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17-year trends in radiological disease burden of multiple sclerosis at presentation

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ABSTRACT

At a population level, MS disease progression appears to have slowed in recent years. This study assessed whether earlier detection of people with potentially milder radiological disease is contributing to these observed trends in MS disease course. The time from MS symptom-onset to the initial brain MRI of the study population alongside the white matter lesion count and volume on this scan had not significantly changed over 17 years (2006 – 2023). The age-related MS Severity Score significantly decreased, and the MS Severity Score remained unchanged throughout the study period. These findings suggest that earlier detection of disease or lower radiological disease burden at presentation do not explain improved outcomes in MS.

1. Background

The progression of physical disability in multiple sclerosis (MS), as measured by the Expanded Disability Status Scale (EDSS) score, appears to have slowed down over recent years (Koch-Henriksen and Magyari, 2021). This trend has been attributed to different factors, such as earlier diagnosis of MS—enabling early initiation of disease-modifying therapies (DMTs) at lower disability levels (Portaccio et al., 2024), the availability of more effective DMTs, better access to healthcare, and adoption of a healthier lifestyle by people with MS (pwMS) (Koch-Henriksen and Magyari, 2021; Stahmann et al., 2024). Improvements in MS diagnosis, through revisions of the MS diagnostic criteria, may have also increased the proportion of people at earlier stages of the disease and with lower levels of disability in recent cohorts of pwMS, influencing MS prognosis through the 'Will Rogers Phenomenon' (Koch-Henriksen and Magyari, 2021; Sormani, 2009). The current pattern of early treatment with DMTs, especially high efficacy DMTs, is thought to have delayed disease progression, mostly through prevention of relapses rather than progression independent of relapses or radiological disease activity. Recognising the factors contributing to the observed trends in MS disease progression can guide the development of targeted interventions to improve its prognosis (Koch-Henriksen and Magyari, 2021; Stahmann et al., 2024).

Lack of awareness of MS symptoms among the public and healthcare professionals and limited access to healthcare or magnetic resonance imaging (MRI) could delay MS diagnosis and, as a result, negatively impact its prognosis. It is unclear whether earlier identification of MS symptoms and improved access to MRI in recent years have affected MS prognosis (Koch-Henriksen and Magyari, 2021; Portaccio et al., 2024; Solomon et al., 2023; Number of MRI Scans Per Year Worldwide: Overview of global MRI utilization, 2024).

Studies have shown that a higher burden of brain white matter lesions on the baseline MRI of people with clinically isolated syndrome or relapsing-remitting MS predicts long-term physical disability and conversion to secondary progressive MS (Rocca et al., 2024; Tintore et al., 2020; Lomer et al., 2024; McNicholas et al., 2017). This study aimed to assess whether, in recent years, pwMS have been presenting earlier on and with a reduced radiological disease burden following the onset of MS-related symptoms, which could be contributing to the reported improved prognosis in MS.

2. Methods

2.1. Study setting and population

This retrospective cross-sectional study includes a randomly selected sample of pwMS from Nottingham University Hospitals NHS Trust who had their 'initial brain MRI' between 1st June 2006 and 30th June 2023.

The 'initial brain MRI' refers to a person's earliest brain MRI scan, at the time of clinical and/or radiological disease presentation, that led to a

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final diagnosis of MS by the start of data collection on 1st October 2023. The diagnosis had been made by the treating neurologist based on established MS diagnostic criteria at the time, i.e., the 2005, 2010, or 2017 revised MS diagnostic criteria (McNicholas et al., 2017).

2.2. Ethics and approvals

PwMS who had provided informed consent, through the UK MS Register (online) or the DELIVER-MS (written) studies, for the use of their clinical data for research purposes were included in this study (Middleton et al., 2018; Ontaneda et al., 2020). The UK MS Register was approved by the South West – Central Bristol Research Ethics Committee (16/SW/0194) on 2nd August 2016 and the DELIVER-MS study (NCT03535298) was approved by the Wales Research Ethics Committee 2 (18/WA/0239) on 3rd August 2018.

