The evolving contribution of MRI measures towards the prediction of secondary progressive multiple sclerosis

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Short Title
Predictive Outcome Models in MS

Key Words
multiple sclerosis, neurodegeneration, inflammation, pathogenesis, clinical outcomes, predictive models

Abstract

Background: In multiple sclerosis (MS), both lesion accrual and brain atrophy predict clinical outcomes. However, it is unclear whether these prognostic features are equally relevant throughout the course of MS. Among 103 participants recruited following a clinically isolated syndrome (CIS) and followed up over 30 years, we explored: (1) whether white matter lesions were prognostically more relevant earlier and brain atrophy later in the disease course towards development of secondary progressive disease; (2) if so, when the balance in prognostic contribution shifts; and (3), whether optimised prognostic models predicting secondary progressive disease should include different features dependent on disease duration.

Methods: Binary logistic regression models were built using age, gender, brain lesion counts and locations, and linear atrophy measures (third ventricular width [TVW] and medullary width [MEDW]) at each timepoint up to 20 years, using either single timepoint data alone or adjusted for baseline measures.

Results: By 30 years, 27 participants remained CIS, while 60 had MS (26 SPMS, 16 MS-related death). Lesions counts were prognostically significant from baseline and at all later timepoints, while linear atrophy measure models reached significance from 5 years. When adjusted for baseline, in combined MRI models including lesion count and linear atrophy measures, only lesion counts were significant predictors. In combined models including relapse measures, expanded disability status scale (EDSS) scores and MRI measures, only infratentorial lesions were significant predictors throughout.

Conclusions: While SPMS progression is associated with brain atrophy, in predictive models only infratentorial lesions were consistently prognostically significant.

Key messages

What is already known on this topic

Both MRI measures of white matter lesion accrual and atrophy predict clinical outcomes in people with multiple sclerosis. However, it is unclear whether both are equally relevant in predicting long-term outcomes (20 years or more) following a first relapse and, in particular, the development of secondary progressive disease. We investigated this, anticipating that white matter lesions may be more relevant earlier, and atrophy measures later, into the disease course.

What this study adds

We found that, while brain atrophy (measured using linear distance between features visible on conventional MRI scans and hence feasible in routine clinical practice) was prognostically relevant to the prediction of secondary progressive disease later in the clinical course of multiple sclerosis, lesion counts were of early and enduring relevance over time. When considered alongside clinical features in predictive models, the only MRI feature that clearly contributed was the presence of infratentorial lesions.

How this study might affect research, practice, or policy

Our findings reinforce previous observations that infratentorial lesions predict worse clinical outcomes and onset of secondary progressive disease, whilst further demonstrating their prognostic relevance even up to 20 years after first symptom onset. They also suggest that linear brain atrophy measures have little to add as prognostic markers in clinical practice.

Introduction

Multiple sclerosis (MS) is clinically highly heterogenous. While some people accrue substantial disability or have a significantly shortened lifespan[1], others develop few detectable long-term neurological deficits[2]. After the first clinical event (a clinically isolated syndrome, CIS), most (~85%) run a relapsing-remitting (RRMS) disease course[3] with many subsequently transitioning to secondary progressive (SP)MS (~50% within 15-20 years)[4,5]. It is during SPMS that individuals acquire most disability.[3,6,7] There is growing evidence that earlier treatment reduces the risk of, or at least significantly delays, SPMS onset[8,9] and hence there is a trend towards treating MS earlier with higher efficacy agents. However, given that a significant proportion may not develop clinically progressive disease or substantial disability[10,11], and the potential for serious harm from disease modifying treatments (DMT), in addition to those with clinically active disease, early use of high efficacy agents would ideally be weighted towards those at the clearest risk of developing SPMS.

Clinical factors associated with a more aggressive MS phenotype include older age at initial presentation, early frequent relapses, and shorter intervals between first and second relapses[2,12,13]. Presenting with an optic neuritis or sensory-predominant CIS has also been linked to a less disabling clinical course, although debated[2,12,14]. Radiological features associated with an aggressive MS phenotype include higher numbers[15] and volumes of white matter[16,17] (WM) and grey matter[18,19] (GM) lesions, the presence of posterior fossa and spinal cord lesions[10], and faster rates of brain atrophy.[20] Transitioning from RRMS to SPMS is associated with declining WM lesion formation and increasing brain atrophy[21], although accelerated brain atrophy still occurs early in MS, particularly among people who eventually develop SPMS[21]. Consistent with this, disability early in RRMS is mainly thought to be due

to relapse activity and WM lesion accrual[10,17], although there is growing recognition that substantial progression independent of relapses may also occur in RRMS[22]. In established SPMS, disability relates more closely to brain atrophy[20,23]. It can therefore be hypothesised that, when predicting SPMS development, WM lesion accrual is more relevant earlier while brain atrophy increases in relevance closer to SPMS onset. However, we have previously shown that brain atrophy independently contributes to prognostic models within the first 5 years after symptom onset[20], so this hypothesis may be incorrect. Systematically investigating prognostic markers for SPMS is difficult as it typically develops 15 or more years after first symptoms onset[24,25], and thus long-term follow-up is required to test this.

We previously reported on a 30-year longitudinal follow-up study of 107 participants presenting with a CIS (by 30 years 28% (n=30) remained CIS, 32.7% (n=35) had RRMS, while 39.3% (n=42) had either SPMS or died due to MS), where we explored the prognostic significance of lesion numbers, location and linear brain atrophy measures in the first 5 years after symptom onset[10,20]. People who transitioned from RRMS to SPMS did so ~17 years after symptom onset and both lesion accrual (in particular, infratentorial lesions) and brain atrophy (measured using medullary width [MEDW], but not third ventricular width [TVW]) predicted SPMS development by 30 years[20].

In the present study, we sought to answer three questions: (1) Are WM lesions more prognostically relevant early, and brain atrophy measures later, in the disease course? (2) If so, how long after disease onset does the balance between them shift? and (3), should optimised prognostic models include different features dependent on disease duration? The main clinical outcome considered was the development of SPMS but to test consistency we also explored other outcome measures (MS-related mortality, and EDSS ≥3.5 by 30 years).

We undertook this with a view to clinical practice, where volumetric brain atrophy measures are not, for practical reasons, routinely assessed. Given that in clinical practice serial scans are often unavailable or acquired using very different machines and protocols, we ran both cross-sectional analyses (using single timepoint data) and longitudinal analyses to determine the added value of serial scanning.

Materials and Methods

Study Participants

The clinical characteristics of this cohort have been previously described.[10] 140 participants were prospectively recruited between 1984-1987 after first presenting with a CIS.[26] Participants underwent radiological (MRI) assessment at 1 year (n=108), with clinical and radiological assessments at 5(n=92), 10(n=66), 14(n=55), 20(n=75) and 30(n=63) years.[10,20] All participants provided informed consent to take part in the study.

Eight participants subsequently found to have a diagnosis other than CIS or MS and were excluded, and by 30 years clinical outcomes were known among 120 and were assessed using the 2010 revised McDonald clinical and MRI criteria.[27] Thirteen participants who died from unrelated causes by 30 years were excluded due to uncertainty in neuroinflammatory outcomes following a CIS. One participant included in our analysis had a diagnosis of idiopathic Parkinson's disease and remained CIS throughout; the remaining cohort had no other known neurodegenerative diseases. Among 107 remaining participants, four (three CIS, one RRMS) had missing or inadequate baseline, 1- or 5-year scans and were excluded from analysis. 103 participants were ultimately included in the present analysis: by 30 years, 27

(26.2%) remained CIS, 34 (33.0%) had RRMS, 26 (25.2%) had SPMS, while 16 (15.5%) had died due to MS (preceded by an SPMS course).

Clinical Assessment

Expanded Disability Status Scores[28] (EDSS) and clinical relapse frequency were determined at baseline, 5, 10, 14, 20 and 30-year visits. Baseline EDSS was calculated retrospectively from review of notes, while 30-year EDSS assessments were undertaken either in person (66 participants) or telephone (25 participants). Where participants were not assessed at a given timepoint, EDSS was inferred from available clinical data and EDSS at adjacent timepoints. 14 participants did not have baseline EDSS retrospectively calculated as these could not be confidently calculated from available records.

Image Acquisition

Image acquisition and analysis protocols have been previously described in detail elsewhere[10,20]. Baseline, 1-year and 5-year timepoint MRI scans were obtained using a 0.5T Picker system (Marconi Medical Systems, Cleveland, OH). 10-, 14- and 20-year timepoint MRI scans were obtained using a 1.5T General Electric Signa system (GE Healthcare, Chicago, IL), while a 3T Philips Achieva system (Philips Healthcare, Best, The Netherlands) was used at the 30-year time point. At each time point, proton density (PD) and/or T2-weighted images were acquired. Baseline, 1-year and 5-year film images were digitised using Vidar Diagnostic Pro Advantage film digitizer (VIDAR Systems, Herndon, VA)[10,29].

Lesions were marked and their location assessed (juxtacortical [JC], periventricular [PV], infratentorial [IT], and deep white matter [DWM])[10]. As baseline, 1-, 5- and 10-year images were not suitable for volumetric MRI analysis, linear atrophy measures were employed. Third

ventricular width (TVW) was measured by drawing a midpoint line running parallel to the long axis of the ventricle on axially acquired PD/T2-weighted MRI scans[20,30]. Medullary width (MEDW) was measured as the dorsoventral medullary diameter on midsagittal imaging (scout images at baseline, 1 and 5 years, and T1-weighted images at subsequent time-points)[20,31].

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics v28.0.0 (IBM Corporation, Armonk, NY).

To answer our questions on the prognostic relevance of WM lesions and brain atrophy measures over time, and whether there was a shift in the balance between them, we built cross-sectional binary logistic regression models using MRI measures from each timepoint. Using the Nagelkerke method, a pseudoR^2 value (pR^2) was calculated as a measure of model fit and the strength of contributory effect (association) of a particular measure towards a given outcome. Models predicting SPMS development were repeated with and without age and gender as additional covariates, with the difference in pR^2 between the two models calculated to determine the sole contribution of each MRI measure over time. To determine the longitudinal effects of MRI measures, models were reran adding their respective baseline MRI measures. Models were not censored: all participants who reached a particular outcome (e.g. SPMS) by an earlier timepoint were included in all subsequent timepoint models (to avoid biasing later models by increasingly including only people at lower risk of SPMS over time).

