

Supplementary Materials

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Supplementary Table 6. Longitudinal analysis between DTI change measures and dementia. Values show the standardized regression coefficients β (SE) for the baseline predictor variables in a cox regression or logistic regression models of dementia conversion. The odds ratio (OR) together with the confidence interval (CI) are shown. The model parameters Hosmer and Lemeshow's R^2 (R^2_L) give an estimated amount of variation in the dependent variable explained by the model. The Area under the curve (AUC) evaluates how well the model classifies dementia conversion and no-dementia conversion at all possible cutoffs respectively. All regression models control for the effects of age, gender and NART-IQ or education.

Supplementary Table 1. MRI acquisition parameters in each cohort study

		SCANS	RUN DMC	HARMONISATION	ASPS-FAM	CADASIL
Sequence						
T1	TR [ms]	11.5	22.50	23.00	1900	22
	TE [ms]	5	3.68	1.9	2.19	6
	Slice [mm]	1.1	1	1	1	1.2
FLAIR	TR [ms]	9000	9000	9000	10000	8402
	TE [ms]	130	84	82	69	151
	Slice [mm]	5	5	3	3	5
DTI	TR [ms]	15600	10200	6800	4900	8300
	TE [ms]	93.4	95	85	81	96
	Slice [mm]	2.5	2.5	3	3	5
	b-value [s/mm ²]	1000	900	1150	1000	1000
	Directions	25	61	61	12	41

TR= repetition time, TE= echo time

Supplementary Table 2. Test scores used for computing Global Cognition or the trail-making test score (TMT-B)

Cohort	Cognitive Index	Task Name	Measure Description
SCANS	Global Cognition	Trail Making Test	Trail-making Test-B: alternating letters and numbers as quickly as possible while still maintaining accuracy
		SL-Verbal Fluency	Timed generation of words beginning with letter: FAS/ BHR
		mWCST	Card Sorting Test involving flexible shifting from learned dimensions
		BMIPB SOIP	Speeded cancellation of second highest of five two-digit numbers
		Digit Symbol	Speeded transcoding task
		Grooved Pegboard	Pick-up, rotation and placement of small pegs.
		Digit Span	Immediate recall of digit strings (forwards & backwards)
		Logical Memory	Immediate and delayed recall of short stories
		Visual Reproduction	Immediate and delayed reproduction of line drawings
RUN DMC	Global Cognition	MST	1-letter Paper-and-Pencil Memory Scanning task: Reaction-time task on detecting memorised letters
		DSST	Symbol-Digit Substitution Task involving match symbols to numbers according to a key
		RAVLT	Rey Auditory Verbal Learning Test involving verbal memory
		ROCF	Rey Complex Figure Task involves reproducing a complicated line drawing, first by copying it freehand (recognition), and then drawing from memory (recall)
		Stroop	Stroop Color Word Test (short form)
		VF	Verbal fluency about naming animals and professions
		VSAT	Verbal Series Attention Test include forward and reverse generation of arithmetic series, days of the week, and months of the year; number-letter sequencing; and auditory vigilance for a spoken target letter
PRESERVE	Global Cognition	TMT-A	Trail-making Test-A: connecting a set of 25 dots as quickly as possible while still maintaining accuracy
		TMT-B	Trail-making Test-B: alternating letters and numbers as quickly as possible while still maintaining accuracy
		WAIS-III	Wechsler Adult Intelligence Coding test involving coding numbers with characters according to a key
		FAS	Verbal fluency Letter subtask involving

			naming letters as soon as possible Verbal fluency Animals subtask involving naming animals as soon as possible
		RAVLT	Rey Auditory Verbal Learning Test involving verbal memory
HARMONISATION	Global Cognition	Global	Combination of 26 cognitive test scores involving executive function, attention, language, verbal memory, visual memory, visual construction, visuomotor speed
ASPS-Fam	Global Cognition	G-Factor	A principal component measure involving figural and verbal memory of the Lern und Gedächtnis Test, Trail-making Test-B, Digit Span backward, Complex reaction time task and Purdue Pegboard Test
CADASIL	Executive function	TMT-B	Trail-making Test-B: alternating letters and numbers as quickly as possible while still maintaining accuracy

