**SUPPLEMENTARY MATERIAL**

**eTable 1. MRI acquisition parameters for SCANS, RUN DMC, HARMONISATION, ASPS-Fam and CADASIL**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  | **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/mm2] | 1000 | 900 | 1150 | 1000 | 1000 |
|  | Directions | 25 | 61 | 61 | 12 | 41 |

**eTable 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 | TMT-B 1 | Trail-making Test-B: alternating letters and numbers as quickly as possible while still maintaining accuracy |
| SL-Verbal Fluency 2 | Timed generation of words beginning with letter: FAS/ BHR |
| mWCST 3 | Card Sorting Test involving flexible shifting from learned dimensions |
| BMIPB SOIP 4 | Speeded cancellation of second highest of five two-digit numbers |
| Digit Symbol 5 | Speeded transcoding task |
| Grooved Pegboard 4 | Pick-up, rotation and placement of small pegs. |
| Digit Span task 6 | Immediate recall of digit strings (forwards & backwards) |
| Logical Memory 6 | Immediate and delayed recall of short stories |
| Visual Reproduction 6 | Immediate and delayed reproduction of line drawings |
| RUN DMC | Global Cognition | MST 7 | 1-letter Paper-and-Pencil Memory Scanning task: Reaction-time task on detecting memorised letters |
| DSST 8 | Letter–Digit Substitution Task involving match letters to numbers according to a key |
| RAVLT 9 | Rey Auditory Verbal Learning Test involving verbal memory |
| ROCF 9,10 | Rey Complex Figure Task involves reproducing a complicated line drawing, first by copying it freehand (recognition), and then drawing from memory (recall) |
| Stroop 11,12 | Stroop Color Word Test (short form) |
| VF 13 | Verbal fluency about naming animals and professions |
| VSAT 14 | 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 1 | Trail-making Test–A: connecting a set of 25 dots as quickly as possible while still maintaining accuracy |
| TMT-B 1 | Trail-making Test-B: alternating letters and numbers as quickly as possible while still maintaining accuracy |
| WAIS-III 6 | Wechsler Adult Intelligence Coding test involving coding numbers with characters according to a key |
| FAS 2 | Verbal fluency Letter subtask involving naming letters as soon as possible  Verbal fluency Animals subtask involving naming animals as soon as possible |
| RAVLT 9 | Rey Auditory Verbal Learning Test involving verbal memory |
| HARMONISATION | Global Cognition | FAB 15 | Frontal Assessment Battery testing executive function |
| Maze Task 16 | Draw around the maze, keeping the pen tip within the maze |
| Digit span task 6 | Participant repeats numbers in the same order and later in the reverse order as read aloud by the examiner |
| Visual memory span task 6 | Patient is asked to redraw a list of stimuli presented to him |
| Auditory detection task 17 | Patients are asked to respond as quickly as possible to presented auditory signals |
| BNT 18 | Boston Naming Test. A test of confrontation naming where patients are asked to name objects presented visually as two dimensional line drawings in a booklet. |
| VF 19 | Verbal fluency task. Assesses spontaneous verbal production. Patients are asked to come up with as many words as possible about a predefined category in a fixed period of time |
| SDMT 20 | Symbol Digit Modality Test. patients are presented with rows of digits and are asked to substitute the corresponding from a key provided above |
| Digit Cancellation task 21 | The subject receives one of more digits he must cross out from a presented list of values |
| WMS-R Visual 22 | Wechsler Memory Scale—Revised (WMS-R) Visual Reproduction Copy task |
| Clock Drawing task 23 | Patient is asked to draw a clock |
| WAIS-R Block task 24 | The patient is asked to replicate a pattern of blocks that the test examiner presents to them |
| Word List Recall task 25 | List of 10 words is presented and immediate recall, delayed recall and delayed recognition is assessed |
| Story Recall task 17 | The subject is asked to recall details of a story that is read to him |
| Picture Recall task 6 | The subject is asked to recall details of one picture among a list of pictures that are shown to him |
| ASPS-Fam | Global Cognition | G-Factor 26 | A principal component measure involving figural and verbal memory of the Lern und Gedaechnis Test, Trail-making Test-B, Digit Span backward, Complex reaction time task and Purdue Pegboard Test |
| CADASIL | Executive function | TMT-B 27 | Trail-making Test-B: alternating letters and numbers as quickly as possible while still maintaining accuracy |

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**eTable 3. MRI acquisition in the multicenter study PRESERVE**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Axial DTI** | **Site 1** | **Site 2** | **Site 3** | **Site 4** | **Site 5** |
| 3 T Scanner(s) | Phillips Achieva TX | Phillips Achieva, Phillips Archieva TX | Phillips Achieva TX | Phillips Ingenia | Siemens Verio Siemens Magnetom Prismafit |
| TR | 6850ms | 6850ms | 6850ms | 9100ms | 11500ms |
| TE | 75ms | 75ms | 75ms | 82ms | 93ms |
| In-plane FOV | 224x224mm2 | 224x224mm2 | 224x224mm2 | 224x224ms2 | 192x192mm2 |
| No slices | 60 | 60 | 60 | 60 | 75 |
| Nob0 | 8 | 8 | 8 | 8 | 2 |
| Max Gradient Strength | 80mT/m | 80mT/m | 80mT/m | 45mT/m | 45/80mT/m |
| Parallel imaging factor | 3 | 3 | 3 | 3 | 2 |
| No headcoil channels | 8 | 8 | 8 | 15 | 32 |
| Number of diffusion gradient directions  (b= 1000 s mm -2) | 32 | 32 | 32 | 32 | 32 |

**eFigure 1. Cognitive profiles between patient cohorts. In SCANS, RUN DMC, ASPS-Fam and CADASIL, the cognitive measure Global or Executive function were split into 3 tertials.** The patients’ MMSE scores were assigned to the tertials and used in the boxplot (panel A). In HARMONISATION and PRESERVE, the MOCA instead of the MMSE scores were used (panel B). In SCANS, RUN DMC, and HARMONISATION, the patients’ MMSE or MOCA scores were additionally split into patients converting vs. not converting to dementia at a later time point (panels C and D).

