The association between disability progression, relapses, and treatment in early relapse onset MS: an observational, multi-center, longitudinal cohort study

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Abstract

The contribution of multiple sclerosis *relapses* to *worsening of disability*, and vice-versa, remains unclear. Vitamin D supplementation (VitD) and disease modifying therapies (DMTs) are potential modulators of this association. Understanding how these endo-phenotypes interact may provide insights to disease pathogenesis and treatment practice. Here, we examined independent associations between *relapses* and *treatment* and the risk of *worsening of disability*, and vice-versa. We find suggestive evidence that early *relapses* predict early *worsening of disability* but do not contribute to long-term worsening. Conversely, the effects of *worsening of disability* on *relapse* risk was pronounced and persisted. VitD and DMTs interacted significantly to markedly reduce the risk of future *relapses* and *worsening of disability*, particularly when commenced early. Personalised real-time survival probabilities revealed individuals having higher risk of future worsening. *Worsening of disability* in ROMS occurs in ways not clearly tied to *relapses* and is strongly linked to an increased risk of future *relapses*.

Introduction

Multiple sclerosis (MS) is clinically a complex disease with 2 seemingly disparate clinical phenotypes characterised by relapses and inexorable disability progression. These 2 features can occur concurrently or be temporally separated, and are the basis for classification of MS into the well-recognised clinical phenotypes of relapsing-onset MS (ROMS) and progression onset MS (POMS). However, despite this dichotomy, the contribution of relapses to disability worsening, and vice-versa, is not well understood. Understanding the interactions between these 2 clinical phenomena; and the temporal interaction with each other and treatment may provide insights into the pathogenesis and treatment of MS disease progression.

Some studies have demonstrated the predictive value of early relapses on worsening of disability in the short[1,2], and long term[3-10]; whereas others[11-14] have reported a dissociating and decreasing impact, of either early or late relapses on longer term disability accrual. However, there is considerable evidence for there being no effect of relapses on long-term disability accrual from observational studies in ROMS[14-19] and secondary progressive (SPMS)[14,20-22]. For instance, in Tremlett *et al.,*[11,23] disability accrual in patients with SPMS was attributed to the effect of chronologic age and disease duration, with the milestones of EDSS (Expanded Disability Status Scale) 4 and 6 being reached on predefined visits not influenced by relapses. In this regard, SPMS can be regarded as ROMS in which the relapsing phase has ended[5,24]. By reasoning, if the progressive accumulation of disability in SPMS or POMS occurs regardless of relapses, then it could be hypothesised that relapses may have little bearing on subsequent worsening events in ROMS. But whether relapses have an independent effect on disability accrual in the relapsing phase of ROMS is unclear. Kappos *et al.,*[17] showed that most disability accumulation was not predicted by relapses; and Ahrweiller *et al.,*[12] demonstrated a decreasing impact of late relapses on disability worsening. An important limitation to all the above cited

studies is that they focused on the direct, rather than the indirect underlying cause. Additionally, most of the direct associations were based on statistically inefficient endpoints (e.g. either 3 or 6 months confirmed disability progression, annualised relapse rates, annualised EDSS) which did not capture the continuous-time evolution of the MS disease course in terms of EDSS transitions, and have been criticised for overestimating disability accrual in short-term clinical trials[25]. Importantly, the indirect residual effects of treatment, including clinical and environmental disease modifiable risk factors such as: age, sex, time-dynamic body mass indices [BMI], smoking status, brain MRI white matter T2 lesion counts, and relapse counts[19], were not estimated out in the models analysing the direct associations, therefore these factors may potentially confound both endpoints[19].

The association between relapses and worsening of disability is methodologically complex. Whether both outcomes are mutually exclusive manifestations of the same underlying disease process without a direct causal-effect relationship, or whether they are cause-effect (or indirectly) related[17]. and in which direction, is unclear. The solution is complex, as the true associations need to be (re)-estimated in the presence of potential confounders (listed above)[19] while adjusting for the dynamic effects of treatments. Notably, most predictive models used in past MS studies have either underestimated the true associations or fail to adjust for treatment effects despite promising results from MS trials. For instance, there is extant evidence from large relatively short phase 3 clinical trials that disease-modifying therapies[8,26-28] (DMTs) (and potentially use of vitamin D [VitD] supplements[29]) approved for the treatment of relapses modulate a variety of largely inflammatory molecular pathways to reduce relapse rates, and the accumulation of disease burden, particularly, as measured by new MRI T2 white matter lesions (T2L)[19,29-31]. However, their effects on long-term disability accrual is less clear, although likely to have a positive long-term benefit[19,31].

VitD deficiency and low sunlight exposure are among the strongest risk factors for developing MS, but the results of VitD supplementation trials in established MS have been underwhelming[29,32,33]. These unexpected results, may be attributed to the timing of supplementation, the dosage used, or that observational studies usually measure ultraviolet B (UVB) derived VitD; whereas clinical trials have used oral VitD supplements[33]. Additionally, many of the completed studies used VitD supplements as add-on therapies to DMTs, and prior work has shown a synergistic effect of VitD and DMTs in modulating relapse risk in cohort studies[34-36]. However, how the use of VitD supplements and DMTs interact to modulate the association between relapses and disability accrual is unknown. The challenge is to accurately model these associations while adjusting for baseline disease burdens. Joint models for analysing associations between a longitudinal biomarker and a survival endpoint are well established[37]; and are useful statistical methods for analysing direct and indirect associations between relapses and worsening of disability in MS patients.

Previously established genetic markers associated with MS risk[38] and disability progression[19] are suitable inputs for joint models[19]. Their cumulative effects [obtained through the construction of genetic prognostic indexes (GPI) that predict relapse risk (relapse-specific GPI, RS-GPI), and worsening risk (worsening-specific GPI, WS-GPI)] are not invariant to MS disease duration under cross-validation[19]. The developed indexes have been shown to predict substantial phenotypic variations in terms of relapse risk (r^2=*73%*) and worsening risk (r^2=69%), and are potentially useful prognostic tools for analysing indirect associations in these endpoints[19].

Therefore, we aim to examine the indirect associations between relapses and worsening of disability by analysing jointly, the individual characteristics of disease progression captured in the GPIs in the presence of potential confounders. We also aim to assess the effects of VitD

supplementation and duration of DMT use, and whether the timing of these interventions affects the relapse rate and risk of disability accrual over time.