As TVW increases with brain atrophy, while MEDW decreases, we present the inverse measure of MEDW (1/MEDW). Linear atrophy models adjusted for baseline are statistically equivalent to modelling the rates of atrophy from baseline. However, for completeness, further models were ran using calculated atrophy rates (see Supplementary Materials).

To determine if prognostic models should include different features dependent on disease duration, we built longitudinal binary logistic regression models using a forward and backward conditional approach including all MRI measures, to determine which covariates were retained for optimal models at each timepoint. Here, we present the full model's pR^2, odds ratio (OR) and the significance of each covariate. With a view to clinical applicability, we manually built additional combined models incorporating both MRI and clinical (age, gender, relapse frequency, EDSS) measures to determine which most optimally predicted ultimate clinical outcomes at each timepoint. The base model started with age and gender, to which we sequentially added MRI and clinical measures, and observed which gave the highest overall pR^2.

We present the results of models predicting SPMS below (models predicting MS-related mortality or EDSS $\geq$3.5 outcomes are presented in Supplemental Materials).

A p-value $\leq$0.05 was considered statistically significant.

Results

We present model pR^2 below (full results in Supplementary Materials). For context, models predicting SPMS based on age (at first CIS) and gender alone had a pR^2=0.029.

Lesion accrual predicting SPMS

Whole brain lesion counts

In cross-sectional models predicting SPMS, whole brain lesion counts were significant at all timepoints (peak contributory effect at 5 years, pR^2=0.377). Contributory effects increased over the first 5 years, then plateaued up to the 14-year timepoint before declining at 20 years. A similar pattern was observed in longitudinal models which included baseline whole brain lesion counts (Figures 1 and 2, and Supplementary Table 4).

Lesion counts by location

Total IT lesion counts peaked in contributory effect at the 1-year timepoint (pR^2=0.417) in cross-sectional models, after which they plateaued before declining at the 20-year timepoint. Total IT lesion count was a significant variable across all cross-sectional models. In longitudinal models (adjusted for baseline IT lesion counts), total IT lesion count was a significant variable at 5- and 14-year timepoints with similar contributory effects (Figures 1 and 2, and Supplementary Table 5).

Cross-sectional models considering either PV or DWM lesion counts both showed increasing contributory effects over the first 5 years, after which their effects plateaued before subsequently declining at 20 years (peak pR^2=0.403 at 14 years for PV models, peak pR^2=0.342 at 5 years for DWM lesion count models). Similar trajectories were noted for longitudinal models adjusted for baseline PV or DWM lesion counts (Figures 1 and 2). PV

and DWM lesion counts remained significant variables across all timepoints in cross-sectional and longitudinal models.

JC lesion count models had the lowest predictive ability towards development of SPMS (peak pR^2=0.152 in cross-sectional models), although significant across all timepoints. In longitudinal models adjusted for baseline, total JC lesion counts were only significant at 20 years (Figures 1 and 2).

Linear atrophy predicting SPMS

Third ventricular width (TVW)

In cross-sectional models, TVW increased in contributory effect of over time, peaking at 14 years (pR^2=0.498). A similar trend was observed in longitudinal models (Figures 1 and 2). TVW was a significant variable in cross-sectional and longitudinal models from the 10-year timepoint onwards.

Medullary width (MEDW)

While MEDW was a significant variable in cross-sectional models at 5, 14 and 20-year timepoints, its predictive power was greatest at the 5- and 20-year timepoints (pR^2=0.221 and 0.260 respectively). A similar trend was observed in longitudinal models adjusted for baseline MEDW, where greatest contributory effect was observed at 5- and 20-year timepoints (and were the only timepoints where MEDW was a significant model variable) (Figures 1 and 2).

Clinical factors predicting SPMS

Relapse frequency was significant in cross-sectional models across all timepoints, with peak associations observed between 5-10 years (pR^2=0.213). Conversely, EDSS increasingly associated with SPMS outcomes over time in cross-sectional models (peak effects at 20 years, pR^2=0.688) and was a significant variable from the 5-year timepoint onwards (see Supplementary Table 6 for full results).

Optimal models predicting SPMS

MRI features alone (Tables 1 & 2)

In combined cross-sectional models (Table 1), at baseline, only IT lesion counts were retained (and significant) (model pR^2=0.174). At the 5-year timepoint, combined models included age, 5-year PV lesion counts and 5-year MEDW (model pR^2=0.595; age and 5-year PV lesion counts were significant variables). At the 10-year timepoint, combined models included 10-year IT lesion counts and 10-year MEDW (model pR^2=0.504; both 10-year IT lesion counts and 10-year MEDW were significant variables). At the 14-year timepoint, combined models only included 14-year TVW and was a significant model variable (model pR^2=0.535). By the 20-year timepoint, the model included 20-year DWM lesion counts and 20-year TVW (model pR^2=0.439; both 20-year DWM lesion counts and 20-year TVW were significant variables).

In combined longitudinal models (including baseline MRI measures, age and gender) (Table 2), at the 5-year timepoint, the model retained 5-year PV lesion counts and 5-year MEDW (model pR^2=0.525; 5-year PV lesion count was a significant variable). At the 10-year

timepoint, only baseline IT lesion count was retained in combined longitudinal models and was a significant variable (model pR^2=0.391). At the 14-year timepoint, combined longitudinal models only retained 14-year PV lesion counts and was a significant variable (model pR^2=0.475). At 20-years, models retained both baseline IT lesion counts and 20-year TVW (model pR^2=0.555; baseline IT lesion counts was a significant variable).

MRI and clinical features (Table 3)

At the 5-year timepoint, combined models retained age, gender, relapse activity between 0-5 years and 1-year IT lesion counts (model pR^2=0.484; age, relapse activity between 0-5 years and 1-year IT lesion counts were significant model variables). At the 10-year timepoint, age, gender, clinical relapse activity between 5-10 years, 1-year IT lesion counts and 10-year EDSS were retained in the model (model pR^2=0.663; 10-year EDSS, relapse activity between 5-10 years, and 1-year IT lesion counts were significant model variables); while at the 14-year timepoint, age, gender, clinical relapse activity between 5-10 years and 14-year IT lesion counts were retained (model pR^2=0.642; age, 14-year IT lesion counts and relapse activity between 5-10 years were significant model variables). At the 20-year timepoint, combined models retained age, gender, 1-year IT lesion counts and 20-year EDSS (model pR^2=0.729; 20-year EDSS and 1-year IT lesion counts were significant model variables).

Table 1 – Lean cross-sectional MRI models (lesions by location, age, gender) predicting 30-year SPMS

Timepoint	n	Model pR^2	Model covariates	Covariate OR (95% CI)	Covariate p=
0 year	**58**	**0.174**	**0-year IT lesion count**	**2.31 (1.13-4.71)**	**0.020***
5 year	**61**	**0.595**	**Age**	**1.14 (1.01-1.28)**	**0.030***
			5-year PV lesion count	**1.40 (1.15-1.70)**	**<0.001***
			5-year MEDW	0.36 (0.13-1.02)	0.055
10 year	**46**	**0.401**	**10-year IT lesion count**	**1.80 (1.16-2.80)**	**0.009***
			10-year MEDW	**0.36 (0.12-1.05)**	**0.060***
14 year	**38**	**0.535**	**14-year TVW**	**2.48 (1.38-4.44)**	**0.002***
20 year	**52**	**0.439**	**20-year DWM lesion count**	**1.02 (1.00-1.05)**	**0.036***
			20-year TVW	**1.48 (1.05-2.10)**	**0.026***

Table 2 – Lean longitudinal MRI models (lesions by location, age, gender) adjusted for baseline MRI measures predicting 30-year SPMS

Timepoint	n	Model pR^2	Model covariates	Covariate OR (95% CI)	Covariate p=
5 year	**43**	**0.525**	**5-year PV lesion count**	**1.27 (1.08-1.51)**	**0.005***
			5-year MEDW	0.26 (0.07-1.02)	0.053
10 year	**27**	**0.391**	**0-year IT lesion count**	**9.25 (1.03-82.9)**	**0.047***
14 year	**22**	**0.475**	**14-year PV lesion count**	**1.20 (1.03-1.39)**	**0.017***
20 year	**31**	**0.555**	**0-year IT lesion count**	**9.61 (1.15-80.5)**	**0.037***
			20-year TVW	1.60 (1.00-2.59)	0.052

Table 3– Lean combined models (clinical and MRI) predicting 30-year SPMS

Timepoint	n	Model pR^2	Model covariates	Covariate OR (95% CI)	Covariate p=
5 year	78	0.484	**Age**	**1.10 (1.00-1.20)**	**0.042***
			Gender	0.70 (0.19-2.52)	0.581
			Number of relapses (0-5 years)	**1.59 (1.08-2.33)**	**0.018***
			1-year IT lesion counts	**4.25 (1.62-11.12)**	**0.003***
10 year	70	0.633	Age	1.12 (1.00-1.26)	0.053
			Gender	0.19 (0.03-1.23)	0.081
			10-year EDSS	**2.09 (1.21-3.62)**	**0.008***
			Number of relapses (5-10 years)	**2.44 (1.20-4.99)**	**0.014***
			1-year IT lesion counts	**5.38 (1.22-23.67)**	**0.026***
14 year	43	0.642	**Age**	**1.23 (1.03-1.47)**	**0.023***
			Gender	0.10 (0.01-1.01)	0.051
			14-year IT lesion counts	**1.92 (1.16-3.17)**	**0.011***
			Number of relapses (5-10 years)	**2.75 (1.16-6.48)**	**0.021***
20 year	82	0.729	Age	1.04 (0.93-1.15)	0.526
			Gender	0.64 (0.13-3.06)	0.572
			20-year EDSS	**2.40 (1.57-3.69)**	**<0.001***
			1-year IT lesion counts	**6.89 (1.83-25.91)**	**0.004***

Discussion

We found that WM lesions were prognostically relevant for the development of SPMS immediately after a CIS and, contrary to our initial hypothesis, remained clinically relevant throughout follow-up. In combined MRI models, linear atrophy measures increasingly contributed towards predictive power at later follow-up points, but when adjusted for baseline MRI measures, only WM lesion counts remained significant. Similarly, when clinical features were introduced into models, among MRI measures, only IT counts remained significant predictors.