MMSE= Mini Mental State Examination, MOCA= Montreal Cognitive Assessment,

tertials 1, 2,3 refer to the lowest cognitive score range, medium cognitive score range and highest cognitive score range

|  |  |
| --- | --- |
| **Chart  Description automatically generatedA** | **Chart, box and whisker chart  Description automatically generatedB** |
| **Chart, box and whisker chart  Description automatically generatedC** | **Chart, box and whisker chart  Description automatically generatedD** |

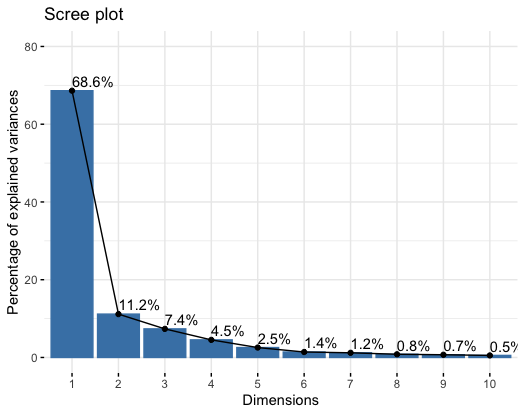
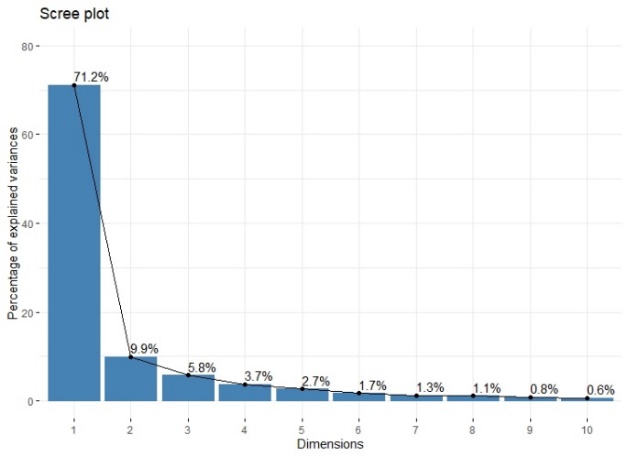
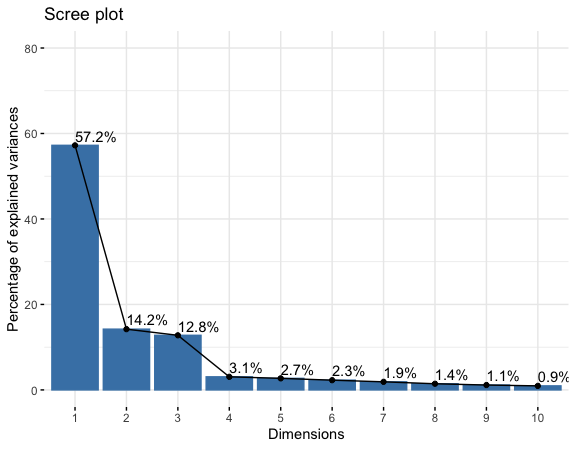
**eTable 4. Clinical information of the subject's reference brain in each cohort used for DSEG** θ

DSEG θ= diffusion tensor segmentation θ, CMB= cerebral microbleeds, CADASIL= Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy

|  |  |
| --- | --- |
| **Cohorts** | **Clinical information of the individual** |
| SCANS | Age= 53, sex= male,  CMB count= 0,  lacune count= 1,  clinical diagnosis= lacunar stroke |
| RUN DMC | Age= 56, sex= female,  CMB count=0,  lacune count= 0 |
| HARMONISATION | Age=61, sex= female,  CMB count=0  lacune count=1 |
| PRESERVE | Age=83, sex= male,  CMB count= 0  lacune count=1,  clinical diagnosis= lacunar stroke |
| ASPS-Fam | Age=69, sex= female,  CMB count= 0  lacune count=0, |
| CADASIL | Age=43, sex= male  CMB count= 0  lacune count=1,  clinical diagnosis= CADASIL |

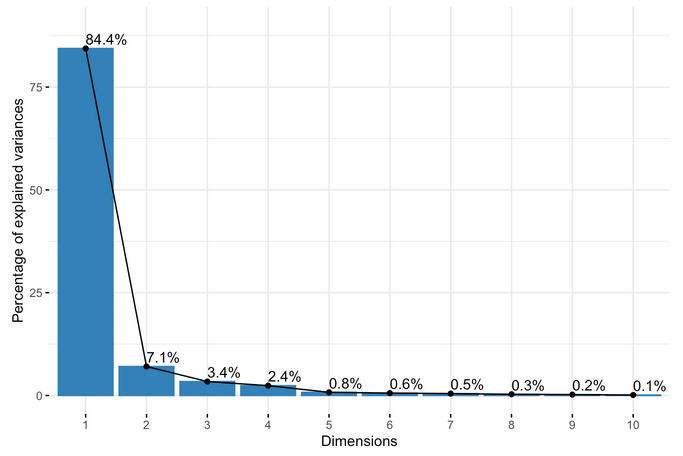
**eFigure 2**: Correlation heatmap between WM DTI histogram markers and percentage of explained variance explained by the principal components. The explained variance was lowest in RUN DMC and highest in HARMONISATION.

|  |  |  |
| --- | --- | --- |
| **SCANS** | **RUN DMC** | **HARMONISATION** |
| SONY_16X:OPTIMAL_11_03_2020:OPTIMAL:SCANS:final data after Eva correction:Heatmap_SCANS_baseline1.png | SONY_16X:OPTIMAL_11_03_2020:Rplot.tiff | Harmony_heatmap_baseline |



Red and blue color on the heatmap refers to a positive and negative association between 2 DTI histogram measures respectively. The strength of the association is illustrated by the marking of the color’s intensity.

|  |  |  |
| --- | --- | --- |
| **PRESERVE** | **ASPS-Fam** | **CADASIL** |
| Heatmap_baseline_PRESERVE | ASPS_FamHeatmap_baseline | Heatmap_DTI_CADASIL |
| PRESERVE_variance_explained_baseline | Graz_baseline_variance_explained |  |

**eFigure 3** Correlation heatmap between WM DTI histogram markers and percentage of explained variance explained by the principal components. The explained variance significantly higher in the severe SVD cohort (PRESERVE) and monogenic SVD cohort (CADASIL) than in the community cohort ASPS-Fam.

Red and blue color on the heatmap refers to a positive and negative association between 2 DTI histogram measures respectively. The strength of the association is illustrated by the marking of the color’s intensity.

eTable 5a. Full linear regression model between DTI, clinical markers, i.e. age, sex and premorbid IQ, and Global Cognition in SCANS

