New regression models for long-term cognitive change in Donepezil treated Alzheimer patients.

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Conclusions

There is considerably heterogeneity in the raw observations of the rate of change. Analyses of the rates of progression in donepezil treated patients showed that the rate of change of ADAS-cog and MMSE scores depends strongly on the current score for the time interval examined. The measured rate of change indicated more rapid improvement for the more severely affected patients. Both quadratic and cubic functions adequately characterize progression of Alzheimer's disease. However, the regression models showed a slower cognitive deterioration in donepezil treated patients compared to earlier studies of untreated patients.

Introduction

The Swedish Alzheimer Treatment Study (SATS) was started in order to describe the long-term effects of cholinesterase inhibitor treatment in patients with Alzheimer's Disease (AD) in a routine clinical setting. Donepezil was the first of the second-generation inhibitors of acetylcholinesterase (ChEI) to get approval in Sweden 1997. Since placebo controlled long term studies in AD treatment are no longer considered ethical, the problem with non-treated groups for comparison exists. Whether it would be feasible for future assessment of new drugs for AD treatment without placebo groups to compare them with ChEI.

Objective

To calculate regression models, which show the development of cognitive function in donepezil treated patients. In addition, to analyse how the patients' baseline scores have an impact on the change in cognition after 6 months of treatment.

Methods and Subjects

SATS is a descriptive, prospective, longitudinal, multicentre study. 435 outpatients with the clinical diagnosis of AD received treatment with donepezil for a period of three years. Among the primary efficacy parameters assessed were MMSE and ADAS cognitive subscale. Patients were assessed at baseline, at 2 months (not ADAS-cog) and every 6 months during the study.
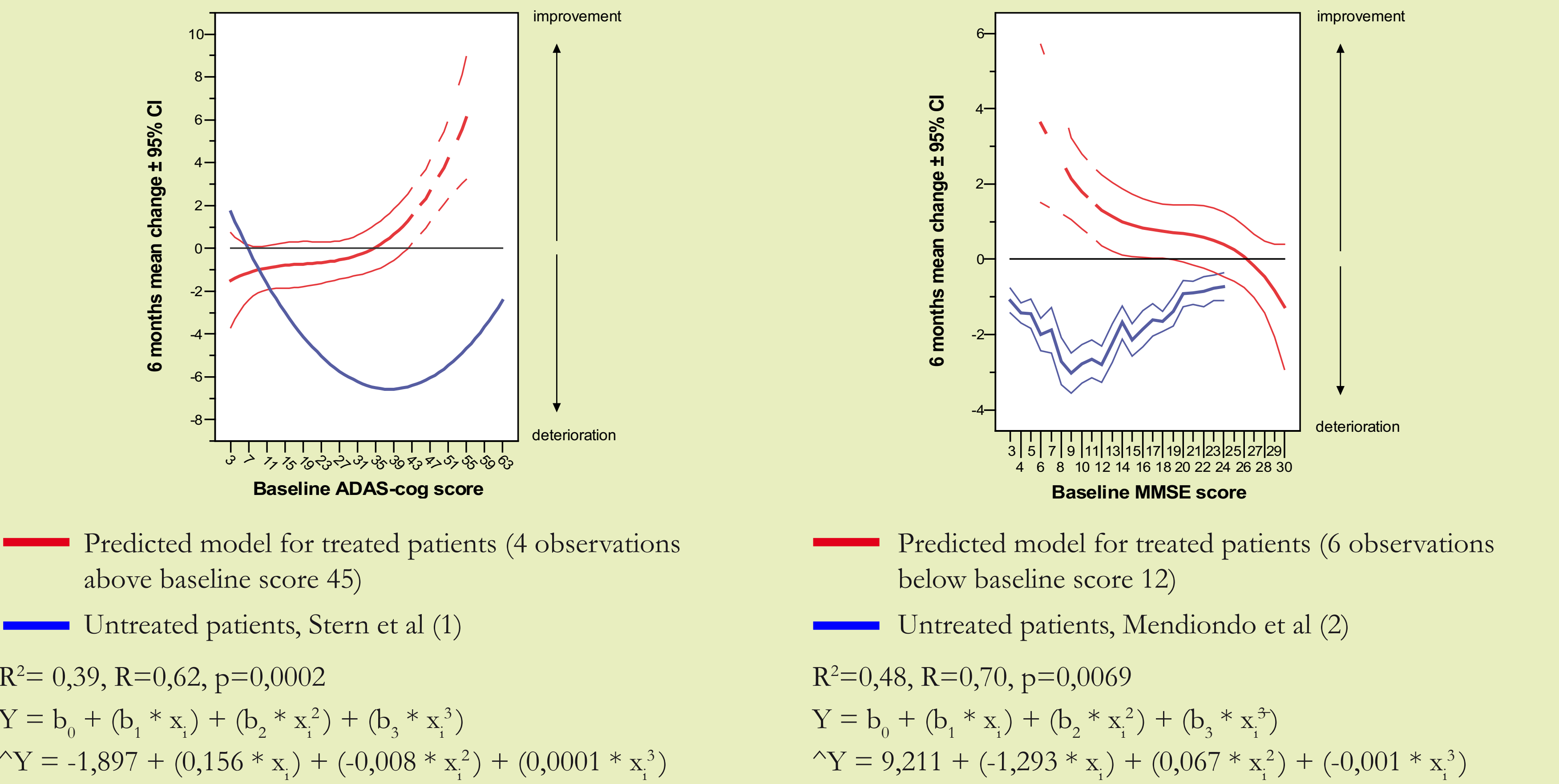
Baseline characteristics	
Gender (males/females)	35%/65%
Age at investigation, mean ± SD, (range)	74.7 ± 6.5, (50 - 87)
Duration, years ± SD	3.1 ± 2.3
MMSE, mean ± SD, (range)	22.0 ± 4.6, (30 - 6)
ADAS-cog (0-70), mean ± SD, (range)	20.7 ± 10.0, (3 - 59)