Lesion counts had greatest prognostic relevance from 5 to 14 years, whilst linear atrophy measures had a more complex relationship with outcomes. TVW was most significantly predictive at 14 years (reaching significance from 10 years), while MEDW was most significantly predictive at 5 and 20 years. While overall this is consistent with lesion accrual being of slightly diminishing clinical relevance over time and atrophy becoming increasingly important[10,20], when models were built with both lesion counts and linear atrophy measures alongside clinical features, only lesion counts independently contributed to the prediction of SPMS. While brain atrophy has been shown to correlate better than lesion accrual with disability in established progressive MS[21,23], our results suggest that linear atrophy measures have lesser value in predicting SPMS onset. In line with previous work[10,32], we found lesion location influenced prognostic relevance, with IT and PV lesions showing similar pR^2 and higher than that observed in DWM and JC lesions respectively. Only IT lesion counts contributed significantly to models that also included clinical measures. Even 20 years after initial CIS, IT lesions continued to have significant prognostic relevance for SPMS by 30 years. While lesion location is clearly relevant to symptoms during a relapse, it remains

unclear why lesion location also influences overall risk of progressive MS. The prognostic significance of TVW increased over time from 5 years, reaching peak contributory effect at 14 years. Medullary thinning had a more complex association with SPMS development, peaking at both 5 and 20 years. It is worth recalling that both TVW and MEDW are regional measures of atrophy: TVW correlates most with brain parenchymal fractions (r=-0.93 at 30-year scanning), whereas MEDW correlates most with cord volumes (r=0.61 at 30-year scanning)[20], and atrophy due to MS preferentially affects different regions of the brain[33] and spinal cord[34] at different stages of disease.

When adjusted for baseline values, MEDW was not a consistent predictor of SPMS. This may be explained by the changes in scanners and scanning protocols which occurred over time (leading to step changes in all measures), measurement noise (initially 2D non-isotropic scans were used, obtained at 0.5T with a 5 mm slice thickness), and differing numbers of participants at each timepoint. However, while these factors will obscure associations, they will not lead to spurious ones being found.

As volumetric atrophy measures could not be applied to early MRI data, we used linear approaches. Compared to volumetric measures they are much easier to undertake, but for the reasons noted earlier we think that associations with clinical outcomes may have been attenuated. In particular, the low resolution of early scans in this study will have been associated with higher partial volume effects when compared with current scans (now very often isotropic and close to 1x1x1mm). Volumetric atrophy measurement approaches can be applied to modern scans, but have a significant computational overhead, and so linear methods may still be more feasible in clinical practice. Given the results of our study, it

would be interesting to compare the sensitivity to change of volumetric and linear measures using current routinely obtained clinical scans.

Another consequence of technical advances since the start of this study was the limited acquisition of other MRI measures that may be of interest in predicting progressive MS, specifically imaging the spinal cord for lesions and measuring atrophy[34,35], or dedicated brain imaging to detect grey matter lesions (which, in the present cohort, was the MRI feature that most distinguished SPMS from RRMS at 30 years[18]). However, none of these are routinely acquired in current clinical practice and does not undermine the relevance of the current findings, although would be of interest in future studies.

It is important to also note that MRI data availability differed between timepoints: for example, at baseline MRI data was available for 103 participants, while at 14 years 52 were scanned. Models based on smaller sample sizes will have less power to detect associations, and so factors not found to be statistically significant in this study may still be clinically relevant (and might have probably been statistically significant if larger sample sizes had been analysed), albeit less so than those where a predictive effect was detected.

Given that we specifically sought to investigate the prognostic relevance of MRI measures towards 30-year outcomes (rather than their direct correlation with disability accrual over time), we used binary logistic regression models to identify which factors significantly contributed towards prognostic power for a given timepoint. However, it is worth noting that there are both biological (e.g., WM lesions disrupting tracts, leading to neurodegeneration and disability) and temporal (WM lesion load, brain atrophy and disability all naturally increase over time) reasons for collinearity between measures, and hence, models may be

dominated by a particular measure with the strongest association towards an outcome at a given time. This does not necessarily mean that other measures are irrelevant to clinical progression *per se*, but rather, they did not contribute to a given prognostic model.

Despite brain atrophy measures increasing in prognostic relevance over time in isolation, they also did not contribute significantly to models including WM lesion and clinical features. While brain atrophy is associated with SPMS, it is also predicted to a degree by preceding WM lesion accrual, and in part it may be argued that atrophy simply reflects a later stage in a pathological cascade from WM lesion formation to tract-mediated damage and eventual brain atrophy (for example[36]). Furthermore, there is growing evidence that with progressive MS, while WM lesion accrual slows, as many as ~30% of lesions transition towards chronic activity[37], and chronic demyelination is also associated with ongoing axonal loss[38]. Based on this, the ultimate effect of early WM lesion accrual on neurodegeneration may take years to manifest (and in previous work with this cohort, associations strengthened over more than a decade[39]).

As expected, relapse activity (as a clinical predictor of 30-year outcomes) followed similar trends to lesion counts over time, increasing in predictive ability up to 5-10 years from first symptom onset, after which its effects progressively diminished. As would be expected based on brain atrophy measures, EDSS also significantly predicted SPMS, increasing in predictive ability from 5 years, although it is important to note that higher EDSS scores per se will increasingly distinguish RR from SPMS, and in combination with other features, has been used as part of an objective definition of SPMS[40].

Our study benefited from 30 years of clinical and radiological data, with clear phenotypic separation by the end of the follow-up period. Licensed DMTs were unavailable when participants were recruited and only introduced a decade or more later, hence most were untreated. Only eleven people (four RRMS, seven SPMS at 30 years) received a DMT at any point, the earliest starting 10 years after MS diagnosis. While this offered a unique insight into the natural history of MS disease progression, it cannot be assumed that MRI prognostic features identified in this cohort are as relevant among people taking current high-efficacy treatments.

In conclusion, while we presupposed a shift between the prognostic relevance of WM lesion accrual and brain atrophy, our results suggest that IT lesions consistently remained prognostically significant towards the development of SPMS in combined clinical and MRI models.

Figures

*For all figures, * indicates a model that was significant at p≤0.05.*
At some timepoints age and gender explained small amounts of the outcome of interest and may therefore not be clearly seen in the Figures. Please see Tables 4 & 5 in supplementary materials for a detailed breakdown of the values.

Figure 1: Cross-sectional models considering contribution of age, gender and MRI measures (total lesion count, lesion by subtype, linear atrophy measures) towards 30-year SPMS

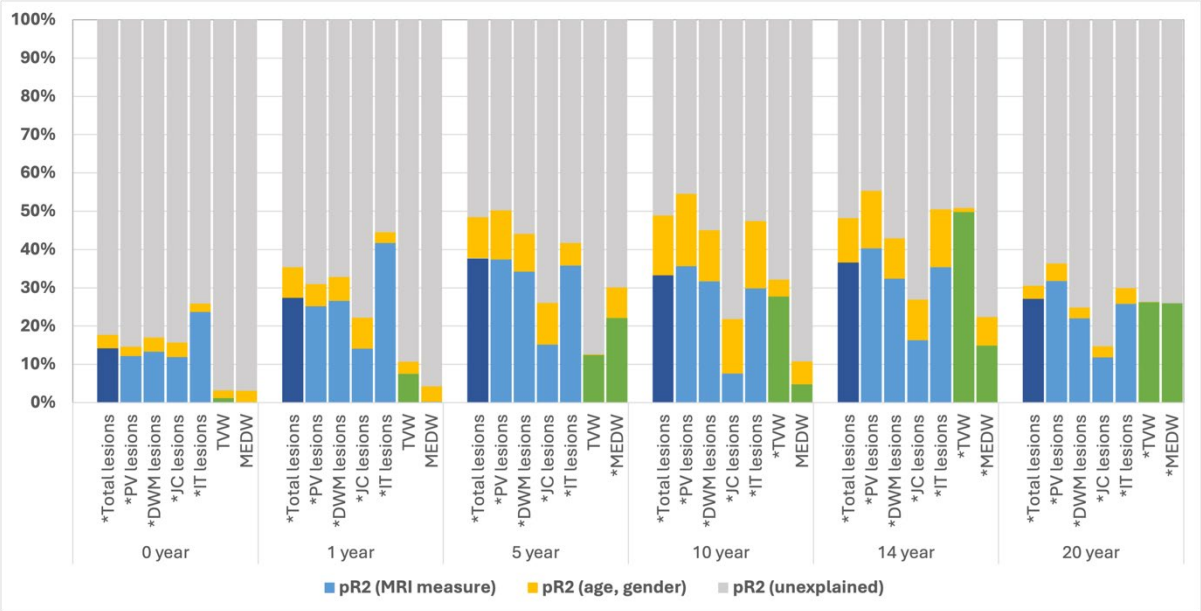
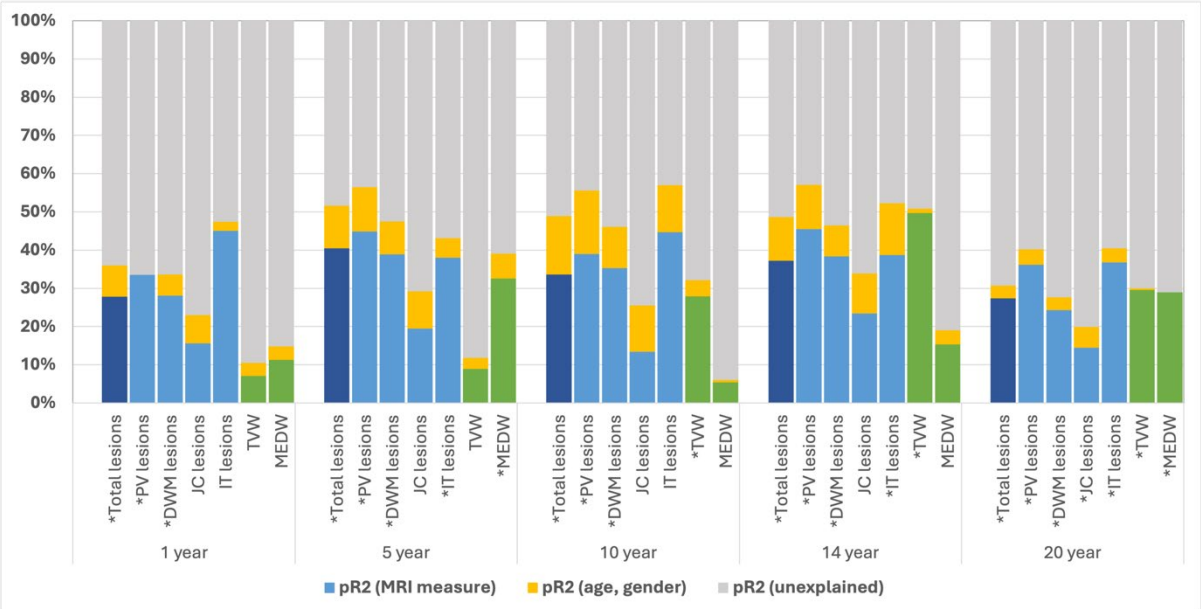


