Original research

Prediction of dementia using diffusion tensor MRI measures: the OPTIMAL collaboration

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ABSTRACT

Objectives It has been suggested that diffusion tensor imaging (DTI) measures sensitive to white matter (WM) damage may predict future dementia risk not only in cerebral small vessel disease (SVD), but also in mild cognitive impairment. To determine whether DTI measures were associated with cognition cross-sectionally and predicted future dementia risk across the full range of SVD severity, we established the International OPtimising mulTImodal MRI markers for use as surrogate markers in trials of Vascular Cognitive Impairment due to cerebrAl small vesseL disease collaboration which included six cohorts.

Methods Among the six cohorts, prospective data with dementia incidences were available for three cohorts. The associations between six different DTI measures and cognition or dementia conversion were tested. The additional contribution to prediction of other MRI markers of SVD was also determined.

Results The DTI measure mean diffusivity (MD) median correlated with cognition in all cohorts, demonstrating the contribution of WM damage to cognition. Adding MD median significantly improved the model fit compared to the clinical risk model alone and further increased in all single-centre SVD cohorts when adding conventional MRI measures. Baseline MD median predicted dementia conversion. In a study with severe SVD (SCANS) change in MD median also predicted dementia conversion. The area under the curve was best when employing a multimodal MRI model using both DTI measures and other MRI measures.

Conclusions Our results support a central role for WM alterations in dementia pathogenesis in all cohorts. DTI measures such as MD median may be a useful clinical risk predictor. The contribution of other MRI markers varied according to disease severity.

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INTRODUCTION

Cerebral small vessel disease (SVD) causes a quarter of all strokes and is the most common pathology underlying vascular cognitive impairment and dementia.[1] Conventional MRI shows characteristic features including lacunar infarcts, white matter hyperintensities (WMH), cerebral microbleeds (CMB) and enlarged perivascular spaces.[2]

It is hypothesised that cognitive impairment results from disruption of neuronal networks due to damage to WM tracts providing their connections, and that this either disrupts efficient processing of information between neurocognitive systems or damages control mechanisms coordinating cognition.[3] A key role of WM damage is suggested by population-based studies showing that WMH burden predicts stroke and dementia.[4] A more sensitive method of identifying WM ultrastructural damage and tract alterations is diffusion tensor imaging (DTI). Studies have shown altered structural integrity within the WM and in areas outside WMH.[5] Cross-sectional studies in SVD show that DTI measures correlate more strongly with cognition than WMH or other conventional SVD markers.[6–8] DTI measures have been shown to predict progression to dementia,[9] but previous prediction studies have been largely limited to single-centre cohorts.

The use of DTI measures may provide better prediction of who will progress to dementia, allowing those at higher risk to be targeted for therapeutic interventions. Recent image analysis techniques allow rapid assessment of DTI measures to be calculated, making it a realistic biomarker for clinical prediction.[8] However, prior to its more widespread use, it is important to demonstrate that DTI measures indeed predict dementia across populations, including patients with varying severity of SVD. Furthermore other markers such as lacunes, WMH, atrophy and CMB have also been associated with cognition in SVD.[7 10] It is important to determine the relative importance of these markers. A combination of DTI and other MRI measures may be needed reflecting the disease heterogeneity beyond microstructural WM damage.

To assess the predictive value of DTI measures across the full range of SVD severity, we formed a collaboration in six cohorts to determine correlations between DTI measures and cognition, and whether baseline and changes in DTI measures predicted dementia conversion. We further determined whether adding conventional MRI markers increased prediction.

METHODS

The OPtimising mulTImodal MRI markers for use as surrogate markers in trials of Vascular Cognitive Impairment due to cerebrAl small vesseL disease (OPTIMAL) collaboration was established to

Table 1 Overview about the cohort studies included in the OPTIMAL project

Cohort	No of patients	Country	Inclusion criteria	Dementia diagnosis	Vascular dementia	Alzheimer's disease
SCANS (St George's cognition and neuroimaging in stroke)	121	UK	Symptomatic SVD defined as a clinical lacunar stroke syndrome with MRI evidence of an anatomically corresponding lacunar infarct, and with confluent regions of WMH graded ≥2 on the modified Fazekas scale.[40]	Diagnostic and Statistical Manual of Mental Disorders V	–	–
PRESERVE (How intensively should we treat blood PRESsure in established cERebral small VEssel disease?')	111	UK	Symptomatic SVD defined as a clinical lacunar stroke syndrome with MRI evidence of an anatomically corresponding lacunar infarct, and with confluent regions of WMH graded ≥2 on the modified Fazekas scale.[40]	–	–	–
RUN DMC (Radboud University Nijmegen Diffusion Imaging and Magnetic Resonance Imaging Cohort)	503	The Netherlands	SVD defined as the presence of lacunes and or WMH on neuroimaging.	Diagnostic and Statistical Manual of Mental Disorders IV	National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherché et l'Enseignement en Neurosciences criteria.[41]	National Institute on Ageing and Alzheimer's Association criteria.[42]
HARMONISATION	127	Singapore	Patients with mild cognitive impairment impaired in at least one cognitive domain of a formal neuropsychological test battery, with or without a history of stroke.	Diagnostic and Statistical Manual of Mental Disorders IV	National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherché et l'Enseignement en Neurosciences criteria.[41]	National Institute on Ageing and Alzheimer's Association criteria.[42]
ASPS-Fam (Austrian stroke prevention family study)	382	Austria	Being free of dementia and stroke as well as demonstrating normal neurological function.	–	–	–
CADASIL (Munich CADASIL cohort)	58	Germany	Diagnosis of CADASIL confirmed by genetic testing or skin biopsy.	–	–	–