2.3. Clinical data

The electronic clinical records of pwMS were reviewed to collect the following data: age at the time of initial brain MRI, sex, the time interval from the onset of typical MS-related symptoms (including unilateral optic neuritis, focal supratentorial syndrome, focal brainstem or cerebellar syndrome, or partial myelopathy) (Thompson et al., 2018) to the initial brain MRI, clinical presentation at the time of the initial brain MRI, most recent EDSS score, the time interval from the initial brain MRI to the first DMT following a diagnosis of MS, the time interval from the first DMT to the most recent EDSS score, and the types of DMTs.

For pwMS who had a typical clinical presentation of MS on the day of or after their initial brain MRI, the time interval from MS symptom-onset to the initial brain MRI was considered zero. The EDSS scores were converted into the age-related MS severity score (ARMSS) and the updated MS severity score (MSSS) (Manouchehrinia et al., 2017; Manouchehrinia et al., 2024; Roxburgh et al., 2005). PwMS were grouped into those who had 1) not been treated with any DMTs, 2) been treated with *only* low-efficacy DMTs (including interferon betas, glatiramer acetate, dimethyl fumarate, diroximel fumarate, and/or teriflunomide,), or 3) been treated with *at least one* high-efficacy DMT (including fingolimod, siponimod, ponesimod, cladribine, alemtuzumab, natalizumab, ocrelizumab, and/or ofatumumab) (Apóstolos et al., 2022; Samjoo et al., 2021; Samjoo et al., 2023).

2.4. MRI data and analysis

Brain white matter lesions, with a long-axis diameter of more than 0.2 cm, were manually identified on axial T2-weighted images of the initial brain MRI and confirmed using sagittal FLAIR images of the same scan. The count of brain white matter lesions was recorded. The slice thickness of each scan was also recorded.

The total volume of brain white matter lesions was measured (in cm^3) on axial T2-weighted images of each scan using an in-house manual image analysis methodology (Fig. 1) (Vernon, 2021). Each lesion was treated as an ellipsoid and its volume (in cm^3) was calculated using the following formulae: $V = \frac{4}{3}\pi abc$, where a = ½ long-axis diameter on axial T2-weigheted images, b = ½ diameter of the axis perpendicular to the long-axis on the same image, and c = ½ the number of slices in which the lesion was visible multiplied by the slice thickness. U-shaped lesions were measured as two ellipsoids for calculating their volume (Vernon, 2021).

A medical student (MT), blinded to the date of the initial brain MRI, performed the MRI analysis after being trained by two neurologists (AG and NE) who also reviewed the output.

2.5. Statistical analysis

Continuous variables with a normal distribution are presented as mean (standard deviation; SD). Continuous variables with non-normal distribution and ordinal variables are presented as median (interquartile range, IQR). Normality was assessed by visual inspection of the data using histograms for each continuous variable. Categorical variables are presented as counts and percentages.

Generalised linear models (GLMs) were used to estimate changes in lesion count (with Negative Binomial distribution), lesion volume, time from MS symptom-onset to the initial brain MRI, and ARMSS and MSSS scores (with Gamma distribution and Log link function) for each year. The results are presented as exponentiated B coefficients (Exp(B)) and their 95 % confidence intervals (95 % CI).

The GLMs for lesion count and volume were adjusted for age, sex, time from MS symptom-onset to the initial brain MRI, and the slice thickness of the scans. To avoid exclusion of cases with no lesions on the initial brain MRI from the analysis—for example, when a person presented with transverse myelitis at the time of their initial brain MRI without brain white matter lesions, 1 cm^3 was added to the lesion volume for all pwMS. One day was added to time from MS symptom-onset to the initial brain MRI for the same reason. The GLM for time from MS

