

# Relationship between brain atrophy and disability in a multi-site multiple sclerosis registry

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## ABSTRACT

**Background** In a retrospective multicentre cohort study, we explored the association between brain atrophy and multiple sclerosis (MS) disability using different MRI scanners and protocols at multiple sites.

**Methods** Relapse-onset MS patients were included if they had two clinical MRIs 12 months apart and  $\geq 2$  Expanded Disability Status Scale (EDSS) scores. Percentage brain volume change (PBVC), percentage grey matter change (PGMC), fluid-attenuated inversion recovery (FLAIR) lesion volume change, whole brain volume (BV), grey matter volume (GMV), FLAIR lesion volume and T1 hypointense lesion volume were assessed by icobrain. Disability was measured by EDSS scores and 6-month confirmed disability progression (CDP).

**Results** Of the 260 relapse-onset MS patients included, 204 (78%) MRI pairs were performed in the same scanner and 56 (22%) pairs were from different scanners. 93% of patients were on treatment and mean PBVC was  $-0.26\%$  ( $\pm 0.52$ ). During the median follow-up of 2.8 years from the second MRI, median EDSS change was 0.0 and 12% patients experienced 6-month CDP. Cross-sectional BV and GMV at the later MRI showed a trend for association with CDP (HR 0.99; 95% CI 0.98 to 1.00;  $p=0.06$ ). Only BV at the later MRI was associated with EDSS score ( $\beta -0.03$ , SE 0.01,  $p<0.001$ ) and the rate of EDSS change over time ( $\beta -0.001$ , SE 0.0003,  $p=0.02$ ). There was no association between longitudinal PBVC or PGMC and CDP or EDSS ( $p>0.05$ ).

**Conclusion** In this highly treated MS cohort with low disability accrual, only cross-sectional BV showed an association with future EDSS scores, while no MRI metric predicted 6-month CDP. These findings highlight the limitations of current clinical MRI measures in predicting disability worsening in real-world settings.

## INTRODUCTION

Disability accrual in multiple sclerosis (MS) is a significant source of personal and societal

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Brain volume is a potential biomarker for multiple sclerosis (MS) disability, but few studies have explored the predictive value of volumetric imaging using different MRI scanners in clinical practice.

## WHAT THIS STUDY ADDS

⇒ Cross-sectional metrics of brain volume were the most robust markers of future disability state and trajectory in our multi-site cohort.  
⇒ Whole brain volume predicted Expanded Disability Status Scale change more than percentage brain volume change over a short observational period.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study provides insight for future volumetric analyses in real-world settings involving multiple imaging sites, MRI protocols and scanner hardware. It suggests that cross-sectional brain volume measurements may be a more useful indicator of future disability than longitudinal measures of brain volume change.  
⇒ This study also demonstrates the limited predictive value of clinical MRI metrics for short-term disability progression in a contemporary, well-treated MS cohort. It highlights the need for future research and validation of these observations.

burden.<sup>1</sup> It is potentially modifiable with appropriate therapy,<sup>2</sup> but early recognition of treatment failure remains complex. Brain volume has been widely studied as a potential biomarker for MS disability, with several studies reporting that early brain atrophy can predict disability progression in the short,<sup>3</sup> medium<sup>4–7</sup> and long term.<sup>8,9</sup> Other MRI measures have also shown

correlation with future disability progression, including grey matter atrophy,<sup>10–13</sup> grey matter volume (GMV),<sup>14</sup> T1 lesion volume,<sup>9 15</sup> T2 or fluid-attenuated inversion recovery (FLAIR) lesion volume,<sup>7 8 15</sup> new T2 lesions,<sup>15 16</sup> gadolinium-enhancing lesions<sup>17 18</sup> and topography of T2 lesions.<sup>19 20</sup>

In prior studies, longitudinal brain imaging has almost exclusively been performed using a single scanner and a single protocol. Few have explored the predictive role of volumetric imaging using serial MRIs performed with various scan protocols and on different scanners.<sup>21 22</sup> However, in the real world, MS clinics often use multiple scanners and multi-centre MS registries cannot control or unify MRI acquisition protocols at their various sites.

In our prior study, we assessed volumetric data from MRIs obtained during routine clinical follow-up at several MSBase sites.<sup>23</sup> Scans were transferred for centralised analysis using icobrain, a commercially available automated software provided by icometrix that assesses global and regional brain volumetric measures.<sup>24</sup> We found that both same-scanner and different-scanner MRI pairs approached the variance of single-centre protocols for percentage brain volume change (PBVC) when they met strict selection criteria.<sup>23</sup>

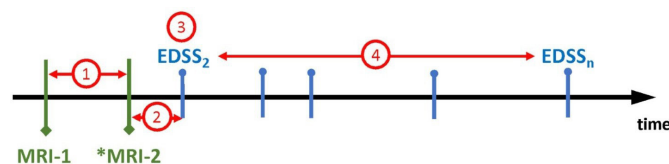
The goal of this study was to assess the association of several quantitative MRI metrics and their 12-month change, in predicting future MS disability. It was conducted using clinical MRIs from an MSBase cohort of patients with relapse-onset MS published previously.<sup>23</sup> In that study, we assessed the quality of brain volume change measures obtained from scan pairs after they were classified in multiple quality control (QC) steps, both automated and manual. We used a subgroup of scan pairs with QC characteristics indicating low PBVC variance for predictive modelling in this study.