Supplementary Table 3. Longitudinal analysis between DTI baseline measures and dementia. Values show the standardized regression coefficients β (SE) for the baseline predictor variables in a cox regression or logistic regression models of dementia conversion. The hazard ratio (HR) or odds ratio (OR) together with the confidence interval (CI) are shown. The model parameters *Nagelkerke's R²* (Ng R²) or Hosmer and Lemeshow's R² (R²_L) give an estimated amount of variation in the dependent variable explained by the model. The Area under the curve (AUC) evaluates how well the model classifies dementia conversion and no-dementia conversion at all possible cutoffs respectively. All regression models control for the effects of age, gender and NART-IQ or education.

	Baseline marker predicting dementia conversion					
Cohort	DTI markers	β (SE)	P-value	HR (95% CI)	Ng R ²	AUC
SCANS	MD Median	0.717 (0.181)	7.1e-05	2.048 (1.438- 2.918)	0.206	0.794
	FA Median	-0.750 (0.251)	0.0028	0.472 (0.289- 0.773)	0.171	0.791
	MDPH	-0.959 (0.256)	0.0002	0.384 (0.232- 0.634)	0.212	0.811
	FAPH	0.782 (0.237)	0.001	2.186 (1.374- 3.478)	0.179	0.754
	MD pkval	0.596 (0.192)	0.002	1.816 (1.248- 2.644)	0.174	0.790
	FA pkval	-0.751 (0.263)	0.004	0.472 (0.282- 0.789)	0.168	0.771
	RUN DMC	MD Median	0.310 (0.136)	0.016	1.364 (1.060-1.755)	0.165
FA Median		0.182 (0.112)	0.105	0.834 (0.670- 1.038)	0.160	0.817
MDPH		-0.812 (0.172)	2.41e-06	0.444 (0.317- 0.622)	0.193	0.847
FAPH		0.192 (0.121)	0.112	1.212 (0.956- 1.536)	0.160	0.818
MD pkval		-0.080 (0.135)	0.554	0.923 (0.708- 1.203)	0.156	0.811

	FA pkval	-0.194 (0.121)	0.108	0.824 (0.650- 1.044)	0.160	0.814
HARMONISATION	MD Median	0.579 (0.253)	0.023	1.784 (1.085- 2.935)	0.096	0.761
	FA Median	-0.259 (0.253)	0.307	0.772 (0.470- 1.268)	0.067	0.722
	MDPH	-0.622 (0.283)	0.028	0.537 (0.308- 0.935)	0.095	0.761
	FAPH	0.309 (0.240)	0.198	1.362 (0.851- 2.180)	0.072	0.738
	MD pkval	0.045 (0.221)	0.840	1.046 (0.678- 1.612)	0.060	0.709
	FA pkval	0.187 (0.214)	0.382	1.206 (0.792- 1.836)	0.065	0.690

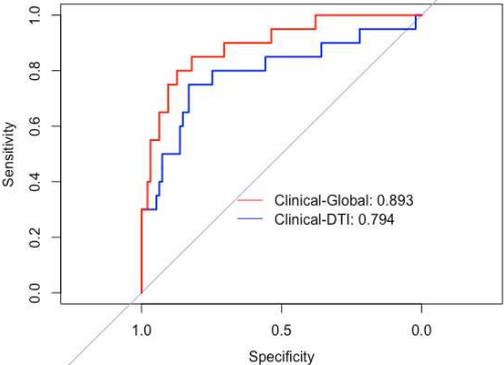
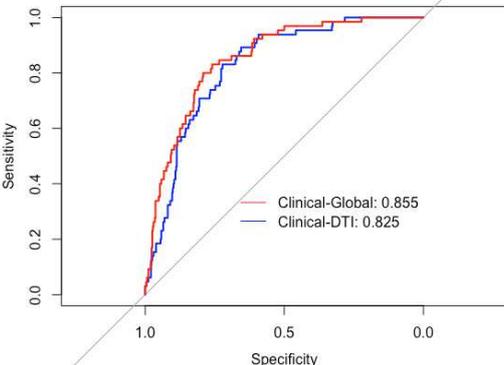
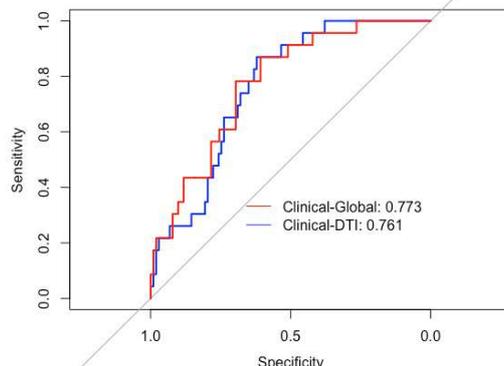
MD= mean diffusivity, FA= fractional anisotropy, PH= normalised peak height of the histogram, pkval= peak value of the histogram