Global= Global cognition, NART= premorbid IQ, MD median= mean diffusivity median of the WM histogram, PC1= scores of the first principal component, PSMD= peak width of skeletonized mean diffusivity, DSEG θ = diffusion tensor image segmentation θ, Geff= global efficiency network measure, β=standardized regression coefficient, 95% CI= 95% confidence interval, AIC= Akaike information criterion, P-Value= statistical value of significance with p < 0.05.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Global** | | | | | | | | | |
| *Predictors* | *β*  *(95% CI)* | *P-Value* | *β*  *(95% CI)* | *P-Value* | *β*  *(95% CI)* | *P-Value* | *β*  *(95% CI)* | *P-Value* | *β*  *(95% CI)* | *P-Value* |
| NART | 0.61  (0.48- 0.75) | **<0.001** | 0.61 (0.48 – 0.74) | **<0.001** | 0.63 (0.51 – 0.76) | **<0.001** | 0.64 (0.51 – 0.76) | **<0.001** | 0.60 (0.48 – 0.73) | **<0.001** |
| Sex [male] | -0.33  (-0.62- -0.05) | **0.02** | -0.36 (-0.64 – -0.08) | **0.01** | -0.31 (-0.59 – -0.03) | **0.03** | -0.12 (-0.40 – 0.17) | 0.43 | -0.50 (-0.78 – -0.22) | **<0.001** |
| Age | -0.12  (-0.26- 0.02) | 0.08 | -0.11 (-0.24 – 0.03) | 0.12 | -0.13 (-0.26 – 0.01) | 0.07 | 0.07 (-0.09 – 0.23) | 0.40 | -0.11 (-0.24 – 0.02) | 0.11 |
| MD median | -0.25  (-0.38- -0.12) | **<0.001** |  |  |  |  |  |  |  |  |
| PC1 |  |  | -0.30 (-0.43 – -0.18) | **<0.001** |  |  |  |  |  |  |
| PSMD |  |  |  |  | -0.30 (-0.42 – -0.17) | **<0.001** |  |  |  |  |
| DSEG θ |  |  |  |  |  |  | -0.38 (-0.53 – -0.23) | **<0.001** |  |  |
| Geff |  |  |  |  |  |  |  |  | 0.35 (0.22 – 0.48) | **<0.001** |
| R2 / R2 adjusted | 0.535 / 0.518 | | 0.562 / 0.546 | | 0.561 / 0.545 | | 0.572 / 0.556 | | 0.585 / 0.569 | |
| AIC | 245.19 | | 238.33 | | 238.67 | | 235.75 | | 232.40 | |

eTable 5b. Full linear regression model between DTI, clinical markers, i.e. age, sex and education, and Global Cognition in RUN DMC

Global= Global cognition, Educ= education, MD median= mean diffusivity median of the WM histogram, PC1= scores of the first principal component, PSMD= peak width of skeletonized mean diffusivity, DSEG θ = diffusion tensor image segmentation θ, Geff= global efficiency network measure, β=standardized regression coefficient, 95% CI= 95% confidence interval, AIC= Akaike information criterion, P-Value= statistical value of significance with p < 0.05.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Global** | | | | | | | | | |
| *Predictors* | *β*  *(95% CI)* | *P-Value* | *β*  *(95% CI)* | *P-Value* | *β*  *(95% CI)* | *P-Value* | *β*  *(95% CI)* | *P-Value* | *β*  *(95% CI)* | *P-Value* |
| (Intercept) | 0.08 (-0.03 – 0.18) | 0.15 | 0.03 (-0.08 – 0.13) | 0.59 | 0.02 (-0.09 – 0.12) | 0.75 | 0.02 (-0.09 – 0.14) | 0.66 | 0.05 (-0.05 – 0.16) | 0.30 |
| Age | -0.32 (-0.41 – -0.23) | **<0.001** | -0.30 (-0.39 – -0.21) | **<0.001** | -0.31 (-0.40 – -0.23) | **<0.001** | -0.37 (-0.47 – -0.28) | **<0.001** | -0.32 (-0.41 – -0.24) | **<0.001** |
| Educ | 0.41 (0.34 – 0.48) | **<0.001** | 0.40 (0.33 – 0.47) | **<0.001** | 0.42 (0.34 – 0.49) | **<0.001** | 0.41 (0.34 – 0.49) | **<0.001** | 0.40 (0.33 – 0.48) | **<0.001** |
| Sex [Male] | -0.14 (-0.28 – 0.00) | 0.06 | -0.05 (-0.20 – 0.09) | 0.47 | -0.03 (-0.18 – 0.11) | 0.67 | -0.05 (-0.20 – 0.11) | 0.57 | -0.10 (-0.24 – 0.04) | 0.16 |
| MD Median | -0.22 (-0.31 – -0.14) | **<0.001** |  |  |  |  |  |  |  |  |
| PC1 |  |  | -0.25 (-0.34 – -0.16) | **<0.001** |  |  |  |  |  |  |
| PSMD |  |  |  |  | -0.24 (-0.33 – -0.16) | **<0.001** |  |  |  |  |
| DSEG θ |  |  |  |  |  |  | -0.12 (-0.22 – -0.02) | **0.02** |  |  |
| Geff |  |  |  |  |  |  |  |  | 0.22 (0.14 – 0.31) | **<0.001** |
| R2 / R2 adjusted | 0.455/ 0.450 | | 0.460/ 0.455 | | 0.461/ 0.456 | | 0.430/ 0.424 | | 0.456/ 0.451 | |
| AIC | 981.32 | | 977.51 | | 976.24 | | 1001.23 | | 980.45 | |

eTable 5c.Full linear regression models between DTI, clinical markers, i.e. age, sex and education, and Global Cognition in HARMONISATION

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Global** | | | | | | | | | | |
| *Predictors* | *β*  *(95% CI)* | *P-Value* | *β*  *(95% CI)* | *P-Value* | *β*  *(95% CI)* | *P-Value* | *β*  *(95% CI)* | *P-Value* | *β*  *(95% CI)* | *P-Value* |
| Age | -0.15 (-0.31 – 0.00) | 0.05 | -0.15 (-0.30 – 0.00) | 0.05 | -0.18 (-0.33 – -0.04) | **0.01** | -0.01 (-0.19 – 0.17) | 0.89 | -0.26 (-0.40 – -0.11) | **<0.001** |
| Sex [Male] | 0.54 (0.25 – 0.84) | **<0.001** | 0.59 (0.29 – 0.89) | **<0.001** | 0.56 (0.27 – 0.85) | **<0.001** | 0.63 (0.33 – 0.92) | **<0.001** | 0.43 (0.12 – 0.73) | **0.01** |
| Educ | 0.45 (0.30 – 0.59) | **<0.001** | 0.43 (0.28 – 0.57) | **<0.001** | 0.42 (0.28 – 0.57) | **<0.001** | 0.46 (0.32 – 0.60) | **<0.001** | 0.43 (0.28 – 0.58) | **<0.001** |
| MD median | -0.31 (-0.47 – -0.15) | **<0.001** |  |  |  |  |  |  |  |  |
| PC1 |  |  | -0.33 (-0.49 – -0.17) | **<0.001** |  |  |  |  |  |  |
| PSMD |  |  |  |  | -0.33 (-0.47 – -0.18) | **<0.001** |  |  |  |  |
| DSEG θ |  |  |  |  |  |  | -0.44 (-0.62 – -0.25) | **<0.001** |  |  |
| Geff |  |  |  |  |  |  |  |  | 0.15 (0.01 – 0.30) | **0.04** |
| R2 / R2 adjusted | 0.435 / 0.417 | | 0.443 / 0.424 | | 0.455 / 0.437 | | 0.462 / 0.444 | | 0.388 / 0.368 | |
| AIC | 296.58 | | 294.92 | | 291.98 | | 290.44 | | 306.64 | |