## METHODS

### Study design and participants

This was a retrospective cohort study of MS patients from four centres: General University Hospital (Prague, Czech Republic), Royal Melbourne Hospital (Melbourne, Australia), Box Hill Hospital (Melbourne, Australia) and Brain and Mind Centre (Sydney, Australia). Eligible patients were enrolled from 18 December 2017 to 13 October 2018. Inclusion criteria were aged  $\geq 18$  years, relapse-onset MS, known date of MS onset and consented to be part of the MSBase Registry.<sup>25</sup>

A total of 6826 clinical MRIs were transferred to icometrix and filtered by image quality. A detailed description of this process is outlined elsewhere.<sup>23</sup> A subgroup of 1885 consecutive MRI pairs (3051 unique MRIs) from 974 patients remained after filtering and was found to have lower PBVC variance compared with the unfiltered dataset.<sup>23</sup> This subgroup represented the best-performing MRI pairs in regard to PBVC variability, and these 974 patients were chosen as the study cohort.



**Figure 1** Selection process for MRIs and follow-up EDSS scores. 1. Time difference between MRIs =  $12 \pm 3$  months (9–15 months inclusive). 2. Time difference between MRI-2 and first EDSS post MRI-2 ( $EDSS_2$ )  $\leq 3$  months. 3. Exclude pts with only 1 EDSS post MRI-2. 4. Time difference between  $EDSS_2$  and  $EDSS_{n(\text{last})} \geq 6$  months. EDSS, Expanded Disability Status Scale;  $EDSS_2$ , the first EDSS after MRI-2; MRI-2, second MRI in pair. \*MRI-2 was defined as the baseline.

Patients with no Expanded Disability Status Scale (EDSS) scores were excluded. Where multiple suitable MRI pairs were available for each patient, the earliest MRI pair was selected. MRI-1 and MRI-2 refer to the first and second MRI of each pair. We further restricted the dataset to patients with MRI scans  $12 (\pm 3)$  months apart and  $\geq 2$  EDSS scores post MRI-2, the first  $\leq 3$  months from MRI-2, with  $\geq 6$  months between the first and last EDSS (figure 1).

Patient demographic and clinical information were obtained from the MSBase Registry including MS course, EDSS scores, relapse dates and use of disease-modifying therapy (DMT).

### Data processing

Brain MRI scans were performed as part of routine clinical care between October 2007 and October 2018. Patients were scanned on any combination of scanners at their site. Inclusion criteria for brain MRIs were 3D T1-weighted (T1) sequence (maximum slice thickness of 1.6 mm) and 3D fluid-attenuated inversion recovery (FLAIR) sequence (or 2D FLAIR with maximum slice thickness of 3 mm).

All MRIs were processed using the icobrain software V.3.1. Scans with suitable volumetric sequences underwent a cross-sectional and longitudinal processing pipeline (icobrain cross and icobrain long) which incorporates automated + visual quality analysis.<sup>24 26</sup> Details of the MRI workflow used in our study have been published previously.<sup>23</sup> Icobrain cross generates segmentation-based measurements for whole brain volume (BV) and GMV normalised for head size, FLAIR lesion volume (FLAIR LV) and T1-hypointense LV (T1LV). Icobrain long provides registration-based measurements for annualised PBVC and percentage grey matter change (PGMC) using Jacobian integration,<sup>20</sup> while absolute change in FLAIR LV was measured using a joint lesion segmentation model assessing difference in images.<sup>27</sup>

### Study outcomes

The study aimed to assess whether quantitative MRI metrics and their 12-month change predict future disability progression in MS. The two primary outcomes were (1) disability progression confirmed at 6 months and

(2) EDSS scores after MRI-2. For the 6-month confirmed disability progression (CDP) analysis, we used a subset of patients with  $\geq 3$  EDSS scores (1 baseline score at MRI-2 and 2 follow-up scores). CDP was defined as an increase in EDSS of 0.5 point (if baseline EDSS  $> 5.5$ ), 1.0 point (if baseline EDSS  $\leq 5.5$ ) or 1.5 point (if baseline EDSS = 0), sustained over  $\geq 6$  months. EDSS scores recorded within 30 days after a relapse were excluded. An EDSS change was considered any difference between baseline and subsequent EDSS score. Therefore, EDSS worsening was defined as an increase of the baseline EDSS score by  $\geq 0.5$ .

To ensure appropriate temporal ordering for prediction, MRI-2 was defined as the baseline imaging time-point, with the first EDSS recorded after MRI-2 used as the baseline EDSS. This approach avoided using clinical information that may have been influenced by disease activity occurring between the two MRIs.

### Statistical analysis

The database was locked for analysis on 1 November 2018. Mean and SD or median and IQR were used to describe data distribution. PBVC and PGMC values reported were annualised. All analyses described below were prespecified.

The association between PBVC and CDP was evaluated with Cox proportional hazards models. The association of other MRI metrics with CDP was also explored: PGMC, FLAIR lesion volume change (LVC), whole BV, GMV, FLAIR LV and T1LV. The segmentation-based measurements (whole BV, GMV, FLAIR LV, T1LV) were assessed on the baseline MRI.