Figure 2: Longitudinal models considering contribution of age, gender and MRI measures (total lesion count, lesion by subtype, linear atrophy measures) towards 30-year SPMS



Ethics

This study was approved by the National Research Ethics Service (15/LO/0650).

Data availability

Anonymised data which is not published in the article can be shared on reasonable request from a qualified investigator.

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Contributorship Statement

PA had full access to the data and was responsible for undertaking data and statistical analysis, along with synthesising the initial draft of the manuscript (along with DTC). NS reviewed the manuscript and contributed towards interpretation of results. KC and LH previously collected clinical and MRI data at the 30-year follow-up for the study (as cited in the manuscript), archiving clinical and MRI data from previous timepoints, image analysis, and review of subsequent drafts. FP participated and supervised in image analysis and interpretation. SAT reviewed the manuscript and contributed towards results interpretation. OC reviewed the manuscript and contributed towards results interpretation. FB supervised image analysis and reviewed the manuscript. CT is joint senior author on the project along with DC, and contributed towards development of research methodology, guiding statistical analysis and manuscript revision. DTC is also senior author and is the guarantor for the project. He had full access to the data, and was responsible for securing funding, data and statistical analysis, interpretation of results, and preparation of the first draft of the manuscript as well as editing subsequent revisions of the manuscript. All coauthors have reviewed and approved the submission of this manuscript.

Competing interests

PA is a clinical research fellow funded by an MS Society grant (Ref: 141) and was previously in a post supported by Merck (supervised by D Chard and SA Trip). He also works as a medical advisor for Mara Health. NS is a clinical research fellow funded by an MRC grant (Ref: MR/W019906/1) and previously in a post support by Merck (supervised by D Chard and SA Trip). KC has received honoraria for participation and attendance of educational events from Novartis, Roche, Biogen and Merck. She has received honoraria for consultancy work from Novartis, Roche, Biogen, Merck and Viatris. LH has no disclosures. FP receives funding from National Institute for Health Research (NIHR), Biomedical Research Centre initiative at University College London Hospitals (UCLH). F.P received a Guarantors of Brain fellowship 2017-2020. (S)AT has received honoraria from Roche, Merck, Novartis, Sanofi-Genzyme and Biogen in the last 3 years and co-supervises a clinical fellowship supported by Merck. OC is a member of independent DSMB for Novartis, gave a teaching talk on McDonald criteria in a Merck local symposium, and contributed to an Advisory Board for Biogen; she is Deputy Editor of Neurology, for which she receives an honorarium. FB is supported by the NIHR biomedical research centre at UCLH. Steering committee or Data Safety Monitoring Board member for Biogen, Merck, ATRI/ACTC and Prothena. Consultant for Roche, Celltrion, Rewind Therapeutics, Merck, IXICO, Jansen, Combinostics. Research agreements with Merck, Biogen, GE Healthcare, Roche. Co-founder and shareholder of Queen Square Analytics LTD. CT has received a Junior Leader La Caixa Fellowship (fellowship code is LCF/BQ/PI20/11760008), awarded by “la Caixa” Foundation (ID 100010434), the 2021 Merck’s Award for the Investigation in MS, awarded by Fundación Merck Salud (Spain) and a grant awarded by the Instituto de Salud Carlos III (ISCIII), Ministerio de Ciencia e Innovación de España (PI21/01860). In 2015, she received an ECTRIMS Post-doctoral Research Fellowship and has received funding from the UK MS Society. She is a member of the Editorial Board of Neurology and Multiple Sclerosis Journal. She has also received honoraria from Roche, Novartis, Bristol Myers Squibb and Merck, and is a steering committee member of the O’HAND trial and of the Consensus group on Follow-on DMTs. DC is a consultant for Hoffmann-La Roche. In the last three years he has been a consultant for Biogen, has received research funding from Hoffmann-La Roche, the International Progressive MS Alliance, the MS Society, the Medical Research Council, and the National Institute for Health Research (NIHR) University College London Hospitals (UCLH) Biomedical Research Centre, and a speaker’s honorarium from Novartis. He co-supervises a clinical fellowship at the National Hospital for Neurology and Neurosurgery, London, which is supported by Merck.

References

1. Scalfari A, Knappertz V, Cutter G, Goodin DS, Ashton R, Ebers GC. Mortality in patients with multiple sclerosis. *Neurology*. Jul 9 2013;81(2):184-92. doi:10.1212/WNL.0b013e31829a3388
2. Ramsaransing GS, De Keyser J. Benign course in multiple sclerosis: a review. *Acta Neurol Scand*. Jun 2006;113(6):359-69. doi:10.1111/j.1600-0404.2006.00637.x
3. Filippi M, Bar-Or A, Piehl F, et al. Multiple sclerosis. *Nat Rev Dis Primers*. Nov 8 2018;4(1):43. doi:10.1038/s41572-018-0041-4
4. Antonio S, Anneke N, Martin D, Paolo Antonio M, George Cornell E. Onset of secondary progressive phase and long-term evolution of multiple sclerosis. *Journal of Neurology, Neurosurgery & Psychiatry*. 2014;85(1):67. doi:10.1136/jnnp-2012-304333
5. Barzegar M, Najdaghi S, Afshari-Safavi A, Nehzat N, Mirmosayyeb O, Shaygannejad V. Early predictors of conversion to secondary progressive multiple sclerosis. *Multiple Sclerosis and Related Disorders*. 2021/09/01/ 2021;54:103115. doi:https://doi.org/10.1016/j.msard.2021.103115
6. Filippi M, Preziosa P, Langdon D, et al. Identifying Progression in Multiple Sclerosis: New Perspectives. *Ann Neurol*. Sep 2020;88(3):438-452. doi:10.1002/ana.25808
7. Weinshenker BG, Bass B, Rice GP, et al. The natural history of multiple sclerosis: a geographically based study. I. Clinical course and disability. *Brain*. Feb 1989;112 (Pt 1):133-46. doi:10.1093/brain/112.1.133
8. Drulovic J, Kostic J, Mesaros S, et al. Interferon-beta and disability progression in relapsing-remitting multiple sclerosis. *Clin Neurol Neurosurg*. Dec 2013;115 Suppl 1:S65-9. doi:10.1016/j.clineuro.2013.09.024
9. 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(2):175-187. doi:10.1001/jama.2018.20588
10. Chung KK, Altmann D, Barkhof F, et al. A 30-Year Clinical and Magnetic Resonance Imaging Observational Study of Multiple Sclerosis and Clinically Isolated Syndromes. *Ann Neurol*. Jan 2020;87(1):63-74. doi:10.1002/ana.25637
11. Sorensen PS, Sellebjerg F, Hartung H-P, Montalban X, Comi G, Tintoré M. The apparently milder course of multiple sclerosis: changes in the diagnostic criteria, therapy and natural history. *Brain*. 2020;143(9):2637-2652. doi:10.1093/brain/awaa145
12. Confavreux C, Vukusic S, Adeleine P. Early clinical predictors and progression of irreversible disability in multiple sclerosis: an amnesic process. *Brain*. Apr 2003;126(Pt 4):770-82. doi:10.1093/brain/awg081
13. Ebers GC. Natural history of multiple sclerosis. *J Neurol Neurosurg Psychiatry*. Dec 2001;71 Suppl 2(Suppl 2):ii16-9. doi:10.1136/jnnp.71.suppl_2.ii16
14. Tintore M, Rovira A, Arrambide G, et al. Brainstem lesions in clinically isolated syndromes. *Neurology*. Nov 23 2010;75(21):1933-8. doi:10.1212/WNL.0b013e3181feb26f
15. Tintore M, Rovira À, Río J, et al. Defining high, medium and low impact prognostic factors for developing multiple sclerosis. *Brain*. Jul 2015;138(Pt 7):1863-74. doi:10.1093/brain/awv105
16. Rudick RA, Lee J-C, Simon J, Fisher E. Significance of T2 lesions in multiple sclerosis: A 13-year longitudinal study. https://doi.org/10.1002/ana.20883. *Annals of Neurology*. 2006/08/01 2006;60(2):236-242. doi:https://doi.org/10.1002/ana.20883
17. Fisniku LK, Brex PA, Altmann DR, et al. Disability and T2 MRI lesions: a 20-year follow-up of patients with relapse onset of multiple sclerosis. *Brain*. Mar 2008;131(Pt 3):808-17. doi:10.1093/brain/awm329