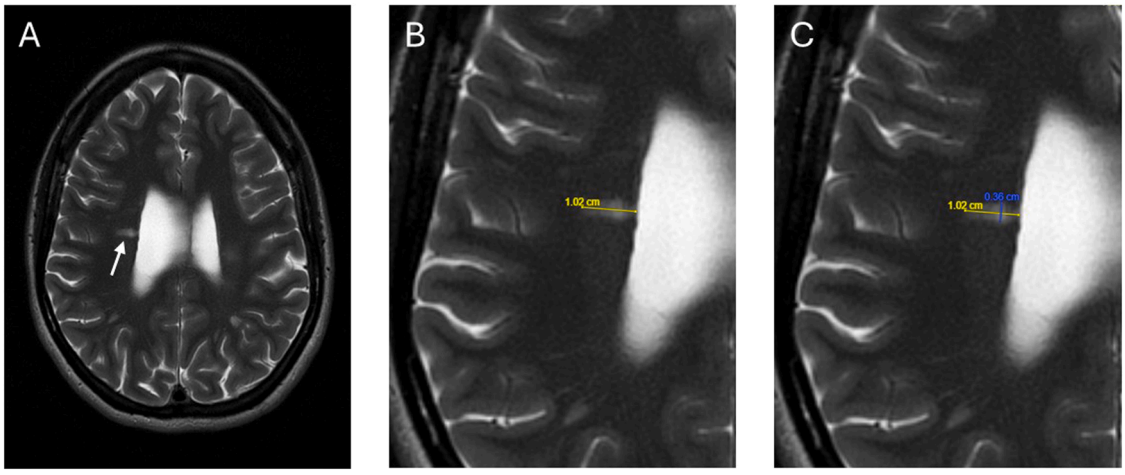

Fig. 1. Manual measurement of the volume of brain white matter lesions on axial T2-weighted magnetic resonance images, using the following formulae: $V = 4/3$ πabc, where a = ½ long-axis diameter, b = ½ diameter of the axis perpendicular to the long-axis, and c = ½ the number of slices in which the lesion is visible multiplied by the slice thickness. (A) A periventricular white matter lesion on an axial T2-weighted brain image (*white arrow*), (B) diameter of its long-axis (*yellow line; 1.02 cm*), and (C) diameter of the axis perpendicular to the long-axis (*blue line; 0.36 cm*).

symptom-onset to the initial brain MRI was adjusted for age and sex. The GLM for ARMSS was adjusted for sex and DMT group. The GLM for MSSS was adjusted for age, sex, and DMT group.

In a sensitivity analysis, the study population was divided into three groups based on the revised MS diagnostic criteria available at the time of their initial brain MRI, i.e., 1) from 1st June 2006 to 29th December 2010 (2005 MS diagnostic criteria group), 2) from 30Th December 2010 to 21st December 2017 (2010 MS diagnostic criteria group), and 3) from 22nd December 2017 to 30th June 2023 (2017 MS diagnostic criteria group) (McNicholas et al., 2017; Thompson et al., 2018). The Kruskal-Wallis H test was used to compare the lesion count, lesion volume, time from MS symptom-onset to the initial brain MRI, time from the initial brain MRI to the first DMT (continuous variables with non-normal distribution), and ARMSSS and MRSS scores (ordinal variables) between the three groups. χ^2 test (Chi-squared test) was used to compare the slice thickness (4 mm or 5 mm) across the three groups.

The statistical analysis was performed using IBM SPSS Statistics Version 29.0.2.0 (20).

3. Results

The initial brain MRI of 223 pwMS, between 14th June 2006 and 10th June 2023, were included in the study. The characteristics of the study population are presented in Table 1. The median (IQR) number of scans per year was 15 (12 – 18). The numbers of scans in the 2005, 2010, and 2017 MS diagnostic groups were 85, 73, and 65, respectively. All scans had been acquired on 3 Tesla MRI scanners. A significantly higher proportion of the 2017 group (91 %) had scans with a thinner slice (i.e., 4 mm) compared to the 2010 (73 %) and 2005 (30 %) groups ($p < 0.001$; Table 2).

The lesion count and volume on the initial brain MRI had not significantly changed over 17 years (Exp(B), 95 % CI = 0.991, 0.958 – 1.024 and 0.966, 0.926 – 1.008 per year, respectively; Fig. 2). There was no significant difference in lesion count ($p = 0.585$) or lesion volume ($p = 0.681$) between the three MS diagnostic criteria groups (Table 2 and Fig. 3).

The time from MS symptom-onset to the initial brain MRI decreased over 17 years, but it was not statistically significant (Exp(B), 95 % CI = 0.967, 0.929 – 1.007; Fig. 2). The time from MS symptom-onset to the initial brain MRI was not significantly different between the three MS diagnostic criteria groups ($p = 0.184$; Table 2 and Fig. 3).