The table shows the number of patients enrolled, the respective inclusion criteria and the type of dementia diagnosis given in each study.
OPTIMAL, OPtimising mulTImodal MRI markers for use as surrogate markers in trials of Vascular Cognitive Impairment due to cerebrAl small vesseL disease; SVD, small vessel disease; WMH, white matter hyperintensity.

determine whether DTI measures predicted dementia in SVD across multiple cohorts.[11]

Subjects

Six cohorts with differing degrees of SVD severity were included

1. Severe symptomatic SVD (SCANS)
2. Severe symptomatic SVD (PRESERVE)
3. Moderate SVD (RUN DMC).
4. Mild cognitive impairment (MCI) (HARMONISATION).
5. Elderly stroke free population based cohort (ASPS-Fam).
6. Monogenic SVD (CADASIL).

Informed consent was obtained from participants. Details were published previously and are summarised in table 1.

Severe symptomatic SVD cohort (SCANS)

MRI scanning took place at baseline and over 3 yearly follow-up sessions on a 1.5 T General Electric Signa HDxt MRI system.[9] Acquisition parameters are presented in online supplemental table 1. Cognition was measured using standardised tests sensitive to SVD.[12] Age-standardised test scores were used to form a measure of Global Cognition (online supplemental table 2).

Multicentre severe symptomatic SVD cohort (PRESERVE)

MRI acquisition took place on eight 3-Tesla MRI scanners (3 Philips Achieva TX, 1 Philips Achieva, 1 Philips Ingenia, 1 Siemens Verio, 1 Siemens Prisma, 1 Siemens Magnetom Prisma fit)[13] as part of the PRESERVE trial. Acquisition parameters across scanners were harmonised (online supplemental table 1). Neuropsychological scores were age standardised to create Global Cognition (online supplemental table 2).

Moderate SVD cohort (RUN DMC)

MRI acquisition was performed on a 1.5 T Siemens Magnetom Avanto MRI machine,[14] using parameters listed in online supplemental table 1). Due to scanner updates, only data from 2011 and 2015 were used for longitudinal analysis, as DTI is sensitive to scanner changes. 258 dementia-free patients with DTI and conventional MRI were still enrolled in 2011. Cognition was assessed using validated cognitive tasks. Age-standardised scores were used to compute a Global Cognition score (online supplemental table 2).

MCI cohort (Harmonisation)

Imaging data were acquired on a 3T Siemens Magnetom Trio Tim system (online supplemental table 1). Baseline and 2 years

follow-up DTI data were available.[15] Patients were tested on neuropsychological test batteries previously validated. Scores were standardised to the mean and SD to form a measure of Global Cognition. More details regarding the test can be found in online supplemental table 2.

Elderly stroke free population-based cohort (ASPS-Fam)

Magnetic resonance acquisition was performed on a 3T Tim Trio whole body scanner (online supplemental table 1). Only baseline DTI measures were used.[16] Global Cognition was created with age-standardised test scores (online supplemental table 2).

Monogenic cohort (CADASIL)

Imaging data were based on a 1.5 T GE Signa system in Munich (online supplemental table 1).[8] To measure the main cognitive deficit in these patients, that is processing speed, the Trail-making test–B was used. The main outcome score was transformed to z-scores using normative data from the literature (online supplemental table 2).[17]

MRI processing

Brain volume and WMH volume

SCANS: Brain volume (BV) was computed from native T1 images as an estimate of brain size relative to the skull size with SIENAX as part of the FMRIB software library.[7] WMH and brain tissues segmentations were carried out using the methods previously described.[18] A measure of WMH, called SVDp, was calculated by taking the ratio of WMH volume to the total cerebral volume composed of the sum of grey matter (GM), WM and WMH.

RUN DMC: Tissue probability maps were calculated employing Statistical Parametric Mapping 12 (SPM12) unified segmentation routine on the T1 MPRAGE images.[19] The GM and WM volumes derived from the sum of the all voxel volumes were added creating a measure of BV. WMH volumes were calculated by a WMH segmentation method[20] and the same measure as in SCANS was used (SVDp).

PRESERVE: T1W scans were segmented into GM, WM and cerebrospinal fluid (CSF) tissue probability maps employing SPM12b (http://www.fil.ion.ucl.ac.uk/spm/). Soft segmentations of the GM and WM tissue probability maps were used to compute BV and an estimate of brain size relative to the skull size with SIENAX was calculated.[13] A semiautomated programme JIM (Xinapse Systems; www.xinapse.com) was used to segment WMH regions. Brain lesion maps were used to compute lesion load as the percentage of WMH lesion volume against BV.[13]

HARMONISATION: Image preprocessing and the tissue classification algorithm have been described elsewhere.[21] Briefly, a k-nearest-neighbour technique was used to classify voxels into CSF, GM and normal appearing WM and volumes were calculated from these measurements. WMH volumes were detected using an adapted threshold technique.[21] Intracranial volume was the sum of the CSF, GM, normal WM and WMH.

ASPS-FAM: Intracranial volume was estimated by FreeSurfer V.6.0. A custom-written Interactive Data Language programme was used to create WMH maps. Segmentation was performed on Fluid-attenuated inversion recovery (FLAIR) images by 2 two raters.[16]

CADASIL: BV was computed from native T1 images as an estimate of size of the brain relative to the skull size with SIENAX as part of the FMRIB software library.[8] WMH segmentations were generated by a semiautomatic pipeline and corrected by trained raters.[8]

Lacune count and CMB count

Lacune and CMB were identified by trained raters blinded to the data.

