

Disability and magnetic resonance imaging as outcome measures in multiple sclerosis clinical trials

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Background

- Unrelenting disability, the key therapeutic target in multiple sclerosis (MS), embodies its prime social, economic, and medical impact and characterises the progressive phase of the disease, which begins on average a decade after onset.
- Relapse frequency, changes in short-term disability scores, and magnetic resonance imaging (MRI) are still unvalidated, yet widely used surrogates for unremitting disability.
- This and the lack of a consensus definition of disability accumulation, even among trials leading to regulatory approval, motivated the assembly of independent databases from randomised trials and from natural history populations.

Aim

The aim of this patient-based meta-analysis is to assess the quality of widely used MRI and disability outcome measures within a unique database of MS clinical trial placebo arms.

Data

- Statistical analysis was based on the Ian McDonald MS Database of the Sylvia Lawry Centre. This database consists of 58 datasets with about 26 100 patients and about 100 600 patient years (as of July 2008) donated from pharmaceutical industry, universities and research institutions.
- To assure the high quality of statistical analyses the database is randomly split into subsets: an open part which is used for model building and hypotheses generation and a closed part used for validation which is administered by data trustees¹.
- Following completion of the analyses in the open part of the database, major findings were summarised. Specific analyses required to confirm these findings were approved by the SLC Publication Committee and then executed in the closed part of the database.

MRI as outcome measure²

Objective

Evaluation of the additional predictive value of cost-intensive MRI information if 'cheap' clinical parameters are available

Methods

Prediction of

On-study relapses Disability

Models

Poisson models Linear and mixed-effects models

Covariates

T1 newly enhancing lesions T2 lesion volume

age, disease duration, gender, pre-study relapses, disease course, baseline EDSS*

* only included in the model for relapse prediction

Results

- Correlation between the number of newly enhancing lesions and the number of on-study relapses: $r = 0.002$ (RRMS), $r = 0.184$ (SPMS). Correlation between the change in T2 lesion volume and worsening in disability: $r = 0.259$ (RRMS), $r = 0.139$ (SPMS).
- No improvement of predictions of on-study relapses (figure 1) and disability (figure 2) when MRI information is included.