The ARMSS score had significantly decreased over 17 years (Exp(B), 95 % CI = 0.969, 0.951 – 0.986 per year; Fig. 2), but the reduction in the MSSS score was not statistically significant (Exp(B), 95 % CI = 0.984, 0.967 – 1.001 per year). The ARMSS score decreased from the 2005 group to the 2017 group ($p < 0.001$; Table 2 and Fig. 3), but the MSSS score was not significantly different between the three groups ($p = 0.117$; Table 2 and Fig. 3). The time form the initial brain MRI to the first DMT ($n = 173$) had significantly decreased from the 2005 group to the 2017 group ($p < 0.001$; Table 2 and Fig. 3).

4. Discussion

There is extensive evidence that a higher burden of brain white matter lesions on the baseline MRI predicts worse disease outcomes in MS (Rocca et al., 2024; McNicholas et al., 2017; Genovese et al., 2019; Van Wijmeersch et al., 2022). It has been suggested that recent cohorts of pwMS have a better disease course than older cohorts (Koch-Henriksen and Magyari, 2021). In theory, one would expect that a modern population of people presenting with radiological evidence of MS for the first time will have a lower load of brain white matter lesions than those who presented decades ago. Recent improvements in MS awareness, access to healthcare, and MRI availability (Koch-Henriksen and Magyari, 2021; Portaccio et al., 2024) —potentially leading to earlier detection of radiological disease, strengthens this hypothesis.

In our study, pwMS who had their initial brain MRI more recently showed lower levels of physical disability compared to those who presented earlier within the 17-year study period, which is in keeping with the trends in MS disease course reported in the literature.[1, 2]Contrary to expectations, this study found no reduction in the MRI burden of brain white matter lesions at the time of first clinical or radiological presentation of MS over 17 years. The interval from the onset of MS-related symptoms to first presentation—which led to acquisition of a brain MRI and a final diagnosis of MS, had also not decreased over 17 years.

Revisions of the MS diagnostic criteria throughout the 17-year study period could have affected the level of physical disability at which people were diagnosed with MS. People who presented in recent years were more likely to have an earlier diagnosis of MS and an improved prognosis due to, for example, earlier initiation of DMTs. To account for this, the study population was divided into three groups based on the MS diagnostic criteria available at the time of the initial brain MRI (i.e., the 2005, 2010, or 2017 MS diagnostic criteria). Comparison of the brain white matter lesion load, the interval from MS symptom-onset to the initial brain MRI, and physical disability levels yielded the same findings as above.

Table 1
Characteristics of the study population ($n = 223$).

Age at initial brain MRI, mean (SD), years	37.5 (11.2)
Female, n (%)	168 (75.3)
Time from MS symptom-onset to initial brain MRI, median (IQR), days	122 (26 – 568)
Time from MS symptom-onset to EDSS measurement, median (IQR), years	10 (5 – 14)
Time from initial brain MRI to first DMT, median (IQR), days	327 (159 – 756)
Most recent EDSS score, median (IQR)	3.5 (1.5 – 6)
ARMSS score, median (IQR)	5.69 (2.71 – 7.37)
MSSS, median (IQR)	6.08 (2.85 – 7.92)
Diagnosis at initial brain MRI, n (%)	
CIS	34 (15.2 %)
RRMS	174 (78 %)
SPMS	1 (0.4 %)
PPMS	14 (6.3 %)
Diagnosis at time of EDSS score, n (%)	
CIS	–
RRMS	184 (82.5)
SPMS	29 (13)
PPMS	10 (4.5)
Lesion count, median (IQR), n	13 (6 – 24)
Lesion count groups, n (%)	
0	7 (3.1)
1 – 3	26 (11.7)
4 – 9	54 (24.2)
≥ 10	136 (61)
Lesion volume, median (IQR), cm^3	0.74 (0.24 – 1.74)
DMT, n (%)	
None	57 (26)
Low efficacy [a]	77 (35)
High efficacy [b]	89 (40)
Presentation at initial brain MRI, n (%)	
Unknown	1 (0.4)
Sensorimotor symptoms [c]	138 (61.9)
Optic neuritis	44 (19.7)
Brainstem or cerebellar syndrome [d]	40 (17.9)

ARMSS: Age-Related Multiple Sclerosis Severity, CIS: Clinically Isolated Syndrome, DMT: Disease-Modifying Therapy, EDSS: Expanded Disability Status Scale, IQR: Inter-Quartile Range, MRI: Magnetic Resonance Imaging, MSSS: Multiple Sclerosis Severity Score, PPMS: Primary Progressive Multiple Sclerosis, RRMS: Relapsing-Remitting Multiple Sclerosis, SD: Standard Deviation, SPMS: Secondary Progressive Multiple Sclerosis.