In SCANS, RUN DMC, HARMONISATION and PRESERVE lacunes were defined as CSF filled cavity within WM or subcortical areas between 3 and 15 mm in diameter on T1-weighted and FLAIR images.[2] In ASPS-Fam lacunes were graded as focal lesions with maximum diameter of 10 mm. In CADASIL lacunes were detected on T1-weighted images with a signal identical to CSF, sharp delineation and diameter >2 mm.

in SCANS, RUN DMC and PRESERVE CMB were identified on T2* weighted Gradient echo (GRE) images as focal spots up to 10 mm in diameter.[7 10] In HARMONISATION rating of the CMB was done on susceptibility-weighted images employing the Microbleed Anatomical Rating Scale.[22 23] In ASPS-Fam CMB were defined as homogeneous rounded lesions with a diameter of 2–5 mm. In CADASIL CMB were graded on GRE sequences as rounded foci <5 mm in diameter.

DTI processing

Six WM histogram measures were computed: mean diffusivity (MD) median (MD median), peak height (PH) and peak location (pkval) and fractional anisotropy (FA) median (FA median), FAPH and FA pkval. The image analysis pipeline has been described previously[13 24 25] and key steps are summarised.

In SCANS, PRESERVE, HARMONISATION and CADASIL the DTI analyses were carried using a standardised protocol either at the central site (SCANS. PRESERVE, HARMONISATION, CADASIL) or under guidance by the central site (ASPS-Fam). The eddy correct software from 'FDT', FMRIB's Diffusion Toolbox, (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT) was employed for DTI preprocessing. In RUN DMC diffusion data analysis was carried prior to OPTIMAL and the imaging data were preprocessed employing in-house developed iteratively reweighted least squares algorithm at the Radboud University Medical Center in Nijmegen.[26] Susceptibility distortions were unwarped by normalising images to the T1 images in the phase-encoding direction. For all datasets MD and FA maps were created with 'DTIFIT'. FLAIR to T1 weighted and T1 weighted to b0 registrations were conducted and the affine transformation matrices were concatenated to generate a FLAIR-to-DTI transformation.[27] Tissue probability maps were registered into DTI space using these transformations. Hard segmentations were used creating maps of tissue classes. Histogram analysis was conducted on the MD and FA maps in in all WM regions. Summary histogram measures were derived from normalised histograms with 1000 bins.

Statistical analysis

The statistical analysis was conducted using R software (V.3.6.3).

Analyses of cross-sectional baseline data

The relationship between the DTI measures and cognition was tested using linear regression controlling for clinical markers (age, sex and premorbid IQ or education). In PRESERVE, the associations were controlled for studysite-related differences. Using a model decomposition method, the amount of variance in cogntion explained was determined.[28] In the CADASIL sample, one patient was excluded as an outlier and the dependent variable was power transformed to meet the statistical assumptions. The statistical assumptions of the linear model were normality of the residuals, homoscedasticity, linearity of the relationship

and no outlier values which were checked through visual plot inspection.

To determine the best model fit, Akaike information criterion (AIC) together with the adjusted variance (Adj R^2) were computed for the following linear regression models: clinical markers only (Clinical), clinical markers plus DTI measures (Clinical-DTI), clinical markers plus conventional MRI markers (BV, WMH, Lacune and CMB) (Clinical-MRI) and clinical markers plus both conventional MRI and DTI measures (Clinical-MRI-DTI). Again, the linear models' assumptions were checked by visual inspection. WMH, lacune and CMB were log10 transformed. Multiple regression models were checked for multicollinearity with the variance inflation factor (VIF) being below a VIF value threshold (VIF <10).[29] To estimate the relative importance of each predictor in the clinical-MRI-DTI model in explaining the overall variance in cognition, a model decomposition method was employed.[28]

Analyses of longitudinal data

The association between baseline DTI measures and dementia conversion was tested using a Cox regression model in SCANS, RUN DMC and HARMONISATION. The clinical markers were added as confounders. The area under the curve (AUC) was computed.[30] To compare the predictive value of DTI measures to cognitive measures, a separate Cox regression model with the clinical markers and global cognition as covariates (Clinical-Global) was computed. The AUC of the Clinical-DTI model was compared with the Clinical-Global model in each cohort.[30]

To determine change in the markers, the difference between two time points was determined using a paired t-test in RUN DMC and HARMONISATION. In SCANS, characterised by four time points, change was estimated by a linear mixed model.[31] The intercept and slope of each participant's linear trajectory were allowed to vary with both fixed and random effects. Fixed effect variation was accounted for by time, and random effect variation allowed for remaining interindividual differences. Change in lacunes and CMB were categorised as dichotomous; that is, change versus no change in counts. Follow-up observations postdementia diagnosis were removed prior to the model's computation.

Employing a Cox or logistic regression the association between the change in DTI measures and dementia was tested while accounting for the clinical markers. Using AIC the DTI model was compared with the clinical model, to the clinical-MRI model and to clinical-MRI-DTI model. The AUC was computed for each model and compared within cohorts.[30]

RESULTS

The cohorts' demographic characteristics are shown in table 2.