18. Haider L, Prados F, Chung K, et al. Cortical involvement determines impairment 30 years after a clinically isolated syndrome. *Brain*. Jun 22 2021;144(5):1384-1395. doi:10.1093/brain/awab033
19. Ziccardi S, Pisani AI, Schiavi GM, et al. Cortical lesions at diagnosis predict long-term cognitive impairment in multiple sclerosis: A 20-year study. *European Journal of Neurology*. 2023/05/01 2023;30(5):1378-1388. doi:https://doi.org/10.1111/ene.15697
20. Haider L, Chung K, Birch G, et al. Linear brain atrophy measures in multiple sclerosis and clinically isolated syndromes: a 30-year follow-up. *J Neurol Neurosurg Psychiatry*. Mar 30 2021;doi:10.1136/jnnp-2020-325421
21. Fisher E, Lee JC, Nakamura K, Rudick RA. Gray matter atrophy in multiple sclerosis: a longitudinal study. *Ann Neurol*. Sep 2008;64(3):255-65. doi:10.1002/ana.21436
22. Tur C, Carbonell-Mirabent P, Cobo-Calvo Á, et al. Association of Early Progression Independent of Relapse Activity With Long-term Disability After a First Demyelinating Event in Multiple Sclerosis. *JAMA Neurology*. 2023;80(2):151-160. doi:10.1001/jamaneurol.2022.4655
23. Fisniku LK, Chard DT, Jackson JS, et al. Gray matter atrophy is related to long-term disability in multiple sclerosis. *Ann Neurol*. Sep 2008;64(3):247-54. doi:10.1002/ana.21423
24. Scalfari A, Neuhaus A, Degenhardt A, et al. The natural history of multiple sclerosis: a geographically based study 10: relapses and long-term disability. *Brain*. Jul 2010;133(Pt 7):1914-29. doi:10.1093/brain/awq118
25. Koch M, Kingwell E, Rieckmann P, Tremlett H, Neurologists UMC. The natural history of secondary progressive multiple sclerosis. *Journal of Neurology, Neurosurgery & Psychiatry*. 2010;81(9):1039-1043. doi:10.1136/jnnp.2010.208173
26. Miller DH, Ormerod IE, Rudge P, Kendall BE, Moseley IF, McDonald WI. The early risk of multiple sclerosis following isolated acute syndromes of the brainstem and spinal cord. *Ann Neurol*. Nov 1989;26(5):635-9. doi:10.1002/ana.410260508
27. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol*. Feb 2011;69(2):292-302. doi:10.1002/ana.22366
28. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology*. Nov 1983;33(11):1444-52. doi:10.1212/wnl.33.11.1444
29. Ebner M, Chung KK, Prados F, et al. Volumetric reconstruction from printed films: Enabling 30 year longitudinal analysis in MR neuroimaging. *Neuroimage*. Jan 15 2018;165:238-250. doi:10.1016/j.neuroimage.2017.09.056
30. Benedict RH, Weinstock-Guttman B, Fishman I, Sharma J, Tjoa CW, Bakshi R. Prediction of neuropsychological impairment in multiple sclerosis: comparison of conventional magnetic resonance imaging measures of atrophy and lesion burden. *Arch Neurol*. Feb 2004;61(2):226-30. doi:10.1001/archneur.61.2.226
31. Chivers TR, Constantinescu CS, Tench CR. MRI-Based Measurement of Brain Stem Cross-Sectional Area in Relapsing-Remitting Multiple Sclerosis. *J Neuroimaging*. Nov-Dec 2015;25(6):1002-6. doi:10.1111/jon.12244
32. Minneboo A, Barkhof F, Polman CH, Uitdehaag BM, Knol DL, Castelijns JA. Infratentorial lesions predict long-term disability in patients with initial findings suggestive of multiple sclerosis. *Arch Neurol*. Feb 2004;61(2):217-21. doi:10.1001/archneur.61.2.217
33. Eshaghi A, Prados F, Brownlee WJ, et al. Deep gray matter volume loss drives disability worsening in multiple sclerosis. *Ann Neurol*. Feb 2018;83(2):210-222. doi:10.1002/ana.25145

34. Casserly C, Seyman EE, Alcaide-Leon P, et al. Spinal Cord Atrophy in Multiple Sclerosis: A Systematic Review and Meta-Analysis. *J Neuroimaging*. Nov 2018;28(6):556-586. doi:10.1111/jon.12553
35. Brownlee WJ, Altmann DR, Alves Da Mota P, et al. Association of asymptomatic spinal cord lesions and atrophy with disability 5 years after a clinically isolated syndrome. *Mult Scler*. Apr 2017;23(5):665-674. doi:10.1177/1352458516663034
36. Bodini B, Chard D, Altmann DR, et al. White and gray matter damage in primary progressive MS: The chicken or the egg? *Neurology*. Jan 12 2016;86(2):170-6. doi:10.1212/wnl.0000000000002237
37. Frischer JM, Weigand SD, Guo Y, et al. Clinical and pathological insights into the dynamic nature of the white matter multiple sclerosis plaque. *Ann Neurol*. Nov 2015;78(5):710-21. doi:10.1002/ana.24497
38. You Y, Barnett MH, Yiannikas C, et al. Chronic demyelination exacerbates neuroaxonal loss in patients with MS with unilateral optic neuritis. *Neurol Neuroimmunol Neuroinflamm*. May 2020;7(3)doi:10.1212/nxi.0000000000000700
39. Chard DT, Brex PA, Ciccarelli O, et al. The longitudinal relation between brain lesion load and atrophy in multiple sclerosis: a 14 year follow up study. *J Neurol Neurosurg Psychiatry*. Nov 2003;74(11):1551-4. doi:10.1136/jnnp.74.11.1551
40. Lorscheider J, Buzzard K, Jokubaitis V, et al. Defining secondary progressive multiple sclerosis. *Brain*. Sep 2016;139(Pt 9):2395-405. doi:10.1093/brain/aww173

Supplementary Material

Table 4 – Total lesion count and linear atrophy models predicting 30-year SPMS outcomes

Table 4a – Cross-sectional models predicting 30-year SPMS outcomes
Adjusted for age and gender

Timepoint	Total Lesion Counts						TVW						MEDW					
	n	MRI measure OR	p=	Model pR^2	MRI measure pR^2	Age and gender pR^2	n	OR	p=	Model pR^2	MRI measure pR^2	Age and gender pR^2	n	OR	p=	Model pR^2	MRI measure pR^2	Age, gender pR^2
0 year	**103**	**1.04 (1.01-1.07)**	**0.004***	**0.177**	**0.142**	**0.035**	87	1.22 (0.77-1.93)	0.409	0.032	0.012	0.02	60	1.05 (0.56-1.95)	0.880	0.031	0	0.031
1 year	**86**	**1.07 (1.03-1.11)**	**0.001***	**0.354**	**0.274**	**0.08**	76	1.55 (0.90-2.65)	0.112	0.107	0.075	0.032	52	1.13 (0.62-2.02)	0.696	0.043	0.002	0.041
5 year	**81**	**1.06 (1.03-1.09)**	**<0.001***	**0.485**	**0.377**	**0.108**	70	1.58 (0.96-2.59)	0.072	0.126	0.124	0.002	**70**	**3.31 (1.56-7.04)**	**0.002***	**0.301**	0.221	0.08
10 year	**62**	**1.04 (1.02-1.07)**	**0.001***	**0.489**	**0.333**	**0.156**	**61**	**1.93 (1.24-3.00)**	**0.004***	**0.321**	0.277	0.044	53	1.39 (0.65-2.97)	0.398	0.108	0.048	0.06
14 year	**52**	**1.03 (1.01-1.05)**	**0.001***	**0.482**	**0.366**	**0.116**	**47**	**2.49 (1.42-4.37)**	**0.001***	**0.508**	0.498	0.01	**47**	**2.60 (1.13-6.02)**	**0.025***	**0.224**	0.149	0.075
20 year	**71**	**1.02 (1.01-1.04)**	**0.001***	**0.305**	**0.271**	**0.034**	**70**	**1.62 (1.21-2.17)**	**0.001***	**0.263**	0.262	0.001	**64**	**7.19 (1.87-27.78)**	**0.004***	**0.260**	0.26	0

Table 4b – Longitudinal models adjusted for baseline predicting 30-year SPMS outcomes
Adjusted for baseline total lesion counts, age and gender

Timepoint	Total Lesion Counts						TVW						MEDW					
	n	OR	p=	Model pR^2	MRI measure pR^2	Age and gender pR^2	n	OR	p=	Model pR^2	MRI measure pR^2	Age and gender pR^2	n	OR	p=	Model pR^2	MRI measure pR^2	Age, gender pR^2
1 year	**86**	**1.10 (1.01-1.21)**	**0.038***	**0.360**	**0.278**	**0.082**	73	1.37 (0.77-2.42)	0.283	0.105	0.071	0.034	41	1.72 (0.66-4.55)	0.266	0.148	0.113	0.035
5 year	**81**	**1.09 (1.04-1.14)**	**<0.001***	**0.516**	**0.405**	**0.111**	67	1.58 (0.90-2.77)	0.113	0.118	0.089	0.029	**50**	**5.10 (1.78-14.49)**	**0.002***	**0.391**	**0.326**	**0.065**
10 year	**62**	**1.04 (1.01-1.08)**	**0.011***	**0.489**	**0.336**	**0.153**	**54**	**1.98 (1.20-3.25)**	**0.007***	**0.321**	**0.279**	**0.042**	32	1.87 (0.55-6.37)	0.315	0.060	0.054	0.006
14 year	**52**	**1.03 (1.01-1.05)**	**0.008***	**0.486**	**0.372**	**0.114**	**46**	**2.55 (1.43-4.55)**	**0.001***	**0.508**	**0.497**	**0.011**	47	2.77 (0.82-9.35)	0.101	0.190	0.153	0.037
20 year	**71**	**1.02 (1.01-1.04)**	**0.001***	**0.307**	**0.274**	**0.033**	**61**	**1.65 (1.20-2.27)**	**0.002***	**0.300**	**0.296**	**0.004**	**64**	**8.85 (1.44-55.56)**	**0.018***	**0.290**	**0.29**	**0**

Table 5 – Lesion count models (separated by location) predicting 30-year SPMS outcomes

Table 5a – Cross-sectional models predicting 30-year SPMS outcomes
Adjusted for age and gender

