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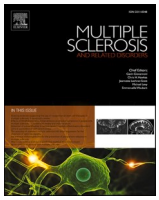

Original article

# A cross-sectional multicentre study of multishell diffusion MRI in multiple sclerosis

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*Abbreviations:* ADC, apparent diffusion coefficient; BIANCA, brain intensity abnormality classification algorithm; CI, cellularity index; CIS, clinically isolated syndrome; dMRI, diffusion MRI; EDSS, expanded disability status scale; DMTs, disease modifying treatments; DTI, diffusion tensor imaging; DWI, diffusion weighted imaging; EPI, echo planar imaging; FA, fractional anisotropy; HC, healthy control; MAGNIMS, magnetic resonance imaging in multiple sclerosis; MD, mean diffusivity; MRI, magnetic resonance imaging; MS, multiple sclerosis; NAGM, normal appearing grey matter; NAWM, normal appearing white matter; ND, neurite density; NODDI, Neurite Orientation Dispersion and Density Imaging; pwMS, persons with multiple sclerosis; RD, radial diffusivity; rD – FA, FA for restricted diffusion compartment; RSI, Restriction spectrum imaging; SE, spin echo; SMT, Spherical Mean Technique; SW, spatial weighting; TBSS, tract-based spatial statistics; WM, white matter; WML, white matter lesion.

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[1] The authors are members of the MAGNIMS network (Magnetic Resonance Imaging in MS; https://www.magnims.eu/), which is a group of European clinicians and scientists with an interest in undertaking collaborative studies using MRI methods in multiple sclerosis, independent of any other organization and is run by a steering committee whose members are: F. Barkhof, N. de Stefano, J. Sastre-Garriga (Co-Chair), O. Ciccarelli, C. Enzinger, M. Filippi, C. Gasperini, L. Kappos, J. Palace, H. Vrenken, À. Rovira, M.A. Rocca (Co-Chair) and T. Yousry

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ABSTRACT

*Background and objectives:* White matter (WM) microstructural properties from advanced multishell diffusion MRI (dMRI) have been linked to clinical disability in multiple sclerosis (MS). This multicentre study used multishell dMRI to compute WM metrics and test for differences between people with MS (pwMS) and healthy controls (HCs).

*Methods:* We included multishell dMRI data from 251 pwMS or clinically isolated syndrome (CIS) (mean age 40.7 years, 72.4 % women, 88.8 % relapsing remitting MS) at six MAGNIMS centres and 543 HCs. Eleven scalar metric maps were estimated from multishell dMRI sequences, based on diffusion tensor imaging (DTI) and restriction spectrum imaging (RSI). The maps were analysed using tract-based spatial statistics (TBSS). The diffusion output was submitted to paired sampled *t*-tests to test for case-control differences and linear regression models to test for associations with Expanded Disability Status Scale (EDSS) scores, while accounting for confounders. In a subsample from Oslo, we tested for correlations between EDSS and dMRI metrics within WM lesions.

*Results:* Significant group differences were found in nine out of eleven dMRI metrics. Linear regression models revealed significant correlations between EDSS and fractional anisotropy (FA) fast ($\beta$=-4.54, $p = 0.01$) and apparent diffusion coefficient (ADC) fast ($\beta$=10.92, $p = 8.7 \times 10^{-3}$).

*Conclusions:* Diffusion MRI based on clinically feasible multishell sequences uncovers WM group differences between pwMS and HCs, but only a selection of the advanced multishell parameters were sensitive to disability, and no statistically significant correlations with disability remained after Bonferroni correction.

## 1. Introduction

The typical white matter (WM) lesions in multiple sclerosis (MS), are shared with many disorders and conditions and lack sensitivity and specificity (Geraldes et al., 2018). The "clinico-radiological paradox", that MRI characteristics only show modest correlation with disability, may be partly explained by occult injury or damage to normal-appearing white or grey matter (NAWM/NAGM), which often remains undetected (Barkhof, 2002; Lublin et al., 2022). Conventional MRI is unable to delineate the exact neuropathological characteristics of MS lesions (Disanto et al., 2018). Hence, there is a need to develop novel imaging-based biomarkers to improve sensitivity and specificity with respect to the microstructural neuropathological processes and to improve the sensitivity to clinical symptoms and disability (Høgestøl et al., 2019).