[a] Included beta-interferons, daclizumab, dimethyl fumarate, diroximel fumarate, glatiramer acetate, methotrexate, and teriflunomide.

[b] Included alemtuzumab, cladribine, fingolimod, natalizumab, ocrelizumab, ofatumumab, ponesimod, and Siponimod.

[c] Included supratentorial and infratentorial lesions.

[d] Included symptoms such as vertigo, imbalance, and diplopia.

Table 2
Characteristics of the 2005, 2010, and 2017 MS Diagnostic Criteria groups.

	2005 $n = 85$	2010 $n = 73$	2017 $n = 65$
Age at initial brain MRI, mean (SD), years	36.8 (11.5)	38.0 (12.7)	35.9 (8.9)
Female, n (%)	66 (77.6)	54 (74.0)	48 (73.8)
Time from MS symptom-onset to initial brain MRI, median (IQR), days	113 (23 – 723)	162 (42 – 635)	100 (18 – 361)
Time from MS symptom-onset to EDSS measurement, median (IQR), years	14.6 (13.2 - 16.1)	8.8 (6.4 - 11.9)	3.4 (1.9 - 5.0)
Time from initial brain MRI to first DMT, median (IQR), days	839 (285 – 1478)	479 (164 – 720)	199 (101 – 299)
Most recent EDSS score, median (IQR)	6 (3 – 6.5)	4 (1.5 - 6)	2 (1 – 3)
ARMSS score, median (IQR)	6.64 (4.63 – 8.17)	5.88 (2.71 – 7.76)	4.23 (2.36 – 6.11)
MSSS, median (IQR)	6.96 (3.84 – 8.25)	6.73 (2.80 – 8.31)	5.23 (2.90 – 7.26)
Diagnosis at initial brain MRI, n (%)			
CIS	14 (16.5)	10 (13.7)	10 (15.3)
RRMS	64 (75.2)	56 (76.7)	54 (83.1)
SPMS	0 (0.0)	1 (1.4)	0 (0.0)
PPMS	7 (8.2)	6 (8.2)	1 (1.5)
Diagnosis at time of EDSS score, n (%)			
CIS	0 (0.0)	0 (0.0)	0 (0.0)
RRMS	61 (71.8)	60 (82.2)	63 (96.9)
SPMS	20 (23.5)	8 (11.0)	1 (1.5)
PPMS	4 (4.7)	5 (6.8)	1 (1.5)
Lesion count, median (IQR), n	11 (5 – 24.5)	15 (7.5 – 24.5)	12 (6.5 – 23.5)
Lesion volume, median (IQR), cm^3	0.83 (0.21 – 1.92)	0.66 (0.30 – 1.72)	0.57 (0.20 – 1.56)
DMT, n (%)			
None	23 (27.1)	21 (28.8)	13 (20.0)
Low efficacy [a]	33 (38.8)	31 (42.5)	13 (20.0)
High efficacy [b]	29 (34.1)	21 (28.8)	39 (60.0)
Presentation at initial brain MRI, n (%)			
Unknown	0 (0.0)	0 (0.0)	1 (1.5)
Sensorimotor symptoms [c]	56 (65.9)	45 (61.6)	37 (56.9)
Optic neuritis	11 (12.9)	14 (19.2)	19 (29.2)
Brainstem or cerebellar syndrome [d]	18 (21.2)	14 (19.2)	8 (12.3)

ARMSS: Age-Related Multiple Sclerosis Severity, CIS: Clinically Isolated Syndrome, DMT: Disease-Modifying Therapy, EDSS: Expanded Disability Status Scale, IQR: Inter-Quartile Range, MRI: Magnetic Resonance Imaging, MSSS: Multiple Sclerosis Severity Score, PPMS: Primary Progressive Multiple Sclerosis, RRMS: Relapsing-Remitting Multiple Sclerosis, SD: Standard Deviation, SPMS: Secondary Progressive Multiple Sclerosis.

[a] Included beta-interferons, daclizumab, dimethyl fumarate, diroximel fumarate, glatiramer acetate, methotrexate, and teriflunomide.

[b] Included alemtuzumab, cladribine, fingolimod, natalizumab, ocrelizumab, ofatumumab, ponesimod, and Siponimod.