Global= Global cognition, Educ= education, MD median= mean diffusivity median of the WM histogram, PC1= scores of the first principal component, PSMD= peak width of skeletonized mean diffusivity, DSEG θ = diffusion tensor image segmentation θ, Geff= global efficiency network measure, β=standardized regression coefficient, 95% CI= 95% confidence interval, AIC= Akaike information criterion, P-Value= statistical value of significance with p < 0.05.

eTable 5d. Full linear regression models between DTI, clinical markers, i.e. age, sex and premorbid IQ, and Global Cognition in PRESERVE

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Global** | | | | | | | | | |
| *Predictors* | *β*  *(95% CI)* | *P-Value* | *β*  *(95% CI)* | *P-Value* | *β*  *(95% CI)* | *P-Value* | *β*  *(95% CI)* | *P-Value* | *β*  *(95% CI)* | *P-Value* |
| Age | 0.31  (0.14 – 0.48) | **<0.001** | 0.32 (0.14 – 0.49) | **<0.001** | 0.32 (0.15 – 0.49) | **<0.001** | 0.24 (0.06 – 0.42) | **0.01** | 0.22 (0.03 – 0.40) | **0.02** |
| NART | 0.37  (0.20 – 0.53) | **<0.001** | 0.37 (0.20 – 0.53) | **<0.001** | 0.36 (0.20 – 0.53) | **<0.001** | 0.37 (0.19 – 0.55) | **<0.001** | 0.39 (0.21 – 0.57) | **<0.001** |
| Sex [Male] | 0.20  (-0.14 – 0.54) | 0.24 | 0.23 (-0.12 – 0.57) | 0.20 | 0.31 (-0.02 – 0.64) | 0.07 | 0.31 (-0.05 – 0.68) | 0.09 | 0.39 (0.02 – 0.76) | **0.04** |
| MD median | -0.39  (-0.57 – -0.22) | **<0.001** |  |  |  |  |  |  |  |  |
| PC1 |  |  | 0.37 (0.20 – 0.54) | **<0.001** |  |  |  |  |  |  |
| PSMD |  |  |  |  | -0.41 (-0.57 – -0.24) | **<0.001** |  |  |  |  |
| DSEG θ |  |  |  |  |  |  | -0.19 (-0.37 – -0.01) | **0.04** |  |  |
| Geff |  |  |  |  |  |  |  |  | -0.19 (-0.36 – -0.01) | **0.04** |
| R2 / R2 adjusted | 0.439 / 0.389 | | 0.426 / 0.375 | | 0.457 / 0.409 | | 0.340 / 0.282 | | 0.340 / 0.281 | |
| AIC | 241.89 | | 244.21 | | 238.73 | | 257.98 | | 258.03 | |

Global= Global cognition, NART= premorbid IQ, MD median= mean diffusivity median of the WM histogram, PC1= scores of the first principal component, PSMD= peak width of skeletonized mean diffusivity, DSEG θ = diffusion tensor image segmentation θ, Geff= global efficiency network measure, β=standardized regression coefficient, 95% CI= 95% confidence interval, AIC= Akaike information criterion, P-Value= statistical value of significance with p < 0.05.

eTable 5e. Full linear regression models between DTI, clinical markers, i.e. age, sex and education, and Global Cognition in ASPS-Fam

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Global** | | | | | | | | | |
| *Predictors* | *β*  *(95% CI)* | *P-Value* | *β*  *(95% CI)* | *P-Value* | *β*  *(95% CI)* | *P-Value* | *β*  *(95% CI)* | *P-Value* | *β*  *(95% CI)* | *P-Value* |
| Age | -0.47  (-0.58 – -0.37) | **<0.001** | -0.51 (-0.62 – -0.41) | **<0.001** | -0.52 (-0.63 – -0.41) | **<0.001** | -0.54 (-0.63 – -0.44) | **<0.001** | -0.48 (-0.57 – -0.38) | **<0.001** |
| Sex [Male] | 0.01 (-0.18 – 0.20) | 0.92 | 0.04 (-0.15 – 0.24) | 0.66 | 0.04 (-0.15 – 0.24) | 0.66 | 0.03 (-0.17 – 0.22) | 0.79 | -0.04 (-0.23 – 0.16) | 0.70 |
| Educ | 0.33 (0.24 – 0.43) | **<0.001** | 0.35 (0.25 – 0.45) | **<0.001** | 0.35 (0.25 – 0.45) | **<0.001** | 0.36 (0.26 – 0.45) | **<0.001** | 0.33 (0.23 – 0.43) | **<0.001** |
| MD median | -0.14  (-0.24 – -0.04) | **0.01** |  |  |  |  |  |  |  |  |
| PC1 |  |  | -0.04 (-0.14 – 0.06) | 0.38 |  |  |  |  |  |  |
| PSMD |  |  |  |  | -0.03 (-0.13 – 0.08) | 0.64 |  |  |  |  |
| DSEG θ |  |  |  |  |  |  | -0.14 (-0.23 – -0.05) | **<0.001** |  |  |
| Geff |  |  |  |  |  |  |  |  | 0.18 (0.09 – 0.28) | **<0.001** |
| R2 / R2 adjusted | 0.525 / 0.516 | | 0.511 / 0.503 | | 0.510 / 0.501 | | 0.529 / 0.521 | | 0.538 / 0.530 | |
| AIC | 488.48 | | 494.77 | | 495.32 | | 486.35 | | 482.02 | |

Global= Global cognition, Educ= education, MD median= mean diffusivity median of the WM histogram, PC1= scores of the first principal component, PSMD= peak width of skeletonized mean diffusivity, DSEG θ = diffusion tensor image segmentation θ, Geff= global efficiency network measure, β=standardized regression coefficient, 95% CI= 95% confidence interval, AIC= Akaike information criterion, P-Value= statistical value of significance with p < 0.05.

eTable 5f. Full linear regression models between DTI, clinical markers, i.e. age, sex and education, and executive function in CADASIL

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **TMT-B** | | | | | | | | | |
| *Predictors* | *β*  *(95% CI)* | *P-Value* | *β*  *(95% CI)* | *P-Value* | *β*  *(95% CI)* | *P-Value* | *β*  *(95% CI)* | *P-Value* | *β*  *(95% CI)* | *P-Value* |
| Age | 0.10  (-0.22 – 0.41) | 0.54 | 0.14 (-0.21 – 0.48) | 0.42 | 0.27 (-0.04 – 0.58) | 0.09 | 0.08 (-0.22 – 0.38) | 0.60 | 0.03 (-0.29 – 0.35) | 0.86 |
| Sex [Male] | 0.08  (-0.61 – 0.45) | 0.76 | -0.07 (-0.61 – 0.46) | 0.79 | -0.02 (-0.50 – 0.46) | 0.93 | 0.10 (-0.41 – 0.62) | 0.69 | -0.34 (-0.95 – 0.28) | 0.27 |
| Educ | 0.24  (-0.06 – 0.55) | 0.11 | 0.25 (-0.06 – 0.56) | 0.11 | 0.23 (-0.05 – 0.50) | 0.10 | 0.24 (-0.05 – 0.54) | 0.11 | 0.23 (-0.09 – 0.55) | 0.15 |
| MD Median | -0.50  (-0.82 – -0.18) | **<0.001** |  |  |  |  |  |  |  |  |
| PC1 |  |  | 0.50 (0.15 – 0.85) | **0.01** |  |  |  |  |  |  |
| PSMD |  |  |  |  | -0.70 (-1.01 – -0.39) | **<0.001** |  |  |  |  |
| DSEG θ |  |  |  |  |  |  | -0.50 (-0.80 – -0.20) | **<0.001** |  |  |
| Geff |  |  |  |  |  |  |  |  | 0.45 (0.09 – 0.82) | **0.02** |
| R2 / R2 adjusted | 0.292 / 0.227 |  | 0.272 / 0.206 | | 0.411 / 0.357 | | 0.313 / 0.251 | | 0.243 / 0.174 | |
| AIC | 133.15 | | 134.50 | | 124.11 | | 131.65 | | 136.43 | |