By assessing the magnitude and direction of water diffusion in vivo, diffusion MRI (dMRI) allows for visualization and quantification of brain microstructural and physiological properties (Le Bihan, 1995). Diffusion tensor imaging (DTI) has been studied extensively in MS (Cercignani and Gandini Wheeler-Kingshott, 2019; Filippi et al., 2001), however, the interpretation of DTI parameters and other imaging parameters is challenging due to crossing fibres and large voxel constraints (Rovaris et al., 2005). In order to model and delineate the signal contributions from intra- versus extra-cellular water compartments, advanced biophysical models leverage dMRI data obtained across a range of directions and b-values. The b-value is a crucial factor in generating diffusion-weighted images as it reflects the strength and timing of the magnetic gradients applied. Higher b-values indicate stronger diffusion effects and thus, images acquired using a combination of lower and higher b-values may provide greater sensitivity to tissue changes. Advanced dMRI has technical limitations and requirements, long scan times, and the model performance in pathological tissue is unclear (Jelescu et al., 2020).

Several multi-compartment models have been developed, particularly Neurite Orientation Dispersion and Density Imaging (NODDI) (Zhang et al., 2012), the Bayesian approach (Reisert et al., 2017) and Spherical Mean Technique (SMT) (Lakhani et al., 2020). Restriction spectrum imaging (RSI) is another advanced dMRI acquisition technique that characterizes tissue microstructure at a sub-voxel level, by leveraging multiple b-values and directions (White et al., 2013). RSI has been studied in various domains including histology validation, tumour delineation, Parkinson's disease and normal aging (White et al., 2014; Brunsing et al., 2017; Hope et al., 2019; Beck et al., 2021). It has the advantage of relatively short scanning time (Hagler et al., 2019). RSI has been suggested as an alternative to NODDI in investigation of persons with MS (pwMS) (Mustafi et al., 2019). One study employed NODDI in a small clinical sample ($n = 5$) (Schneider et al., 2017). Two other studies looked at microstructural abnormalities in cortical lesions and normal appearing grey matter (Preziosa et al., 2022), and the contribution of focal lesions and normal-appearing (NA) tissue microstructural abnormalities to cognitive impairment in MS (Preziosa et al., 2023). Another study applied myelin water and multishell diffusion imaging to quantify the relative damage to myelin and axons among different lesion types, in normal-appearing tissue, and across MS clinical subtypes and healthy controls (HCs) (Rahmanzadeh et al., 2021). One study reported a correlation between disability and RSI parameters among pwMS but did not compare patients to HCs (Sowa et al., 2019). Other studies have also investigated diffusion MRI parameters in pwMS and found clinical correlations and explored disease pathology, both cross sectional and longitudinal, and also in combination with other MRI modalities (York et al., 2022; Yoon et al., 2022; Kato et al., 2022; Schiavi et al., 2023). In summary, there is a focus on advanced dMRI, highlighting its potential to explore the microstructural abnormalities in pwMS.

Our main hypothesis in this study was that applying diffusion tensor and microstructural measures on our multicentre MRI and clinical data may offer novel insights into MS. We hypothesize that applying ComBat harmonization to address site-specific variability in dMRI metrics, followed by a unified post-processing pipeline, enables us to combine data across sites and to differentiate between pwMS and HCs. Secondly, we aimed to assess the sensitivity to disability, measured with the Expanded Disability Status Scale (EDSS), across the dMRI metrics.

## 2. Materials and methods

### 2.1. Study design and participants

In this cross sectional retrospective multicentre study of pwMS, we acquired MRI and clinical data from six centres of the Magnetic Resonance Imaging in MS (MAGNIMS) consortium. The centres in alphabetical order: Hospital Clínic, IDIBAPS, Barcelona, Spain; IRCCS San Raffaele Scientific Institute, Milan, Italy; Oslo University Hospital, Oslo, Norway; University Medical Center of the Johannes Gutenberg University, Mainz, Germany; UCL Queen Square Institute of Neurology, London, United Kingdom; Vall d'Hebron University Hospital, Barcelona. Spain. Inclusion criteria were a confirmed MS or CIS diagnosis according to the 2017 McDonalds criteria (Thompson et al., 2018), age between 18 and 80 years, multishell dMRI data, and clinical and demographic information. No exclusion criteria for pwMS were added in addition to the inclusion criteria. We included 543 HCs from four sites: 505 from Oslo, 30 from Mainz, and four each from Barcelona and Milan (Fig. 1). The

HCs had no medical issues affecting brain structure and function or any known neurological disorder. Exclusion criteria for the HCs are listed in the supplementary material. The HCs and the pwMS were scanned on the same scanner at each centre using identical parameters (Richard et al., 2018). The project was open for participation in MAGNIMS from January 2021 until June 2022. MRI scans were acquired between October 2014 and September 2021.

Mean age was 40.7 years (range 19–76 years), there were 72.4 % women, 88.8 % had relapsing-remitting MS (RRMS) and mean disease duration was 6.4 years for pwMS. Disability status was measured with EDSS (median 2.0, interquartile range 1.0–3.0) (Table 1).

