Appendix e-5

<u>Calculation of Rate of Change</u>: For each subject, the rate of change was calculated as the slope of the individual changes in test score over time, which was then converted to a z-score, i.e., a 'normed' slope. The following procedure was used: (1) the cognitive test score at each follow-up time (time t) minus the cognitive test score at baseline was calculated, and divided by the difference in the time between these two measurements {(measurement at follow-up time t) - (measurement at baseline 0)} /t. (2) each of these individual slope values were then centered and standardized across subjects; thus, the rate of change had a mean of zero and a variance of 1.

The standardized slope values were then used as time-dependent covariates in the Cox regression models, with each subject contributing a standardized slope value for each follow-up assessment that was available (e.g., 0-1, 0-2, 0-3, 0-4, etc). These measurements were not smoothed, but were instead treated as a 'step function', where the rate of change was not varied between the individual follow-up intervals.