Global= Global cognition, Educ= education, MD median= mean diffusivity median of the WM histogram, PC1= scores of the first principal component, PSMD= peak width of skeletonized mean diffusivity, DSEG θ = diffusion tensor image segmentation θ, Geff= global efficiency network measure, β=standardized regression coefficient, 95% CI= 95% confidence interval, AIC= Akaike information criterion, P-Value= statistical value of significance with p < 0.05.

eTable 6a. Full Cox regression models between baseline imaging marker, clinical markers and later dementia conversion in SCANS

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Dementia conversion** | | | | | | | | | |
| *Markers* | *HR*  *(95% CI)* | *P-Value* | *HR*  *(95% CI)* | *P-Value* | *HR*  *(95% CI)* | *P-Value* | *HR*  *(95% CI)* | *P-Value* | *HR*  *(95% CI)* | *P-Value* |
| Age | 1.73  (0.96 – 3.11) | 0.07 | 1.71 (0.94 – 3.11) | 0.08 | 1.79 (0.98 – 3.28) | 0.06 | 0.94 (0.50 – 1.77) | 0.86 | 1.68 (0.94 – 3.03) | 0.10 |
| Sex [Male] | 5.76  (1.23 – 26.85) | 0.03 | 6.11 (1.32 – 28.18) | **0.02** | 5.73 (1.26 – 25.95) | **0.02** | 2.15 (0.42 – 10.98) | 0.36 | 8.56 (1.90 – 38.66) | **0.01** |
| NART | 0.71  (0.43 – 1.16) | 0.17 | 0.64 (0.39 – 1.05) | 0.08 | 0.61 (0.37 – 1.03) | **0.06** | 0.74 (0.45 – 1.22) | 0.24 | 0.59 (0.36 – 0.97) | **0.04** |
| MD median | 2.19  (1.51 – 3.16) | **<0.001** |  |  |  |  |  |  |  |  |
| PC1 |  |  | 2.28 (1.51 – 3.44) | **<0.001** |  |  |  |  |  |  |
| PSMD |  |  |  |  | 1.74 (1.29 – 2.34) | **<0.001** |  |  |  |  |
| DSEG θ |  |  |  |  |  |  | 3.52 (2.09 – 5.92) | **<0.001** |  |  |
| Geff |  |  |  |  |  |  |  |  | 0.37 (0.23 – 0.61) | **<0.001** |
| AIC | 138.37 | | 139.60 | | 143.70 | | 128.21 | | 138.39 | |

NART= premorbid IQ, MD Median= mean diffusivity median of the WM histogram, PC1= scores of the first principal component, PSMD= peak width of skeletonized mean diffusivity, DSEG θ = diffusion tensor image segmentation θ, Geff= global efficiency network measure, AIC= Akaike information criterion, HR= hazard ratio, AIC= Akaike information criterion, 95% CI= 95% confidence interval, P-Value= statistical value of significance with p < 0.05

eTable 6b Full Cox regression model between baseline imaging marker, clinical markers and later dementia conversion in RUN DMC

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Dementia conversion** | | | | | | | | | |
| *Markers* | *HR*  *(95% CI)* | *P-Value* | *HR*  *(95% CI)* | *P-Value* | *HR*  *(95% CI)* | *P-Value* | *HR*  *(95% CI)* | *P-Value* | *HR*  *(95% CI)* | *P-Value* |
| Age | 3.15 (2.08 – 4.76) | **<0.001** | 2.84 (1.87 – 4.31) | **<0.001** | 3.14 (2.11 – 4.68) | **<0.001** | 3.18 (2.06 – 4.90) | **<0.001** | 2.97 (1.98 – 4.45) | **<0.001** |
| Sex [Male] | 1.15 (0.65 – 2.04) | 0.62 | 1.01 (0.57 – 1.78) | 0.98 | 0.94 (0.53 – 1.68) | 0.83 | 0.90 (0.48 – 1.69) | 0.74 | 1.03 (0.58 – 1.82) | 0.93 |
| Educ | 0.97 (0.74 – 1.27) | 0.81 | 0.98 (0.74 – 1.28) | 0.86 | 0.96 (0.73 – 1.26) | 0.75 | 0.98 (0.75 – 1.28) | 0.87 | 0.99 (0.76 – 1.30) | 0.97 |
| MD Median | 1.33 (1.00 – 1.76) | 0.05 |  |  |  |  |  |  |  |  |
| PC1 |  |  | 1.57 (1.15 – 2.14) | **<0.001** |  |  |  |  |  |  |
| PSMD |  |  |  |  | 1.45 (1.14 – 1.83) | **<0.001** |  |  |  |  |
| DSEG θ |  |  |  |  |  |  | 1.33 (0.91 – 1.93) | 0.14 |  |  |
| Geff |  |  |  |  |  |  |  |  | 0.64 (0.46 – 0.89) | **0.01** |
| AIC | 515.69 | | 511.60 | | 511.51 | | 517.17 | | 512.59 | |

Educ= education, MD Median= mean diffusivity median of the WM histogram, PC1= scores of the first principal component, PSMD= peak width of skeletonized mean diffusivity, DSEG θ = diffusion tensor image segmentation θ, Geff= global efficiency network measure, AIC= Akaike information criterion, HR= hazard ratio, AIC= Akaike information criterion, 95% CI= 95% confidence interval, P-Value= statistical value of significance with p < 0.05

eTable 6c. Full Cox regression model between baseline imaging marker, clinical markers and later dementia conversion in HARMONISATION