### 2.2. Standard protocol approvals, registrations, and patient consents

The project was approved by the Regional Committee for Medical and Health Research Ethics of South East Norway (REK2011–1846A and REK2016/102). Study participants were recruited within the MAGNIMS general framework agreement, with approvals from the regional ethical committees at all local centres. Study participants provided signed informed consent prior to study enrolment at the respective sites according to the Declaration of Helsinki.

### 2.3. MRI acquisition, processing and data preparation

All centres performed a 3T MRI scan of the brain for all participants. In Supplementary Table 1, details regarding the available DWI sequence parameters are listed. MRI data from 291 pwMS were processed. A total of 40 pwMS or CIS were removed due to MRI artifacts or missing data (28 from IDIBAPS, eight from Oslo, two from both Mainz and London), leaving 251 pwMS (121 from Oslo, 49 from Mainz, 38 from IDIBAPS, 16 from Milan, 15 from Barcelona and 12 from London). One HC from Milan was removed from image processing due to MRI artifacts.

We performed quality control, mostly visual assessments, data inspection and detection of outliers at all stages in the data processing pipeline. Image processing was done using an in-house pipeline in MATLAB (Maximov et al., 2019). In brief, the pipeline includes corrections for noise (Veraart et al., 2016), Gibbs ringing (Kellner et al., 2016), susceptibility-induced and eddy current distortions and motion using FSL function topup (topup - FslWiki (ox.ac.uk)) and eddy (eddy - FslWiki (ox.ac.uk)) (Andersson and Sotiropoulos, 2016) in the case of available opposite phase-encoding images (Jenkinson et al., 2012). Isotropic Gaussian smoothing was carried out with the FSL function *fslmaths* (Jenkinson et al., 2012) with a Gaussian kernel of 1 $mm^3$.

### 2.4. Imaging derived parameters from multishell diffusion

After the post-processing of the data, the pipeline included dMRI metrics from 11 parameters from the WM. Conventional DTI parameters acquired from b-values $\leq$ 1000, included fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), radial diffusivity (RD), which were estimated using DTIFit in FSL (FDT/UserGuide - FslWiki (ox.ac.uk). RSI parameters (FA fast, FA slow, ADC fast, ADC slow, Cellularity index, neurite density (ND) and rD-FA), were estimated using in-house Matlab tools (White et al., 2014). Cellularity index is the water signal from the spherically restricted diffusion compartment, while neurite density reflects the relative density of neuronal processes (Hope et al., 2019). rD-FA is FA from restricted diffusion compartment (White et al., 2013). ADC fast is a measure of the diffusion of extracellular water, while slow ADC is a measure of the effective diffusion coefficient of intracellular water (Sowa et al., 2019).

The diffusion metric maps were analysed using Tract-based Spatial Statistics (TBSS) (Smith et al., 2006). All volumes were aligned to the FMRI58_FA template, supplied by FSL (Smith et al., 2004), using a non-linear transformation implemented by FNIRT (Smith et al., 2004). Next, a mean FA image was obtained and thinned in order to create mean FA skeleton. Afterwards, all subject's FA values were projected onto the mean skeleton, by filling the skeleton with FA values from the nearest relevant tract centre. The skeleton-based analysis allows one to minimise confounding effects due to partial voluming and any residual misalignments originating from non-linear spatial transformations. Additionally, the TBSS derived skeleton was used for averaging of diffusion metrics over the skeleton. This procedure was performed for all diffusion metrics using tbss_non_FA script from FSL (TBSS/UserGuide - FslWiki (ox.ac.uk)).

To account for site effects across the multi-site MRI dataset, we applied the ComBat harmonization technique (Orlhac et al., 2022). ComBat is a well-established method designed to remove batch effects in high-dimensional data, such as neuroimaging, while preserving biological variability. The adjustment was performed using the ComBat function from the sva package in R, with parametric empirical Bayes to stabilize the estimates across sites.

### 2.5. Statistical analyses

For analyses and illustrations we used R (version 4.4.0) (Team, 2013), mainly adhering to common standard approaches. Diffusion MRI metrics averaged across the WM skeleton were used in paired sample *t*-tests to test for group differences among the pwMS compared with HCs. Pearson's correlation coefficients were estimated where appropriate. We