Supplementary Table 4. The association between global cognition at baseline and future dementia risk. The model included age, sex, NART/education and baseline global cognition. Values show standardised regression coefficients: β (SE) for predictor variables in the Cox regression models of later dementia conversion. There was a significant association between Global cognition and dementia conversion independently of age, sex and premorbid IQ (NART) or education in the SVD cohorts.

	SCANS			RUN DMC			HARMONISATION		
	β (SE)	HR (95% CI)	p-value	β (SE)	HR (95% CI)	p-value	β (SE)	HR (95% CI)	p-value
Age	0.505 (0.291)	1.657 (0.936, 2.932)	0.083	0.974 (0.173)	2.648 (1.886- 3.717)	1.83e-08	0.268 (0.271)	1.308 (0.769, 2.224)	0.322
Sex, male	0.970 (0.649)	2.638 (0.739, 9.414)	0.135	0.017 (0.257)	1.017 (0.614, 1.684)	0.948	-0.524 (0.520)	0.592 (0.214, 1.641)	0.314
NART/Educ	0.585 (0.304)	1.795 (0.990, 3.256)	0.054	0.448 (0.142)	1.565 (1.184, 2.068)	0.002	0.095 (0.260)	1.100 (0.661, 1.831)	0.714
Global	-2.215 (0.439)	0.109 (0.046, 0.258)	4.58e-07	-1.270 (0.212)	0.281 (0.185, 0.426)	2.09e-09	-0.499 (0.264)	0.607 (0.361, 1.019)	0.059

Global= Global Cognition, NART= premorbid IQ score, Educ= Education, HR= Hazard ratio, CI = confidence interval, statistical significance P-value < 0.05

Supplementary Figure 1. Comparing the area under the curve (AUC) for the baseline Clinical-DTI model and the baseline Clinical-Global model predicting later dementia conversion. In all three cohorts the AUC estimates between the two predictive models were not significantly different.

Cohort	ROC with the AUC listed in the figures	DeLong test for 2 correlated ROC curves
SCANS		$Z = -1.567$ $p = 0.117$
RUN DMC		$Z = -1.818$ $p = 0.069$
HARMONISATION		$Z = -0.232$ $p = 0.816$

Supplementary Table 5. DTI all Histogram and MRI change over time. Values show the change in MD median and MRI markers over time. The p-value below 0.05 indicates that there was a significant change over time. The number of patients showing in an increase in lacune count and CMB count over time is also shown.

	Cohort					
	SCANS N= 99		RUN DMC N= 257		ARMY N= 120	
MRI parameter change	Est· annual mean change (SE)	p-value	Abs· Mean change (SD)	p-value	Abs· Mean change (SD)	p-value
MD Median (mm²/s)	5.37e-06 (5.42e-07)	2.97e-06	3.34e-06 (1.26e-05)	3.15e-05	2.30e-05 (3.69e-05)	4.04e-10
FA Median (mm²/s)	-2.05e-03 (4.26e-04)	8.16e-06	0.002 (0.021)	0.19	-5.62e-03 (1.72e-02)	4.90e-04
MDPH (mm²/s)	-3.87e-04 (3.32e-05)	<2e-16	-1.14e-04 (1.17e-03)	0.12	-6.05e-04 (1.27e-03)	8.11e-07
FAPH (mm²/s)	-1.44e-06 (5.00e-06)	0.77	9.62e-05 (2.77e-04)	6.60e-08	2.00e-04 (5.77e-04)	2.25e-04
MD pkval (mm²/s)	2.77e-06 (6.59e-07)	4.95e-05	-2.67e-06 (2.54e-05)	0.09	8.67e-06 (3.07e-05)	2.47e-03
FA pkval (mm²/s)	-6.44e-03 (1.69e-03)	2.76e-04	-3.00e-03 (7.56e-02)	0.52	-8.00e-04 (1.66e-02)	0.60
BV (ml)	-8.88 (0.86)	<2e-16	-22.39 (19.95)	< 2.2e-16	-16.00 (132.86)	0.19
WMH	0.08 ^a (0.01) ^c	<2e-16	0.32 ^a (0.46)	< 2.2e-16	2.56 ^b (9.53)	3.85e-03
MRI incidence	Number of patients (Proportion %)		Number of patients (Proportion %)		Number of patients (Proportion %)	
Lacune count	27 (0.27)		30 (0.12)		10 (0.08)	
CMB count	36 (0.36)		32 (0.12)		24 (0.20)	