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Dementia conversion** | | | | | | | | | |
| *Markers* | *HR*  *(95% CI)* | *P-Value* | *HR*  *(95% CI)* | *P-Value* | *HR*  *(95% CI)* | *P-Value* | *HR*  *(95% CI)* | *P-Value* | *HR*  *(95% CI)* | *P-Value* |
| Age | 1.24 (0.76 – 2.05) | 0.39 | 1.25 (0.75 – 2.08) | 0.40 | 1.32 (0.82 – 2.13) | 0.25 | 1.05 (0.59 – 1.89) | 0.86 | 1.60 (0.96 – 2.68) | 0.07 |
| Sex [Male] | 0.30 (0.11 – 0.82) | **0.02** | 0.29 (0.11 – 0.82) | **0.02** | 0.29 (0.10 – 0.81) | **0.02** | 0.32 (0.12 – 0.84) | **0.02** | 0.38 (0.14 – 0.98) | **0.05** |
| Educ | 0.84 (0.53 – 1.35) | 0.48 | 0.85 (0.53 – 1.35) | 0.49 | 0.82 (0.51 – 1.31) | 0.41 | 0.79 (0.49 – 1.28) | 0.34 | 0.88 (0.57 – 1.36) | 0.57 |
| MD Median | 1.78 (1.08 – 2.93) | **0.02** |  |  |  |  |  |  |  |  |
| PC1 |  |  | 1.74 (1.03 – 2.92) | **0.04** |  |  |  |  |  |  |
| PSMD |  |  |  |  | 1.73 (1.13 – 2.65) | **0.01** |  |  |  |  |
| DSEG θ |  |  |  |  |  |  | 1.94 (1.06 – 3.53) | **0.03** |  |  |
| Geff |  |  |  |  |  |  |  |  | 0.79 (0.49 – 1.30) | 0.36 |
| AIC | 173.51 | | 174.17 | | 172.71 | | 173.67 | | 177.58 | |

Educ= education, MD Median= mean diffusivity median of the WM histogram, PC1= scores of the first principal component, PSMD= peak width of skeletonized mean diffusivity, DSEG θ = diffusion tensor image segmentation θ, Geff= global efficiency network measure, AIC= Akaike information criterion, HR= hazard ratio, AIC= Akaike information criterion, 95% CI= 95% confidence interval, P-Value= statistical value of significance with p < 0.05

|  |  |  |
| --- | --- | --- |
| **Diagram  Description automatically generated**  (A) | **Diagram  Description automatically generated**  (B)  (B)  (C) | **Chart, diagram, scatter chart  Description automatically generated**  (C) |
| Panel (A), panel (B) and panel (C) show dementia cases and no dementia cases on the first and second principal component in SCANS (A), RUN DMC (B) and HARMONISATION (C). Panel (D) and panel (E) show no dementia cases and the dementia subtype cases on the first and second principal components in RUN DMC (D) and HARMONISATION (E)  Dim 1= 1st principal component, Dim 2= 2nd principal component, AD= Alzheimer’s disease, VD= Vascular Dementia, AD/VD= Mixed dementia with Alzheimer’s and vascular dementia, LBD= Lewy body dementia | **Chart, scatter chart  Description automatically generated**  (D) | **Chart, scatter chart  Description automatically generated**  (E) |

**eFigure 4. There were no patterns showing that dementia cases or dementia subtypes were better represented on the second instead of the first principal component dimension.**

**eFigure 5. Rates of dementia conversion in the cohorts with dementia conversion. The rate of dementia conversion was higher in HARMONISATION than in SCANS or RUN DMC**

**Chart, line chart

Description automatically generated**

Stage 1= Baseline- year 1, Stage 2= year 1-2, Stage 3= year 2-3, Stage 4= year 3-4, Stage 5= year 4- 5, Stage 6= year 5-6, Stage 7= year 6-7, Stage 8= year 7-8, Stage 9= year 8-9

**eFigure 6. Differences between vascular dementia (VD) and Alzheimer’s disease (AD) over 3 years intervals in RUN DMC.** The DTI baseline measures PC1, MD median, PSMD were overall higher and Geff lower for VD than AD subtype across the different time intervals.

MD Median= mean diffusivity median of the WM histogram, PC1= scores of the first principal component, PSMD= peak width of skeletonized mean diffusivity, DSEG θ = diffusion tensor image segmentation θ, Geff= global efficiency network measure, VD= vascular dementia, AD/VD= mixed Alzheimer’s and vascular dementia, AD= Alzheimer’s disease

|  |  |  |
| --- | --- | --- |
| **Chart, scatter chart, box and whisker chart  Description automatically generated**  (A) | **Chart, box and whisker chart  Description automatically generated**  (B) | **Chart, scatter chart, box and whisker chart  Description automatically generated**  (C) |
| **Chart, box and whisker chart  Description automatically generated**  (D) | **Chart, box and whisker chart  Description automatically generated**  (E) | Panel A-E show the baseline DTI measures for each of the dementia subtypes across the 3-years time intervals.  AD= Alzheimer’s disease, VD= Vascular Dementia, AD/VD= Mixed dementia with Alzheimer’s and vascular dementia |

**eTable 7: Change in the WM DTI histogram measures in PRESERVE**

|  |  |  |  |
| --- | --- | --- | --- |
| **DTI all WM marker** | **Mean baseline value (SD)** | **Mean 2 year change (SD)** | **P-Value** |
| **MD pkval** | 7.64e-04  (4.12e-05) | 3.70e-06  (2.31e-05) | 0.15 |
| **MD PH** | 1.33e-02  (2.45e-03) | -8.29e-04  (1.22e-03) | **3.39e-08** |
| **MD Median** | 7.88e-04  (4.61e-05) | 8.31e-06  (1.70e-05) | **3.35e-05** |
| **MD kurtosis** | 10.00  (4.83) | -1.41  (1.76) | **3.04e-10** |
| **MD skew** | 2.37  (0.58) | -0.23  (0.28) | **3.67e-10** |
| **FA pkval** | 0.31  (4.84e-02) | -3.49e-03  (3.97e-02) | **4.31e-01** |
| **FA PH** | 3.22e-03  (2.38e-04) | -3.48e-05  (1.77e-04) | **8.03e-02** |
| **FA Median** | 3.34e-01  (2.81e-02) | -3.46e-03  (1.29e-02) | **1.83e-02** |
| **FA kurtosis** | 0.52  (0.34) | 4.83e-02  (0.18) | **1.51e-02** |
| **FA skew** | 0.67  (0.15) | 2.27e-02  (6.93e-02) | **4.22e-03** |
| **AxD pkval** | 1.03e-03  (5.51e-05) | 1.40e-05  (5.14e-05) | **0.02** |
| **AxD PH** | 7.50e-03  (8.46e-04) | -2.78e-04  (5.00e-04) | **3.7e-06** |
| **AxD Median** | 1.10e-03  (5.17e-05) | 1.11e-05  (2.31e-05) | **4.8e-05** |
| **AxD kurtosis** | 3.73  (1.43) | -1.66  (0.80) | **< 2e-16** |
| **AxD skew** | 1.38  (0.26) | -0.36  (0.19) | **< 2e-16** |
| **RD pkval** | 6.12e-04  (4.62e-05) | 4.70e-06  (2.80e-05) | 0.14 |
| **RD PH** | 1.18e-02  (1.60e-03) | -4.94e-04  (8.03e-04) | **4.52e-07** |
| **RD Median** | 6.33e-04  (4.70e-05) | 7.90e-06  (1.69e-05) | **7.74e-05** |
| **RD kurtosis** | 8.50  (3.56) | -0.28  (1.41) | **8.26e-02** |
| **RD skew** | 2.08  (0.43) | -3.87e-02  (0.23) | 0.14 |

