Relationship of Pre-morbid IQ and Education to Progression of Alzheimer's Disease

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Background

- Education is a strong predictor of AD incidence
- Education and tests of cognitive performance are highly correlated
- Studies of the role of education on rate of cognitive decline after a diagnosis of AD have not yielded consistent results
- Since education and pre-morbid intellectual functioning are highly correlated, a direct measure of pre-morbid IQ may be better than education as a predictor of cognitive decline in AD

Hypothesis

- Pre-morbid IQ is a better predictor of cognitive decline, global progression, and overall survival than education in patients with probable AD

Methods

- **Setting and Study Population**
  - –Baylor Alzheimer's Disease Center, Houston
  - –Electronic database of initial and follow-up clinical and neuropsychological assessments maintained for more than 1600 patients diagnosed according to NINCDS-NDRDA criteria
  - –Database established in 1989, new patients accrued continuously since that time
  - –Vital status of all patients ascertained through phone follow-up of contacts and/or death index searches
- **Inclusion criteria**
  - –Diagnosis of probable AD
  - –An AMNART test administered within six months of the baseline visit
  - –At least one annual follow-up visit with neuropsychological assessment

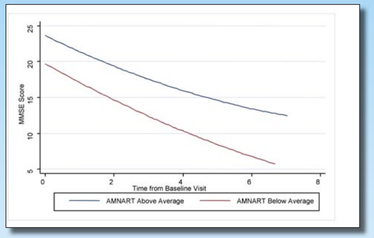
Study Variables

- **Outcome Variables**
  - –Baseline and follow-up MMSE scores
  - –Baseline and follow-up ADAS-Cog scores
  - –Baseline and follow-up Clinical Dementia Rating (CDR) scores
  - –Vital status
- **Predictor Variables**
  - –Age at baseline visit to center
  - –Sex
  - –Race/ethnicity
  - –Years of education
  - –Estimated duration of symptoms before baseline visit
  - –Nelson Adult Reading Test (American version) raw score
- **Statistical Analysis**
  - –Analysis was restricted to the first six testing sessions, since the small number of individuals with more than six assessments could distort regression model fit
  - –Linear random effects models used to test hypotheses regarding education, pre-morbid cognitive ability and decline on MMSE and ADAS-Cog scores
  - –Cox proportional hazards regression with robust variance estimation used to identify predictors of all-cause mortality
  - –Quadratic term for time included to account for non-linear change
  - –Time by baseline AMNART and time by education interaction terms tested as warranted
  - –Graphs of fitted regression lines produced using STATA

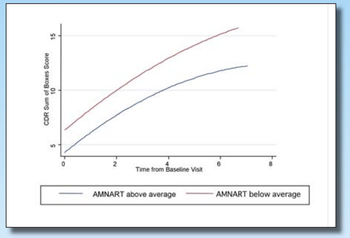
Results

- 478 patients met inclusion criteria. Baseline characteristics of the study population shown in Table 1.
- When the raw AMNART score was not in the model, education was a significant predictor of cognitive performance, but was not associated with differential rate of decline (education by time interaction term not significant).
- The raw baseline AMNART was significantly associated with performance on the MMSE, ADAS-Cog and CDR Sum of Boxes scores, and the rate of decline was more rapid in persons with a below average AMNART score (see Table 2 and graphs of fitted regression lines).
- Education was not a significant predictor of test performance or global function when the raw baseline AMNART was included in the regression models.
- Neither education nor the baseline AMNART score were significant predictors of all cause mortality (Table 3).

Change in MMSE Score by Level of Baseline AMNART



Change in CDR Sum of Box Score by Level of Baseline AMNART



Change in ADAS–Cog Score by Level of Baseline AMNART

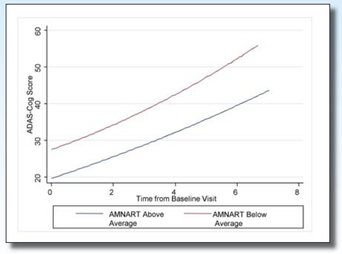


Table 1. Baseline Characteristics of Study Population (All with Diagnosis of Probable AD)