Cross-sectional association between imaging markers and cognition

The DTI measure MD median showed the most consistent associations with the largest effect size, being related to cognition in all cohorts (table 3), and was taken forward as the

Table 2 Demographic, imaging and cognition measures in each cohort studies

	Cohort					
	SCANS	RUN DMC	HARMONISATION	PRESERVE	ASPS-Fam	CADASIL
Demographics	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Age (years)	70.01 (9.75)	65.62 (8.81)	72.23 (8.47)	68.07 (9.11)	65.43 (10.67)	47.90 (9.77)
Sex, male (%)	78 (0.65)	284 (0.57)	57 (0.45)	43 (0.39)	139 (0.40)	26 (0.45)
Included in cross-sectional analysis	Yes	Yes	Yes	Yes	Yes	Yes
Sample size with complete DTI and MRI baseline	115	499	127	101	243	54
Included in longitudinal analysis	Yes	Yes	Yes	No	No	No
Dementia cases with baseline MRI and DTI measures	20	65	23	–	–	–
Sample size in longitudinal dementia analysis with complete repeated MRI and DTI	99	257	120	–	–	–
Dementia cases with repeated MRI and DTI measures	18	12	21	–	–	–
Baseline complete DTI, MRI parameter	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
MD median (mm^2/s)	8.00e-04 (4.08–05)	8.30e-04 (3.71e-05)	8.82e-04 (6.08e-05)	7.87e-04 (4.39e-05)	7.69e-04 (3.03e-05)	8.89e-04 (1.30e-04)
Brain volume (mL)	1295.94 (92.37)	1060.82 (80.15)	1088.87 (128.83)	1349.19 (104.26)	1460.02 (144.38)	1171.88 (113.51)
Baseline MRI count parameter	Median (range)	Median (range)	Median (range)	Median (range)	Median (range)	Median (range)
WMH	3.11 (0.29–23.23)*	0.34 (0.01–12.93)*	2.70 (0–82.89)†	2.90 (0.29–9.32)*	3.90 (0.07–137.16)†	95.24 (0.66–307.18)†
Lacune	2 (0–27)	0 (0–11)	0 (0–8)	2 (0–23)	0 (0–7)	2.5 (0–32)
CMB	0 (0–144)	0 (0–54)	0 (0–95)	0 (0–44)	0 (0–9)	0 (0–16)
Baseline cognition with complete imaging	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Global cognition	−0.654 (0.833)	−0.015 (0.728)	−0.582 (0.892)	−0.789 (0.957)	0.033 (1.028)	–
TMT-B	–	–	–	–	–	−2.88 (4.08)

*% ratio of WMH volume to the total cerebral volume.
†WMH volume in mL.
CMB, cerebral microbleeds; DTI, diffusion tensor imaging; MD, mean diffusivity; TMT-B, Trail-making Test version B; WMH, white matter hyperintensity.

Table 3 Cross-sectional analysis between DTI measures and Global Cognition or TMT-B (CADASIL) independently of the clinical markers

	SCANS*	RUN DMC*	HARMONISATION*	PRESERVE*	ASPS-Fam*	CADASIL†
MD median	−0.232 (0.068), p=**0.001** Adj. R^2=0.478, Norm. Cont R^2 (95% CI)=0.170 (0.030 to 0.330)	−0.218 (0.040), p=**8.76e-08** Adj. R^2=0.454, Norm. Cont R^2 (95% CI)=0.237 (0.167 to 0.317)	−0.344 (0.077), p=**1.98e-05** Adj. R^2=0.456, Norm. Cont R^2 (95% CI)=0.192 (0.076 to 0.336)	−0.410 (0.087), p=**9.19e-06** Adj. R^2=0.373, Norm. Cont R^2 (95% CI)=0.297 (0.105 to 0.464)	−0.149 (0.055), p=**0.008**, Adj. R^2=0.516, Norm. Cont R^2 (95% CI)=0.173 (0.093 to 0.273)	−0.516 (0.177), p=**0.0055** Adj. R^2=0.235, Norm. Cont R^2 (95% CI)=0.650 (0.235 to 0.812)
FA median	0.267 (0.069), p=**0.0002** Adj. R^2=0.492, Norm. Cont R^2 (95% CI)=0.200 (0.066 to 0.342)	0.098 (0.034), p=**0.004** Adj. R^2=0.431, Norm. Cont R^2 (95% CI)=0.025 (0.002 to 0.072)	0.268 (0.072), p=**0.0003** Adj. R^2=0.433, Norm. Cont R^2 (95% CI)=0.171 (0.057 to 0.324)	0.400 (0.082), p=**4.08e-06** Adj. R^2=0.383, Norm. Cont R^2 (95% CI)=0.394 (0.156 to 0.562)	0.119 (0.051), p=**0.020**, Adj. R^2=0.512, Norm. Cont R^2 (95% CI)=0.100 (0.037 to 0.203)	0.515 (0.162), p=**0.0027** Adj. R^2=0.257, Norm. Cont R^2 (95% CI)=0.677 (0.299 to 0.789)
MDPH	0.315 (0.067), p=**7.17e-06** Adj. R^2=0.520, Norm. Cont R^2 (95% CI)=0.231 (0.091 to 0.389)	0.210 (0.043), p=**1.25e-06** Adj. R^2=0.448, Norm. Cont R^2 (95% CI)=0.244 (0.175 to 0.314)	0.338 (0.077), p=**2.36e-05** Adj. R^2=0.455, Norm. Cont R^2 (95% CI)=0.188 (0.082 to 0.337)	0.316 (0.090), p=**0.001** Adj. R^2=0.314, Norm. Cont R^2 (95% CI)=0.195 (0.032 to 0.371)	0.009 (0.050), p=0.865 Adj. R^2=0.500, Norm. Cont R^2 (95% CI)=0.026 (0.008 to 0.075)	0.451 (0.179), p=**0.015** Adj. R^2=0.202, Norm. Cont R^2 (95% CI)=0.609 (0.207 to 0.747)
FAPH	−0.249 (0.069), p=**0.001** Adj. R^2=0.484, Norm. Cont R^2 (95% CI)=0.122 (0.028 to 0.263)	−0.093 (0.034), p=**0.006** Adj. R^2=0.430, Norm. Cont R^2 (95% CI)=0.012 (0.002 to 0.044)	−0.239 (0.076), p=**0.002** Adj. R^2=0.416, Norm. Cont R^2 (95% CI)=0.156 (0.053 to 0.304)	−0.374 (0.083), p=**1.72e-05** Adj. R^2=0.364, Norm. Cont R^2 (95% CI)=0.357 (0.126 to 0.545)	0.022 (0.050), p=0.664 Adj. R^2=0.500, Norm. Cont R^2 (95% CI)=0.020 (0.006 to 0.072)	−0.454 (0.154), p=**0.005** Adj. R^2=0.237, Norm. Cont R^2 (95% CI)=0.630 (0.209 to 0.797)
MD pkval	−0.178 (0.069), p=**0.011** Adj. R^2=0.456, Norm. Cont R^2 (95% CI)=0.110 (0.010 to 0.280)	−0.146 (0.040), p=**2.69e-04** Adj. R^2=0.437, Norm. Cont R^2 (95% CI)=0.174 (0.112 to 0.249)	−0.099 (0.073), p=0.177 Adj. R^2=0.377, Norm. Cont R^2 (95% CI)=0.027 (0.003 to 0.152)	−0.365 (0.089), p=**8.53e-05** Adj. R^2=0.343, Norm. Cont R^2 (95% CI)=0.254 (0.076 to 0.444)	−0.109 (0.054), p=**0.044** Adj. R^2=0.509, Norm. Cont R^2 (95% CI)=0.130 (0.065 to 0.216)	−0.610 (0.173), p=**0.001** Adj. R^2=0.241, Norm. Cont R^2 (95% CI)=0.757 (0.214 to 0.904)
FA pkval	0.228 (0.069), p=**0.001** Adj. R^2=0.476, Norm. Cont R^2 (95% CI)=0.053 (0.009 to 0.123)	0.006 (0.037), p=0.864 Adj. R^2=0.421, Norm. Cont R^2 (95% CI)=0.037 (0.017 to 0.078)	0.095 (0.077), p=0.216 Adj. R^2=0.375, Norm. Cont R^2 (95% CI)=0.021 (0.005 to 0.123)	0.257 (0.088), p=**0.004** Adj. R^2=0.288, Norm. Cont R^2 (95% CI)=0.197 (0.016 to 0.427)	0.086 (0.048), p=0.072 Adj. R^2=0.507, Norm. Cont R^2 (95% CI)=0.057 (0.010 to 0.142)	0.159 (0.144), p=0.274 Adj. R^2=0.0655, Norm. Cont R^2 (95% CI)=0.305 (0.028 to 0.656)

