Midsagittal corpus callosum area and conversion to multiple sclerosis after clinically isolated syndrome: a multicenter Australian cohort study

Running title: Midsagittal corpus callosum area and conversion to MS after clinically isolated syndrome

Cara Odenthal^{1,2}, Steve Simpson Jr³, Justin Oughton^{1,2}, Ingrid van der Mei³, Stephen Rose^{2,4}, Jurgen Fripp^{2,4}, Robyn Lucas⁵, Bruce Taylor³, Keith Dear⁶, Anne-Louise Ponsonby⁷, Alan Coulthard^{1,2} and the Ausimmune and AusLong Investigator Groups

¹(Department of Medical Imaging) Royal Brisbane and Women's Hospital, Brisbane, Australia

²(School of Medicine) The University of Queensland, Brisbane, Australia

³Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia

⁴ICT – Australian e-Health Research Centre, Brisbane, Australia

⁵National Centre for Epidemiology and Population Health, Australian National University, Canberra, Australia

⁶Duke Kunshan University, Kunshan, China

⁷Murdoch Children's Research Institute, Royal Children's Hospital, University of Melbourne, Australia

Corresponding author:

Cara Odenthal, Department of Medical Imaging, Royal Brisbane and Women's Hospital, Cnr Butterfield St and Bowen Bridge Rd, Herston QLD Australia 4029

Email: caraodenthal@yahoo.com.au Ph: +61 438 455 460 Fax: +61 3646 0862

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Abstract

Introduction: Patients presenting with clinically isolated syndrome (CIS) may proceed to clinically definite multiple sclerosis (CDMS). Midsagittal corpus callosum area (CCA) is a surrogate marker for callosal atrophy, and can be obtained from a standard MRI study. This study explores the relationship between CCA measured at CIS presentation (baseline) and at 5 years post presentation, and conversion from CIS to CDMS. The association between CCA and markers of disability progression is explored.

Method: CCA was measured on MRI scans at presentation and five-year review following diagnosis of a first demyelinating event, or evidence of progressive MS, in 143 participants in the Ausimmune/AusLong Study. Relationships between CCA (at baseline and follow-up) and clinical outcomes were assessed.

Results: Mean CCA at baseline study was 6.63cm² (SD 1.01). Patients who converted to MS by five-year review (n=100) had a significantly smaller mean CCA at follow-up (6.22 vs. 6.74, p=0.007). Greater CCA reduction was associated with higher annualized relapse rate over follow-up.

Conclusion: Baseline CCA obtained from standard MRI protocols may be compared with subsequent MRI examinations as a surrogate for neurodegeneration and cerebral atrophy in patients with MS. This study demonstrates an association between CCA and disability in individuals presenting with CIS who convert to MS.

Introduction

Patients with longstanding multiple sclerosis (MS) demonstrate neuronal loss and cerebral atrophy, with reduced brain volume being regarded as a surrogate marker for neurodegeneration.¹⁻³ The pathophysiological processes underpinning cerebral atrophy are not limited to those that occur during the acute demyelinating episode, as cellular inflammation and neuronal loss persist long after the acute relapse is complete.⁴ Whether cerebral atrophy is detectable at the time of the earliest demyelinating event has not yet been clearly elucidated.⁵

The corpus callosum, as the largest bundle of white matter tracts in the brain, is a region of particular interest in multiple sclerosis. Pathology within the corpus callosum may reflect both local and distant processes, through demyelination, inflammation and secondary Wallerian degeneration.^{6,7} Unlike many other brain regions, however, the corpus callosum is not well suited to volumetric analysis, due to inherent difficulty in defining its lateral margins.^{8,9} Fortuitously, midsagittal corpus callosum area (CCA) is a validated method of quantifying atrophy of the corpus callosum.⁷⁻¹⁶

The aim of the present study was to determine whether CCA at first demyelinating event is a marker of disease progression at five years, including conversion to MS, clinical relapses and disability, and whether CCA at 5 years differs between patients who convert to MS and those who do not.

Materials and Methods

Subjects

The Ausimmune Longitudinal (AusLong) Study was designed to study environmental, genetic and personal risk factors for the onset and progression of MS¹⁷ in a large cohort of patients who had

1 initially presented with clinically isolated syndrome and been recruited into the multicenter
2 Ausimmune study. Patients were eligible for the current study if they had sagittal MRI imaging data
3 available at baseline imaging and at 5 year follow up. All patients signed written informed consent.
4 The study had multicenter ethics approval.