^a % of brain volume

^b volume in ml

^c log₁₀ transformed

MD= mean diffusivity, BV= brain volume, WMH= white matter hyperintensity, CMB= cerebral microbleeds, NART= premorbid IQ score, pkval= peak value of the histogram, PH= normalised peak height of the histogram

Supplementary Table 6. Longitudinal analysis between DTI change measures and dementia. Values show the standardized regression coefficients β (SE) for the baseline predictor variables in a cox regression or logistic regression models of dementia conversion. The odds ratio (OR) together with the confidence interval (CI) are shown. The model parameters Hosmer and Lemeshow's R^2 (R^2_L) give an estimated amount of variation in the dependent variable explained by the model. The Area under the curve (AUC) evaluates how well the model classifies dementia conversion and no-dementia conversion at all possible cutoffs respectively. All regression models control for the effects of age, gender and NART-IQ or education.

Change marker predicting dementia conversion						
Cohort	DTI change markers	β (SE)	P-value	HR/ OR (95% CI)	Ng R^2 / R^2_L	AUC
SCANS	MDPH	-0.674 (0.243)	0.006	0.510 (0.317- 0.820)	0.119	0.750
	FAPH	0.652 (0.235)	0.006	1.919 (1.211- 3.041)	0.112	0.715
	MD Median	0.951 (0.226)	2.49e-05	2.588 (1.663- 4.027)	0.202	0.785
	FA Median	-0.388 (0.205)	0.059	0.679 (0.454- 1.014)	0.078	0.713
	MD pkval	0.388 (0.212)	0.067	1.474 (0.9727- 2.234)	0.077	0.678
	FA pkval	-0.686 (0.215)	0.001	0.504 (0.331- 0.767)	0.131	0.769
	RUN DMC	MDPH	-0.409 (0.417)	0.327	0.665 (0.289- 1.482)	0.257
FAPH		0.005 (0.356)	0.990	0.995 (0.483- 1.910)	0.247	0.895
MD Median		-0.068 (0.305)	0.825	0.935 (0.498- 1.667)	0.248	0.891
FA Median		-0.043 (0.356)	0.905	0.958 (0.496- 1.934)	0.247	0.896
MD pkval		-0.175 (0.277)	0.528	0.839 (0.475- 1.428)	0.251	0.894
FA pkval		0.015 (0.369)	0.967	1.015 (0.485- 2.069)	0.247	0.895

HARMONISATION	MDPH	-0.059 (0.251)	0.816	0.943 (0.570 1.545)	0.076	0.682
	FAPH	0.375 (0.242)	0.120	1.455 (0.911- 2.389)	0.097	0.704
	MD Median	0.453 (0.237)	0.056	1.573 (0.998- 2.597)	0.109	0.738
	FA Median	-0.134 (0.245)	0.585	0.875 (0.538- 1.420)	0.078	0.693
	MD pkval	0.309 (0.245)	0.207	1.362 (0.847- 2.234)	0.090	0.704
	FA pkval	0.005 (0.267)	0.986	1.005 (0.599- 1.722)	0.075	0.685

MD= mean diffusivity, FA= fractional anisotropy, PH= normalised peak height of the histogram, pkval= peak value of the histogram