Values show standardised regression coefficients: β (SE) for predictor variables in linear regression models of Global Cognition or TMT-B in CADASIL. P-value < 0.05 are marked in bold. Adjusted R^2 refers to the overall explained variance adjusted for the number of predictors in the model. DTI's normalised R^2 contribution to the overall model together with the 95% CI is also shown.

*Linear regression analysis with Global cognition as outcome measure

†Linear regression analysis with TMT-B as outcome measure

DTI, diffusion tensor imaging; FA, fractional anisotropy; MD, mean diffusivity; PH, peak height; pkval, peak value of the histogram; TMT-B, Trail-making Test version B.

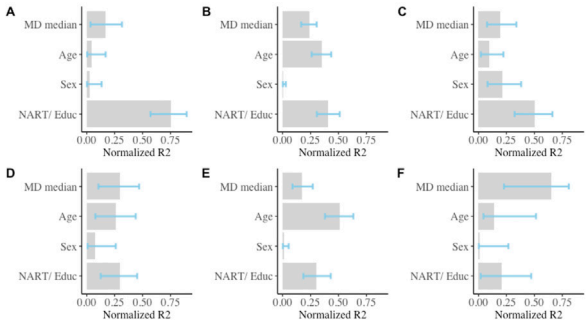

Figure 1 Normalised contribution of the individual marker to the unadjusted explained variance in cognition in the Clinical-DTI model. In the sporadic SVD and MCI cohorts normalised DTI's contribution to the overall explained variance varied around 20%. DTI's contribution to the model was significant higher for CADASIL. Across all non-monogenic cohorts clinical markers explained a significant proportion of the model's explained variance. Panels: A=SCANS, B=RUN DMC, C=HARMONISATION, D=PRESERVE, E=ASPS Fam, F=CADASIL. Lines refer to 95% CIs after bootstrapping. Overall unadjusted R^2 variance explained by the Clinical-DTI model: SCANS=0.496, RUN DMC=0.458, HARMONISATION=0.474, PRESERVE=0.409, ASPS-Fam=0.524, CADASIL=0.299 MD median=median of the normalised mean diffusivity histogram, NART= premorbid IQ, Educ= education, R^2= explained variance of the model, DTI= diffusion tensor imaging; MCI= mild cognitive impairment; MD= mean diffusivity; SVD= small vessel disease.

DTI marker used in further analyses. The Clinical-DTI model explained 0.454–0.516 of variance in the single non-monogenic centre cohorts, but less variance in the multicentre cohort (adj R^2=0.373) (table 3). The adjusted variance in the CADASIL cohort was 0.235 due the low variance explained by the clinical model in this cohort. DTI's normalised R^2 contribution was highest in CADASIL (figure 1).