The association of the MRI metrics with EDSS score over time was evaluated with ordinal mixed-effect models. The models included a random intercept for patient and an interaction term for the MRI variable of interest and follow-up time (from MRI-2 to EDSS score) to evaluate the associations between MRI metrics at baseline with EDSS trajectory over time. The relationship between the primary variable of interest and the interaction is denoted in the tables by 'slope', which indicates the rate of EDSS change.

All models were adjusted for proportion of time spent on DMT between MRI-1 and MRI-2. Whole BV or GMV at MRI-1 was adjusted for as potential confounders when modelling PBVC and PGMC, respectively. Models assessing the EDSS score over time were adjusted for baseline EDSS. No corrections were made for multiple comparisons as the number of p values reported was limited and the risk of false discovery rate inflation was low.

Six prespecified sensitivity analyses were performed for PBVC, the primary MRI metric of interest. First, we adjusted the models for sex and age at MRI-2. Second, we excluded MRI pairs with a relapse within 30 days prior to MRI-1 or MRI-2. Third, we replaced EDSS with the Multiple Sclerosis Severity Score (MSSS) as the outcome variable. MSSS uses EDSS to rank patients relative to a normative population with the same time from MS

onset.<sup>28</sup> We used a recently updated normative population with relapse-onset MS.<sup>29</sup> Fourth, we replaced EDSS with the Age Related Multiple Sclerosis Severity (ARMSS) score which ranks EDSS scores based on the patient's age at the time of assessment.<sup>30</sup> Fifth, we compared patients in the best versus the worst quartiles of PBVC and assessed PBVC as a binary variable. Sixth, we combined the first three MRI scans, that is, two consecutive MRI pairs, to create 'MRI triplets' for each patient. We obtained the annualised PBVC for each triplet using the mean PBVC of the two MRI pairs. The scan interval between MRI-1 and MRI-2 was set to 0.75–3 years.

Minimum detectable effect sizes were estimated using 200 simulations at  $\alpha=0.05$  and  $1-\beta=0.80$ . All statistical analyses were performed in R, V.3.6.0.

## RESULTS

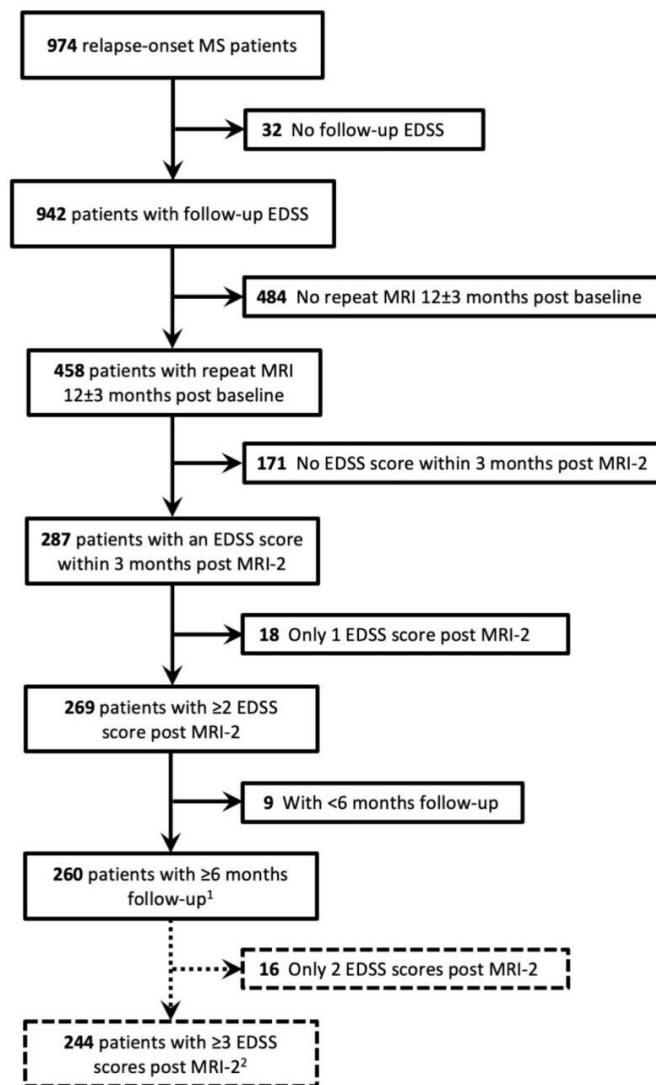
### Cohort characteristics

Of 974 patients with relapse-onset MS in the study cohort, 260 patients met the inclusion criteria (figure 2). The MRI pairs for these 260 patients consisted of 204 (78%) same-scanner pairs and 56 (22%) different-scanner pairs (online supplemental table S1). The demographic, clinical and MRI characteristics of the included patients are summarised in table 1. The majority of patients (95%) had relapsing-remitting MS (RRMS) and the mean (SD) age at RRMS diagnosis was 32.2 (9.9) years. At MRI-1, the mean (SD) age of the cohort was 39.4 (10.4) years and mean (SD) disease duration from clinically isolated syndrome was 9.8 (6.8) years. Almost all patients were treated with DMTs (93%) between MRI-1 and MRI-2 (online supplemental table S2). The median follow-up time was 3.8 years from MRI-1 to last EDSS, or 2.8 years from MRI-2 (baseline) to last EDSS. The median (IQR) EDSS score at MRI-2 was 2.0 (1.5–3.5) and the median EDSS change from MRI-2 to last follow-up visit was 0.0 (range –2.0 to 4.0).