[c] Included supratentorial and infratentorial lesions.

[d] Included symptoms such as vertigo, imbalance, and diplopia.

The interval between the first radiological presentation to the initiation of treatment with DMTs reduced from the 2005 MS diagnostic criteria group to the 2017 group. The use of high efficacy DMTs had almost doubled in the 2017 MS diagnostic group compared to the 2005 and 2010 groups. These findings suggest that earlier diagnosis and treatment of MS and the growing use of high efficacy DMTs may explain some of the improvements in disease outcomes in recent years. Other factors such as advances in neurorehabilitation and adoption of a healthier lifestyle may have also played a role (Koch-Henriksen and Magyari, 2021; Portaccio et al., 2024; Stahmann et al., 2024; Ontaneda et al., 2020; Giovannoni et al., 2016; Amatya et al., 2019). However, the current study was not designed to assess the effect of the above factors on MS prognosis.

These findings suggest that earlier detection of white matter lesions on brain MRI and identification of cases with a lower radiological disease burden does not explain recent improvements in physical disability outcomes in MS.

4.1. Limitations

MRI scanners and techniques have clearly advanced over the past two decades, resulting in improved image quality in modern cohorts of pwMS. All the scans in the current study were performed using 3 Tesla MRI, but recent scans had images with a thinner slice. Although, the study adjusted for changes in slice thickness when analysing trends of the burden of brain white matter lesions over time, other variables that could have influenced image quality were not accounted for. Some white matter lesions of earlier scans may have not been identified due to their poorer image quality, while most lesions on recent scans would have been detected due to their higher quality. This could have resulted in an apparently consistent white matter lesion load over 17 years. Studies with a larger sample size, powered to detect changes in the brain white matter lesion load while accounting for variations in scanner types and image quality, are required for generalisable results.

Age-adjusted EDSS scores (i.e., ARMSS) seems to perform better when comparing levels of physical disability across a heterogeneous population of pwMS than EDSS scores adjusted for disease duration (i.e., MSSS), as disease duration can highly depend on subjective recall of historical MS symptoms. This could explain the finding in this study that ARMSS decreased over 17 years but not MSSS. A larger sample size is required to detect changes in MSSS due to its variability. Also, the longer follow-up of people who presented earlier may have contributed to higher ARMSS, but not MSSS which is adjusted for disease duration, in earlier years. However, inclusion of disease duration as a covariate in the analysis resulted in a similar finding.

It is known that the location of white matter lesions is an important determinant of physical disability and disease progression, for example, spinal cord lesions predict worse disease outcomes (Rocca et al., 2024; van der et al., 2018; Granberg et al., 2013; Minneboo et al., 2004; AlTokhis et al., 2022). This study was not powered to take into account the location of white matter lesions in the analysis.

5. Conclusion

This study suggests that earlier detection of white matter lesions on brain MRI and identification of cases with a lower radiological disease burden do not explain recent improvements in physical disability outcomes in MS. Larger studies that account for advancements in MRI techniques and scanners are needed to confirm these findings. The role of other potential factors contributing to the observed improvements in MS prognosis also needs to be further investigated.

Ethical considerations

The UK MS Register was approved by the South West – Central Bristol Research Ethics Committee (16/SW/0194) on 2/08/2016 and the DELIVER-MS study (NCT03535298) was approved by the Wales Research Ethics Committee 2 (18/WA/0239) on 3/08/2018.

Consent to participate

Participants of the UK MS Register and DELIVER-MS study had, respectively, provided online and written informed consent for the use of their data for research purposes.

Consent for publication

Not applicable.