The variance in cognition explained by the different models is shown in table 4. The additional variance explained by adding conventional MRI markers to the DTI-clinical model varied but was greatest in SCANS and CADASIL, while little or no additional variance was added in HARMONISATION and ASPS-Fam. In all models VIF was below 3. Relative contributions of the different imaging markers of SVD to cognition in the Clinical-DTI-MRI model were determined (figure 2). This varied according to SVD severity. In SCANS and in CADASIL, this was greatest for BV, lacunes and the DTI measure. In contrast, in milder SVD (ASPS-FAM and HARMONISATION), the DTI measure contributed most, and BV and lacunes contributed little (figure 2). Of the clinical markers, age was the most important predictor in the ASPS-Fam, whereas education or premorbid IQ explained most variance in the non-monogenic cohorts.

Longitudinal association between baseline imaging marker and dementia conversion

Dementia incidence together with DTI measures was available for three studies: SCANS, 5 years follow-up, 20 (17%) dementia cases, all vascular dementia (VD); RUN DMC, 9 years follow-up, 65 (13%) dementia cases, (21 VD), 30 Alzheimer's disease (AD), 10 AD/VD, 1 Frontotemporal dementia, 1 Lewy body, 1 progressive supranuclear palsy, 1 unknown) and HARMONISATION, 2 years follow-up, 23 (18 %) dementia cases, (3 VD, 20 AD).

In all three cohorts, higher MD median was associated with a higher risk of dementia after controlling for the clinical markers (SCANS: HR (95% CI)=2.048 (1.438 to 2.918), p=7.1e-05, AUC=0.794; RUN DMC: HR (95% CI)=1.364 (1.060 to 1.755), p=0.016, AUC=0.825; HARMONISATION: HR (95% CI)=1.784 (1.085 to 2.935), p=0.023, AUC=0.757) (table 5). Associations for the other DTI measures are shown in online supplemental table 3.

The baseline Clinical-Global model predicted dementia to a roughly similar degree to the Clinical-DTI model in all cohorts (online supplemental table 4). There were no significant differences in AUC between the Clinical-Global and Clinical-DTI

Table 4 Predictive model comparisons at baseline

Model summary measure	Model	SCANS	RUN DMC	HARMONISATION	PRESERVE	ASPS-Fam	CADASIL
AIC	Clinical	283.45	1148.17	304.77	261.09	496.22	131.10
	Clinical-DTI	255.59	1121.22	287.73	243.55	503.45	124.44
	Clinical-MRI	204.45	1119.72	303.27	247.49	493.74	123.15
	Clinical-MRI-DTI	199.54	1113.17	293.52	246.02	502.68	122.64
Adj R^2	Clinical	0.420	0.422	0.373	0.229	0.502	0.107
	Clinical-DTI	0.478	0.454	0.456	0.373	0.516	0.235
	Clinical-MRI	0.570	0.459	0.398	0.365	0.513	0.292
	Clinical-MRI-DTI	0.564	0.467	0.447	0.391	0.523	0.311

Employing the AIC and the adjusted R^2 variance (Adj R^2), the model fits and the Adj R^2 of the Clinical model (Clinical: age and sex and education/premorbid IQ), the Clinical-DTI model (age and sex and education/premorbid IQ+MD median), the Clinical-MRI model (age and sex and education/premorbid IQ and BV and WMH and lacune count and CMB) and the Clinical-MRI-DTI model (age and sex and education/premorbid IQ & BV and WMH and lacune count and CMB and MD median) were compared. AIC was lowest (reflecting best model fit) for the DTI+MRI + clinical model in all single-centre SVD cohorts (SCANS, RUN DMC and CADASIL) indicating that this is the best model dealing with the trade-off between the goodness of fit of the model and the simplicity of the model. The multimodal MRI's Adj R^2 ranged between 0.311 and 0.564 across the cohorts.
AIC, Akaike information criterion; BV, brain volume; CMB, cerebral microbleeds; DTI, diffusion tensor imaging; MD, mean diffusivity; Adj. R^2, adjusted R^2 variance; SVD, small vessel disease; WMH, white matter hyperintensities.

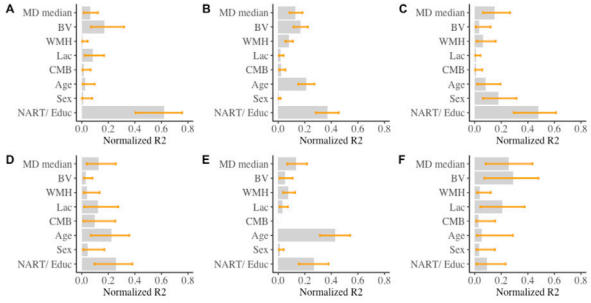

Figure 2 Normalised contribution of the individual marker to the unadjusted explained variance in cognition in the Clinical-MRI-diffusion tensor imaging (DTI) model. In single-centre small vessel disease (SVD) () cohorts (SCANS, RUN DMC, CADASIL), brain volume (BV) and DTI explained a significant variance among all imaging markers. The importance of lacune count as factor varied according to the vascular disease severity with being high in SCANS, PRESERVE and CADASIL and low in RUN DMC, HARMONISATION and ASPS-Fam. In all but ASPS-Fam premorbid IQ explained most of the variance among the clinical markers. The importance of DTI was high and of clinical markers low in CADASIL. Cerebral microbleed (CMB) was not included in the model for ASPS-Fam. Panels: A=SCANS, B=RUN DMC, C=HARMONISATION, D=PRESERVE, E=ASPS Fam, F=CADASIL. Lines refer to 95% CIs after bootstrapping. CMB was excluded in the ASPS-Fam Clinical-MRI-DTI model. Overall unadjusted R^2 variance explained by the Clinical-MRI-DTI model: SCANS=0.595, RUN DMC=0.475, HARMONISATION=0.483, PRESERVE=0.453, ASPS-Fam=0.538, CADASIL=0.426. MD median=median of the normalised MD histogram, Lac=lacune count, NART=premorbid IQ score, R^2=explained variance of the model. MD= mean diffusivity; WMH= white matter hyperintensity.

models on formal statistical testing (online supplemental figure 1).