### Confirmed disability progression

244 patients had at least 3 EDSS scores during follow-up and were included in the CDP analysis. Only 29 of 244 (12%) patients experienced a 6-month confirmed EDSS progression event over 2.8 years mean follow-up time from MRI-2 to last visit. The characteristics of these 29 patients are displayed in online supplemental table S3. Of these 29 patients, 9 were in the worst PBVC quartile and 7 were in the best PBVC quartile. We did not find evidence for association between any of the MRI metrics and the risk of subsequent EDSS progression events (table 2). The main MRI metrics of interest, annualised PBVC and PGMC, were not associated with 6-month CDP. However, cross-sectional whole BV (HR 0.99; 95% CI 0.99 to 1.00;  $p=0.06$ ) and GMV (HR 0.99; 95% CI 0.98 to 1.00;  $p=0.06$ ) at MRI-2 showed a trend towards association with EDSS progression (table 2).

The minimum detectable effect sizes for the volumetric MRI variables and the CDP are presented in online supplemental table S4.



**Figure 2** Consort diagram for inclusion. EDSS, Expanded Disability Status Scale; MRI-2, second MRI in pair; MS, multiple sclerosis. The dotted lines represent the subgroup of patients used in the confirmed disability progression analysis. <sup>1</sup>n=260 used in EDSS analysis. <sup>2</sup>n=244 used in confirmed disability progression (CDP) analysis.

### EDSS and its change

In general, whole BV, GMV, FLAIR LV, T1LV and LVC were associated with absolute EDSS score (table 3). Whole BV and PBVC were predictive of future EDSS slope. Only whole BV was associated with both EDSS score ( $\beta$   $-0.03$ , SE  $0.01$ ,  $p < 0.001$ ) and the slope of EDSS change over time ( $\beta$   $-0.001$ , SE  $0.0003$ ,  $p = 0.02$ ) (table 3). For example, every 33 mL reduction in the whole BV would be associated with a mean 1-step higher EDSS overall, and more rapidly increasing EDSS by 0.03 steps per year. Our results mean that after 30 years, the EDSS would be predicted to increase by 1 step for every 33 mL lower baseline brain volume. See online supplemental figures S1, S2 for estimated EDSS trajectories over time for PBVC and BV quartiles.

**Table 1** Demographic, clinical and MRI characteristics of included patient cohort

| Characteristics                                       | N=260                           |
|-------------------------------------------------------|---------------------------------|
| <i>Clinical</i>                                       |                                 |
| Sex (female)                                          | 202 (78%)                       |
| Age (years) at                                        |                                 |
| CIS diagnosis                                         | 29.6 ( $\pm 10.0$ )             |
| RRMS diagnosis                                        | 32.2 ( $\pm 9.8$ )              |
| MRI-1 scan; range                                     | 39.4 ( $\pm 10.4$ ); 18 to 72   |
| Disease type at MRI-1                                 |                                 |
| CIS                                                   | 3 (1.1%)                        |
| RRMS                                                  | 248 (95.4%)                     |
| SPMS                                                  | 9 (3.5%)                        |
| Disease duration from CIS to MRI-1 (years)            | 9.8 ( $\pm 6.8$ )               |
| Follow-up length* (years); range                      | 2.8 (2.0–3.7); 0.5 to 7.9       |
| Number of EDSS scores (post-MRI-2); range             | 6 (4–13); 2 to 35               |
| Patients on DMT during MRIs                           | 242 (93%)                       |
| Proportion of time spent on DMT during MRIs (%); mean | 100 (98.8–100); 88.5            |
| <i>Disability</i>                                     |                                 |
| EDSS score at MRI-2; range                            | 2.0 (1.5–3.5); 0.0 to 7.0       |
| EDSS change from MRI-2 to last follow-up; range       | 0.0 (0.0 to +0.5); –2.0 to +4.0 |
| Number of patients reaching CDP                       | 29/244 (12%)                    |
| <i>MRI measures</i>                                   |                                 |
| PBVC between MRI-1 and MRI-2 (%/year)                 | –0.26 ( $\pm 0.52$ )            |
| PGMC between MRI-1 and MRI-2 (%/year)                 | –0.34 ( $\pm 0.54$ )            |
| LVC between MRI-1 and MRI-2 (mL)                      | 0.01 ( $\pm 0.65$ )             |
| BV at MRI-1 (mL)                                      | 1535 ( $\pm 81$ )               |
| GMV at MRI-1 (mL)                                     | 907 ( $\pm 57$ )                |
| BV at MRI-2 (mL)                                      | 1530 ( $\pm 70$ )               |
| GMV at MRI-2 (mL)                                     | 906 ( $\pm 49$ )                |
| FLAIR LV at MRI-2 (mL)                                | 5.64 ( $\pm 5.56$ )             |
| T1LV at MRI-2 (mL)                                    | 3.57 ( $\pm 3.94$ )             |

Data are given as mean ( $\pm$ SD), median (IQR) and number (%) unless otherwise stated.

\*Follow-up length from MRI-2 (baseline) to last visit with EDSS score. BV, whole brain volume; CDP, 6-month confirmed disability progression; CIS, clinically isolated syndrome; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; GMV, grey matter volume; FLAIR LV, fluid-attenuated inversion recovery lesion volume; LVC, fluid-attenuated inversion recovery lesion volume change; MRI-1, first MRI in pair; MRI-2, second MRI in pair; PBVC, annualised percentage brain volume change; PGMC, annualised percentage grey matter change; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; T1LV, T1-hypointense lesion volume.