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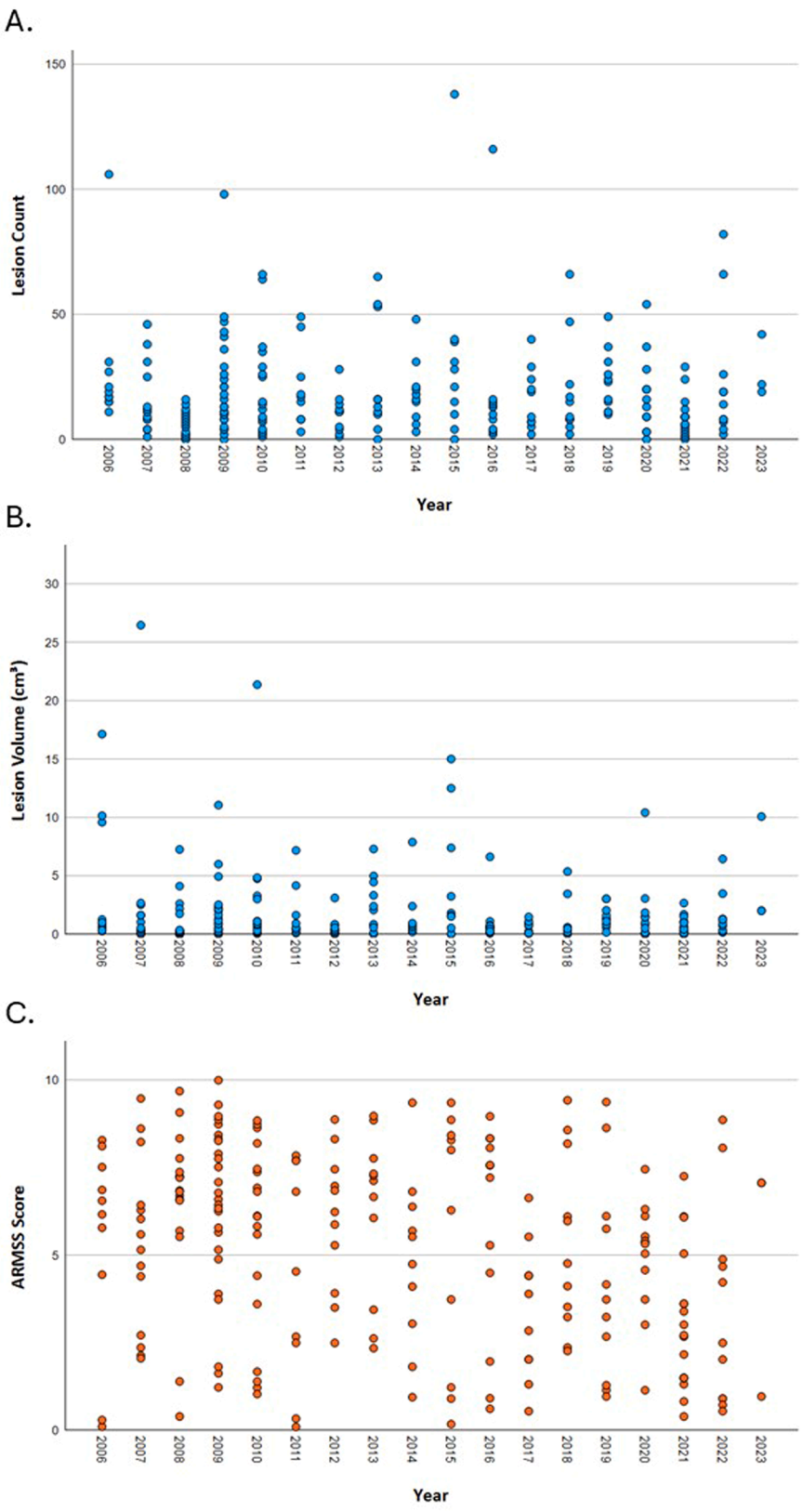

Fig. 2. The trends in white matter lesion count (A) and volume (B) on the initial brain MRI of the study population and their ARMSS score (C), based on the most recent EDSS score, from 2006 to 2023. ARMSS: Age-related Multiple Sclerosis Severity, EDSS: Expanded Disability Status Scale, MRI: Magnetic Resonance Imaging.