Longitudinal association between change in imaging marker and dementia conversion

Complete longitudinal data with repeat conventional MRI and DTI were available for SCANS (N=99), RUN DMC (N=257) and HARMONISATION (N=120) and for incident dementia cases: SCANS 18; RUN DMC 12; HARMONISATION 21. There was a change in DTI in all cohorts (online supplemental table 5).

Change in MD median over 3 years predicted dementia conversion over 5 years in SCANS (HR (95% CI)=2.588 (1.663 to 4.027), p=2.49e-05, AUC=0.785) but not in RUN DMC (OR (95% CI)=0.935 (0.498 to 1.667), p=0.825, AUC=0.924) or in HARMONISATION (OR (95% CI)=1.573 (0.998 to 2.597), p=0.056, AUC=0.738) (table 5). Although adding MD median increased the AUC from 0.684 to 0.738 in HARMONISATION, this increase was not significant. There was no increase in prediction in RUN-DMC (figure 3). Associations between other DTI markers and dementia conversion are in online supplemental table 6. In SCANS, adding the conventional MRI measures added prediction over the clinical-DTI model with the AUC increasing from 0.785 to 0.872 (p=0.054) (figure 3).

DISCUSSION

This analysis, across a number of cohorts at risk of dementia but with differing degrees of SVD, confirms the central importance of diffuse WM damage, measured by DTI, as a major determinant of cognitive impairment and dementia. It further validates the use of DTI measures as a marker to predict future dementia risk. The DTI measure also correlated with cognition in all cohorts demonstrating the contribution of WM damage to cognitive impairment across all grades of SVD disease severity. The relative contribution of the conventional markers varied according to disease severity. In all SVD cohorts (SCANS, RUN DMC and CADASIL), BV and the DTI measures were strong imaging predictors of cognition. In contrast, in the normal elderly (ASPS-Fam) and the MCI cohort (HARMONISATION), the DTI measure was the strongest imaging predictor, and there was little predictive value from brain atrophy and lacunes. This may partly reflect the fact that lacunes are more common in severe SVD. The DTI measure added a similar level of prediction

Table 5 Higher median MD is related to higher risk of dementia while accounting for clinical markers

	Baseline marker predicting dementia conversion				
Cohort	**β (SE)**	**P value**	**HR (95% CI)**	**Ng R^2**	**AUC**
SCANS	0.717 (0.181)	**7.1e-05**	2.048 (1.438 to 2.918)	0.206	0.794
RUN DMC	0.310 (0.136)	**0.016**	1.364 (1.060 to 1.755)	0.165	0.825
HARMONISATION	0.579 (0.253)	**0.023**	1.784 (1.085 to 2.935)	0.096	0.761
	Change in DTI predicting dementia conversion				
Cohort	**β (SE)**	**P value**	**HR/OR (95% CI)**	**Ng R2 / $R2_L$**	**AUC**
SCANS	0.951 (0.227)	**2.49e-05**	2.588 (1.663 to 4.027)	0.202	0.785
RUN DMC	−0.068 (0.305)	0.825	0.935 (0.498 to 1.667)	0.248	0.891
HARMONISATION	0.453 (0.237)	0.056	1.573 (0.998 to 2.597)	0.109	0.738

Values show standardised regression coefficients β (SE) for the predictor variables in the Cox regression or logistic regression models of dementia conversion. P-value < 0.05 are marked in bold. The HR or OR together with the CI are shown. The model parameters Nagelkerke's R^2 (Ng R^2) or Hosmer and Lemeshow's R^2 (R^2_L) give an estimated amount of variation in the dependent variable explained by the model. The AUC evaluates how well the model classifies dementia conversion vs. no-dementia conversion at all possible cutoffs respectively. All regression models control for the effects of age, sex and NART-IQ or education.
Statistical significance p<0.05.
AUC, area under the curve; DTI, diffusion tensor imaging; MD, mean diffusivity; Ng R^2, Nagelkerke R^2; R^2_L, Hosmer and Lemeshow's R^2.