Materials and Methods

Data, study cohort, and inclusion criteria

We used clinical data pooled from the multi-centre (Brisbane, Newcastle, Geelong and Western Victoria, and Tasmania) Australian Longitudinal Prospective Cohort Study (AUSLONG) of MS participants enrolled between 2003 and 2006[39]. We analysed 253 (N=2453 EDSS transitions) cases with up to 10 years of follow-up after their first clinical presentation with central nervous system demyelination (FDE); and who had been diagnosed as either ROMS (N=219) or remained as clinically isolated syndrome (CIS) by 10 years (N=34). All cases were defined using the 2017 McDonald criteria[40].

Endpoint definitions

Confirmed MS relapses*:* MS relapses were defined as the appearance of new or worsening neurological symptoms, or worsening of previously stable or improving pre-existing neurological deficits (not caused by fever or a known infection), and lasting more than 24 hours. Confirmed MS relapses were defined as MS relapses accompanied by a clinically meaningful change in EDSS (e.g., a 0.5-point increase in EDSS) or functional scores (including new MRI T2 white matter lesions), and confirmed by trained and certified neurologists. All investigator-reported relapses were included in the statistical analysis.

Worsening of disability*:* EDSS scores were measure by trained and certified neurologists face-to-face at baseline, 2-3yrs, 5yrs, and 10yrs; and validated telephone EDSS was measured at intervening yearly time points. All face-to-face EDSS were confirmed at each clinical visit, while the telephone

EDSS were validated according to previous MS studies[41-45]. Worsening events were based on EDSS, and were statistically defined using a first-order Markov assumption that captures the continuous-time evolution of EDSS.[19] Specifically, we posit that the current EDSS score depended on the previous score, and the time between observations is continuous rather than discrete[46]. Definition of a "*worsening*" (increase in EDSS) versus "*improved*" (decrease in EDSS) events was achieved through data transformation using the "*msm2Surv*" survival function in *mstate* R-package[47]. Because participants entered the study at different times, we defined the *time-to-worsening* of disability *t*, as the continuous time elapsed since MS diagnosis until the current observation. By default, *t*=0 at study entry to enable comparison of the baseline hazards. At stable-state transitions (*no change in EDSS*) we assumed there was no improvement or disability progression; and therefore, were considered non-informative censoring events. Because the latter events could lead to "*likelihood drainage*", and potentially alter the associations, they were excluded from the analysis. Unless specifically noted, we considered a decrease in EDSS as informative censoring in the survival analysis.

Statistical Analysis

Analysing the time-to-relapse

The association between confirmed MS relapsing events (Y) and worsening of disability events (X) is graphically depicted on Fig. 1. In the first instance, we let X to be our exposure variable of interest, and Y as the endpoint in the relationship $X \rightharpoonup Y$, assessing the indirect effects of worsening events MS relapses. The residual effects estimate $\beta_{XY}^{(x)}$ representing this association was obtained using a three-stage procedure.

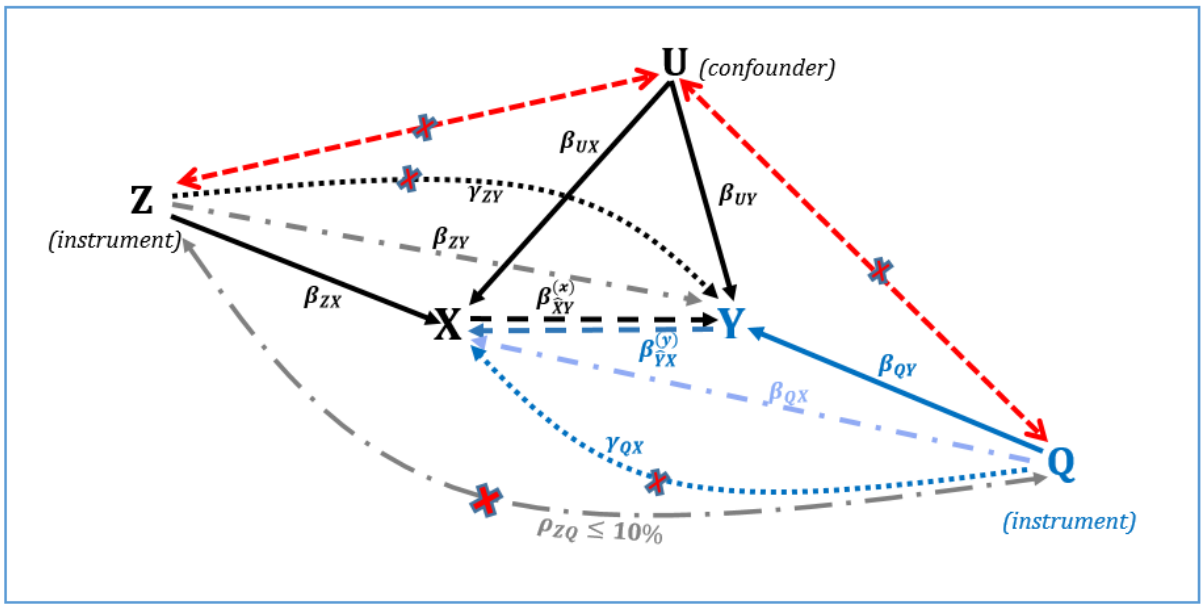

Figure 1. A graphical depiction of the complex relationship between relapses (Y) and worsening of disability (X). $\beta_{\tilde{X}Y}^{(x)}$ and $\beta_{\tilde{Y}X}^{(y)}$ are the indirect association parameters, all other parameters represent direct associations. Associations not allowed are indicated by red cross. The correlation ρ_{ZQ} between the genetic instruments Q and Z is kept below 10%.

Stage 1: Constructing a time-dependent WS-GPI. A Cox model was used to construct a time-dependent *WS-GPI* for the exposure X, which is independent of a defined set of potential clinical and environmental confounders U, by regressing X on a pre-determined set of genetic markers Z that were predictive of X. The set Z of genetic markers used were those related to MS risk,[38] and long-term disability progression[19]. By definition, a factor was considered a potential confounder and included in the set U, if it was directly associated with both X (β_{UX}) and Y (β_{UY}). Based on our previous analyses[19]; the age at FDE, sex, BMI, relapse counts, and T2L counts were potentially confounding. Specifically, smoking status did not pass the threshold (P<0.05) for inclusion despite its clinical relevance[19].