MD= mean diffusivity, FA= fractional anisotropy, AxD= axial diffusivity, RD= radial diffusivity, pkval= peak value, PH= normalized peak height, P-Value= statistical value of significance with p < 0.05

**eTable 8a Change in WM DTI measures over time in SCANS**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **DTI all WM marker** | **Estimated mean baseline value (SE)** | **Estimated mean annual change (SE)** | **Wald-test** | **P-Value** |
| **MD pkval** | 7.70e-04 (3.18e-06) | 2.94e-06 (6.50e-07) | 4.52 | **1.39e-05** |
| **MD PH** | 1.52e-02 (2.84e-04) | -3.84e-04 (3.28e-05) | -11.70 | **< 0.001** |
| **MD Median** | 7.98e-04 (4.07e-06) | 5.43e-06 (6.06e-07) | 8.96 | **< 0.001** |
| **MD kurtosis** | 15.22  (0.66) | -0.32  (0.13) | -2.36 | **0.02** |
| **MD skew** | 2.75  (0.06) | 0.02  (0.01) | 1.44 | 0.15 |
| **FA pkval** | 0.27  (0.01) | -6.18e-03 (1.80e-03) | -3.43 | **< 0.001** |
| **FA PH** | 3.05e-03 (2.17e-05) | 1.32e-06 (5.42e-06) | 0.24 | 0.807 |
| **FA Median** | 0.29  (2.86e-03) | -2.16e-03 (4.41e-04) | -4.90 | **< 0.001** |
| **FA kurtosis** | 0.52  (0.03) | 0.02  (6.62e-03) | 2.23 | **0.03** |
| **FA skew** | 0.68  (0.01) | 0.01  (2.39e-03) | 4.54 | **< 0.001** |
| **AxD pkval** | 1.01e-03 (3.62e-06) | 3.71e-06 (1.16e-06) | 3.19 | **0.002** |
| **AxD PH** | 8.44e-03 (8.90e-05) | -1.28e-04 (1.20e-05) | -10.63 | **< 0.001** |
| **AxD kurtosis** | 5.20  (0.15) | 0.25  (0.04) | 6.56 | **< 0.001** |
| **AxD skew** | 1.51  (2.43e-02) | 6.32e-02 (7.05e-03) | 8.96 | **< 0.001** |
| **RD pkval** | 6.42e-04 (3.84e-06) | 4.67e-06 (1.39e-06) | 3.37 | **0.001** |
| **RD PH** | 1.26e-02 (1.81e-04) | -2.77e-04 (2.44e-05) | -11.34 | **< 0.001** |
| **RD Median** | 6.65e-04 (4.57e-06) | 6.30e-06 (1.31e-06) | 4.80 | **< 0.001** |
| **RD kurtosis** | 12.06  (0.46) | -0.11  (0.11) | -1.10 | 0.27 |
| **RD skew** | 2.37  (0.04) | 0.04  (0.01) | 3.70 | **< 0.001** |

MD= mean diffusivity, FA= fractional anisotropy, AxD= axial diffusivity, RD= radial diffusivity, pkval= peak value, PH= normalized peak height, P-Value= statistical value of significance with p < 0.05

**eTable 8b Change in WM DTI histogram measures over time in RUN DMC**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **DTI all WM histogram marker** | **Mean baseline value (SD)** | **Mean 5 year change (SD)** | **Paired t-test** | **P-Value** |
| **MD pkval** | 7.81e-04 (3.43e-05) | -2.12e-06 (2.55e-05) | 1.37 | 0.17 |
| **MD PH** | 1.36e-02 (2.20e-03) | -1.49e-04 (1.20e-03) | 2.04 | **0.04** |
| **MD Median** | 7.98e-04 (3.44e-05) | 3.43e-06 (1.25e-05) | -4.50 | **1.01e-05** |
| **MD kurtosis** | 18.53 (6.39) | 6.72e-03  (4.49) | -0.025 | 0.98 |
| **MD skew** | 3.10  (0.61) | 7.21e-02 (0.43) | -2.78 | **0.01** |
| **FA pkval** | 0.33  (6.70e-02) | -3.10e-03 (7.46e-02) | 0.68 | 0.50 |
| **FA PH** | 3.36e-03 (2.97e-04) | 9.60e-05 (2.76e-04) | -5.72 | **2.89e-08** |
| **FA Median** | 0.34  (2.87e-02) | 1.85e-03 (2.09e-02) | -1.45 | 0.15 |
| **FA kurtosis** | 0.43  (0.34) | 4.84e-02 (0.21) | -3.80 | **1.81e-04** |
| **FA skew** | 0.67  (0.14) | 1.48e-02 (8.60e-02) | -2.82 | **5.17e-03** |
| **AxD pkval** | 1.06e-03 (5.07e-05) | 3.42e-06 (5.04e-05) | -1.12 | 0.27 |
| **AxD PH** | 8.80e-03 (8.80e-04) | 4.13e-05 (8.29e-04) | -0.82 | 0.41 |
| **AxD Median** | 1.12e-03 (3.87e-05) | 7.96e-06 (2.00e-05) | -6.54 | **3.08e-10** |
| **AxD kurtosis** | 9.02  (2.42) | 0.29  (2.06) | -2.30 | **0.02** |
| **AxD skew** | 2.04  (0.33) | 9.25e-02 (0.29) | -5.23 | **3.45e-07** |
| **RD pkval** | 6.29e-04 (4.35e-05) | 3.16e-07 (3.31e-05) | -0.16 | 0.88 |
| **RD PH** | 1.02e-02 (1.16e-03) | 1.40e-05 (8.68e-04) | -0.27 | 0.79 |
| **RD Median** | 6.42e-04 (3.79e-05) | 2.04e-06 (1.57e-05) | -2.14 | **0.03** |
| **RD kurtosis** | 1.28  (3.92) | 0.70  (3.47) | -3.29 | **0.01** |
| **RD skew** | 2.38  (0.41) | 0.14  (0.38) | -6.05 | **4.79e-09** |

MD= mean diffusivity, FA= fractional anisotropy, AxD= axial diffusivity, RD= radial diffusivity, pkval= peak value, PH= normalized peak height, P-Value= statistical value of significance with p < 0.05