Timepoint	PV lesions						DWM lesions					
	n	MRI measure OR	p=	Model pR^2	MRI measure pR^2	Age and gender pR^2	n	OR	p=	Model pR^2	MRI measure pR^2	Age and gender pR^2
0 year	**97**	**1.17 (1.04-1.31)**	**0.007***	**0.146**	**0.122**	**0.024**	**97**	**1.06 (1.02-1.10)**	**0.006***	**0.170**	**0.133**	**0.037**
1 year	**82**	**1.25 (1.10-1.42)**	**<0.001***	**0.310**	**0.252**	**0.058**	**82**	**1.10 (1.04-1.17)**	**0.001***	**0.328**	**0.266**	**0.062**
5 year	**81**	**1.34 (1.16-1.54)**	**<0.001***	**0.502**	**0.374**	**0.128**	**81**	**1.07 (1.03-1.11)**	**<0.001***	**0.441**	**0.342**	**0.099**
10 year	**62**	**1.29 (1.12-1.48)**	**<0.001***	**0.545**	**0.356**	**0.189**	**62**	**1.06 (1.02-1.10)**	**0.001***	**0.450**	**0.317**	**0.133**
14 year	**52**	**1.22 (1.09-1.37)**	**<0.001***	**0.553**	**0.403**	**0.150**	**52**	**1.05 (1.02-1.08)**	**0.001***	**0.429**	**0.324**	**0.105**
20 year	**71**	**1.14 (1.07-1.22)**	**<0.001***	**0.363**	**0.318**	**0.045**	**71**	**1.03 (1.01-1.05)**	**0.002***	**0.248**	**0.22**	**0.028**

Timepoint	JC lesions						IT lesions					
	n	MRI measure OR	p=	Model pR^2	MRI measure pR^2	Age and gender pR^2	n	OR	p=	Model pR^2	MRI measure pR^2	Age and gender pR^2
0 year	**97**	**1.54 (1.13-2.11)**	**0.007***	**0.157**	**0.119**	**0.038**	**96**	**3.03 (1.48-6.20)**	**0.002***	**0.259**	**0.237**	**0.022**
1 year	**82**	**1.49 (1.11-2.01)**	**0.008***	**0.222**	**0.141**	**0.081**	**82**	**5.10 (2.01-12.93)**	**<0.001***	**0.445**	**0.417**	**0.028**
5 year	**81**	**1.24 (1.06-1.46)**	**0.007***	**0.261**	**0.152**	**0.109**	**78**	**2.30 (1.39-3.81)**	**0.001***	**0.417**	**0.358**	**0.059**
10 year	**61**	**1.09 (1.01-1.17)**	**0.025***	**0.218**	**0.076**	**0.142**	**55**	**1.96 (1.18-3.26)**	**0.01***	**0.474**	**0.298**	**0.176**
14 year	**50**	**1.10 (1.02-1.18)**	**0.016***	**0.269**	**0.163**	**0.106**	**47**	**1.90 (1.25-2.89)**	**0.003***	**0.505**	**0.354**	**0.151**
20 year	**69**	**1.08 (1.01-1.15)**	**0.021***	**0.147**	**0.118**	**0.029**	**64**	**1.45 (1.12-1.89)**	**0.005***	**0.299**	**0.258**	**0.041**

Table 5b – Longitudinal models adjusted for baseline predicting 30-year SPMS outcomes
Adjusted for baseline lesion counts (with respect to location), age and gender

Timepoint	PV lesions						DWM lesions					
	n	MRI measure OR	p=	Model pR^2	MRI measure pR^2	Age and gender pR^2	n	OR	p=	Model pR^2	MRI measure pR^2	Age and gender pR^2
1 year	**81**	**1.53 (1.12-2.09)**	**0.008***	**0.335**	**0.335**	**0.000**	**81**	**1.16 (1.01-1.32)**	**0.035***	**0.475**	**0.281**	**0.055**
5 year	**80**	**1.60 (1.25-2.03)**	**<0.001***	**0.565**	**0.449**	**0.116**	**80**	**1.12 (1.04-1.20)**	**0.002***	**0.336**	**0.389**	**0.086**
10 year	**61**	**1.31 (1.11-1.55)**	**0.002***	**0.556**	**0.39**	**0.166**	**61**	**1.06 (1.01-1.12)**	**0.016***	**0.461**	**0.353**	**0.108**
14 year	**51**	**1.25 (1.09-1.43)**	**0.001***	**0.571**	**0.455**	**0.116**	**51**	**1.04 (1.01-1.08)**	**0.025***	**0.464**	**0.384**	**0.080**
20 year	**67**	**1.17 (1.07-1.28)**	**<0.001***	**0.402**	**0.362**	**0.040**	**67**	**1.03 (1.01-1.05)**	**0.006***	**0.276**	**0.243**	**0.033**

Timepoint	JC lesions						IT lesions					
	n	MRI measure OR	p=	Model pR^2	MRI measure pR^2	Age and gender pR^2	n	OR	p=	Model pR^2	MRI measure pR^2	Age and gender pR^2
1 year	81	1.44 (0.85-2.41)	0.173	0.230	0.156	0.074	80	2.32 (0.79-6.81)	0.126	0.474	0.45	0.024
5 year	80	1.17 (1.00-1.38)	0.056	0.292	0.195	0.097	**77**	**2.10 (1.15-3.85)**	**0.016***	**0.431**	**0.38**	**0.051**
10 year	60	1.04 (0.97-1.13)	0.274	0.255	0.134	0.121	54	1.34 (0.92-1.97)	0.132	0.570	0.447	0.123
14 year	50	1.06 (0.98-1.14)	0.129	0.339	0.234	0.105	**47**	**1.66 (1.02-2.70)**	**0.041***	**0.522**	**0.387**	**0.135**
20 year	**66**	**1.07 (1.00-1.15)**	**0.044***	**0.199**	**0.145**	**0.054**	60	1.31 (0.98-1.75)	0.070	0.405	0.368	0.037

Table 6 – Clinical measures models predicting 30-year SPMS outcomes

Table 6a – Relapse activity models predicting 30-year SPMS outcomes
Adjusted for age and gender

Timepoint	n	Relapse activity OR	p=	Model pR^2	Relapse activity pR^2	Age and gender pR^2
0-5 years	**95**	**1.81 (1.29-2.54)**	**<0.001***	**0.251**	**0.213**	**0.038**
5-10 years	**87**	**2.57 (1.56-4.22)**	**<0.001***	**0.260**	**0.246**	**0.014**
10-20 years	**94**	**1.47 (1.04-2.08)**	**0.029***	**0.096**	**0.058**	**0.038**

Table 6b – EDSS models predicting 30-year SPMS outcomes
Adjusted for age and gender

Timepoint	n	EDSS OR	p=	Model pR^2	EDSS pR^2	Age and gender pR^2
0 year	100	1.23 (0.89-1.69)	0.207	0.051	0.023	0.028
1 year (nadir)	105	1.25 (0.92-1.71)	0.154	0.058	0.045	0.013
5 year	**105**	**1.89 (1.38-2.59)**	**<0.001***	**0.307**	**0.303**	**0.004**
10 year	**106**	**2.46 (1.71-3.53)**	**<0.001***	**0.512**	**0.501**	**0.011**
14 year	**106**	**2.13 (1.58-2.87)**	**<0.001***	**0.519**	**0.503**	**0.016**
20 year	**107**	**2.83 (1.93-4.17)**	**<0.001***	**0.694**	**0.688**	**0.006**

Table 7 – Additional linear atrophy models predicting 30-year SPMS outcomes

Table 7a – Models considering absolute difference in linear atrophy measures from baseline predicting 30-year SPMS outcomes
Adjusted for age and gender

Timepoint	TVW						MEDW					
	n	MRI measure OR	p=	Model pR^2	MRI measure pR^2	Age and gender pR^2	n	OR	p=	Model pR^2	MRI measure pR^2	Age and gender pR^2
5 year	67	1.32 (0.83-2.09)	0.241	0.081	0.046	0.035	**50**	**0.29 (0.12-0.67)**	**0.004***	**0.344**	**0.281**	**0.063**
10 year	**54**	**1.67 (1.13-2.46)**	**0.01***	**0.239**	**0.199**	**0.040**	32	0.61 (0.20-1.83)	0.374	0.051	0.046	0.005
14 year	**46**	**2.34 (1.39-3.96)**	**0.001***	**0.468**	**0.456**	**0.012**	28	0.45 (0.15-1.33)	0.150	0.125	0.093	0.032
20 year	**61**	**1.51 (1.15-2.00)**	**0.003***	**0.239**	**0.225**	**0.014**	39	0.57 (0.24-1.37)	0.209	0.074	0.066	0.008

Table 7b – Models considering rates of linear atrophy (mm/year x100)* from baseline predicting 30-year SPMS outcomes
Adjusted for age and gender

Timepoint	TVW						MEDW					
	n	MRI measure OR	p=	Model pR^2	MRI measure pR^2	Age and gender pR^2	n	OR	p=	Model pR^2	MRI measure pR^2	Age and gender pR^2
5 year	67	1.01 (0.99-1.04)	0.241	0.081	0.046	0.035	**50**	**0.94 (0.90-0.98)**	**0.004***	**0.344**	**0.281**	**0.063**
10 year	**54**	**1.05 (1.01-1.09)**	**0.01***	**0.239**	**0.199**	**0.040**	32	0.95 (0.85-1.06)	0.374	0.051	0.046	0.005
14 year	**46**	**1.13 (1.05-1.21)**	**0.001***	**0.468**	**0.456**	**0.012**	28	0.89 (0.77-1.04)	0.150	0.125	0.093	0.032
20 year	**61**	**1.09 (1.03-1.15)**	**0.003***	**0.239**	**0.225**	**0.014**	39	0.89 (0.75-1.07)	0.209	0.074	0.066	0.008

$$Rate\ of\ atrophy\ = \frac{Linear\ atrophy\ measure\ at\ a\ given\ time\ time\ point - Linear\ atrophy\ measure\ at\ baseline}{Time\ (years\ from\ baseline\ measure)}\ X\ 100$$