Stage 2: Predicting the evolution of the WS-GPI. A Bayesian mixed-effect longitudinal sub-model was then used to estimate the non-linear subject-specific profiles (predicted values) of the *WS-GPI* over natural cubic splines of time, with two internal knots placed at the 33rd and 66th percentile of the follow-up times. Boundary knots were set at 0.5 and 13 years.

Stage 3: Estimating association parameters. The final step was to estimate the association parameter $\beta_{\hat{X}Y}^{(x)}$. To achieve this, the predicted values of the *WS-GPI* obtained from stage 2 were then regressed against Y to predict the risk for relapse, using a univariate constant coefficient joint model (CCJM). Because EDSS evolves continuously in time, we fitted flexible univariate varying coefficient joint model (VCJM)[37,48], and compared their predictive performance with the CCJM. Because different features of the *WS-GPI* could indirectly influence the relapse-free survival process, we examined three hypothesises, each relating the underlying residual (indirect) effects of the worsening events (captured in the *WS-GPI*) to the risk of relapse. Specifically, we hypothesised that relapse risk depends on the (1) *current value* (CV*)*, (2) *current value and slope* (CVS), and (3) *cumulative effects* (CE) of the predicted value of *WS-GPI*, respectively. To allow comparison between CCJM and VCJM, we approximated the baseline hazards of the CCJM with penalized P-splines[48].

Analysis of time-to-worsening of disability

Note that the analysis of the *time-to-worsening of disability* is the exact opposite and replica of the analysis of *time-to-relapse* described above. In other words, we analysed the *time-to-worsening of disability* now considering a reversed direction of the association ($X \leftarrow Y$) between the endpoints, wherein X (worsening events) is now our endpoint of interest, and Y (relapse) is the exposure variable. Similarly, we constructed a *RS-GPI* by regressing Y on a different set of predetermined genetic markers Q (where $Q \notin Z$, and the correlation coefficient $\rho_{QZ} \leq 10\%$) that were predictive of Y in the presence of potential confounders U (mentioned above). The parameter $\beta_{\hat{Y}X}^{(y)}$ representing the reversed association $X \leftarrow Y$ (relapses predict worsening events) was estimated using two statistical formulations in both the CCJM and VCJM. In the first model, we posit that the risk for the worsening endpoint X depends on the CV, CVS, and the CE of the *RS-GPI*; while in the second model, we posit that it depends on

the 3- and 6-months' time-lagged values of *RS-GPI*, achieved using time-lagged survival models. Lagging the actual times 3 and 6 months to observing a worsening events reduces the influence of the direct effects of relapses (captured in *RS-GPI*) on EDSS scores measured during the relapse phase[5,17]. This time-lagged survival analysis gives an unbiased estimate of the association parameters ($\beta_{\hat{Y}X}^{(y)}$ at 3 months versus $\beta_{\hat{Y}X}^{(y)}$ at 6 months) and avoid overestimating the long-term effects of worsening events on future relapses, and vice-versa[19,25].

Adjusting for (dynamic) treatment effects

We included in our joint model interactions of the *WS(RS)-GPI* with VitD supplements only, DDMT only, and VitD×DDMT; and determine the best component using deviance information criterion (DIC). The DMT variables used were the duration of 1st-line therapy (interferons and glatiramer acetate), 2nd-line therapy (oral therapies teriflunomide, and dimethyl fumarate), and 3rd-line therapy (natalizumab alemtuzumab and fingolimod). As this cohort was recruited before routine use of 2nd and 3rd-line therapies, there were too few cases on 2nd line therapy to be included; and therefore, the time spent without medication (duration of disease without DMT) formed our reference category. To assess whether earlier effects of treatment affected the (relapse)worsening-free survival, we fitted time-lagged survival models as above, and estimated the time-dynamic profiles of both treatments (including interactions) under the CCJMs assumption using non-parametric bootstrap resampling. Specifically, we estimate the effects of treatment at intervals of 30 days apart, assuming 365.25 days per year, to 2 years from FDE.

Statistical software and inference

The Bayesian approach to estimation of joint models implemented in the "*JMBayes2*" Rpackage[49] was used to analyse the data. We trained mixed-effects and survival models using observations at the current visit (the current epoch) and used it predict future outcomes. That

is at each participant visit, we fitted joint models (described above) and dynamically updated the predictions using future outcomes; and obtained person-specific survival probabilities in real-time. The posterior means and 95% credible intervals were used to ascertain the statistical significance. The time-dynamic area under the receiver operating characteristic curve (AUC(t, Δt)) and dynamic prediction errors (PE$(t, \Delta t)$) were used to assess model performance in real-time. We used follow-up times t=2.5, 5, 7.5 years, and a prediction window of width Δt =2.5 years.

Data availability

The R-codes and Outputs are given in the supplementary material (Web-Appendix A). The AUSLONG data are not publicly available due to privacy and ethical restrictions but can be obtained from the AUSLONG Investigators

Results

Cohort characteristics

Participants across the four centres had similar baseline characteristics. In the analysis cohort, the mean age at study entry was 37 years (SD=9 years). Additional characteristics are given in Table 1.

Table 1. Cohort characteristics, demographics, and follow-up times

Female/male	*196/57*
Mean age at onset female/male (yrs)	*37.6/37.4*
Median EDSS at onset female/male	*1.5/1.0*
Median EDSS at diagnosis female/male	*2.0/1.5*
Median EDSS at year 10 female/male	*2.0/2.0*
Average follow-up from onset female/male (yrs)	*8.8/8.2*
Average follow-up from diagnosis female/male (yrs)	*7.1/7.9*
Average time to first relapse female/male (mnths)	*8.4/6.7*
Mean T2L count at baseline female/male	*8.5/8.0*
Mean T2L count at year 10 female/male	*9.1/8.4*
Relapse rates per year female/male	*0.2/0.2*
Mean body mass index at baseline female/male	*26.4/28.9*
Mean body mass index at year 10 female/male	*27.0/28.3*
Average disease duration at year 10 female/male (yrs)	*9.9/8.6*

Model selection

We observed better discriminative capability and prediction accuracy for the VCJM compared to the CCJM (Table S1). Based on higher AUC and smaller PE values, the CVS models are preferred. Also, the VCJM is preferred over the CCJM in explaining the relapse dynamics. Fig. S1 provide further evidence that favours the use of a VCJM over CCJM. In the CCJMs (CVS model), interactions of VitD and DDMT is preferred (see DIC on Table S2). Table S3 gives estimates for the parameters describing the non-linear profile of the *WS*- and *RS-GPIs* over time, with good discriminative capabilities.