5 6 MRI acquisition

7 MRI data collected as part of the multicentre Ausimmune and AusLong Studies was used^{17 18}. For
8 Ausimmune, the baseline MRI was a clinical scan obtained using the MRI protocol of choice of the
9 referring centre¹⁷. Patients recruited into the subsequent Auslong study were scanned according to a
10 defined study protocol which included a sagittal FLAIR sequence¹⁸. Inclusion in the current study
11 required a sagittal FLAIR sequence at the five-year time point plus any sagittal sequence at
12 baseline. Where FLAIR sagittal was not performed at baseline, a sagittal T1 sequence was used. An
13 intra rater study was obtained on a subset of the data to establish the validity of substituting a T1
14 sequence in the absence of a baseline FLAIR sequence (see below). Image quality was assessed by
15 two experienced radiological observers (CO, AC) with each image being assigned 'poor', 'fair' or
16 'good' based on subjective assessment of image interpretability. Features of images of 'poor
17 quality' included subjective low signal-to-noise ratio, low spatial and contrast resolution, and the
18 presence of artifact. Data from participants whose scans were of 'poor' image quality at both
19 baseline and five-year analysis were excluded; data from participants with at least one study
20 assigned 'fair' or 'good' was retained.

21 Participant data was not excluded on the basis of scanner manufacturer or software.

22 23 MRI analysis

24 Image analysis was performed using OsiriX DICOM Viewer (Pixme Sarl, Bernex, Switzerland), on
25 Mac OS (Extended) (Apple Inc., Cupertino, CA, USA). The best mid-sagittal image was selected;
26 landmarks used to identify the best mid-sagittal image included vessels within the sagittal fissure,
27 the great cerebral vein, and the cerebral aqueduct. Midline sagittal corpus callosum area (CCA) was

outlined manually three times using a tablet digitiser (Wacom Technology Corporation, Vancouver, WA, USA) and the mean value calculated (Figure 1). Mid sagittal intracranial area (ICA) was obtained from the same image for use as a control variable^{18, 19, 20}

Validation of CCA measurement on different imaging sequences

The equivalence of CCA measurements using two different MRI sequences was studied using data from 30 randomly selected participants who had both mid-sagittal FLAIR and T1 images at baseline. Repeat CCA measurements were obtained by a single observer and intraclass correlation coefficients were calculated.

Intra-and inter-rater variation of CCA measurement

A subset of 30 MRI studies were selected at random. A single observer (CO) measured CCA on each MRI on two occasions, separated by 7 days.

Validation of 2D CCA measurement using 3D data

A validation study was performed to test the association between automatically derived corpus callosum area (CCA), intracranial area (ICA), corpus callosum volume (CCV) and intracranial volume within a healthy population using scans from a separate cohort of healthy people acquired as part of the Australian Imaging, Biomarker and Lifestyle Flagship Study of Ageing (AIBL).¹⁹ Automatically extracted mid-sagittal CCA and ICA were correlated with corpus callosum volume (CCV) and intracranial volume (ICV). T1-weighted volumes were prepared for processing and segmentation using the MILXView neuroimaging platform (AEHRC, Brisbane, QLD, Australia), which aligns MRI data to Montreal Neurological Institute and Hospital (MNI) coordinates prior to mid-slice extraction and mid-sagittal measurement.²⁰

Clinical measurements

1 Conversion to clinically definite MS (CDMS) was defined as the occurrence of two or more clinical
2 demyelinating episodes, thus satisfying the diagnostic requirements of dissemination in space and
3 time, or a single episode plus paraclinical evidence, as per the 2005 McDonald criteria²¹ (a minority
4 of cases (n=20) were diagnosed following MRI based on this latter criterion). Conversion to CDMS
5 was reported at annual review and crosschecked against neurological records. A relapse was defined
6 according to the 2001 McDonald Criteria²² as the acute or subacute appearance or reappearance of a
7 neurological abnormality (lasting at least 24 hours) in the absence of other potential explanatory
8 factors. Relapses were reported at annual review; only relapses that were diagnosed and verified by
9 a neurologist were included in the analysis. Disability was assessed at follow-up by the Kurtzke
10 Expanded Disability Status Scale (EDSS)²³.