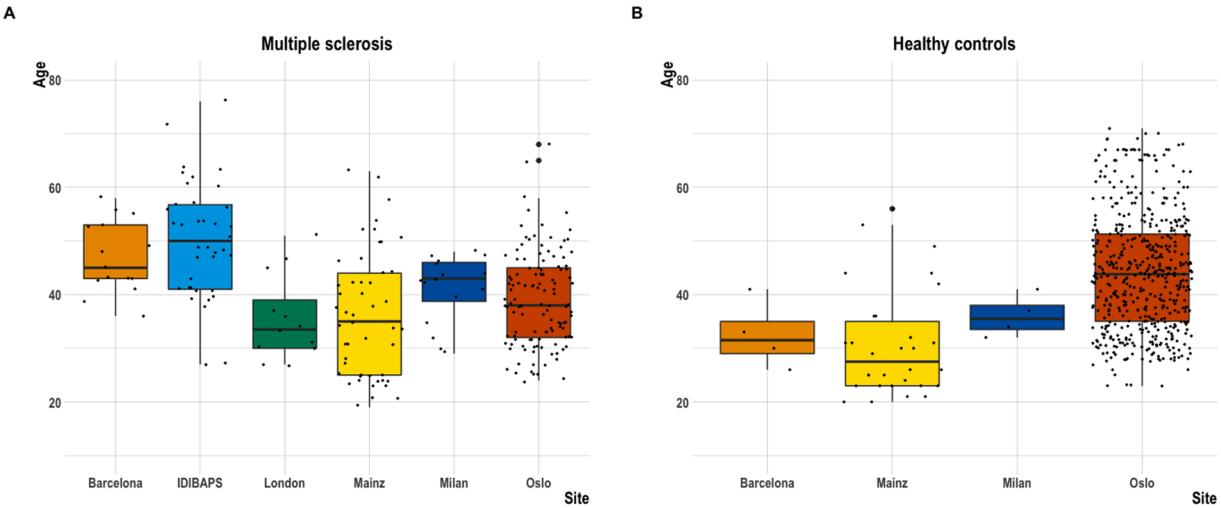


**Fig. 1.** Age distribution of the people with MS in A) and healthy controls in B) across all the participating sites.

**Table 1**
Overview of the demographic and clinical features of the complete cohort.

| *Centre* | *Barcelona* | *IDIBAPS* | *London* | *Mainz* | *Milan* | *Oslo* | *All* |
|---|---|---|---|---|---|---|---|
| N - MS | 15 | 38 | 12 | 49 | 16 | 121 | 251 |
| N - HC | 4 | 0 | 0 | 30 | 4 | 505 | 543 |
| Mean age (SD) at MRI - MS | 47.5 (±6.8) | 50.3 (±10.8) | 35.7 (±8.0) | 36.7 (±11.7) | 41.6 (±6.2) | 39.8 (±8.8) | 40.7 (±10.5) |
| Mean age (SD) at MRI - HC | 32.9 (±6.3) | – | – | 31.3 (±10.1) | 36.5 (±4.0) | 44.2 (±10.9) | 43.3 (±11.3) |
| Female - MS | 60 % | 68.4 % | 50 % | 63.7 % | 56.3 % | 60.5 % | 72.4 % |
| Female - HC | 50 % | – | – | 50 % | 75 % | 50.2 % | 55.7 % |
| Median EDSS (IQR) | 2.0 (1.0–2.5) | 3.0 (2.0–4.0) | 1.5 (0.5–2.0) | 1.0 (1.0–2.5) | 4.0 (2.0–6.5) | 2.0 (1.5–2.5) | 2.0 (1.0–3.0) |
| Disease duration, mean years (SD) | 10.7 (±5.2) | – | 1.1 (±0.1) | 4.9 (±5.7) | 8.8 (±9.2) | 6.1 (±4.6) | 6.4 (±5.6) |
| **Disease course** | | | | | | | |
| CIS, n ( %) | – | – | 2 (16.7) | – | – | – | 2 (0.8) |
| RRMS, n ( %) | 12 (80.0) | 28 (73.7) | 10 (83.3) | 49 (100) | 8 (50.0) | 116 (95.9) | 223 (88.8) |
| SPMS, n ( %) | 3 (20.0) | 10 (26.3) | – | – | 8 (50.0) | 5 (4.1) | 26 (10.4) |
| **Disease modifying treatment** | | | | | | | |
| No treatment, n ( %) | 3 (20.0) | 12 (31.6) | 6 (50.0) | 1 (2.0) | 5 (31.2) | 41 (33.9) | 68 (27.1) |
| Low-efficacy treatment, n ( %) | 5 (33.3) | 11 (28.9) | 6 (50.0) | 32 (65.3) | 4 (25.0) | 41 (33.9) | 99 (39.4) |
| *Interferon, n ( %)* | – | *2 (5.3)* | *3 (25.0)* | *7 (14.6)* | – | *3 (2.8)* | *15 (6.0)* |
| *Glatiramer acetate, n ( %)* | *1 (6.7)* | *2 (5.3)* | *1 (8.3)* | *5 (10.2)* | – | *16 (13.2)* | *25 (10.0)* |
| *Dimethyl fumarate, n ( %)* | *2 (13.3)* | *1 (2.6)* | *2 (17.0* | *17 (34.8)* | *3 (18.8)* | *2 (1.7)* | *27 (10.8)* |
| *Teriflunomide, n ( %)* | *2 (13.3)* | *6 (15.7)* | – | *1 (2.0)* | *1 (6.3)* | *20 (16.5)* | *25 (10.0)* |
| *Daclizumab, n ( %)* | – | – | – | *2 (4.0)* | – | – | *2 (0.8)* |
| High-efficacy treatment, n ( %) | 7 (46.7) | 15 (39.5) | 0 (0.0) | 16 (32.7) | 7 (43.8) | 39 (32.2) | 84 (33.5) |
| *Fingolimod, n ( %)* | *2 (13.3)* | *5 (13.2)* | – | *5 (10.2)* | *3 (18.8)* | *25 (20.7)* | *40 (15.9)* |
| *cladribine (Cladribine), n ( %)* | – | – | – | *1 (2.0)* | – | – | *1 (0.4)* |
| *Alemtuzumab, n ( %)* | *1 (6.7)* | *2 (5.3)* | – | *2 (4.0)* | *1 (6.3)* | *10 (4.0)* | *16 (6.4)* |
| *Natalizumab, n ( %)* | *1 (6.7)* | *2 (5.3)* | – | *5 (10.2)* | *2 (12.6)* | *4 (3.3)* | *14 (5.6)* |
| *Ocrelizumab, n ( %)* | *2 (13.3)* | *2 (5.3)* | – | *2 (4.0)* | *1 (6.3)* | – | *7 (2.8)* |
| *Rituximab, n ( %)* | *1 (6.7)* | *3 (7.9)* | – | *1 (2.0)* | – | – | *5 (2.0)* |
| *Ofatumumab, n( %)* | – | *1 (0.4)* | – | – | – | – | *1 (0.4)* |