Estimation of potential confounding effects

We have previously shown that disability worsening has a direct significant impact on relapse risk (HR=1.60; P≤0.01), but the reverse was not supported when predicting the risk for worsening (HR=1.12, P=0.34)[19]. In that study, we estimated the direct effects of factors including sex, age at FDE, relapse counts, and BMI in each survival endpoint. In this study (Table 2), these factors were used as potential confounders, and we observed consistent effects when estimating the association parameters. Particularly, we found positive effects of baseline T2L counts on relapse risk without adjustment for treatment, a statistically non-significant effect in the presence of VitD supplementation, and a borderline effect after adjusting for DDMT. A non-significant hazard was obtained after adjusting for the combination of treatment effects. These results suggest that the combined effects of VitD supplementation and DMTs is required to fully mitigate the effects of baseline T2L counts on subsequent relapse events. We also observed positive effects of baseline T2L count on the risk of worsening regardless of the beneficial effects of treatment. These results suggest a strong persistent effect of baseline T2L count on the risk of future worsening events.

Table 2. Constant coefficient joint models: Posterior means (Est) and 95% credible intervals (C.I) for the parameters in the current value (CV) and current slope (CS) models with and without adjustment for the effects of vitamin D supplementation (VitD) and duration of disease-modifying therapies (DDMT).

Mean components:	Unadjusted		VitD-adjusted		DDMT-adjusted		VitD & DDMT-adjusted	
Effects	Est	(95% C.I)	Est	(95% C.I)	Est	(95% C.I)	Est	(95% C.I)
Analysing time-to-relapses (N =856 relapsing events)								
Confounding effects								
Sex(Male)	-0.471	(-0.497; -0.445)	-0.262	*(-0.832; 0.179)*	-0.186	*(-0.205; -0.168)*	-0.331	*(-0.358; -0.304)*
Age at FDE	0.009	*(0.008; 0.010)*	0.012	*(-0.012; 0.032)*	-0.015	*(-0.016; -0.013)*	-0.012	*(-0.013; -0.011)*
Body mass index	-0.114	*(-0.159; -0.069)*	-0.062	*(-0.590; 0.481)*	0.374	*(0.322; 0.426)*	0.887	*(0.849; 0.926)*
Relapse counts	0.312	*(0.303; 0.320)*	0.226	*(-0.024; 0.443)*	0.390	*(0.379; 0.402)*	0.356	*(0.346; 0.366)*
T2 lesion counts	0.182	*(0.154; 0.210)*	0.045	*(-0.266; 0.427)*	0.020	*(0.009; 0.031)*	-0.003	*(-0.014; 0.009)*
Association parameters								
WS-GPI_Value	0.919	*(0.892; 0.945)*	0.811	*(0.238; 1.287)*	1.086	*(1.068; 1.104)*	1.001	*(0.987; 1.014)*
WS-GPI_Slope	0.895	*(0.652; 1.138)*	1.685	*(1.623; 1.748)*	1.207	*(1.063; 1.351)*	1.084	*(0.968; 1.199)*
WS-GPI_Value×VitD(Yes)			-0.745	*(-0.759; -0.730)*			-0.541	*(-0.572; -0.510)*
WS-GPI_Slope×VitD(Yes)			-1.021	*(-1.110; 0.931)*			-0.580	*(-0.861; -0.299)*
WS-GPI_Value×DDMT(Cat. 1)					-0.387	*(-0.542; -0.233)*	-0.018	*(-0.109; 0.073)*
WS-GPI_Slope×DDMT(Cat. 1)					-0.648	*(-0.879; -0.417)*	-0.646	*(-0.854; -0.437)*
WS-GPI_Value×DDMT(Cat. 3)					-0.984	*(-1.142; -0.827)*	-1.032	*(-1.159; -0.905)*
WS-GPI_Slope×DDMT(Cat. 3)					1.207	*(1.063; 1.351)*	-1.105	*(-1.330; -0.879)*
WS-GPI_Value×VitD(Yes)×DDMT(Cat. 1)							-0.877	*(-1.109; -0.644)*
WS-GPI_Slope×VitD(Yes)×DDMT(Cat. 1)							-0.200	*(-0.414; 0.015)*
WS-GPI_Value×VitD(Yes)×DDMT(Cat. 3)							-0.354	*(-0.604; -0.104)*
WS-GPI_Slope×VitD(Yes)×DDMT(Cat. 3)							-0.855	*(-1.054; -0.655)*
Analysing time-to-worsening of disability (N = 481 worsening events)								
Confounding effects								
Sex(Male)	-1.908	*(-1.948; -1.868)*	-1.464	*(-1.506; 1.421)*	-1.431	*(-1.472; -1.390)*	-1.718	*(-1.761; -1.676)*
Age at FDE	-0.014	*(-0.015; -0.013)*	-0.016	*(-0.016; 0.015)*	-0.015	*(-0.015; -0.014)*	-0.023	*(-0.024; -0.022)*
Body mass index	0.025	*(0.022; 0.027)*	0.024	*(0.023; 0.025)*	0.018	*(0.017; 0.020)*	0.006	*(0.005; 0.007)*
Relapse counts	0.080	*(0.067; 0.094)*	0.037	*(0.027; 0.046)*	-0.005	*(-0.014; 0.004)*	0.052	*(0.041; 0.063)*
T2 lesion counts	0.949	*(0.920; 0.977)*	0.611	*(0.588; 0.635)*	0.613	*(0.587; 0.639)*	1.100	*(1.070; 1.130)*
Association parameters								
RS-GPI_Value	1.513	*(1.436; 1.589)*	1.113	*(1.074; 1.153)*	1.238	*(1.192; 1.284)*	2.759	*(2.688; 2.829)*
RS-GPI_Slope	-2.517	*(-3.259; -1.774)*	-1.401	*(-1.683; 1.119)*	-1.580	*(-1.880; -1.280)*	-1.729	*(-2.041; -1.417)*
RS-GPI_Value×VitD(Yes)			-0.143	*(-0.172; 0.114)*			-0.933	*(-0.968; -0.898)*
RS-GPI_Slope×VitD(Yes)			0.152	*(-0.736; 1.039)*			1.234	*(0.706; 1.762)*
RS-GPI_Value×DDMT(Cat. 1)					-0.302	*(-0.365; -0.239)*	-0.954	*(-1.219; -0.689)*
RS-GPI_Slope×DDMT(Cat. 1)					-0.648	*(-0.879; -0.417)*	-0.454	*(0.115; 0.793)*
RS-GPI_Value×DDMT(Cat. 3)					-0.984	*(-1.142; -0.827)*	-0.729	*(-1.159; -0.905)*
RS-GPI_Slope×DDMT(Cat. 3)					0.443	*(-0.151; 1.037)*	0.454	*(0.115; 0.793)*
RS-GPI_Value×VitD(Yes)×DDMT(Cat. 1)							-0.768	*(-1.173; -0.367)*
RS-GPI_Slope×VitD(Yes)×DDMT(Cat. 1)							0.302	*(-0.031; 0.635)*
RS-GPI_Value×VitD(Yes)×DDMT(Cat. 3)							-0.670	*(-0.911; -0.429)*
RS-GPI_Slope×VitD(Yes)×DDMT(Cat. 3)							-0.407	*(-0.745; -0.069)*