**eTable 8c Change in WM DTI histogram measures over time in HARMONISATION**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **DTI all WM marker** | **Mean baseline value (SD)** | **Mean 2 year change (SD)** | **Paired t-test** | **P-Value** |
| **MD pkval** | 7.68e-04 (3.76e-05) | 8.25e-06 (3.02e-05) | -3.08 | **2.58e-03** |
| **MD PH** | 0.012 (2.13e-03) | -6.30e-04 (1.26e-03) | 5.65 | **1.00e-07** |
| **MD Median** | 8.82e-04 (6.08e-05) | 2.24e-05 (3.62e-05) | -6.96 | **1.65e-10** |
| **MD kurtosis** | 8.71  (2.52) | -0.69  (1.33) | 5.80 | **4.97e-08** |
| **MD skew** | 2.94  (0.41) | -0.12  (0.22) | 6.22 | **6.76e-09** |
| **FA pkval** | 0.07  (0.02) | -1.10e-03 (0.02) | 0.75 | 0.45 |
| **FA PH** | 5.32e-03 (6.53e-04) | 1.76e-04 (5.83e-04) | -3.39 | **9.37e-04** |
| **FA Median** | 0.19  (0.02) | -5.33e-03 (0.02) | 3.53 | **5.77e-04** |
| **FA kurtosis** | 0.99  (0.82) | 0.13  (0.63) | -2.36 | **0.02** |
| **FA skew** | 1.28  (0.26) | 0.06  (0.19) | -3.22 | **1.64e-03** |
| **AxD pkval** | 1.03e-03 (5.30e-05) | 1.10e-05 (5.14e-05) | -2.41 | **0.02** |
| **AxD PH** | 8.22e-03 (1.00e-03) | -2.52e-04 (7.83e-04) | 3.63 | **4.08e04** |
| **AxD Median** | 1.13e-03 (5.49e-05) | 2.01e-05 (2.86e-05) | -7.93 | **1.00e-12** |
| **AxD kurtosis** | 3.72  (0.924) | -0.27  (0.60) | 5.13 | **1.09e-06** |
| **AxD skew** | 2.16  (0.22) | -0.07  (0.14) | 5.78 | **5.66e-08** |
| **RD pkval** | 6.49e-04 (4.78e-05) | 1.40e-05 (4.15e-05) | -3.80 | **2.26e-04** |
| **RD PH** | 8.94e-03 (1.38e-03) | -4.05e-04 (8.74e-04) | 5.23 | **7.00e-07** |
| **RD Median** | 7.80e-04 (6.57e-05) | 2.34e-05 (3.99e-05) | -6.62 | **9.50e-10** |
| **RD kurtosis** | 5.09  (1.51) | -0.37  (0.82) | 5.05 | **1.53e-06** |
| **RD skew** | 2.35  (0.31) | -0.09  (0.17) | 5.61 | **1.25e-07** |

MD= mean diffusivity, FA= fractional anisotropy, AxD= axial diffusivity, RD= radial diffusivity, pkval= peak value, PH= normalized peak height, P-Value= statistical value of significance with p < 0.05

**eFigure 7**: Correlation heatmap & Percentage of explained variance by the Principal component in change in WM DTI histogram measures. The percentage of explained variance was higher in HARMONISATION than in SCANS or RUN DMC

|  |  |  |
| --- | --- | --- |
| **SCANS** | **RUN DMC** | **HARMONISATION** |
| C:\Users\me417\AppData\Local\Microsoft\Windows\INetCache\Content.Word\SCANS_heatmap_changes_updated.jpeg | RUN_DMC_heatmap_sorted_updated | C:\Users\me417\AppData\Local\Microsoft\Windows\INetCache\Content.Word\HARMY_changes_DTI.jpeg |
| **SCANS_60** | **C:\Users\me417\AppData\Local\Microsoft\Windows\INetCache\Content.Word\60_pca_RUN DMC.jpeg** | C:\Users\me417\AppData\Local\Microsoft\Windows\INetCache\Content.Word\Singapore_change_scores_pca.jpeg |

Red and blue color on the heatmap refers to a positive and negative association between 2 DTI histogram measures respectively. The strength of the association is illustrated by the marking of the color’s intensity

**eFigure 8. There were no site-related differences for DTI change when controlling for baseline DTI measure in the multicenter study PRESERVE.**

|  |  |
| --- | --- |
| DTI measure | Differences in mean levels of site with 95% family-wise confidence level |
| MD median | Chart, line chart, scatter chart  Description automatically generated |
| PC1 | Chart, line chart, box and whisker chart  Description automatically generated |
| PSMD | Chart, scatter chart, box and whisker chart  Description automatically generated |
| DSEG θ | Chart, line chart, scatter chart, box and whisker chart  Description automatically generated |
| Geff | Chart, line chart, scatter chart, box and whisker chart  Description automatically generated |

eTable 9. Estimated change in DTI markers after removal of imaging measures post dementia diagnosis in SCANS

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Estimated mean baseline value (SE)** | **Estimated mean annual change (SE)** | **Wald-test** | **p-value** |
| MD Median | 7.98e-04  (3.92e-06) | 5.37e-06  (5.42e-07) | 9.92 | **< 0.001** |
| PSMD | 3.78e-04  (1.05e-05) | 1.36e-05  (1.89e-06) | 7.21 | **<0.001** |
| DSEG θ | 20.19  (0.84) | 1.17  (0.09) | 13.42 | **<0.001** |
| Geff | 8.12  (0.23) | -0.18  (0.03) | -6.68 | **<0.001** |

MD Median= mean diffusivity median of the all WM histogram, PC1= scores of the first principal component, PSMD= peak width of skeletonized mean diffusivity, DSEG= diffusion tensor image segmentation, Geff= global efficiency network measure, SE= standard error, statistically significant p < 0.05

**eTable 10. Firth's Bias-Reduced Logistic Regression between DTI’s change and dementia conversion in RUN DMC.** There was no significant association between change in DTI and dementia conversion.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Dementia conversion** | | |
|  | *RUN DMC* | | |
| *Change*  *Markers* | *Estimate*  *(95% CI)* | *Chi-square* | *P-Value* |
| MD median | -0.085  (-0.670- 0.444) | 0.094 | 0.760 |
| PC1 | 0.251  (-0.527- 0.899) | 0.416 | 0.519 |
| PSMD | 0.151  (-0.381- 0.569) | 0.390 | 0.532 |
| DSEG θ | 0.381  (-0.273- 1.109) | 1.261 | 0.261 |
| Geff | -0.269  (-0.836- 0.348) | 0.794 | 0.373 |

MD Median= mean diffusivity median of the all WM histogram, PC1= scores of the first principal component, PSMD= peak width of skeletonized mean diffusivity, DSEG= diffusion tensor image segmentation, Geff= global efficiency network measure, β=standardized regression coefficient, 95% CI= 95% confidence interval, statistically significant p < 0.05

**eFigure 9. Change in Mean Skeletonized mean Diffusivity (MSMD) vs. Peak width Skeletonized mean Diffusivity (PSMD) in PRESERVE**. In contrast to PSMD (panel B), there was a significant difference in MSMD (panel A) between baseline and follow-up 2 years.

|  |
| --- |
| Chart, scatter chart  Description automatically generatedA) |
| Chart, scatter chart  Description automatically generatedB) |

MSMD= Mean skeletonized mean diffusivity, PSMD= Peak width skeletonized mean diffusivity, T-test= paired t-test, TP= time point