MS = multiple sclerosis, HC = healthy control, MRI = magnetic resonance imaging, EDSS = Expanded disability status scale, IQR = inter quartile range, CIS = clinically isolated syndrome, RRMS = relapsing remitting multiple sclerosis, SPMS = secondary progressive multiple sclerosis.

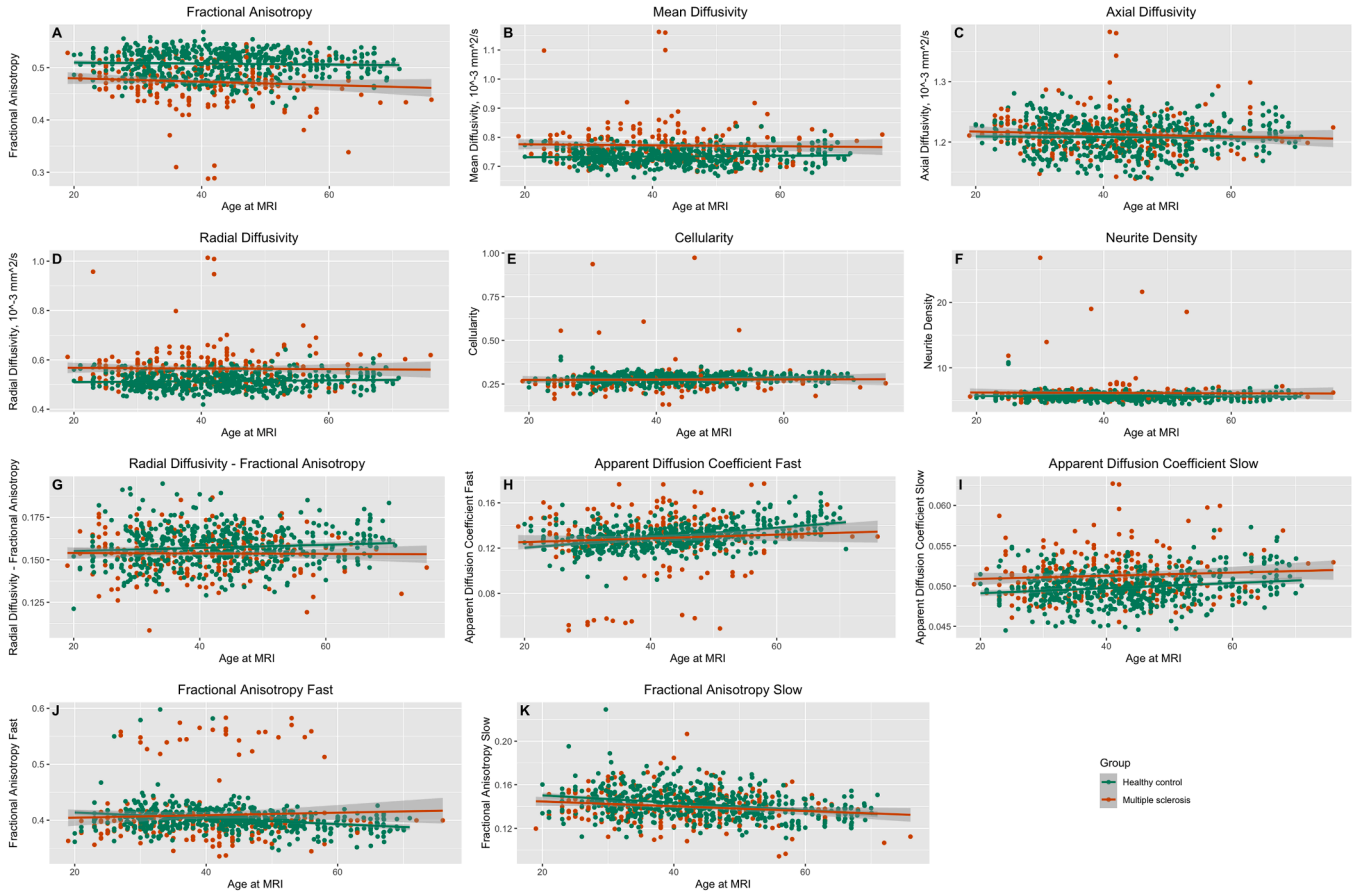


**Fig. 2.** Visualizing the resulting ComBat-adjusted multishell diffusion weighted parameters across people with MS and healthy controls.

compared the demographic and clinical features between the sites with either ANOVA for continuous variables or Chi-Square Test for categorical variables. To assess clinical correlations we ran linear regression models with only fixed effects, including relevant confounding factors, such as age and sex (Bates et al., 2014). Cohen's d was computed when appropriate to evaluate effect size. In the linear models, we also standardized the EDSS, the dMRI metrics and age by using the built in scale function in R using the formula: x-*scaled* = (x – x-*mean*) / x-*SD*, to convert each value into a z-score. Linear model setup:

$$\text{Response variable (EDSS)} \sim \text{dMRI metric} + \text{age} + \text{sex}$$

To account for multiple comparisons, we used a Bonferroni correction, which divides the significance threshold (usually 0.05) by the number of tests performed, thereby reducing the risk of false positives among all significant tests. To investigate the potential interaction between age and each predictor variable, we included an interaction term between age and the predictor variable of interest in our linear regression model.

## 3. Results

### 3.1. Case-control differences

We found significant differences between pwMS and HC for most metrics for all sites, except for Cellularity and ADC fast. Fig. 2 and Table 2 summarize the case-control differences in all dMRI metrics. The general diffusion parameters of FA (Cohen's $d = 1.16$) and RD (Cohen's $d = -1.03$) exhibited the highest effect sizes in dMRI metrics between pwMS and HC. The age trajectories for all the diffusion parameters are shown in Fig. 2 and Supplementary Figure 1, showing some outliers and for some diffusion parameters (FA fast and ADC fast) large scanner and site dependent differences also seen in Supplementary Table 2.