DDMTs (Cat. 1): duration of DMT category 1; DDMTs (Cat. 3): duration of DMT category 3; Each column represents a CCJM with (without) adjustment for treatment, and parameters not included in that model have empty cells. Association parameters *WS-GPI_(.)* and *RS_GPI_(.)* are allowed to interact with VitD and/or DDMT.

The indirect effects of worsening events on relapse risk

The association parameters relating the indirect effects of worsening events (captured in *WS-GPI*) with the risk for relapse under the CCJM are shown in Table 2. After adjusting for combined treatment effects (Table 2), we found positive associations between the value and slope of *WS-GPI* and the risk for relapse. For every 1 year post FDE, each 1-unit increase in the value of the *WS-GPI* is associated with a 2.72-fold increase in a person's relapse risk without VitD supplementation and DMT use; a 1.58-fold increase on VitD supplementation alone; a 2.67-fold increase for on 1st-line DMT alone; a 0.97-fold decrease on 3rd-line DMT alone; a 0.65-fold decrease on both VitD supplementation and 1st-line DMT combined; and a 0.40-fold decrease in relapse risk with VitD supplementation and 3rd-line DMT combined (See Web-Appendix B on how to compute these values using Table 2). Similar observations were made regarding the associations between the slope of *WS-GPI* and risk of relapse with(without) treatment effect, respectively.

Graphical estimates of the VCJM (Table S4) are shown on Fig. 2A. From FDE (*t=0*), we observed non-linear effects for increasing values of *WS-GPI* on the relapse-free survival, whereas the effect of the slope increased linearly with time. Specifically, 3 years post FDE, for individuals having the same sex, BMI score, T2L counts, relapse counts, and same value of *WS-GPI* at baseline, the log-hazard ratio for 1-unit increase in the slope of *WS-GPI* is 2.4. However, 6 years post FDE, this effect increases to 4.6. These results suggest that worsening events are predictive of relapses (indirectly via the *WS-GPI*) and increases the risk of subsequent relapses with time. These effects were modulated and reversed by individual and combined treatment effects, respectively.

The indirect effects of relapses on worsening risk

There were no significant differences in the association parameters obtained before and after lagging the survival times, suggesting no bias in the EDSS scores that could be attributed to concurrent relapses. The results of the models without lagging the survival times are presented in Table 2. The CSV of *RS-GPI* were associated with the risk of worsening under the CCJM. Whereas the current values increased the risk for early worsening, we observed an inverse relationship with the slopes. Each 1-unit increase in the value of *RS-GPI* is associated with a 15.78-fold increase in worsening risk without VitD supplementation and DMT use; a 6.21-fold increase with VitD supplementation alone; a 6.08-fold increase on 1^{st}-line DMT alone; a 7.61-fold increase on 3^{rd}-line DMT alone; a 1.11-fold increase on VitD supplementation and 1^{st}-line DMT combined; and a 1.53-fold increased risk for worsening with VitD supplementation and 3^{rd}-line DMT combined.

Graphical estimates of the VCJM results (Table S5) are shown in Fig. 2B. Specifically, holding all other effects constant, the residual effects of relapses (captured in the *RS-GPI*) have a decreasing impact on the worsening-free survival from FDE ($t=0$) with an initial log-hazard of 3.4, trending towards the null (log-hazard$\simeq$0) at $\simeq$2.5 years post FDE. Hereinafter, these effects diminish with subsequent worsening events. A similar trend is observed with the slopes. These results suggest that relapses have a decreasing impact on worsening events over time, and do not positively impact worsening after 2.5 years post FDE, and are significantly mitigated by individual, and combined treatment.

