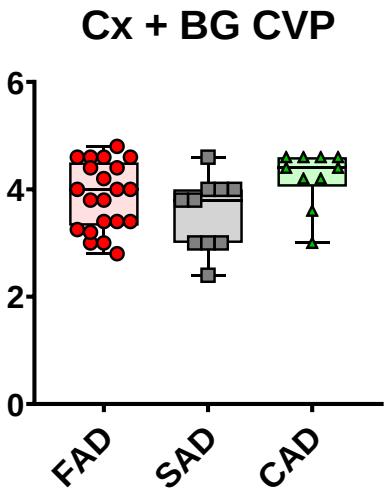

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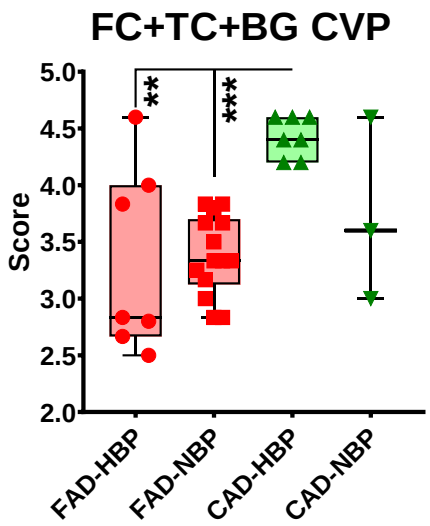

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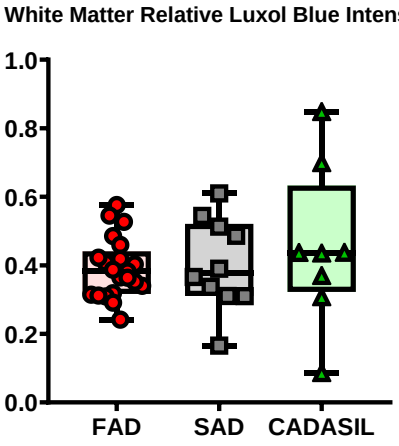

Supplementary Figure 4

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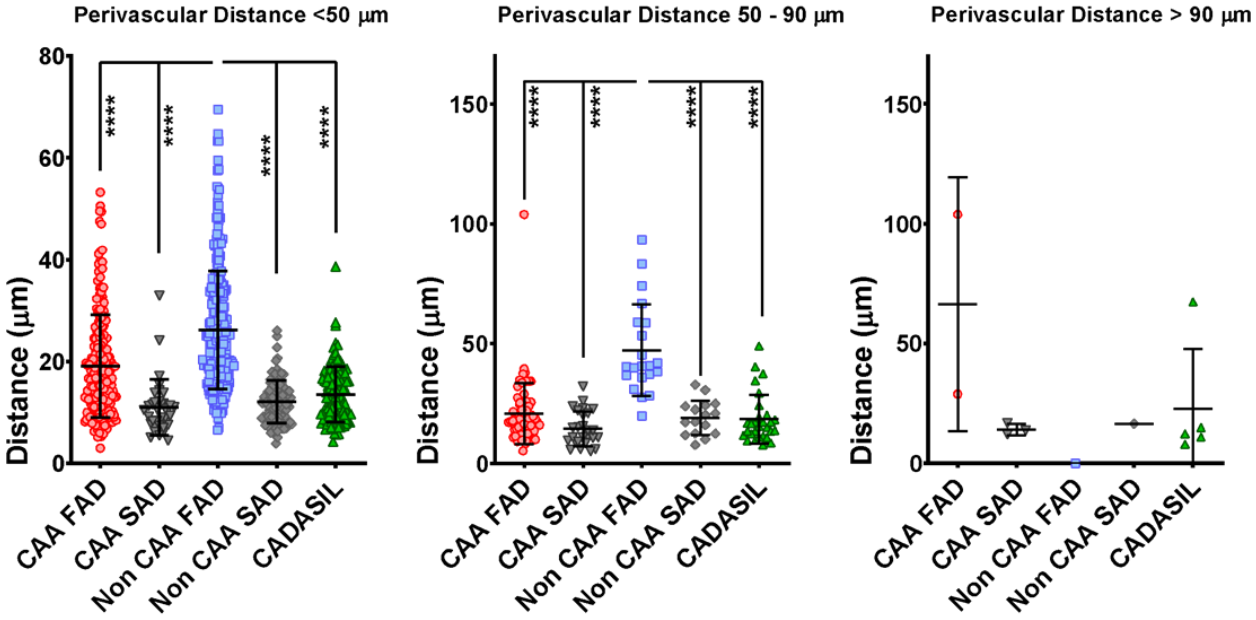

