AUTHORS: DiGregorio, D[1]., Negash, S[1]., Blattner, R[1]., and Randolph, C.[1]

RBANS as a Predictor of Disease Progression in Early Symptomatic Alzheimer's Disease

Background

The Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB) is used almost exclusively as the primary endpoint in clinical trials of putative disease-modifying therapies for early symptomatic Alzheimer's Disease (AD) clinical trials. This diagnostic staging semi-structured interview is also used as a key inclusion criterion in most trials. Clinical trials of putative disease-modifying therapies typically involve very large samples of participants for large commitments of time, usually followed at least over an 18-month period. This is necessary to observe sufficient placebo decline to detect slowing of progression in the treatment group. Clinical factors that are predictive of placebo decline may be useful in enriching trial samples or serving as stratification variables for earlier phase trials with smaller samples. We decided to explore the utility of typical screening measures used in trials of early symptomatic AD to determine the degree to which they were predictive of progression on the typical sole primary endpoint in such trials, the CDR-SB.

Methods

Data from 3,606 participants were collated across six early symptomatic AD studies which included the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Delayed Memory Index (DMI) cutoff of 85 or less, and the Mini Mental Status Examination (MMSE) cutoff of 20+ for inclusion. Forward and backward stepwise regressions were carried out to identify the best model for predicting change in CDR-SB from screening to month 18. The metrics selected as predictor variables were all measured at screening and included RBANS total scale index score, the RBANS DMI, MMSE total, CDR-SB, and age (the only demographic variable accessible). At each step, variables were chosen based on Akaike Information Criterion (AIC). The final model identified by the stepwise regressions was then evaluated using a linear regression to determine the magnitude and direction coefficients for the predictor variables.

Results

The final model identified by both the forward and backward stepwise regressions included all possible variables save RBANS DMI (Table 1). When subjected to linear regression, this model was found to be statistically significant (adjusted R2 = 0.1216; p-value < .0001). Participant age was positively associated to change in CDR-SB (coefficient = 0.007), while RBANS total scale index score (coefficient = -0.057), MMSE total (coefficient = -0.121), and screening CDR-SB (coefficient = -0.087) were negatively associated (Figure 1).

Table 1

	ESTIMATE	STD. ERROR	T VALUE	P
Intercept	8.520884	0.57273	14.878	< 2e-16
Total Scale	-0.05685	0.003465	-16.409	<2e-16
MMSE Total	-0.12069	0.018351	-6.577	5.5e-11
Sum of Box	-0.08698	0.030777	-2.826	0.00474
Subject Age	0.007287	0.00479	1.521	0.1283

Conclusions

Screening measures such as the RBANS, MMSE, and CDR are typically utilized in trials of disease modifying therapies. This current data shows that clinical screening data including RBANS total scale index score, MMSE total, CDR-SB, and age are predictive of disease progression. The measure with the strongest relationship to progression on CDR-SB was the RBANS total scale index score. Participants in the lowest quartile on the measure progressed more than 2.5 times the rate of progression for participants in the highest quartile. These data may be useful in future clinical trial design, either for enriching study samples for faster progression or for the purposes of stratification.

Keywords

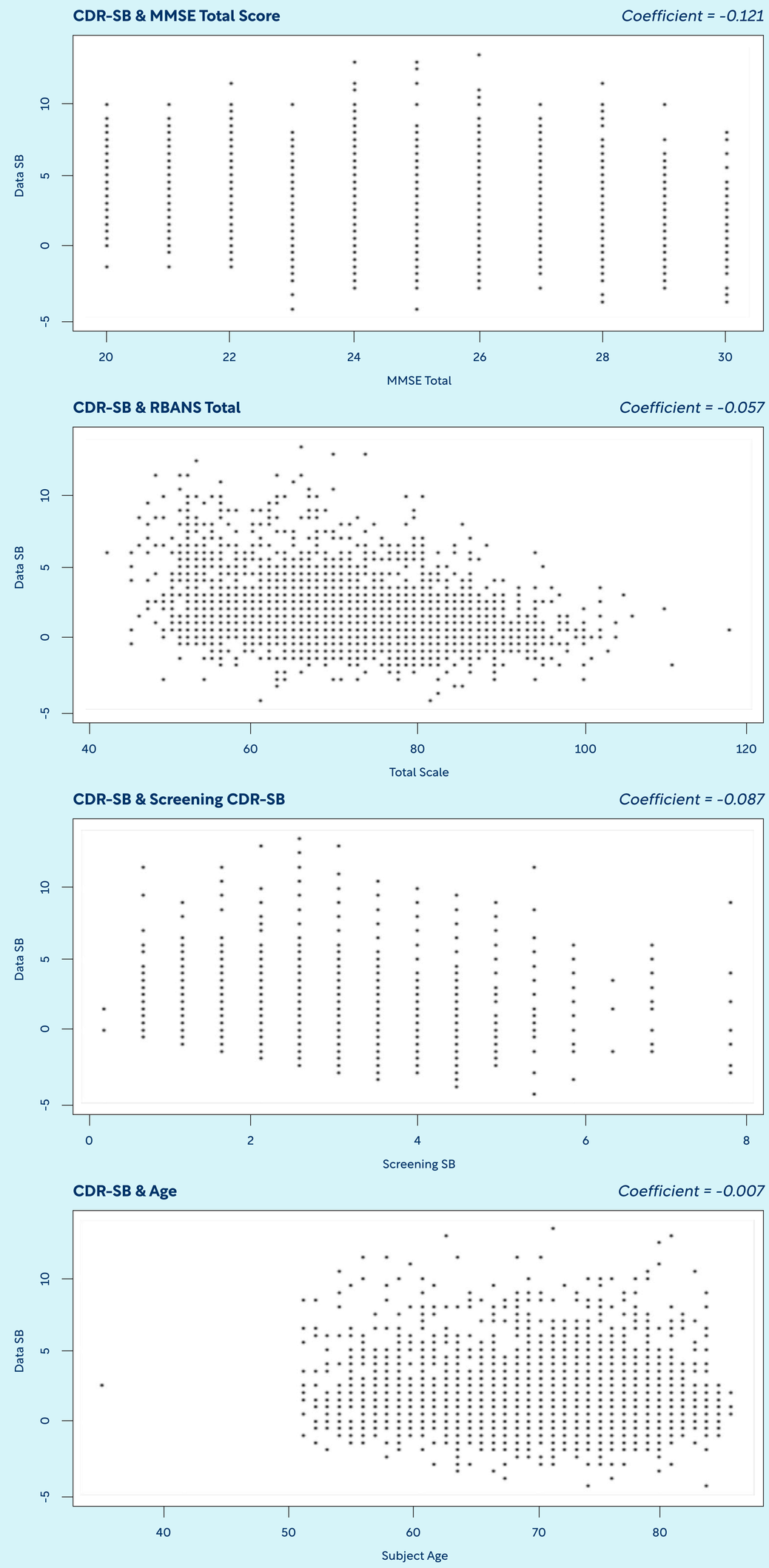
Alzheimer's Disease, Clinical Dementia Rating Scale-Sum of Boxes, Repeatable Battery for the Assessment of Neuropsychological Status, Mini Mental Status Examination.

Disclosures

Authors are employees of WCG. Dr. Randolph is the author of the RBANS and receives royalties from the copyright holder, Pearson.

[1]WCG CLINICAL, INC., PRINCETON, NJ, USA

Figure 1: Scatterplots for Relationships between variables



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