When the analyses were repeated within the Oslo cohort (Supplementary Table 3), the effect sizes were generally larger, especially for FA (Cohen's $d = 2.03$) and RD (Cohen's $d = -1.91$). The Oslo cohort had more robust and pronounced differences, particularly in FA and RD. Despite this, the overall patterns of diffusion abnormalities in pwMS relative to HCs remain consistent across both the entire cohort and the Oslo subgroup (Supplementary Figure 2).

### 3.2. Clinical correlations with the dMRI features

Linear regression models revealed significant associations between EDSS and FA fast ($\beta = -4.54$, $p = 0.01$) and ADC fast ($\beta = 10.92$, $p = 8.7 \times 10^{-3}$). Lower FA fast and increased ADC fast levels were associated with higher disability. None of the dMRI features remained significant after adjustment for multiple comparisons. Table 3 summarizes the results from linear regression models testing for associations between EDSS and the dMRI metrics, accounting for age, sex. We also explored the clinical correlations with disease course added as a fixed effect in Supplementary Table 4.

## 4. Discussion

In this cross-sectional study of pwMS collected at six MAGNIMS centres, we have analysed 11 dMRI parameters from multishell diffusion of the brain compared to HCs. Our main findings are significant differences in the WM between pwMS and HC for most dMRI metrics, except for cellularity and fast ADC. Our case-control findings indicate that while multi-site data offers broader generalizability, site-related variations can moderate the magnitude of observed effects. Repeating the analysis within the Oslo cohort showed that the observed trends are not