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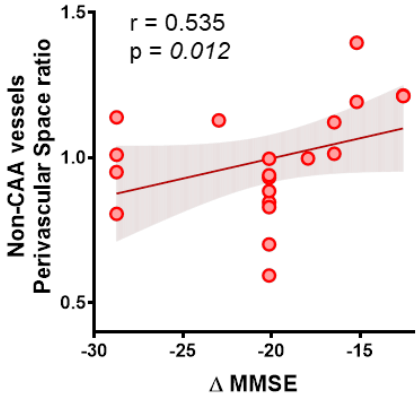

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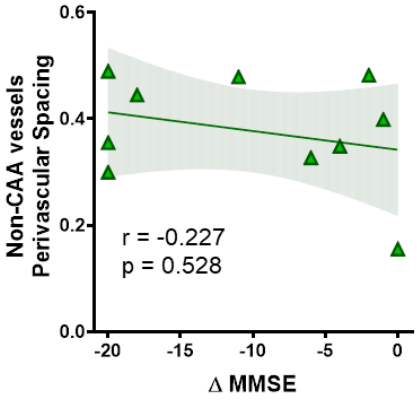
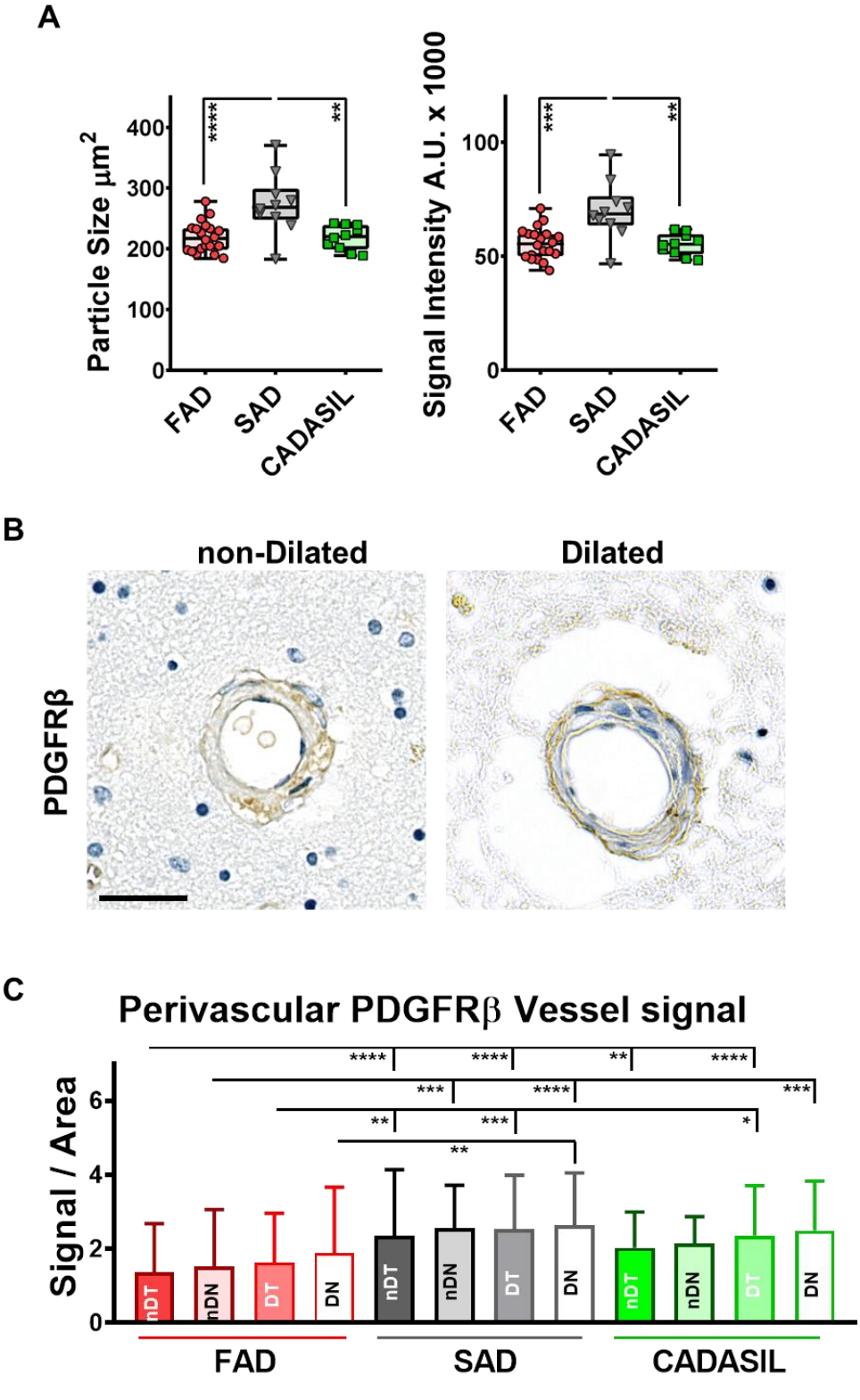
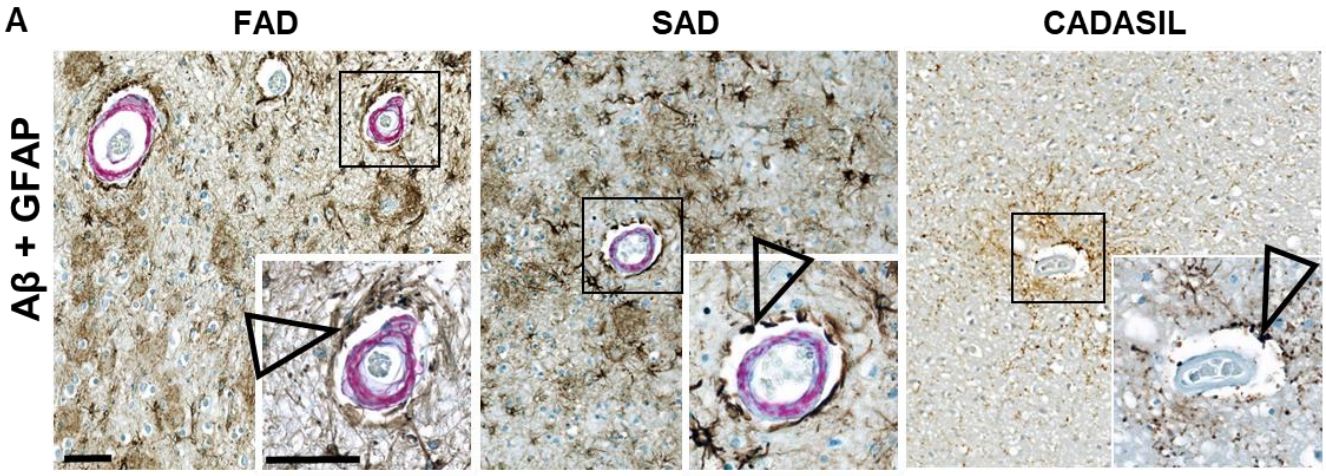
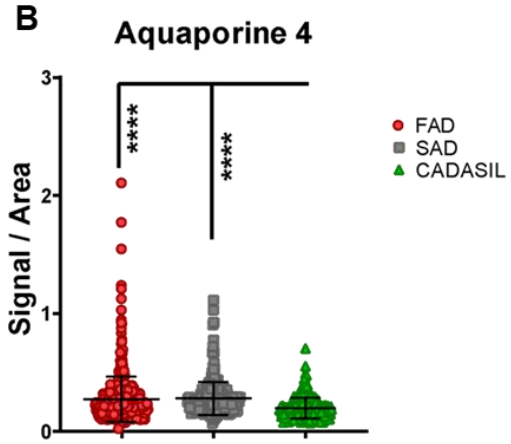


Supplementary Figure 5



Supplementary Figure 6





Supplementary Figure 7