To simplify comparisons, change of score in this poster is calculated so that all positive values indicate improvement and all negative values indicate worsening. We computed the difference between baseline i.e. start of donepezil treatment and the 6 months score and then calculated a mean for every possible baseline score. To avoid using test scores that had reached a floor, we truncated each patient's record by censoring data points after the ADAS-cog score first reached 70 or the MMSE score first reached zero. We have only 4 patients with baseline ADAS-cog scores above 45 and 6 patients with MMSE scores below 12.

Reference List
(1) Stern R.G., Mohs R.C., Davidson M., Schmeidler J., Silverman J., Kramer-Ginsberg E. et al. A longitudinal study of Alzheimer's disease: Measurement, rate and predictors of cognitive deterioration. Am J Psychiatry 1994 March;151(3):390-6.
(2) Mendiondo M.S., Wesson Ashford J., Kryscio R.J., Schmitt F.A. Modelling Mini Mental State Examination changes in Alzheimer's disease. Statist. Med. 2000; 19:1607-1616
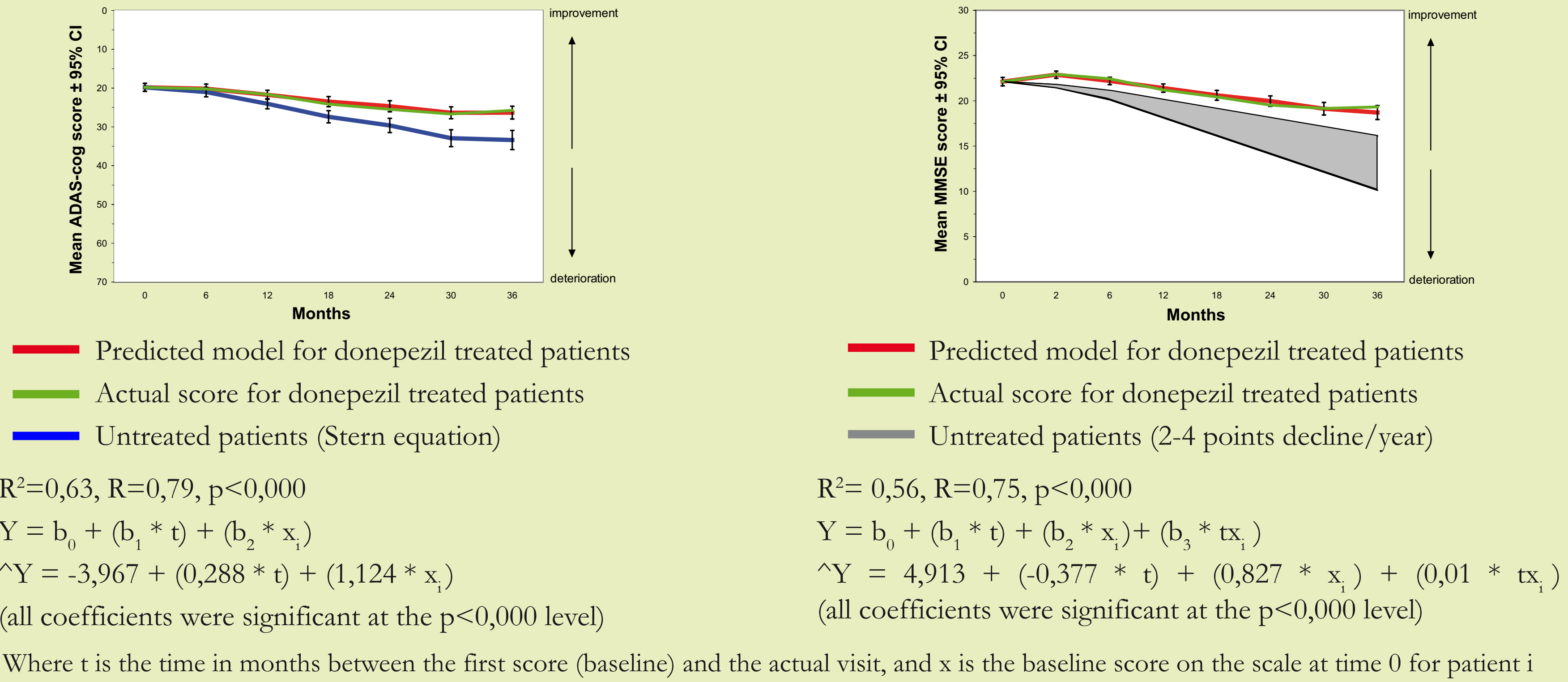
Results