**Table 2**
ComBat adjusted dMRI metrics across multiple sclerosis subjects and healthy controls.

| | Multiple sclerosis | Healthy controls | *t* | *p* | *Cohen's d* |
|---|---|---|---|---|---|
| FA, mean (SD) | 0.47 (±0.04) | 0.51 (±0.02) | 13.0 | **$1.6 \times 10^{-31}$** | 1.16 |
| MD, mean $10^{-3}$mm$^2$/s (SD) | 0.77 (±0.06) | 0.73 (±0.03) | −9.3 | **$2.7 \times 10^{-18}$** | −0.92 |
| AD, mean $10^{-3}$mm$^2$/s (SD) | 1.21 (±0.03) | 1.21 (±0.03) | −2.1 | **0.03** | −0.17 |
| RD, mean $10^{-3}$mm$^2$/s (SD) | 0.57 (±0.07) | 0.51 (±0.03) | −10.5 | **$6.0 \times 10^{-22}$** | −1.03 |
| Cellularity, mean (SD) | 0.27 (±0.08) | 0.28 (±0.03) | 1.1 | 0.28 | 0.11 |
| ND, mean (SD) | 6.16 (±2.17) | 5.64 (±0.55) | −3.8 | **$2.2 \times 10^{-4}$** | −0.40 |
| rD – FA, mean (SD) | 0.15 (±0.01) | 0.16 (±0.01) | 4.1 | **$5.2 \times 10^{-5}$** | 0.32 |
| FA fast, mean (SD) | 0.41 (±0.05) | 0.40 (±0.02) | −2.2 | **0.03** | −0.21 |
| FA slow, mean (SD) | 0.14 (0 ± 0.01) | 0.14 (0 ± 0.01) | 2.1 | **0.04** | 0.16 |
| ADC fast, mean (SD) | 0.13 (±0.02) | 0.13 (±0.01) | 1.3 | 0.2 | 0.12 |
| ADC slow, mean (SD) | 0.05 (±0.0) | 0.05 (0.0) | 7.5 | **$4.2 \times 10^{-13}$** | −0.65 |

FA = fractional anisotropy, MD = mean diffusivity, AD = axial diffusivity, RD = radial diffusivity, ND = neurite density, ADC = apparent diffusion coefficient rD - FA= FA for restricted diffusion compartment. Significant differences in bold.

**Table 3**
Linear regression models showing correlation between EDSS and the ComBat-adjusted dMRI metrics in people with MS.

| | Linear regression model: EDSS with DWI feature, age and sex | | | | |
|---|---|---|---|---|---|
| | Estimates | *CI* | *t* | *p* | *p adjusted* |
| FA | −2.17 | −6.92 - 2.58 | −0.90 | 0.37 | 1.0 |
| MD | −1.07 | −4.04 – 1.89 | −0.71 | 0.48 | 1.0 |
| AD | 1.27 | −4.39 – 6.92 | 0.44 | 0.66 | 1.0 |
| RD | −0.73 | −3.21 – 1.74 | −0.58 | 0.56 | 1.0 |
| Cellularity | 1.39 | −0.97 – 3.74 | 1.16 | 0.25 | 1.0 |
| ND | 0.06 | −0.03 - 0.14 | 1.29 | 0.20 | 1.0 |
| rD - FA | 1.07 | −14.65 – 16.79 | 0.13 | 0.89 | 1.0 |
| **FA fast** | **−4.54** | **−8.01 – −1.07** | **−2.58** | **0.01** | **0.11** |
| FA slow | −8.73 | −21.4 0– 3.94 | −1.36 | 0.18 | 1.0 |
| **ADC fast** | **10.92** | **2.78 – 19.06** | **2.64** | **$8.7 \times 10^{-3}$** | **0.10** |
| ADC slow | 40.98 | −25.71 – 107.68 | 1.21 | 0.23 | 1.0 |

FA = fractional anisotropy, MD = mean diffusivity, AD = axial diffusivity, RD = radial diffusivity, ND = neurite density, ADC = apparent diffusion coefficient, rD - FA= FA for restricted diffusion compartment. Significant associations in bold.

driven by site-specific confounds, but the effect sizes are amplified when analyzed in a more homogeneous setting. This suggests that scanner and site variability, present in the cohort, may attenuate some of the observed group differences when multiple centers are combined.

Analyses revealed significant associations between EDSS and FA fast and ADC fast in the whole sample, where lower FA fast and increased ADC fast were associated with higher disability. The largest effect sizes for parameters showing significant differences between HC and pwMS were observed in the main diffusion metrics. However, it is important to note that only the advanced multishell diffusion parameters demonstrated significant clinical correlations with EDSS, both in the full cohort and in the Oslo cohort.

Subtle damage outside of visible lesions, in the NAWM, is also prevalent in pwMS (Cercignani and Gandini Wheeler-Kingshott, 2019). Our main finding of significant differences in the WM between pwMS and HCs is therefore not surprising. These findings also agree with previous ex-vivo spinal-cord MS studies (Grussu et al., 2015) and previous studies of brain DTI in MS (Mustafi et al., 2019; Kolasa et al., 2019). Our analysis revealed group differences in metrics assumed to be sensitive to damage to both myelin (e.g. FA, MD, RD, AD) and axons (e.g. rD-FA, ADC), but no difference between cellularity and ADC fast parameters.