11 Statistical analysis

12 The distribution of covariates by study site was evaluated by Chi-square test for categorical
13 variables, and t-test for continuous terms. Associations between MRI measures and clinical course
14 were analysed by linear regression for continuous outcomes and log-binomial regression for
15 dichotomous outcomes, the latter essentially analogous in its interpretation to logistic regression but
16 more appropriate for the cross-sectional nature of the analysis. Multiplicative interaction was
17 assessed by the creation of a product term between the two parameters being evaluated, with the
18 significance of the product term denoting the significance of the interaction. Linearity of effects was
19 evaluated by categorising the independent variable in quartiles and testing for trend across these
20 categories. Cronbach's alpha was used for the reliability studies. A one-way random effects model,
21 single measures, was used for the intra-rater reliability, and a two-way random effects model, single
22 measures, for the inter-rater reliability. Spearman's correlation was used for the validation study.
23 The different parametric and nonparametric statistical methods used were appropriate for the
24 various purposes entailed, with the former used where measures of association were desired, e.g. for
25 clinical outcomes like relapse rate and disability accumulation, while nonparametric methods were
26

1 used where only tests of significance were desired, e.g. in comparing scans in the validation
2 studies.

3
4 Change in parameters between baseline and five-year review were calculated as follows:

- 5 • change in CCA (Δ CCA): 5-year CCA minus baseline CCA; absolute annualised change in
6 CCA was calculated by dividing this value by the time in years from baseline to 5-year review; and
7 annualised percentage change by calculating the annualized change as a percent of baseline CCA.
- 8 • change in disability was taken as the 5-year EDSS, under the assumption that the EDSS on
9 the day before the first event was 0; annualised change in disability was calculated by dividing this
10 value by the duration between the day before the first demyelinating event and the 5-year review to
11 yield the annualised percentage change.
- 12 • annualised relapse rate was calculated by dividing the total number of relapses by the time
13 in years from baseline to 5-year review.

14
15 All multivariable models include age, sex and study site. Statistical analyses were performed using
16 Stata Version 12.1 (StataCorp, College Station, TX, USA).

17 18 **Results**

19 Cohort Characteristics

20 Cohort characteristics are presented in Table 1. Of the 282 participants with a first clinical
21 diagnosis of CNS demyelination recruited into the Ausimmune Study, 143 had complete imaging
22 and clinical data available from baseline and 5 year review. These 143 patients formed the study
23 group. The cohort included 113 females (age 34.13 ± 9.39 years), and 30 males (age 33.11 ± 8.31
24 years). The 143 participants resided in four Australian states: Queensland (n=32), New South Wales
25 (n=24), Victoria (n=49) and Tasmania (n=38). There was no significant variation in sex ratio
26 between sites (p=0.22).

Validation studies

For the CCA measurement technique, intra rater reliability was 0.84 ($p<0.001$) and inter rater reliability was 0.93 ($p<0.001$). CCA measurements on T1 versus FLAIR images showed a high intraclass correlation of 0.97 (95% CI: 0.94, 0.99).

Correlation between automatically derived CCA and CCV was performed in a separate, healthy cohort. Positive correlation was found between automatically derived CCA and CCV ($r=0.78$), in addition to between automatically derived ICA and ICV ($r=0.88$).

Corpus callosum area (CCA)

Mean baseline CCA was 6.63 (SD 1.01) cm^2 . There was no association between patient age and baseline CCA ($p=0.98$). Baseline CCA was significantly smaller among females than males (β : -0.57 (95% CI: -0.97, -0.17) cm^2 , $p=0.006$), as was baseline intracranial area (ICA) (β : -11.94 (95% CI: -15.93, -7.95) cm^2 , $p<0.001$). Similar differences by sex were seen for five-year CCA and ICA. Mean time between MRI scans was 5.48 (SD 1.05) years.

Mean CCA at 5 year follow-up was 6.34 (SD 0.98) cm^2 . Mean total ΔCCA was -0.28 (SD 0.91) cm^2 , or -3.37% (SD 13.59); this equated to mean annual ΔCCA of -0.57% (SD 2.91). Mean relapse number by follow-up was 2.56 (SD 3.48), with a mean annualised relapse rate of 0.30 (SD: 0.42) per year.