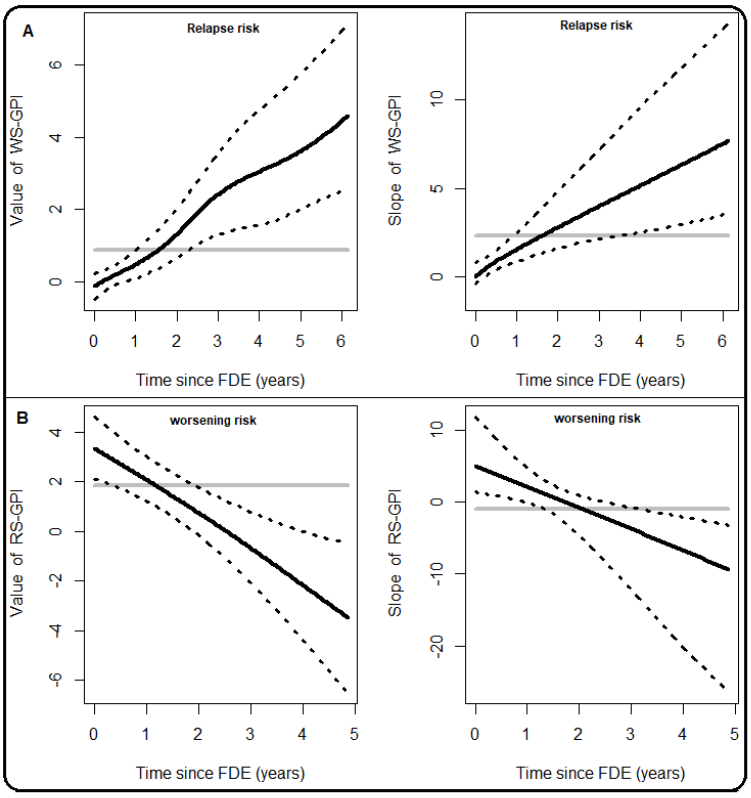

Figure 2. Time-dynamic association estimates. (A). The estimated residual effects ($\beta_{\tilde{X}Y}^{(x)}$) of worsening events on relapse risk. B. The estimated residual effects ($\beta_{\tilde{Y}X}^{(y)}$) of relapses on worsening risk. The posterior means (black lines) and 95% credible intervals (dash lines) obtained from the VCJM are presented. The grey solid lines denote the mean residual estimates obtained from CCJM.

Timing of treatment effects on relapse and worsening risk

Time-dynamic associations and treatment effects are presented in Fig. 3. Each point on the plot represents the histories of *RS-GPI* and *WS-GPI*, each adjusted for treatment effects. We observed stronger evidence of *earlier* versus *current* values of *WS-GPI* and *RS-GPI* effect on the relapse-free (Fig. 3A) and worsening-free survival (Fig. 3B). Regarding the *earlier* versus *current* effects of all treatments, we recorded marginal benefits within 2 years from FDE in terms of the relapse-free survival (Fig. 3C), but not on the worsening-free survival (Fig. 3D).

Thus, a longer duration of treatment is required to marginally reduce the risk of worsening. Overall, the timing of treatment is important in reducing the risk of disability progression.

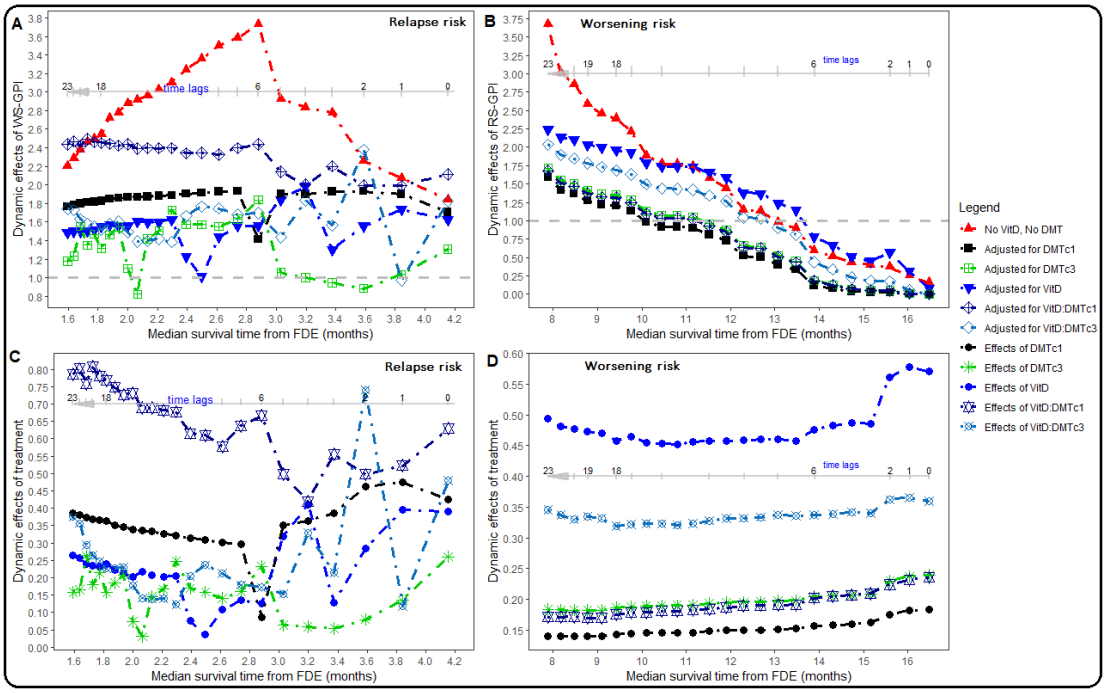

Figure 3. Time-dynamic association parameters for the current value of the WS-GPI (A) & RS-GPI (B), adjusted for dynamic treatment histories (C & D). Each point on the plot is a doubly-robust estimate obtained from bootstrapping the posterior means.

Person-specific dynamic time-course predictions.

In Fig. 4, we present real-time personalised predictions for a 35 years old male who was diagnosed with MS 7 years after his FDE. Each time he was assessed, his relapse-free (Fig. 2A) and worsening-free (Fig. 4B) survival probabilities were updated simultaneously. Specifically, 2 years after observing his first value for *WS-GPI*, his relapse-free probability is ≃0.82, while 2 years after his last visit, this probability is ≃0.31. Conversely, his worsening-free probability (Fig. 4B) is ≃0.96 2 years after observing his first value for *RS-GPI*, and ≃0.71 2 years after observing the last value. Similar observations were made for the remaining participants in our study. These personalised predictions further confirm the observation that

current and future relapses are driven by worsening events, whereas relapses have little bearing on subsequent worsening. These results further suggest that subsequent worsening of disability in ROMS participants occurs in ways not clearly tied to relapses, and depends on the previous worsening status.