### Sensitivity analysis

The results of the sensitivity analyses are shown in table 4. First, adjusting the models of PBVC for sex and age did not change the findings of the primary analysis. Second, excluding MRIs acquired immediately after a relapse

**Table 2** Association between MRI volumetric measurements and 6-month confirmed disability progression

| MRI metric            | HR (95% CI)         | P value |
|-----------------------|---------------------|---------|
| PBVC*, %              | 0.89 (0.45 to 1.75) | 0.73    |
| PGMC†, %              | 0.93 (0.45 to 1.91) | 0.83    |
| LVC*, %               | 1.64 (0.69 to 3.97) | 0.26    |
| BV‡ (MRI-2), mL       | 0.99 (0.99 to 1.00) | 0.06    |
| GMV‡ (MRI-2), mL      | 0.99 (0.98 to 1.00) | 0.06    |
| FLAIR LV‡ (MRI-2), mL | 1.03 (0.97 to 1.10) | 0.38    |
| T1LV‡ (MRI-2), mL     | 1.06 (0.97 to 1.15) | 0.21    |

Volumes are in mL.

\*Adjusted for BV at MRI-1 and proportion of time spent on DMT during MRIs.

†Adjusted for GMV at MRI-1 and proportion of time spent on DMT during MRIs.

‡Adjusted for proportion of time spent on DMT between MRI-1 and MRI-2.

BV, whole brain volume; GMV, grey matter volume; FLAIR LV, fluid-attenuated inversion recovery lesion volume; LVC, fluid-attenuated inversion recovery lesion volume change; MRI-2, second MRI in pair (baseline); PBVC, percentage brain volume change; PGMV, percentage grey matter change; T1LV, T1-hypointense lesion volume.

resulted in a cohort of 239 patients for the EDSS analysis (8 had relapses pre-MRI-1 and 13 had relapses pre-MRI-2) and 224 patients for the CDP analysis. We did not find any associations between PBVC and CDP or PBVC and EDSS in this subgroup. Third, no association was found between PBVC and future MSSS. Fourth, there was no relationship between PBVC and ARMSS scores. In the fifth sensitivity analysis, we explored the extremes of PBVC. We found that 25% of patients with the highest PBVC loss ( $\leq -0.56\%$ ) were more likely to have a faster rate of EDSS worsening than those in the lowest quartile ( $\geq 0.07\%$ ) of PBVC loss ( $\beta$  0.26, SE 0.07,  $p < 0.001$ ). However, we did not identify a relationship between the worst PBVC quartile and the overall EDSS scores or 6-month CDP. Finally, among the 306 patients with three MRI scans (triplets) available, the mean (SD) PBVC of the MRI triplets was  $-0.24$  (0.39). We did not find any associations between PBVC and CDP or PBVC and EDSS.

## DISCUSSION

In this real-world cohort of 260 patients with relapse-onset MS followed at multiple sites and scanned in multiple MRI scanners, we found associations between cross-sectional volumetric brain MRI metrics and future EDSS scores. BV, GMV, lesion volume change and the volumes of FLAIR and T1 lesions were associated with EDSS scores recorded over the median 2.8 years after the second MRI brain scan. In addition, BV at the second MRI was predictive of future EDSS trajectory. We were unable to identify an association between PBVC or PGMV recorded over 1 year with subsequent disability. We also did not

**Table 3** Association between MRI volumetric measurements and EDSS scores

| MRI metric*           | Estimate (SE)   | P value |
|-----------------------|-----------------|---------|
| PBVC†, %              | -0.08 (0.16)    | 0.61    |
| Slope                 | -0.07 (0.05)    | 0.15    |
| PGMC‡, %              | -1.39 (0.92)    | 0.13    |
| Slope                 | -0.15 (0.07)    | 0.03    |
| LVC†, %               | 0.40 (0.15)     | 0.01    |
| Slope                 | -0.07 (0.06)    | 0.24    |
| BV§ (MRI-2), mL       | -0.03 (0.01)    | <0.001  |
| Slope                 | -0.001 (0.0003) | 0.02    |
| GMV§ (MRI-2), mL      | -0.05 (0.01)    | <0.001  |
| Slope                 | -0.001 (0.001)  | 0.33    |
| FLAIR LV§ (MRI-2), mL | 0.46 (0.09)     | <0.001  |
| Slope                 | -0.0002 (0.006) | 0.97    |
| T1LV§ (MRI-2), mL     | 0.55 (0.12)     | <0.001  |
| Slope                 | 0.01 (0.01)     | 0.53    |

Volumes are in mL.

All the models adjusted for baseline EDSS.

\*Slope refers to the interaction term between the MRI metric and follow-up time (i.e. time between MRI-2 and EDSS score), which indicates whether the rate of that MRI variable changes over time.

†Adjusted for BV at MRI-1 and proportion of time spent on DMT during MRIs.

‡Adjusted for GMV at MRI-1 and proportion of time spent on DMT during MRIs.

§Adjusted for proportion of time spent on DMT between MRI-1 and MRI-2.