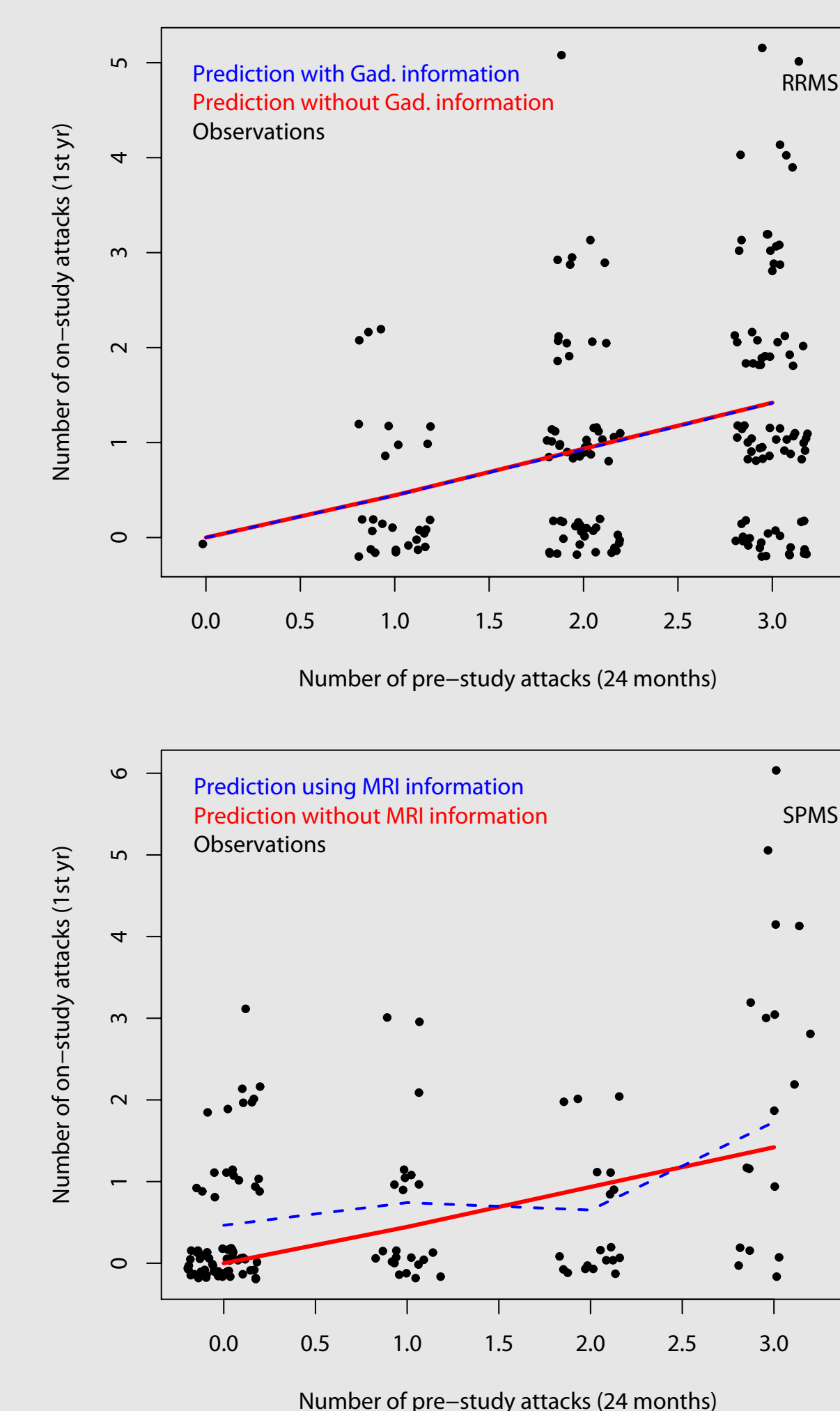


Figure 1: Prediction of on-study relapse rates using Poisson regression models for patients with relapsing-remitting MS (RRMS, N = 120) and secondary progressive MS (SPMS, N = 151).