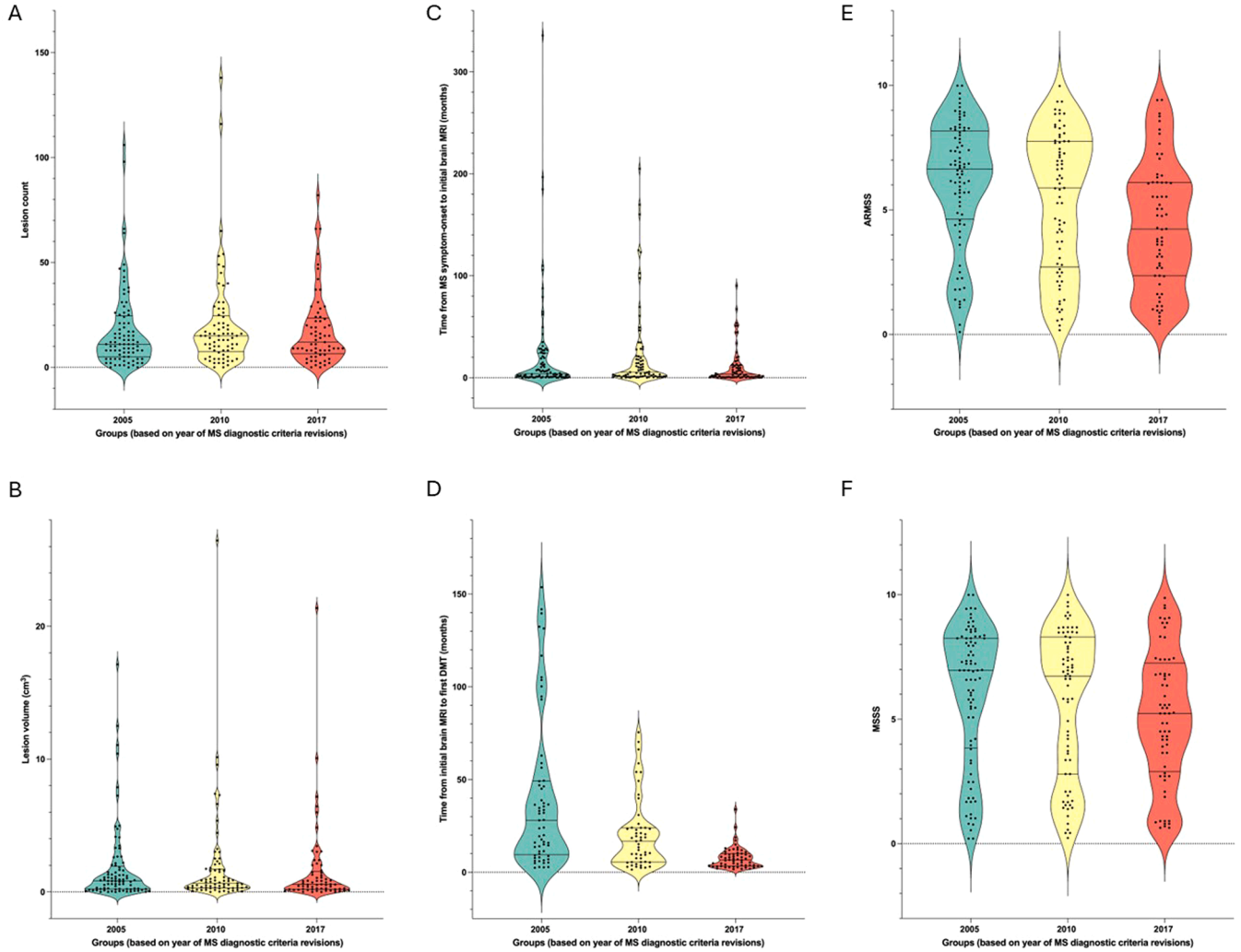

Fig. 3. Violin plots depicting the distribution of the white matter lesion count (A) and volume (B) on the initial brain MRI, the time from MS symptom-onset to the initial brain MRI (C), the time from the initial brain MRI to the first DMT (D), and ARMSSS (E) and MRSS (F) scores of the three study groups, based on the revised MS diagnostic criteria available at the time of initial brain MRI. The violin plots were generated using GraphPad Prism which uses a concept known as kernel density estimation (KDE). Apparent negative values reflect KDE smoothing and do not indicate actual negative data. ARMSS: Age-related Multiple Sclerosis Severity, DMT: Disease-Modifying Therapy, EDSS: Expanded Disability Status Scale, MRI: Magnetic Resonance Imaging.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

CRediT authorship contribution statement

Millie Taylor: Writing – original draft, Investigation, Formal analysis, Data curation. **Omar Alrawashdeh:** Investigation, Data curation. **Nikos Evangelou:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Afagh Garjani:** Writing – review & editing, Validation, Supervision, Methodology, Formal analysis.

Declaration of competing interest

Millie Taylor: Nothing to declare.

Omar Alrawashdeh: Nothing to declare

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Afagh Garjani: Nothing to declare.

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