Relationships between MRI and clinical parameters

Associations between baseline CCA and subsequent MRI and clinical variables are presented in Table 2. Baseline CCA was a significantly predictor of five-year CCA; five-year CCA increased by $\sim 0.6\text{cm}^2$ for every 1cm^2 increase in baseline CCA. The size of this effect increased following adjustment (Figure 2). Greater baseline CCA was also predictive of a greater reduction in CCA by follow-up, in terms of absolute annualised change (β : -0.09 (95% CI: -0.12, -0.06), $p<0.001$) and annualised percentage change (β : -1.19 (95% CI: -1.63, -0.76), $p<0.001$).

Baseline CCA was associated with risk of subsequent conversion to CDMS, however, this did not persist following adjustment for age. There was no association between baseline CCA and progression in disability scores. Higher baseline CCA was associated with a significantly increased relapse rate; however, this association was strongly influenced by an individual with a very high relapse rate (3.62 relapses/yr). Excluding the outlier abrogated this association (IRR: 1.03 (95% CI: 0.93, 1.15), $p=0.58$).

Patients who were shown to have converted to MS at five-year review had a significantly reduced CCA (-0.52 , $p=0.007$) at 5 years (Table 3). Higher annual relapse rate was predictive of a smaller CCA at five-year review ($p=0.001$) and a greater rate of CCA reduction ($p=0.024$); however, this association was lost following exclusion of data from the outlier with very high relapse rate ($p=0.12$). Greater EDSS at five-year review was significantly associated with a greater rate of CCA reduction, and smaller CCA at follow-up.

Discussion

In current practice, MRI reporting in individuals with CIS and MS is based upon the subjective, semi-quantitative assessment of T2 hyperintense and T1 hypointense lesions within the cerebrum and spinal cord.²² However, there is argument for more standardised, quantitative MRI data.²⁴ Until such time as automated analytical software is a standard inclusion in MRI packages, midsagittal CCA is a valid, reliable tool with clinical relevance in the assessment of individuals presenting with CIS.

In this cohort of Australian individuals with CIS, a higher CCA at baseline was associated with a greater annual reduction in CCA, while not being associated with other markers of clinical course such as disability progression. Participants who converted to CDMS demonstrated greater rates of

1 corpus callosum atrophy, and a smaller mean CCA at five-year review. Relapse rate was associated
2 with a greater rate of CCA reduction. Further, higher disability scores at 5 years were associated
3 with a smaller CCA at five years.

4
5 Few studies have addressed whether corpus callosum atrophy precedes the clinical diagnosis of MS.
6 In our cohort, after adjusting for demographics and baseline ICA, those who converted to CDMS
7 demonstrated a significantly greater rate of corpus callosum atrophy by five-year review. In
8 contrast, a 2012 study found no significant difference in CCA between MS converters at 2 years
9 compared to non-converters.²⁵ These conflicting results may be attributable to varying rates of
10 callosal atrophy following CIS. In their longitudinal study, Kalincik et al performed serial MRIs at
11 3-6 month intervals from initial CIS presentation. They concluded that the rate of callosal atrophy
12 was inconstant over time, with early reduction in CCA being most strongly associated with
13 conversion to MS by two years (being adjusted for age, gender and changes in treatment).²⁵ As
14 CCA was measured at only two timepoints in this study, we cannot define when greatest change in
15 CCA occurred, nor conclude whether CCA change is a linear process.

16
17 An important finding from this study was that a higher relapse rate was predictive of a greater
18 annualised change in CCA, and smaller CCA at five-year follow-up. This supports the concept that
19 in earliest MS, cellular processes leading to brain atrophy are exacerbated by acute inflammatory
20 activity (i.e. relapses).⁴ These findings are in concordance with those of previous authors.²⁵

21
22 MRI volumetric analysis has previously provided insight into the associations between cerebral
23 atrophy and disability in patients with CIS.²⁶ However, MRI volumetric analysis is complex, time-
24 consuming, and reliant upon specialised MRI sequences usually reserved for research protocols.¹⁵
25 In contrast, CCA is a simple, robust method for quantification of callosal atrophy which may be
26 easily incorporated into diagnostic protocols by the everyday radiologist.¹⁵ Interestingly, CCA