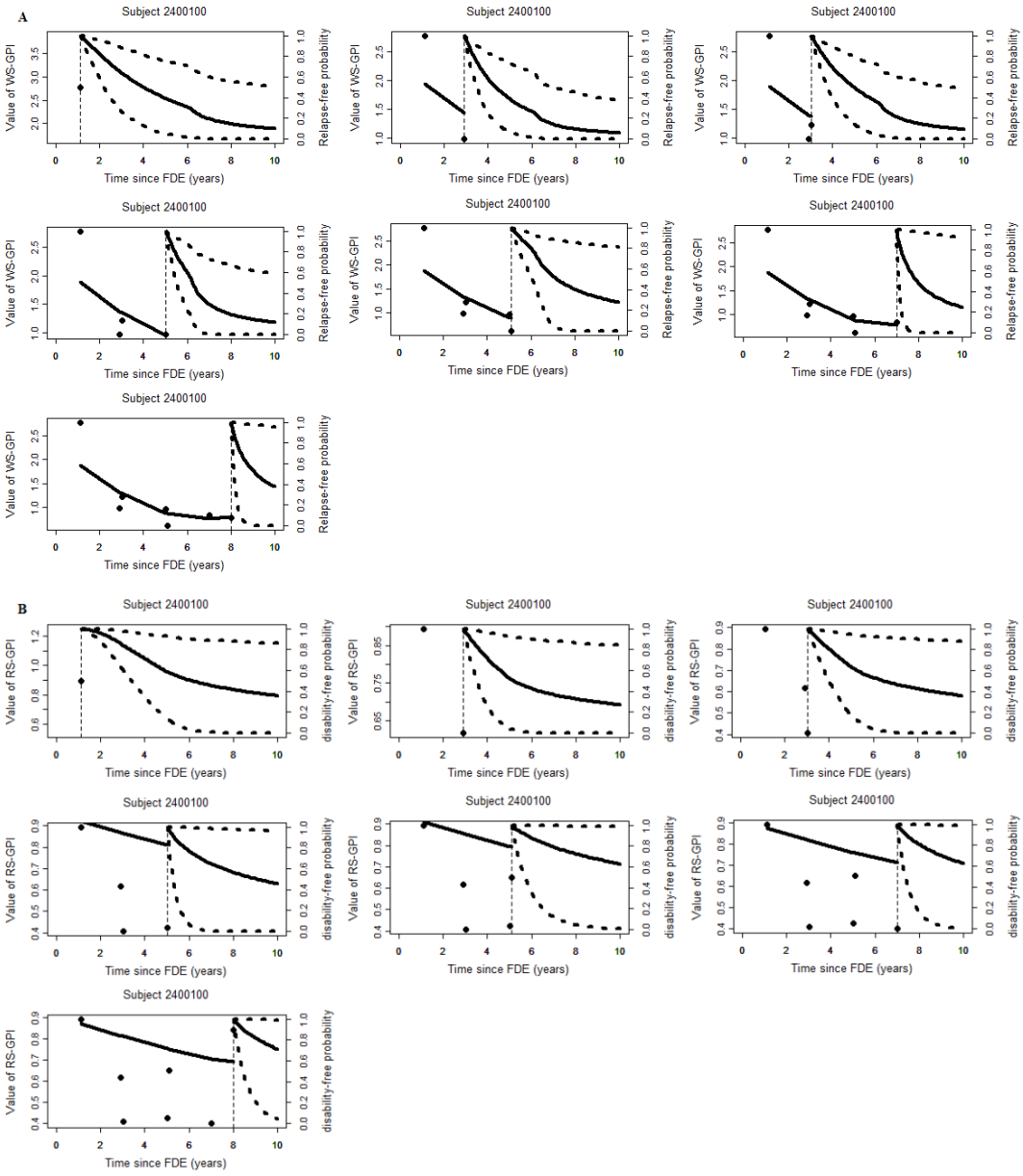

Figure 4. Real-time dynamic predictions for a 35 years old male (AUSLONG ID=2400100). (A). Relapse-free survival, (B). Worsening/disability-free survival. Vertical dotted lines denote the time point of the last EDSS measurement. The fitted longitudinal profile of the WS-GPI (A) and RS-GPI (B) is presented (left of vertical line). Solid lines denote the mean survival estimate, while dashed lines are the corresponding 95% credible intervals.

Discussion

We analysed a multicentre longitudinal prospective data consisting of new ROMS and CIS cases and examined indirectly the relationship between relapses and worsening of disability via the use of genetic prognostic indices predictive of these endpoints. We found that the effects of relapses on worsening of disability, and vice versa, were time dynamic. Relapses predicted worsening of disability in the early years of disease activity, but their longer-term impact on disability worsening diminished significantly with time. Conversely, disability worsening significantly increased relapse risk in the short and long-term. We also showed that early treatment with DMTs and early supplementation with VitD particularly in combination could completely mitigate relapse risk and significantly reduce the risk of worsening of disability.

Predictors of ROMS dynamics

There were strong associations between baseline MRI T2L counts and relapse risk, and long-term worsening of disability that were significantly modulated by DMT usage and by the type and duration of the DMT used. We found that at least 1 year use of any DMT combined with VitD supplements was required to completely mitigate the direct effects of baseline T2L count on relapse risk. However, the effects of baseline T2L count on worsening risk (although significantly mitigated) persisted each year despite treatment combination. These observations were consistent with previous studies[50,51] that examined the role of DMTs in modulating the associations between T2L counts and disability progression. Our analysis adds to these studies by including the therapeutic effects of VitD supplements, and the combined therapeutic actions of both VitD and DMTs in reducing long-term disability accrual. Particularly in those having higher baseline T2L counts, early treatment combination after FDE could provide the best chance of mitigating future disability accrual. This work supports previous finding from

observational studies[52-55] regarding the synergistic effect of VitD and DMTs in modulating relapse risk.