There was a significant quadratic and cubic component between baseline scores on ADAS cog or MMSE versus 6 months mean cognitive change. Linear and several nonlinear models were also tested but these models were not significant. Here we present the cubic models which have most of the variation explained by the model, i.e. the best fit.

Predicted model for treated patients (4 observations above baseline score 45)
Untreated patients, Stern et al (1)

$R^2 = 0,39$, $R = 0,62$, $p = 0,0002$
$Y = b_0 + (b_1 * x_i) + (b_2 * x_i^2) + (b_3 * x_i^3)$
$\hat{Y} = -1,897 + (0,156 * x_i) + (-0,008 * x_i^2) + (0,0001 * x_i^3)$

Predicted model for treated patients (6 observations below baseline score 12)
Untreated patients, Mendiondo et al (2)

$R^2 = 0,48$, $R = 0,70$, $p = 0,0069$
$Y = b_0 + (b_1 * x_i) + (b_2 * x_i^2) + (b_3 * x_i^3)$
$\hat{Y} = 9,211 + (-1,293 * x_i) + (0,067 * x_i^2) + (-0,001 * x_i^3)$

Where x is the baseline score on the scale at time 0 for patient i

The first 6 months rate of cognitive change in donepezil treated patients was strongly dependent of the baseline scores. The predicted mean rate of change with 95 % confidence intervals showed more rapid improvement for the more severely affected patients with 30 and above on the ADAS cognitive subscale or 17 and below on the MMSE scale. This indicates a different slope and cognitive development compared to earlier studies of untreated patients.

For patients with at least 3 assessments each we predicted a longitudinal regression model for the dependent variable ADAS-cog score (330 patients, 1402 observation points), and for the variable MMSE score (390 patients, 1955 observation points) at different intervals. Several different linear and non-linear models were tested but these models showed the best fit.

Predicted model for donepezil treated patients
Actual score for donepezil treated patients
Untreated patients (Stern equation)

$R^2 = 0,63$, $R = 0,79$, $p < 0,000$
$Y = b_0 + (b_1 * t) + (b_2 * x_i)$
$\hat{Y} = -3,967 + (0,288 * t) + (1,124 * x_i)$
(all coefficients were significant at the $p < 0,000$ level)

Predicted model for donepezil treated patients
Actual score for donepezil treated patients
Untreated patients (2-4 points decline/year)

$R^2 = 0,56$, $R = 0,75$, $p < 0,000$
$Y = b_0 + (b_1 * t) + (b_2 * x_i) + (b_3 * tx_i)$
$\hat{Y} = 4,913 + (-0,377 * t) + (0,827 * x_i) + (0,01 * tx_i)$
(all coefficients were significant at the $p < 0,000$ level)

Where t is the time in months between the first score (baseline) and the actual visit, and x is the baseline score on the scale at time 0 for patient i

The left figure shows a comparison between the treated patients' predicted mean ADAS-cog scores from our regression model with 95% confidence intervals, and the mean predicted scores from the Stern equation calculated from untreated patients. Our model shows a favourable effect on cognition in donepezil treated patients with significant differences between the ADAS mean scores from 6 months and onwards (p<0,000). The right figure shows the mean predicted MMSE score with 95% confidence intervals from our multiple non-linear regression model calculated from donepezil treated patients. The shadow area shows the decline of 2-4 MMSE points/year based on historical untreated patients.