1 measurement has recently been demonstrated to outperform several volumetric measures in
2 predicting physical and cognitive impairment in patients with established MS.^{3, 15}

3
4 Similarly to MRI brain volumetrics, two-dimensional cerebral atrophy measures may be affected by
5 transient physiological and pathological factors, such as oedema and gliosis.⁸ Random measurement
6 error is also a potential source of error. In our cohort, 56 participants demonstrated an increased
7 CCA over the five-year period, with mean CCA increase within this subgroup being 0.63 (SD 0.42)
8 cm². This may be explained by: transient pathological phenomena, scanner heterogeneity,
9 additional/alternative pathological processes or operator error.

10
11 Our study possesses some limitations. First, due to its multi-centre design, there was inevitable
12 heterogeneity in MRI field strength and sequences.²⁷ As baseline MRI was not performed according
13 to a defined study protocol, there was some unavoidable variation in slice thickness and separation.
14 In our reliability assessment, we found CCA measurements between MRI sequences (T1 and
15 FLAIR) to have good agreement, with heterogeneity of slice thickness and spacing among the
16 sample group, which was reflective of the total cohort. Second, participant data were not excluded
17 on the basis of time interval between the clinical and MRI examination; prolonged time to follow-
18 up is likely to counter this potential source of error. Third, relapse assessment and conversion to MS
19 were assessed retrospectively, through annual patient assessment and review of clinical records.
20 Finally, due to missing/inadequate MRI data, analysis is restricted to a subsample of cases from the
21 Ausimmune Study, with varied site retention being a potential source of bias. However, with
22 retention rate in the Ausimmune/AusLong Study being 84.6%, this effect is likely to be minimal.

23
24 In this group of Australians presenting with CIS, we applied a validated, simple method to quantify
25 corpus callosum atrophy over five years. The authors propose CCA measurement may provide
26 clinicians with a useful MRI marker to estimate corpus callosum volume loss in patients presenting
27 with CIS. Future directions of the current study include inclusion of a healthy cohort, and serial

CCA measurement at more regular, shorter intervals from CIS presentation to explore temporal variation corpus callosum atrophy over time.

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Conflicts of Interest and Sources of Funding

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Table 1 Cohort characteristics for 143 persons with MRI data at baseline and 5-year review. Results presented as mean (SD).

				Converter	Non- converter
	All persons	Males	Females	s (n=110)	s (n=33)
Baseline CCA (cm ²)	6.63 (1.01)	7.07 (1.09)	6.51 (0.96)	6.54 (1.02)	6.92 (0.91)
Follow-up CCA (cm ²)	6.34 (0.98)	6.77 (0.76)	6.23 (0.94)	6.22 (0.98)	6.74 (0.89)
Baseline ICA (cm ²)	157.79 (10.95)	167.23 (10.95)	155.29 (9.49)	157.24 (11.25)	159.62 (9.81)
Total ΔCCA (%)	-3.37 (13.59)	-2.69 (14.27)	-3.56 (13.47)	-3.87 (13.78)	-0.18 (0.88)
Mean annualised ΔCCA (%)	-0.57 (2.91)	-0.64 (2.79)	-0.54 (2.96)	-0.64 (3.05)	-0.32 (2.42)

Abbreviations: CCA = Corpus callosal area; ICA = Intracranial area.

Table 2. Baseline CCA (continuous and quartile categorical) as predictor of subsequent MRI and clinical course parameters.