Table 8 – Total lesion count and linear atrophy models predicting 30-year MS-related mortality outcomes

Table 8a – Cross-sectional models predicting 30-year MS-related mortality outcomes
Adjusted for age and gender

Timepoint	Total Lesion Counts						TVW						MEDW					
	n	MRI measure OR	p=	Model pR^2	MRI measure pR^2	Age and gender pR^2	n	OR	p=	Model pR^2	MRI measure pR^2	Age and gender pR^2	n	OR	p=	Model pR^2	MRI measure pR^2	Age, gender pR^2
0 year	**103**	**1.03 (1.01-1.06)**	**0.006***	**0.197**	**0.099**	**0.098**	87	1.00 (0.54-1.83)	0.989	0.067	0	0.067	60	1.37 (0.55-3.40)	0.496	0.256	0.001	0.255
1 year	**86**	**1.04 (1.01-1.07)**	**0.005***	**0.243**	**0.131**	**0.112**	76	1.10 (0.64-1.90)	0.721	0.112	0.013	0.099	**52**	**0.39 (0.15-0.99)**	**0.048***	**0.302**	**0.103**	**0.199**
5 year	**81**	**1.03 (1.01-1.05)**	**0.001***	**0.379**	**0.228**	**0.151**	70	1.08 (0.62-1.87)	0.797	0.207	0.046	0.161	70	0.92 (0.38-2.22)	0.845	0.198	0.002	0.196
10 year	**62**	**1.04 (1.01-1.06)**	**0.004***	**0.560**	**0.162**	**0.398**	61	1.30 (0.90-1.86)	0.164	0.254	0.079	0.175	53	1.24 (0.36-4.29)	0.737	0.342	0.019	0.323
14 year	**52**	**1.03 (1.01-1.05)**	**0.013***	**0.480**	**0.144**	**0.336**	**47**	**1.70 (1.06-2.73)**	**0.028***	**0.405**	**0.301**	**0.104**	47	2.59 (0.74-9.00)	0.137	0.325	0.055	0.270
20 year	**71**	**1.03 (1.01-1.05)**	**0.004***	**0.477**	**0.161**	**0.316**	**70**	**1.99 (1.19-3.35)**	**0.009***	**0.524**	**0.377**	**0.147**	**64**	**17.2 (2.28-125.00)**	**0.006***	**0.509**	**0.416**	**0.093**

Table 8b – Longitudinal models adjusted for baseline predicting 30-year MS-related mortality outcomes
Adjusted for baseline, age and gender

Timepoint	Total Lesion Counts						TVW						MEDW					
	n	OR	p=	Model pR^2	MRI measure pR^2	Age and gender pR^2	n	OR	p=	Model pR^2	MRI measure pR^2	Age and gender pR^2	n	OR	p=	Model pR^2	MRI measure pR^2	Age, gender pR^2
1 year	86	1.058 (0.99-1.13)	0.088	0.249	0.134	0.115	73	1.08 (0.58-2.01)	0.799	0.107	0.01	0.097	41	0.96 (0.26-3.52)	0.951	0.292	0.054	0.238
5 year	**81**	**1.04 (1.01-1.07)**	**0.010***	**0.400**	0.254	0.146	67	1.18 (0.64-2.16)	0.597	0.218	0.066	0.152	50	0.75 (0.24-2.36)	0.619	0.372	0.022	0.350
10 year	**62**	**1.05 (1.01-1.09)**	**0.027***	**0.566**	0.168	0.398	54	1.29 (0.86-1.93)	0.223	0.241	0.067	0.174	32	2.07 (0.20-21.3)	0.538	0.692	0.05	0.642
14 year	52	1.02 (0.99-1.06)	0.237	0.488	0.146	0.342	**46**	**1.68 (1.05-2.70)**	**0.030***	**0.414**	**0.309**	**0.105**	28	3.21 (0.28-37.0)	0.351	0.629	0.052	0.577
20 year	**71**	**1.03 (1.01-1.06)**	**0.008***	**0.481**	0.168	0.313	**61**	**1.98 (1.14-3.44)**	**0.016***	**0.511**	**0.366**	**0.145**	-	-	-	-	-	-

Table 9 – Lesion count models (separated by location) predicting 30-year MS-related mortality outcomes

Table 9a – Cross-sectional models predicting 30-year MS-related mortality outcomes
Adjusted for age and gender

Timepoint	PV lesions						DWM lesions					
	n	MRI measure OR	p=	Model pR^2	MRI measure pR^2	Age and gender pR^2	n	OR	p=	Model pR^2	MRI measure pR^2	Age and gender pR^2
0 year	**97**	**1.13 (1.01-1.26)**	**0.030***	**0.162**	0.087	0.075	**97**	**1.04 (1.01-1.08)**	**0.015***	**0.175**	0.071	0.104
1 year	**82**	**1.17 (1.05-1.31)**	**0.006***	**0.260**	0.172	0.088	**82**	**1.05 (1.01-1.09)**	**0.016***	**0.211**	0.096	0.115
5 year	**81**	**1.11 (1.02-1.20)**	**0.020***	**0.237**	0.124	0.113	**81**	**1.04 (1.02-1.06)**	**<0.001***	**0.365**	0.215	0.150
10 year	**62**	**1.23 (1.07-1.40)**	**0.003***	**0.485**	0.103	0.382	**62**	**1.04 (1.01-1.08)**	**0.006***	**0.519**	0.168	0.351
14 year	52	1.09 (1.00-1.19)	0.057	0.368	0.081	0.287	**52**	**1.04 (1.01-1.07)**	**0.012***	**0.462**	0.150	0.312
20 year	**71**	**1.29 (1.08-1.53)**	**0.005***	**0.637**	0.258	0.379	**71**	**1.04 (1.01-1.06)**	**0.008***	**0.403**	0.126	0.277

Timepoint	JC lesions						IT lesions					
	n	MRI measure OR	p=	Model pR^2	MRI measure pR^2	Age and gender pR^2	n	OR	p=	Model pR^2	MRI measure pR^2	Age and gender pR^2
0 year	**97**	**1.37 (1.04-1.81)**	**0.027***	**0.157**	**0.057**	**0.100**	**96**	**2.10 (1.29-3.43)**	**0.003***	**0.298**	0.201	0.097
1 year	82	1.23 (0.98-1.54)	0.074	0.159	0.035	0.124	**78**	**2.26 (1.40-3.65)**	**<0.001***	**0.450**	0.345	0.105
5 year	81	1.11 (0.98-1.25)	0.096	0.227	0.085	0.142	**82**	**1.83 (1.26-2.66)**	**0.001***	**0.557**	0.426	0.131
10 year	61	1.07 (0.98-1.17)	0.128	0.248	0.003	0.245	**55**	**1.86 (1.23-2.82)**	**0.003***	**0.695**	0.363	0.332
14 year	50	1.06 (0.97-1.16)	0.214	0.289	0.009	0.280	**47**	**2.75 (1.03-7.29)**	**0.043***	**0.778**	0.361	0.417
20 year	69	1.06 (0.98-1.15)	0.167	0.234	0.014	0.220	**64**	**1.67 (1.15-2.43)**	**0.008***	**0.572**	0.240	0.332

Table 9b – Longitudinal models adjusted for baseline predicting 30-year MS-related mortality outcomes
Adjusted for baseline lesion counts (with respect to location), age and gender

Timepoint	PV lesions						DWM lesions					
	n	MRI measure OR	p=	Model pR^2	MRI measure pR^2	Age and gender pR^2	n	OR	p=	Model pR^2	MRI measure pR^2	Age and gender pR^2
1 year	**81**	**1.45 (1.10-1.91)**	**0.008***	**0.319**	0.200	0.119	81	1.04 (0.94-1.15)	0.422	0.209	0.096	0.113
5 year	**80**	**1.34 (1.10-1.63)**	**0.004***	**0.354**	0.185	0.169	**80**	**1.05 (1.01-1.09)**	**0.007***	**0.385**	0.243	0.142
10 year	**61**	**1.20 (1.04-1.38)**	**0.015***	**0.505**	0.115	0.390	**61**	**1.06 (1.01-1.11)**	**0.022***	**0.535**	0.187	0.348
14 year	51	1.08 (0.95-1.23)	0.242	0.376	0.092	0.284	51	1.03 (0.99-1.07)	0.145	0.476	0.147	0.329
20 year	**67**	**1.28 (1.06-1.54)**	**0.011***	**0.642**	0.254	0.388	**67**	**1.04 (1.01-1.07)**	**0.011***	**0.405**	0.137	0.268

Timepoint	JC lesions						IT lesions					
	n	MRI measure OR	p=	Model pR^2	MRI measure pR^2	Age and gender pR^2	n	OR	p=	Model pR^2	MRI measure pR^2	Age and gender pR^2
1 year	81	1.23 (0.72-2.10)	0.444	0.158	0.038	0.12	**80**	**1.97 (1.15-3.39)**	**0.014***	**0.456**	**0.359**	**0.097**
5 year	80	1.14 (0.97-1.34)	0.111	0.238	0.097	0.141	**77**	**1.64 (1.14-2.37)**	**0.008***	**0.569**	**0.428**	**0.141**
10 year	60	1.05 (0.94-1.17)	0.391	0.263	0.005	0.258	**54**	**1.68 (1.03-2.75)**	**0.039***	**0.702**	**0.385**	**0.317**
14 year	50	1.03 (0.91-1.15)	0.659	0.341	0.044	0.297	47	1.84 (0.79-4.30)	0.158	0.794	0.398	0.396
20 year	66	1.06 (0.96-1.16)	0.249	0.235	0.017	0.218	60	1.51 (0.91-2.51)	0.114	0.575	0.323	0.252

Table 10 – Total lesion count and atrophy models predicting 30-year EDSS ≥3.5 outcomes

Table 10a – Cross-sectional models predicting 30-year EDSS ≥3.5 outcomes
Adjusted for age and gender