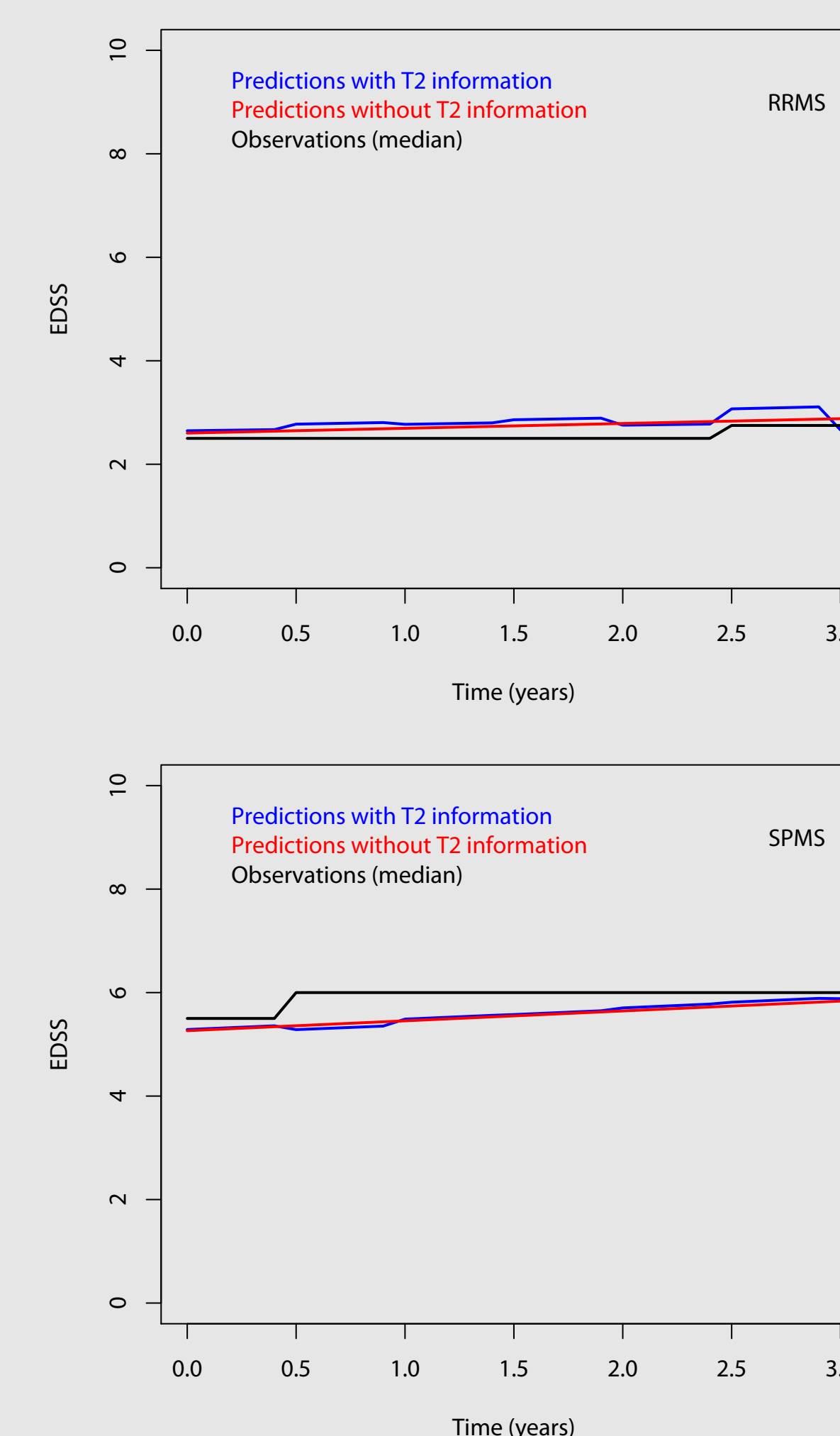


Figure 2: Prediction of the longitudinal EDSS course using linear mixed effects models for patients with relapsing-remitting MS (RRMS, N = 559) and secondary progressive MS (SPMS, N = 544).

Disability as outcome measure³

Objective

Disability is measured on a ordinal 10-point ambulation-centred scale (EDSS). Serial in-trial changes of 0.5 or 1.0 points on this scale, unconfirmed or confirmed for 3-6 months, are frequently used as endpoint in clinical trials. **Is it justified to use short-term changes in disability to demonstrate treatment efficacy in a long-term disease?**

Methods

Comparison of the probability of worsening vs improvement in disability to measure how much worsening was attributable to noise (random variation, measurement error, ...)

Results

In relapsing-remitting MS disability progression is no more likely than similarly defined improvement. Many patients who meet frequently used disability criteria for treatment failure in MS trials must do so by random variation/measurement error.

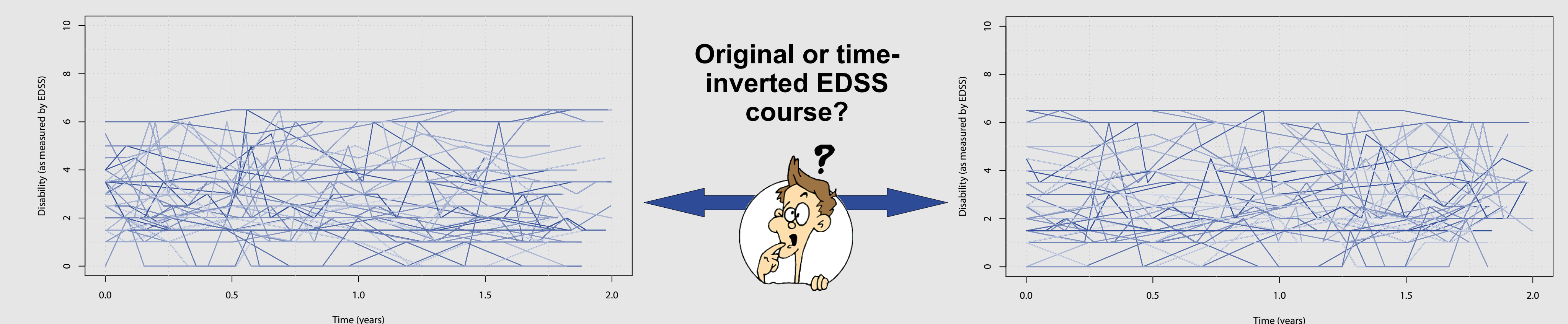


Figure 3: Disability evolution of 50 randomly selected placebo patients with relapsing-remitting MS during a clinical trial (data truncated at 2 years to simulate a 2-year trial). Which figure shows the original EDSS course and which the time-inverted course?

Conclusions/Outlook

- If information on demographic and clinical parameters is available, MRI information has no additional predictive value for the prediction of relapses and disability in a trial context.
- Short-term changes in disability may be attributable to noise and are therefore not justified to be used as surrogate marker for unremitting disability.
- There are severe deficits in the quality of widely used outcome measures in MS clinical trials. The analyses highlight the difficulty in determining effectiveness of therapy in chronic diseases. We believe that IT platforms to measure physical activity, such as actiBelt^{®4}, have great potential to be developed in meaningful, patient-oriented outcome measures and can moreover be used as monitoring tool for exercise therapy^{5,6}.

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