Later Relapses do not contribute to long-term disability accrual

Although relapses were associated with worsening of disability during the early years of clinical disease activity, later relapses did not contribute to subsequent disability accrual. In fact, their effects diminished significantly with time. In contrast to our results, early natural history studies suggested that relapse frequency and incomplete recovery from relapses within the first few years of disease predicted long-term disability accrual[13,56-60]. However, the current study suggests that this predictive effect is lost after 2.5 years of disease duration and may interestingly reverse in direction thereafter. Our findings are comparable to those from previous studies that reported relapses accrued early[1,14], or within the first 2[20] and 5 years[11-14] of disease onset predicted short-term disability progression, and then lost their predictive value thereinafter. This dissociating and decreasing impact of relapses on disability accrual could be attributed to the indirect, short-term effects mediated by clinical and environmental modifiable risk factors such as adiposity-associated inflammation and increased pro-inflammatory states associated with low VitD/low sunlight exposure.[19] Also, the increasing use of DMTs that directly suppress relapses and the natural decrease with time in relapse rates may mitigate any long-term associations[8,26,27,61-64]. Although long-term disability accrual may result from the accumulation of fixed sequelae following each inflammatory attack due to neuronal and glial cell damage[4,65,66], the latter process can also occur without a clinical sequela, as in new enlarging T2 lesions on MRI. T2L counts at baseline have been shown in this study and others to have significantly impact long-term disability accrual despite treatment combination. Thus our discovery that late relapses have no effect on later worsening events, and may in fact mitigate against them, is of interest.[1] Our data also supports the concept that the majority of inflammatory activities in ROMS manifests as new or evolving T2 lesions on brain MRI and

not clinical relapses, but does result in clinically observable changes in the functional system (EDSS).

Worsening events predict the risk of future relapses

Current worsening events were associated with shorter *time-to-relapse*, and increased the risk associated with future relapses, shown in Fig. 2A. However, these time-dynamic actions were not observed until, on average, 3 months after the first relapse. Limited studies[1,17,67] have investigated association of the current worsening status on the risk of future relapses in ROMS. Our analysis provides strong evidence suggesting that future relapses occur as a consequence of the current and previous disability scores (EDSS), and the magnitude of the change that occur between observation times, and that subsequent worsening outcomes in ROMS occurs in ways not tied to relapses[17,67]. Compared to these studies[17,67], we provided quantitative measures of both constant and time-dynamic associations in Fig. 2B, and personalised real-time survival probabilities in Fig. 4A to support findings.

Relapses are thought to occur when inflammatory activity approaches a threshold that causes clinically noticeable alterations, such that the person with MS is aware of a sudden change in their clinical status (EDSS). Inflammatory episodes frequently happen without a clinical sequela as in new or enlarging T2 lesions on MRI. Such attacks can occur when auto antigens are presented to the immune system following neuronal and glial cell injury. As a result, those with a higher pace of neurodegeneration are potentially more likely to expose auto antigens to the immune system, thus increasing inflammatory activity, relapses, and MRI activity. In other words, there may be a negative feedback loop in which neurodegeneration leads to an increase in inflammatory activity, which causes further neurodegeneration and, eventually, irreversible disability accumulation. Overall, our findings suggest that neurodegeneration causes disability

progression through inflammatory-driven cell death, which then increases subsequent relapse activity.

Timing of treatment is important in reducing the risk of disease progression

Results from the time-lagged joint models suggests that VitD supplements and DMTs could mitigate the risk associated with future relapses and worsening events. These results corroborates findings cohort studies from published meta-analyses which suggest that potentially VitD supplements[29,53] or DMTs[31] have a therapeutic role in the prevention of relapses, although there is uncertainty with regards to the dosage and timing. Our study provides strong evidence regarding the timings of VitD and DMTs administration and the consequence on risk reduction. Specifically, early use of VitD supplements and DMTs provided significant benefits in reducing relapse risk, compared to delayed use. These results align with prior findings in MS cohort studies[17,27,63,64,67].

Clinical implications, strengths, and limitations

Our study is limited by its observational non-randomised longitudinal cohort design. VitD supplements and DMTs were initiated at the discretion of the treating physicians, or by self-administration in the case of VitD. However, in this context, a longitudinal 10 year cohort study does provide the best methodology to ascertain these associations as it would be unethical and infeasible to undertake a 10 years placebo-controlled intervention study. Additionally, there is also likely to be indication bias where higher efficacy DMTs are given to those with worse markers of disease activity. However, the availability of prospectively collected long-term data with repeated measures significantly enhances the power of this study.

The lack of an external validation cohort is another limitation of this study, and we are unaware of a similarly conducted prospective cohort with all investigated factors measured. However, our study demonstrates real-world clinical application by providing unbiased estimates of person-specific real-time survival probabilities for predicting future disability outcomes in MS. These dynamic predictions could be deployed into clinical practice via a web application delivering equal prediction accuracy like the original model. Clinicians could utilise these predictions (provided genotyping was available) and identify those at higher risk of future disability progression or relapses, and employ higher efficacy DMTs as early as possible. Thus, by observing snapshots of the progression process in real-time, data-driven treatment assignment and shared decision making is highly supported.

Additionally, our model adjusts for potential confounding effects established in our previous studies,[19] but many clinical and environmental risk factors exist, which could possibly enhance the association found here. Specifically, the dosage of VitD supplements were not specified for most of our participants but were usually in the form of multivitamin supplements in the order of 200- 400IU daily. There was limited information on cases using 2nd-line DMTs in this study, and therefore we cannot comment on the effects of these drugs. Furthermore, the ability to show that the relationship between relapses and worsening of disability only exist in the presence of significant SNP-outcome associations (shown on Fig. 2), as opposed to non-significant ones (shown on Fig. S2.) is novel and validates our findings. Complex gene-environment interactions that could further enhance the associations could not be assessed.

Conclusion

We examined the complex relationship between relapses and worsening of disability and provided robust measures of associations adjusted for treatment effects and potential confounders. We presented evidence that relapses do not contribute to long-term disability

accrual in ROMS. These findings were further supported by evaluating person-specific real-time survival probabilities for predicting future progression outcomes. Furthermore, combining VitD supplements with DMTs could effectively mitigate the effect of higher MRI T2L counts on the risk for relapse and disability worsening. While the timing for the maximal effects of VitD supplements might be difficult to achieve practically, our study strongly suggests that early treatment soon after FDE with combined DMT and VitD has the highest chance of positively modulating subsequent disease activity. The personalised predictions obtained from our study could be translated into clinical practice via a web application predicting future disease course in real-time, while providing clinicians the option to intervene to mitigate disease progression.

Group.

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Contributions

AUSLONG investigators group designed the study; BVT supervised the study; VFN performed data analysis, wrote the manuscript, and completed revisions; JC, YZ, IVM, PEM, SAB, ALP, SSY, and JLS, also contributed revisions of the manuscript. All authors read the manuscript draft, contributed edits, and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Supplementary material

The online supplementary materials contain additional tables, explanation on how to compute estimates presented in the main tables, and R-codes to replicate the analysis.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

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