BV, whole brain volume; EDSS, Expanded Disability Status Scale; GMV, grey matter volume; FLAIR LV, fluid-attenuated inversion recovery lesion volume; LVC, fluid-attenuated inversion recovery lesion volume change; MRI-2, second MRI in pair (baseline); PBVC, percentage brain volume change; PGMV, percentage grey matter change; T1LV, T1-hypointense lesion volume.

find evidence for an association between any of the MRI metrics in predicting subsequent 6-month CDP.

Brain volume change has been proposed as an important MRI metric for monitoring the course of MS and to guide decisions on treatment.<sup>31</sup> Currently, three outcomes are used to assess absence of detectable disease activity<sup>32</sup> (No Evidence of Disease Activity-3): relapses, active MRI lesions and disability progression. Brain atrophy reflects decline in neurological capacity<sup>3-6 8 9</sup> and there have been recommendations to incorporate it as an additional component in the No Evidence of Disease Activity-4.<sup>31</sup> A meta-analysis of 13 clinical trials showed that treatment effects on brain atrophy explained 48% of the variance in the effect of treatment on disability progression over 2 years.<sup>3</sup>

Our study highlights the limitations of using clinical MRI metrics for prediction of clinical worsening. The absence of association between PBVC and disability progression may be partially explained by the low rate of brain atrophy seen in our cohort over a 1-year period. An annualised PBVC rate of  $-0.4\%$  (using SIENA software) was shown to provide 80% specificity in discriminating the presence of pathological brain atrophy in patients

with MS.<sup>33</sup> Another study suggested a PBVC cut-off of  $-0.86\%$  (specificity  $71\%$ ) for predicting CDP in interferon  $\beta$ -treated patients.<sup>6</sup> Although an equivalent cut-off value has not yet been explored for the icobrain software, our cohort's PBVC of  $-0.26\%$  is within the range reported for healthy individuals ( $0.1\%$ – $0.3\%$ ).<sup>34</sup> The absence of association with PGMV was consistent with some prior studies,<sup>6 15</sup> but contrasts with others that have reported predictive value for PGMV in identifying future disability progression.<sup>11 12</sup>

Our cohort was characterised by low baseline EDSS and minimal EDSS change over time, likely reflecting the high proportion of patients on effective DMTs. These favourable clinical outcomes limited the capacity to detect associations between serial MRI change and disability, particularly over a relatively short time interval. Only  $12\%$  of participants reached 6-month CDP, and post-hoc power calculations indicated that the available power was moderate to low. This underscores the challenges of low signal-to-noise ratio in clinically acquired MRI scans across scanners and protocols and of using the derived metrics to predict disability progression in contemporary, well-treated MS cohorts.

**Table 4** Sensitivity analyses for annualised PBVC

| Sensitivity analysis                      | 6-month CDP               |         | EDSS                                   |                    |
|-------------------------------------------|---------------------------|---------|----------------------------------------|--------------------|
|                                           | HR (95% CI)               | P value | Estimate (SE)                          | P value            |
| Adjusted for age and sex*                 | 0.86 (0.44 to 1.70)       | 0.67    | $-0.04$ (0.16)<br>Slope $-0.07$ (0.05) | 0.82<br>0.12       |
| Excluding relapse pre-MRI-1 and MRI-2†    | 0.81 (0.40 to 1.65)       | 0.56    | $-0.08$ (0.17)<br>Slope $-0.08$ (0.05) | 0.63<br>0.11       |
| MSSS as outcome instead of EDSS           | –                         | –       | $0.28$ (0.28)<br>Slope $-0.01$ (0.02)  | 0.32<br>0.60       |
| ARMSS as outcome instead of EDSS          | –                         | –       | $0.03$ (0.28)<br>Slope $-0.02$ (0.02)  | 0.91<br>0.33       |
| PBVC worst quartile‡<br>Ref=best quartile | $7.20$ (0.69 to $75.12$ ) | $0.10$  | $-0.07$ (0.24)<br>Slope $0.26$ (0.07)  | $0.78$<br>$<0.001$ |
| Using MRI triplets instead of pairs§      | $0.92$ (0.48 to $1.77$ )  | $0.81$  | $0.12$ (0.14)<br>Slope $-0.03$ (0.04)  | $0.38$<br>$0.39$   |

Models using EDSS as the outcome were adjusted for baseline EDSS.

\*Adjust for age at MRI-2, sex, BV at MRI-1 and proportion of time spent on DMT during MRIs.

†Number of patients in CDP analysis=224 (27 reached CDP); number of patients in EDSS analysis=239.

‡Number of patients in CDP analysis=125 (10 reached CDP); number of patients in EDSS analysis=131. PBVC worst quartile were PBVC values  $\leq -0.56\%$ ; best quartile were PBVC values  $\geq 0.07\%$ .

§Number of patients in CDP analysis=263; number of patients in EDSS analysis=306.

CDP, confirmed disability progression at 6 months; EDSS, Expanded Disability Status Scale; MRI-1, first MRI in pair; MRI-2, second MRI in pair; MSSS, Multiple Sclerosis Severity Score; PBVC, percentage brain volume change; ref, reference.