	5-year CCA		Annualised change in CCA		Annualised percentage change in CCA*	
	Univariable	Adjusted ^a	Univariable	Adjusted ^a	Univariable	Adjusted ^a
Baseline CCA, continuous	0.56 (0.43, 0.69) <i>p</i> <0.001	0.69 (0.57, 0.81) <i>p</i> <0.001	-0.09 (-0.12, -0.06) <i>p</i> <0.001	-0.06 (-0.09, -0.03) <i>p</i> <0.001	-1.19 (-1.63, -0.76) <i>p</i> <0.001	-0.77 (-1.19, -0.35) <i>p</i> <0.001
Baseline CCA 3.82 – 5.83	5.57 (5.30, 5.85)	5.39 (5.15, 5.64)	0.04 (-0.01, 0.10)	0.01 (-0.05, 0.06)	0.83 (-0.04, 1.70)	0.23 (-0.55, 1.02)
>5.83 – 6.60	+0.68 (0.28, 1.07)	+0.86 (0.52, 1.21)	-0.03 (-0.11, 0.05)	+0.01 (-0.07, 0.08)	-0.56 (-1.80, 0.67)	-0.06 (-1.17, 1.05)
>6.60 – 7.37			-0.11 (-0.19, -0.03)	-0.06 (-0.13, 0.01)	-1.70 (-2.93, -0.47)	-1.03 (-2.12, 0.06)
>7.37 – 8.78	+1.08 (0.68, 1.48)	+1.29 (0.95, 1.63)	0.03	-0.17 (-0.25, -0.09)	0.47	-2.14 (-3.33, -0.95)
Trend:	+1.33 (0.94, 1.73) <i>p</i> <0.001	+1.67 (1.29, 2.04) <i>p</i> <0.001	0.17 <i>p</i> <0.001	<i>p</i> <0.001	2.12 <i>p</i> <0.001	<i>p</i> <0.001
	Conversion to CDMS		Relapse rate FDE to 5-year review		Annualised change in EDSS	
	Univariable	Adjusted ^a	Univariable	Adjusted ^a	Univariable	Adjusted ^b
Baseline CCA, continuous	0.92 (0.84, 1.00) <i>p</i> =0.048	0.96 (0.88, 1.05) <i>p</i> =0.34	1.09 (0.98, 1.21) <i>p</i> =0.097	1.18 (1.05, 1.32) <i>p</i> =0.007	+0.01 (-0.05, 0.07) <i>p</i> =0.72	+0.002 (-0.06, 0.07) <i>p</i> =0.95

Baseline CCA

3.82 – 5.83	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	0.04 (-0.08, 0.15)	0.02 (-0.10, 0.13)
>5.83 – 6.60	1.00 (0.81, 1.23)	1.09 (0.87, 1.37)	0.97 (0.71, 1.31)	1.23 (0.89, 1.69)	-0.06 (-0.23, 0.11)	-0.01 (-0.18, 0.16)
>6.60 – 7.37	0.87 (0.68, 1.11)	0.93 (0.73, 1.18)	0.90 (0.66, 1.23)	1.04 (0.75, 1.43)	+0.01 (-0.16, 0.18)	+0.01 (-0.17, 0.18)
>7.37 – 8.78	0.82 (0.63, 1.08)	0.95 (0.73, 1.24)	1.42 (1.07, 1.87)	1.86 (1.37, 2.53)	+0.05 (-0.12, 0.22)	+0.03 (-0.16, 0.22)
Trend:	<i>p</i> =0.087	<i>p</i> =0.48	<i>p</i>=0.024	<i>p</i>=0.001	<i>p</i> =0.48	<i>p</i> =0.78

Abbreviations: CCA = Corpus callosal area; FDE = First demyelinating event; EDSS = Expanded Disability Status Scale.

Analyses predicting continuous outcomes (5-year CCA, change in CCA, change in EDSS) evaluated by linear regression, presented as the geometric mean (95% CI) of the reference and coefficients relative to the reference (95% CI) for subsequent levels. Analyses predicting dichotomous outcomes (conversion to CDMS) evaluated by log-binominal regression, presented as prevalence ratios (95% CI) relative to the reference. Analyses predicting count-based outcomes (relapse rate) evaluated by Poisson regression, presented as incidence rate ratios (95% CI) relative to the reference.

^aAdjusted for age, sex, study site and baseline intracranial area.

^bAdjusted for age, sex, study site, baseline intracranial area and whether participants were having a relapse at the time of their 5-year disability measure.

*see methods for calculation of annualized percentage change

Table 3. Clinical course parameters as predictors of 5-year CCA, and annualised change in CCA.