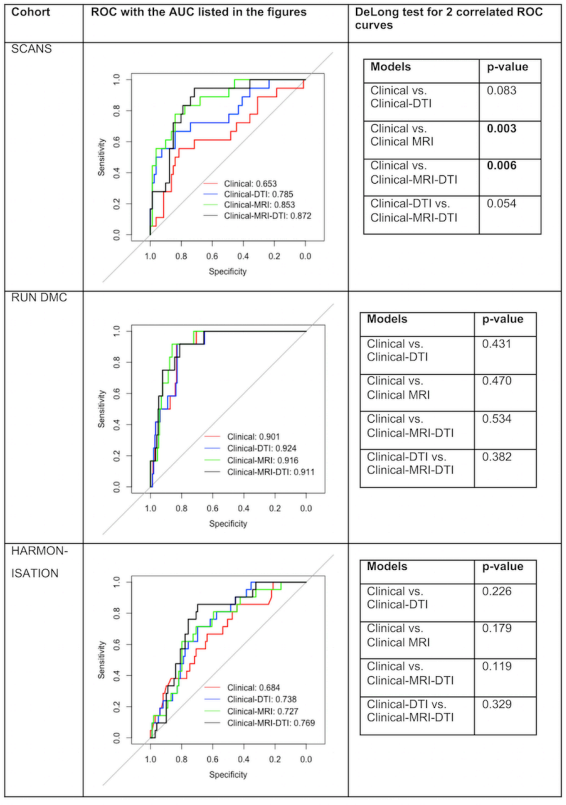

Figure 3 Change in multimodal imaging resulted in the largest area under the curve (AUC) only in severe small vessel disease. Values show the AUC for the Cox regression and logistic regression models: Clinical: Clinical markers alone, Clinical-DTI: Change in DTI combined with clinical markers, Clinical-MRI: Change in MRI markers combined with clinical markers, Clinical-MRI-DTI: All markers included. AUC evaluates how well the model classifies dementia conversion and no-dementia conversion at all possible cutoffs respectively. Differences in AUC between the models were tested. Clinical=model with clinical markers, Clinical-DTI=model with clinical markers and DTI marker, Clinical-MRI=model with clinical markers and conventional MRI markers, Clinical-MRI-DTI=model with clinical markers, conventional markers and DTI marker. DTI, diffusion tensor imaging; ROC, receiver operating cruve.

to the simple clinical model as did inclusion of the global cognitive score.

Our results are consistent with WM damage leading to disruption of WM pathways and disconnection of brain networks underlying cognition, playing a crucial role in cognitive impairment and dementia. Data directly supporting this hypothesis comes from recent studies of brain networks. Tractography techniques can be used to generate brain networks from DTI data, and network measures have been shown to both correlate with cognition cross-sectionally and predict future dementia risk, in patients with SVD.[3 32 33] Mediation analysis demonstrated that conventional markers of SVD such as WM damage, lacunes and CMB impair cognition through disruption of network integrity.[3] Our data emphasise the importance of this process across various patient groups, not only those with prominent SVD, but also those with MCI in whom the predominant pathology is likely to be AD. Recent studies have emphasised the importance of WM alterations contributing to cognitive impairment in AD-like dementia.[34 35]

DTI measures have been proposed not only as a predictor of future dementia risk, but also a surrogate marker which could be used in clinical trials to evaluate new therapies in phase 2 studies.[8 36] Cognition has been shown to be insensitive to change in longitudinal studies in SVD, and therefore, require very large sample sizes to detect change.[12] In the severe SVD cohort SCANS but not in RUN DMC or HARMONISATION significant change in DTI measures predicted future dementia risk. The AUC significantly increased by adding the MRI markers. Taking all this evidence together suggests that trials using DTI measures together with conventional MRI markers as surrogate markers are likely to be more successful in more severe cohorts of SVD with the vascular factor being the primary determinant for dementia conversion.

We used a histogram analysis measuring alterations in the whole WM which has been previously used to estimate DTI parameters.[7 9 36–38] We chose MD median as our primary measure as this showed consistent associations across the different cohorts, and since previous evidence has shown a high immediate reproducibility.[37] It might be expected that FA would provide a more direct measure of WM track damage, but associations with cognition were less consistent with FA parameters, being strong in some cohorts, but weaker than MD in others. The reasons for this are unknown, but it suggests MD may be a more robust marker for use in clinical trials. However, all WM histogram analyses are time-consuming and require multiple MRI sequences. New methods of analysing DTI have been developed which would be quicker and potentially more robust for application in large datasets, including the fully automatic peak width of skeletonised MD,[8] relying on tract-based spatial statistics and the semiautomatic DTI segmentation technique-based discrete segments describing brain microstructure of healthy and/or damaged tissue .[39] These make the implementation of DTI measures in clinical and research prediction simpler. It is, however, important to determine how these operate across different SVD and MCI populations, between single versus multicentre studies and across different scanner types.

A major strength of this study is the validation of MRI markers across independent populations. The study also has limitations. Although these cohort studies were designed to analyse the association between imaging and clinical outcome measures, the underlying study design and image analysis were not the same across data. First, the different cohorts had different lengths of follow-up, and number of follow-up MR scans. In RUN DMC, we could only include time points 2011 and 2015 in the longitudinal DTI-change analysis due to scanner upgrades between 2006 and 2011. Second, different MRI scanners and different field strengths were employed (1.5 vs 3 Tesla). Third, different MRI analyses were used in quantifying the imaging measures. Fourth, the computation of cognitive scores and criteria for dementia diagnosis were different across cohorts which, however, may be strength as it shows the generalisability of the associations across a variety of methods.

In conclusion, our study across multiple cohorts with differing severity of SVD demonstrates the central role for diffuse WM microstructure alterations in cognitive impairment and future dementia. Our results demonstrate that DTI measures allow prediction of future dementia risk, and combining it with conventional markers provides additional predictive values in cohorts with severe SVD.

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Ethics approval All studies were approved by the ethics committees of the respective institutions. SCANS was approved by the London–Wandsworth ethics committee (ukctg.nihr.ac.uk; study iD: 4577). RUN DMC was approved by the Medical Review Ethics Committee region Arnhem-Nijmegen (No. 2005/256). HARMONISATION was approved by the National Healthcare Group Domain-Specific Review Board (DSRB reference No. 2010/00017). PRESERVE was approved by the Harrow National Research Ethics Service committee (No: 11/LO/0458). ASPS-Fam was approved by the ethics committee of the Medical University of Graz, Austria (comission registration No. IRB00002556). CADASIL was approved by the LMU medical faculty (No. 299/03).

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