Studies have investigated the relation between disability and DTI/dMRI metrics for over two decades (Filippi et al., 2001; Liu et al., 2012; Bergsland et al., 2015; Rimkus Cde et al., 2013; Bezukladova et al., 2020; Tovar-Moll et al., 2009). One study showed association between baseline mean diffusivity values and EDSS at follow-up 4 years later. Brain FA in WM tracts explained 18 % of the variance in future EDSS values (Lopez-Soley et al., 2023). Another study found associations between DTI indices in the corpus callosum and EDSS progression (Kolasa et al., 2019). We also found associations between disability and FA fast and ADC fast. These associations may be used for follow-up and prediction of disease progression in the future, however different methodology e.g. measuring changes in all WM versus specific areas of the WM and using different diffusion techniques is challenging. Future studies should use both longitudinal as well as cross sectional design and include both regional and global dMRI metrics both in GM and WM structures.

The main limitation of this study is the collection of patient samples using non-identical MRI protocols. However, multicentre studies are useful to increase statistical power, although they often increase heterogeneity. Multicentre studies require statistically complex analyses due to site-specific effects and methodological differences (Zhou et al., 2018). These factors can be even more challenging in advanced dMRI research, since added layers of complexity are introduced by differences in the implementation of MRI sequences, diffusion gradient configurations and processing pipelines. We applied harmonized analytical pipelines, both in the imaging analyses and the statistical methods, and we could not identify differences in acquisition parameters that could explain the difference in the resulting data (Maximov et al., 2019). However, an unexpected finding like the lack of difference in cellularity between pwMS and HC, may be related to methodologic factors related to the use of standard dMRI sequences instead of the RSI acquisitions (Pinto et al., 2020). Common statistical and post-processing pipelines are needed to be able to adapt to many different diffusion acquisitions and reduce variability by the abovementioned acquisition variability.

A limitation of this study is the lack of differentiation between the NAWM and WML, since the study's original design did not include FLAIR sequence or lesion masks, and it was not feasible to expand this analysis at a later stage for the whole sample. Future studies of advanced diffusion in NAGM could help elucidate progression of the disease in different forms (i.e. relapsing versus progressive and smouldering MS) (Eshaghi et al., 2018). Furthermore, relying solely on EDSS to measure disability does not capture the full spectrum of MS-related disability. Future studies should also aim to include assessments of cognition, fatigue, and patient-reported outcomes to provide a more comprehensive evaluation (Giovannoni et al., 2016). A precise characterization of lesions, including lesion types and locations, could yield more findings in future studies. Lastly, the variable number of subjects and controls included at each site may also be a limitation of this study.

## 5. Conclusions

This study provides insight into microstructural changes both in WM in the brain of pwMS. This adds important information to the growing body of literature of the utility of advanced dMRI in pwMS. Our findings suggest that a majority of multishell diffusion parameters in the WM of the brain significantly differ between pwMS and HCs. Correlations between disability and the imaging parameters were found, but after correcting for multiple testing with Bonferroni correction no significant correlations with disability remained. Restricting the analyses to one clinical cohort, increased the correlations for some diffusion parameters. More studies using similar or improved pipelines for acquisition, post-processing and extraction of dMRI metrics are needed.

## CRediT authorship contribution statement

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## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Hanne Flinstad Harbo reports financial support was provided by South Eastern Regional Health Authority of Norway. Sergiu Groppa reports financial support was provided by Deutsche Forschungsgemeinschaft. Einar August Hoegestoel reports a relationship with Biogen that includes: speaking and lecture fees. Einar August Hoegestoel reports a relationship with Merck that includes: funding grants and speaking and lecture fees. Einar August Hoegestoel reports a relationship with Sanofi-Genzyme that includes: board membership and speaking and lecture fees. Piotr Sowa reports a relationship with Merck that includes: speaking and lecture fees and travel reimbursement. Elisabeth Gulowsen Celius reports a relationship with BMS that includes: speaking and lecture fees. Elisabeth Gulowsen Celius reports a relationship with Biogen that includes: speaking and lecture fees. Elisabeth Gulowsen Celius reports a relationship with Janssen that includes: speaking and lecture fees. 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*Declaration of generative AI and AI-assisted technologies in the writing process*

During the preparation of this work the author used ChatGPT 4o in order to improve readability. After using this tool, the author reviewed and edited the content as needed and take full responsibility for the content of the publication.

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*Data availability statement*

The dataset used and analyses during the current study are available from the corresponding author and the respective local project leaders upon on reasonable request.

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Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2025.106435.

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