	Five-year CCA		Annualised change in CCA	
	Univariable	Adjusted ^a	Univariable	Adjusted ^a
Conversion to CDMS by 5-yr review				
Yes	-0.52 (-0.90, -0.15) <i>p=0.007</i>	-0.56 (-0.93, -0.19) <i>p=0.003</i>	-0.02 (-0.10, 0.06) <i>p=0.60</i>	-0.07 (-0.14, -0.01) <i>p=0.035</i>
Relapse rate, FDE to 5-yr review	-0.55 (-0.94, -0.17) <i>p=0.005</i>	-0.45 (-0.83, -0.07) <i>p=0.021</i>	-0.02 (-0.06, 0.02) <i>p=0.42</i>	-0.12 (-0.19, -0.05) <i>p=0.001</i>
0 – 0.10	6.68 (6.36, 7.00)	6.65 (6.34, 6.96)	-0.01 (-0.08, 0.05)	-0.01 (-0.06, 0.05)
>0.10 – 0.14	-0.42 (-0.90, 0.06)	-0.20 (-0.67, 0.27)	-0.08 (-0.17, 0.03)	-0.06 (-0.15, 0.02)
>0.14 – 0.44	-0.22 (-0.65, 0.22)	-0.29 (-0.71, 0.12)	-0.01 (-0.10, 0.08)	-0.02 (-0.10, 0.06)
>0.44 – 3.62	-0.66 (-1.11, -0.20)	-0.61 (-1.08, -0.15) <i>p=0.010</i>	-0.10 (-0.19, -0.00)	-0.12 (-0.21, -0.04)
Trend:	<i>p=0.016</i>		<i>p=0.14</i>	<i>p=0.024</i>
5-yr EDSS	-0.18 (-0.28, -0.08)	-0.19 (-0.28, -0.10)	-0.01 (-0.03, 0.01)	-0.02 (-0.04, -0.00)

	<i>p=0.001</i>	<i>0.09)</i> <i>p<0.001</i>	<i>p=0.24</i>	<i>p=0.023</i>
0 – 1	6.68 (6.41, 6.95)	6.74 (6.49, 7.00)	-0.06 (-0.12, -0.01)	-0.03 (-0.08, 0.02)
>1 – 1.5	-0.25 (-0.70, 0.20)	-0.42 (-0.85, 0.02)	+0.07 (-0.02, 0.16)	+0.00 (-0.08, 0.08)
>1.5 – 2.5	-0.50 (-0.92, -0.09)	-0.58 (-0.97, -	+0.03 (-0.05, 0.12)	-0.01 (-0.08, 0.06)
>2.5 – 7.0	-0.78 (-1.22, -0.34)	0.19)	-0.06 (-0.15, 0.04)	-0.09 (-0.16, -0.01)
<i>Trend:</i>	<i>p<0.001</i>	-0.84 (-1.26, - 0.41) <i>p<0.001</i>	<i>p=0.37</i>	<i>p=0.046</i>
Annualised changed in EDSS	-0.11 (-0.66, 0.45)	-0.23 (-0.79, 0.33)	-0.07 (-0.18, 0.04)	-0.07 (-0.17, 0.03)
	<i>p=0.71</i>	<i>p=0.41</i>	<i>p=0.18</i>	<i>p=0.14</i>
-1.30, -0.19	6.55 (6.19, 6.91)	6.64 (6.29, 6.98)	-0.04 (-0.11, 0.03)	-0.03 (-0.09, 0.03)
>-0.19, 0	-0.18 (-0.65, 0.29)	-0.29 (-0.75, 0.17)	+0.03 (-0.06, 0.12)	+0.03 (-0.06, 0.11)
>0, 0.20	+0.33 (-0.28, 0.95)	+0.34 (-0.23, 0.91)	+0.11 (-0.01, 0.23)	+0.11 (0.01, 0.22)
>0.20, 1.18	-0.41 (-0.91, 0.09)	-0.58 (-1.07, -0.10)	-0.04 (-0.13, 0.06)	-0.06 (-0.15, 0.03)
<i>Trend:</i>	<i>p=0.23</i>	<i>p=0.10</i>	<i>p=0.56</i>	<i>p=0.28</i>

Abbreviations: CCA = Corpus callosal area; FDE = First demyelinating event; EDSS = Expanded Disability Status Scale.

Analyses predicting continuous outcomes (5-year CCA, change in CCA, change in EDSS) evaluated by linear

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^aAdjusted for age, sex, study site and 5-year intracranial area. Analyses of disability also adjusted for whether participants were having a relapse at the time of their 5-year disability measure.

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Author/s:

Odenthal, C;Simpson, S;Oughton, J;van der Mei, I;Rose, S;Fripp, J;Lucas, R;Taylor, B;Dear, K;Ponsonby, A-L;Coulthard, A

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