Timepoint	Total Lesion Counts						TVW						MEDW					
	n	MRI measure OR	p=	Model pR^2	MRI measure pR^2	Age and gender pR^2	n	OR	p=	Model pR^2	MRI measure pR^2	Age and gender pR^2	n	OR	p=	Model pR^2	MRI measure pR^2	Age, gender pR^2
0 year	**103**	**1.04 (1.01-1.07)**	**0.005***	**0.169**	**0.034**	**0.135**	87	1.06 (0.67-1.66)	0.807	0.021	0.001	0.020	60	0.79 (0.42-1.46)	0.447	0.031	0.016	0.015
1 year	**86**	**1.07 (1.03-1.11)**	**0.001***	**0.318**	**0.076**	**0.242**	76	1.51 (0.89-2.57)	0.129	0.095	0.066	0.029	52	0.96 (0.53-1.72)	0.884	0.020	0.001	0.019
5 year	**81**	**1.06 (1.03-1.09)**	**<0.001***	**0.489**	**0.111**	**0.378**	70	1.37 (0.86-2.17)	0.187	0.088	0.053	0.035	**70**	**3.83 (1.73-8.47)**	**<0.001***	**0.333**	**0.270**	**0.063**
10 year	**62**	**1.05 (1.02-1.07)**	**<0.001***	**0.543**	**0.197**	**0.346**	**61**	**2.11 (1.28-3.46)**	**0.003***	**0.377**	**0.290**	**0.087**	53	1.24 (0.59-2.62)	0.574	0.151	0.049	0.102
14 year	**52**	**1.05 (1.02-1.07)**	**<0.001***	**0.606**	**0.164**	**0.442**	**47**	**3.22 (1.58-6.58)**	**0.001***	**0.592**	**0.536**	**0.056**	47	2.00 (0.91-4.41)	0.085	0.197	0.105	0.092
20 year	**71**	**1.03 (1.01-1.05)**	**<0.001***	**0.389**	**0.025**	**0.364**	**70**	**2.14 (1.45-3.15)**	**<0.001***	**0.426**	**0.423**	**0.003**	**64**	**13.5 (2.75-66.67)**	**0.001***	**0.335**	**0.328**	**0.007**

Table 10b – Longitudinal models adjusted for baseline predicting 30-year EDSS ≥3.5 outcomes
Adjusted for baseline, age and gender

Timepoint	Total Lesion Counts						TVW						MEDW					
	n	OR	p=	Model pR^2	MRI measure pR^2	Age and gender pR^2	n	OR	p=	Model pR^2	MRI measure pR^2	Age and gender pR^2	n	OR	p=	Model pR^2	MRI measure pR^2	Age, gender pR^2
1 year	81	1.06 (0.98-1.15)	0.136	0.318	0.242	0.076	73	1.46 (0.80-2.67)	0.213	0.084	0.055	0.029	41	1.28 (0.49-3.33)	0.613	0.185	0.175	0.010
5 year	**86**	**1.10 (1.04-1.16)**	**<0.001***	**0.526**	**0.413**	**0.113**	67	1.42 (0.83-2.44)	0.198	0.087	0.050	0.037	**50**	**12.99 (2.79-62.50)**	**0.001***	**0.565**	**0.526**	**0.039**
10 year	**62**	**1.06 (1.02-1.10)**	**0.005***	**0.553**	**0.366**	**0.187**	**54**	**2.23 (1.26-3.96)**	**0.006***	**0.381**	**0.291**	**0.090**	32	2.38 (0.59-9.52)	0.220	0.199	0.189	0.010
14 year	**52**	**1.05 (1.02-1.08)**	**0.002***	**0.607**	**0.442**	**0.165**	**46**	**3.52 (1.67-7.44)**	**<0.001***	**0.618**	**0.549**	**0.069**	28	2.92 (0.77-11.11)	0.116	0.221	0.174	0.047
20 year	**71**	**1.03 (1.02-1.05)**	**<0.001***	**0.397**	**0.375**	**0.022**	**61**	**2.25 (1.46-3.47)**	**<0.001***	**0.476**	**0.463**	**0.013**	**39**	**21.73 (2.07-250.00)**	**0.010***	**0.415**	**0.395**	**0.020**

Table 11 – Lesion count models (separated by location) predicting 30-year EDSS ≥3.5 outcomes

Table 11a – Cross-sectional models predicting 30-year SPMS outcomes
Adjusted for age and gender

Timepoint	PV lesions						DWM lesions					
	n	MRI measure OR	p=	Model pR^2	MRI measure pR^2	Age and gender pR^2	n	OR	p=	Model pR^2	MRI measure pR^2	Age and gender pR^2
0 year	**97**	**1.16 (1.04-1.31)**	**0.01***	**0.135**	**0.110**	**0.025**	**97**	**1.06 (1.02-1.11)**	**0.008***	**0.166**	**0.130**	**0.036**
1 year	**82**	**1.22 (1.08-1.38)**	**0.001***	**0.263**	**0.209**	**0.054**	**82**	**1.10 (1.03-1.17)**	**0.003***	**0.297**	**0.240**	**0.057**
5 year	**81**	**1.28 (1.13-1.45)**	**<0.001***	**0.432**	**0.314**	**0.118**	**81**	**1.08 (1.04-1.13)**	**<0.001***	**0.470**	**0.366**	**0.104**
10 year	**62**	**1.25 (1.11-1.40)**	**<0.001***	**0.522**	**0.298**	**0.224**	**62**	**1.08 (1.03-1.12)**	**<0.001***	**0.540**	**0.363**	**0.177**
14 year	**52**	**1.22 (1.09-1.37)**	**<0.001***	**0.576**	**0.378**	**0.198**	**52**	**1.08 (1.03-1.13)**	**<0.001***	**0.619**	**0.455**	**0.164**
20 year	**71**	**1.13 (1.06-1.20)**	**<0.001***	**0.319**	**0.282**	**0.037**	**71**	**1.04 (1.02-1.07)**	**<0.001***	**0.366**	**0.346**	**0.020**

Timepoint	JC lesions						IT lesions					
	n	MRI measure OR	p=	Model pR^2	MRI measure pR^2	Age and gender pR^2	n	OR	p=	Model pR^2	MRI measure pR^2	Age and gender pR^2
0 year	**97**	**1.50 (1.09-2.05)**	**0.012***	**0.138**	**0.102**	**0.036**	**96**	**2.66 (1.34-5.29)**	**0.005***	**0.221**	**0.196**	**0.025**
1 year	**82**	**1.49 (1.09-2.05)**	**0.013***	**0.206**	**0.132**	**0.074**	**82**	**4.09 (1.69-9.88)**	**0.002***	**0.374**	**0.346**	**0.028**
5 year	**81**	**1.25 (1.06-1.49)**	**0.009***	**0.255**	**0.148**	**0.107**	**78**	**2.20 (1.33-3.67)**	**0.002***	**0.381**	**0.316**	**0.065**
10 year	**61**	**1.09 (1.01-1.17)**	**0.025***	**0.264**	**0.072**	**0.192**	**55**	**2.02 (1.15-3.55)**	**0.014***	**0.508**	**0.260**	**0.248**
14 year	**50**	**1.10 (1.02-1.19)**	**0.018***	**0.318**	**0.156**	**0.162**	**47**	**2.19 (1.33-3.61)**	**0.002***	**0.592**	**0.350**	**0.242**
20 year	**69**	**1.09 (1.01-1.16)**	**0.018***	**0.162**	**0.137**	**0.025**	**64**	**1.67 (1.15-2.42)**	**0.007***	**0.348**	**0.307**	**0.041**

Table 11b – Longitudinal models adjusted for baseline predicting 30-year SPMS outcomes
Adjusted for baseline lesion counts (with respect to location), age and gender

Timepoint	PV lesions						DWM lesions					
	n	MRI measure OR	p=	Model pR^2	MRI measure pR^2	Age and gender pR^2	n	OR	p=	Model pR^2	MRI measure pR^2	Age and gender pR^2
1 year	**81**	**1.34 (1.02-1.76)**	**0.036***	**0.266**	**0.210**	**0.056**	81	1.10 (0.97-1.25)	0.128	0.296	0.244	0.052
5 year	**80**	**1.42 (1.17-1.73)**	**<0.001***	**0.469**	**0.363**	**0.106**	**80**	**1.16 (1.06-1.26)**	**<0.001***	**0.517**	**0.426**	**0.091**
10 year	**61**	**1.25 (1.09-1.43)**	**0.002***	**0.525**	**0.323**	**0.202**	**61**	**1.10 (1.04-1.18)**	**0.002***	**0.564**	**0.436**	**0.128**
14 year	**51**	**1.25 (1.09-1.43)**	**0.002***	**0.584**	**0.418**	**0.166**	**51**	**1.09 (1.03-1.15)**	**0.002***	**0.633**	**0.505**	**0.128**
20 year	**67**	**1.15 (1.06-1.25)**	**<0.001***	**0.342**	**0.310**	**0.032**	**67**	**1.05 (1.02-1.07)**	**<0.001***	**0.401**	**0.382**	**0.019**

Timepoint	JC lesions						IT lesions					
	n	MRI measure OR	p=	Model pR^2	MRI measure pR^2	Age and gender pR^2	n	OR	p=	Model pR^2	MRI measure pR^2	Age and gender pR^2
1 year	81	1.58 (0.87-2.89)	0.136	0.215	0.146	0.069	80	1.96 (0.76-5.05)	0.166	0.405	0.379	0.026
5 year	80	1.19 (0.99-1.42)	0.059	0.274	0.179	0.095	**77**	**2.13 (1.15-3.91)**	**0.015***	**0.387**	**0.332**	**0.055**
10 year	60	1.05 (0.97-1.14)	0.257	0.287	0.120	0.167	54	1.39 (0.86-2.22)	0.177	0.568	0.376	0.192
14 year	50	1.06 (0.98-1.15)	0.155	0.381	0.223	0.158	**47**	**2.08 (1.16-3.75)**	**0.014***	**0.593**	**0.358**	**0.235**
20 year	**66**	**1.08 (1.01-1.16)**	**0.033***	**0.199**	**0.156**	**0.043**	**60**	**1.52 (1.05-2.22)**	**0.029***	**0.398**	**0.353**	**0.045**