We tested several MRI measures at baseline and longitudinally, and identified BV as the most consistent correlate of future EDSS scores and EDSS trajectory. Brain volume measurements are likely to be more robust to the inter-scanner and inter-protocol errors than registration-based methods assessing serial worsening over short time periods. This observation is consistent with a cross-sectional study using icobrain, that identified correlations of decreased BV and GMV with higher disability.<sup>35</sup> On the other hand, a recent study that also used clinical MRIs assessed by icobrain, but a different analytical methodology with stratification of a smaller number of patients into quartiles by BV, did not show any association between baseline brain volume and EDSS progression.<sup>21</sup> Overall, the results of the present study are consistent with previous research suggesting that low brain parenchymal fraction in patients with RRMS may be associated with increased risk of disability worsening in 5–8 years.<sup>4 7</sup>

This study has several limitations. First, there are technical limitations due to the different scanners used among study sites, with a proportion of scan pairs completed under different scanning conditions. However, our prior study showed that the variance of PBVC is acceptable in the subgroup of MRI pairs strictly selected based on automated±manual QC processes.<sup>23</sup> Second, the number of EDSS progression events in our cohort was low, and we were underpowered to detect an association between PBVC and CDP as discussed earlier. Third, we did not have access to segmentation-based measurements for other brain regions that have demonstrated associations with disability in other studies, such as corpus callosum and thalamic fraction<sup>15</sup> or lateral ventricular volume.<sup>8</sup> Fourth, we did not have data available to adjust the models for other baseline clinical and MRI measures, such as education<sup>9 21</sup> or spinal cord lesions/atrophy<sup>36</sup> which affect disability. Fifth, there are limitations to using EDSS as a disability outcome, despite it being the gold standard for assessing disability in MS.<sup>37</sup> It is problematic as it is a nonlinear ordinal scale, is biased towards mobility impairment and does not detect subclinical progression. Sixth, we did not have cognitive outcomes available, such as the Symbol Digit Modalities Test or components of the Multiple Sclerosis Functional Composite. Cognitive measures may be more appropriate clinical outcomes for grey matter atrophy, due to their strong correlation with grey matter pathology.<sup>10 11 38</sup> Seventh, there was no placebo or healthy control group to help distinguish between the natural history of brain atrophy using icobrain versus response to DMT. Eighth, we did not exclude MRIs where DMT was recently commenced, in order to eliminate the risk of capturing pseudoatrophy. However, in our sensitivity analysis, we did use the mean annualised PBVC generated from MRI triplets to improve signal-to-noise ratio for the detection of true decline in the volume of nervous tissue.

## CONCLUSION

In conclusion, while our findings do not support the use of clinically acquired MRI volumetrics for short-term prediction of confirmed disability progression, they highlight potential value in cross-sectional brain volume measures for characterising future disability state. These results should be interpreted as exploratory and hypothesis-generating, and underscore the limitations of clinical MRI data for population-level and individual-level prognostication. Further validation in larger cohorts with longer follow-up is needed to clarify the predictive value of MRI volumetrics in real-world settings.

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## REFERENCES

- 1 GBD 2016 Multiple Sclerosis Collaborators. Global, regional, and national burden of multiple sclerosis 1990–2016: a systematic

- analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 2019;18:269–85.
- 2 Brown JWL, Coles A, Horakova D, et al. Association of Initial Disease-Modifying Therapy With Later Conversion to Secondary Progressive Multiple Sclerosis. *JAMA* 2019;321:175–87.
- 3 Sormani MP, Arnold DL, De Stefano N. Treatment effect on brain atrophy correlates with treatment effect on disability in multiple sclerosis. *Ann Neurol* 2014;75:43–9.
- 4 Fisher E, Rudick RA, Simon JH, et al. Eight-year follow-up study of brain atrophy in patients with MS. *Neurology (EConicon)* 2002;59:1412–20.
- 5 Rojas JL, Patrucco L, Besada C, et al. Brain atrophy at onset and physical disability in multiple sclerosis. *Arq Neuropsiquiatr* 2012;70:765–8.
- 6 Pérez-Mirallés FC, Sastre-Garriga J, Vidal-Jordana A, et al. Predictive value of early brain atrophy on response in patients treated with interferon  $\beta$ . *Neurol Neuroimmunol Neuroinflamm* 2015;2:e132.
- 7 Bakshi R, Healy BC, Dupuy SL, et al. Brain MRI Predicts Worsening Multiple Sclerosis Disability over 5 Years in the SUMMIT Study. *J Neuroimaging* 2020;30:212–8.
- 8 Popescu V, Agosta F, Hulst HE, et al. Brain atrophy and lesion load predict long term disability in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2013;84:1082–91.
- 9 Dekker I, Eijlers AJC, Popescu V, et al. Predicting clinical progression in multiple sclerosis after 6 and 12 years. *Eur J Neurol* 2019;26:893–902.
- 10 Geurts JGG, Calabrese M, Fisher E, et al. Measurement and clinical effect of grey matter pathology in multiple sclerosis. *Lancet Neurol* 2012;11:1082–92.
- 11 Rudick RA, Lee JC, Nakamura K, et al. Gray matter atrophy correlates with MS disability progression measured with MSFC but not EDSS. *J Neurol Sci* 2009;282:106–11.
- 12 Fisniku LK, Chard DT, Jackson JS, et al. Gray matter atrophy is related to long-term disability in multiple sclerosis. *Ann Neurol* 2008;64:247–54.
- 13 Roosendaal SD, Bendfeldt K, Vrenken H, et al. Grey matter volume in a large cohort of MS patients: relation to MRI parameters and disability. *Mult Scler* 2011;17:1098–106.
- 14 Filippi M, Preziosa P, Copetti M, et al. Gray matter damage predicts the accumulation of disability 13 years later in MS. *Neurology (EConicon)* 2013;81:1759–67.
- 15 Uher T, Vaneckova M, Sobisek L, et al. Combining clinical and magnetic resonance imaging markers enhances prediction of 12-year disability in multiple sclerosis. *Mult Scler* 2017;23:51–61.
- 16 Sormani M, Rio J, Tintoré M, et al. Scoring treatment response in patients with relapsing multiple sclerosis. *Mult Scler* 2013;19:605–12.
- 17 Uher T, Horakova D, Kalincik T, et al. Early magnetic resonance imaging predictors of clinical progression after 48 months in clinically isolated syndrome patients treated with intramuscular interferon  $\beta$ -1a. *Eur J Neurol* 2015;22:1113–23.
- 18 Prosperini L, De Angelis F, De Angelis R, et al. Sustained disability improvement is associated with T1 lesion volume shrinkage in natalizumab-treated patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2015;86:236–8.
- 19 Galassi S, Prosperini L, Logoteta A, et al. A lesion topography-based approach to predict the outcomes of patients with multiple sclerosis treated with Interferon Beta. *Mult Scler Relat Disord* 2016;8:99–106.
- 20 Dekker I, Sombekke MH, Balk LJ, et al. Infratentorial and spinal cord lesions: Cumulative predictors of long-term disability? *Mult Scler* 2020;26:1381–91.
- 21 D'hooghe MB, Gielen J, Van Remoortel A, et al. Single MRI-Based Volumetric Assessment in Clinical Practice Is Associated With MS-Related Disability. *J Magn Reson Imaging* 2019;49:1312–21.
- 22 Huppertz HJ, Kröll-Seger J, Klöppel S, et al. Intra- and interscanner variability of automated voxel-based volumetry based on a 3D probabilistic atlas of human cerebral structures. *Neuroimage* 2010;49:2216–24.
- 23 Nguyen A-L, Sormani MP, Horakova D, et al. Utility of icobrain for brain volumetry in multiple sclerosis clinical practice. *Mult Scler Relat Disord* 2024;92:106148.
- 24 Jain S, Sima DM, Ribbens A, et al. Automatic segmentation and volumetry of multiple sclerosis brain lesions from MR images. *Neuroimage Clin* 2015;8:367–75.
- 25 Butzkueven H, Chapman J, Cristiano E, et al. MSBase: an international, online registry and platform for collaborative outcomes research in multiple sclerosis. *Mult Scler* 2006;12:769–74.
- 26 Smeets D, Ribbens A, Sima DM, et al. Reliable measurements of brain atrophy in individual patients with multiple sclerosis. *Brain Behav* 2016;6:e00518.

- 27 Jain S, Ribbens A, Sima DM, *et al.* Two Time Point MS Lesion Segmentation in Brain MRI: An Expectation-Maximization Framework. *Front Neurosci* 2016;10:576.
- 28 Roxburgh RHRSR, Seaman SR, Masterman T, *et al.* Multiple Sclerosis Severity Score: using disability and disease duration to rate disease severity. *Neurology (Echronicon)* 2005;64:1144–51.
- 29 Zhou Y, Claflin SB, Stankovich J, *et al.* Redefining the Multiple Sclerosis Severity Score (MSSS): The effect of sex and onset phenotype. *Mult Scler* 2020;26:1765–74.
- 30 Manouchehrinia A, Westerlind H, Kingwell E, *et al.* Age Related Multiple Sclerosis Severity Score: Disability ranked by age. *Mult Scler* 2017;23:1938–46.
- 31 Kappos L, De Stefano N, Freedman MS, *et al.* Inclusion of brain volume loss in a revised measure of 'no evidence of disease activity' (NEDA-4) in relapsing–remitting multiple sclerosis. *Mult Scler* 2016;22:1297–305.
- 32 Banwell B, Giovannoni G, Hawkes C, *et al.* Editors' welcome and a working definition for a multiple sclerosis cure. *Mult Scler Relat Disord* 2013;2:65–7.
- 33 De Stefano N, Stromillo ML, Giorgio A, *et al.* Establishing pathological cut-offs of brain atrophy rates in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2016;87:93–9.
- 34 Opfer R, Ostwaldt A-C, Sormani MP, *et al.* Estimates of age-dependent cutoffs for pathological brain volume loss using SIENA/FSL-a longitudinal brain volumetry study in healthy adults. *Neurobiol Aging* 2018;65:1–6.
- 35 Fragoso YD, Wille PR, Abreu M, *et al.* Correlation of clinical findings and brain volume data in multiple sclerosis. *J Clin Neurosci* 2017;44:155–7.
- 36 Andelova M, Uher T, Krasensky J, *et al.* Additive Effect of Spinal Cord Volume, Diffuse and Focal Cord Pathology on Disability in Multiple Sclerosis. *Front Neurol* 2019;10:820.
- 37 Kalincik T, Sormani MP, Tur C. Has the Time Come to Revisit Our Standard Measures of Disability Progression in Multiple Sclerosis? *Neurology (Echronicon)* 2021;96:12–3.
- 38 Uher T, Vanneckova M, Sormani MP, *et al.* Identification of multiple sclerosis patients at highest risk of cognitive impairment using an integrated brain magnetic resonance imaging assessment approach. *Eur J Neurol* 2017;24:292–301.