Variable	n with value	Mean ± SD or Percent	Range
Age at Diagnosis	478	74.5 ± 8.0	46-93
Sex (% female)	478	67.4%	n/a
Race/Ethnic Group :	478		n/a
–White		433 (90.6%)	
–Black		27 (5.6%)	
–Hispanic		13 (2.7%)	
–Other		5 (1.15%)	
Years of Education	478	13.9 ± 3.4	0-29
Baseline MMSE	468	21.8 ± 5.1	2-30
Baseline MMSE Classification	468		n/a
Mild (>=20 points)		324 (69.2%)	
Moderate (10-19 points)		129 (27.6%)	
Severe (<10 points)		15 (3.2%)	
CDR Sum of Boxes	460	5.2 (3.5)	0-15
First AMNART (estimated IQ)	478	108.2 ± 10.3	76-155
Raw Baseline AMNART (AMNART errors)		21.5 ± 10.3	1-45
Baseline ADAS Cog	381	22.1 ± 11.4	1-64
Estimated duration of disease before diagnosis	474	3.5 ± 2.20	0.5 –13.0
Years of active follow-up	478	3.2 ± 2.00	0.7 – 11.9
Proportion deceased as of censoring date	478	161 (34%)	n/a
Years of survival from diagnosis to death	478	5.0 ± 2.4	1.0 – 12.7

Table 2. Random Effects Models Predicting Change in Each Outcome Measure

	MMSE Score			ADAS-Cog Score			CDR Sum of Boxes Score		
	Beta	SE	p	Beta	SE	p	Beta	SE	p
Model 1 (demographics, duration of symptoms, years from baseline)									
Age at diagnosis	-.01	.03	.74	.04	.08	.65	0.05	.02	.02
Sex (1=male; 0=female)	1.03	.58	.08	-0.55	1.32	.68	-0.28	.39	.47
Race/Ethnicity (1=non-Hispanic white; 0=other)	1.96	.92	.03	-5.60	2.10	<.01	-1.50	.62	.02
Education (yrs)	0.35	.08	<.01	-0.45	.19	.02	-0.17	.06	<.01
Duration of Symptoms Before Diagnosis (yrs)	-0.43	.12	<.01	1.01	.28	<.01	0.23	.08	<.01
Time (yrs)	-2.76	.19	<.01	4.32	.43	<.01	2.19	.14	<.01
Time Squared (quadratic term)	0.14	.04	<.01	-0.12	.10	.21	-0.14	.03	<.01
Education x Time Interaction	0.04	.03	.16	-0.08	.06	.16	-0.03	.02	.11
Intercept	17.07			27.7			4.11		
Total Variance Explained	.184			.109			.206		
Model (Model 2 plus Raw Baseline AMNART, time x AMNART interaction)									
Age at diagnosis	-0.01	.03	.83	0.03	.07	.63	0.05	.02	.02
Gender	1.23	.54	.02	-1.16	1.26	.36	-0.37	.38	.33
Race/Ethnicity (1=non-Hispanic white; 0=otherwise)	0.37	.87	.67	-2.51	2.03	.22	-0.77	.61	.21
Education (yrs)	0.13	.08	.10	-0.01	.19	.96	-0.08	.06	.16
Duration of Symptoms Before Diagnosis (yrs)	-0.33	.11	<.01	0.81	.26	<.01	0.19	.08	.02
Baseline AMNART (raw score)	-0.21	.03	<.01	0.41	.06	<.01	0.09	.02	<.01
Time (yrs)	-2.16	.25	<.01	3.34	.60	<.01	1.92	.19	<.01
Time Squared (quadratic term)	0.13	.04	<.01	-0.10	.10	.30	-0.13	.03	<.01
Baseline AMNART x Time Interaction	-.03	.01	<.01	0.046	.02	.02	0.01	.01	.04
Intercept	25.2			10.74			.645		
Total Variance Explained	.280			.189			.25		

Table 3. Relative Hazard Ratios for Mortality Associated with Study Variables

	Univariate Hazard Ratio (95% CI)	p	Multivariate Adjusted Hazard Ratio (95% CI)[a]	p
Age at diagnosis	1.01 (0.99, 1.03)	.26	1.02 (1.00, 1.05)	.04
Gender (1=male, 0=female)	1.72 (1.25, 2.38)	<.01	1.75 (1.24, 2.44)	<.01
Race/Ethnicity (1=white, 0 otherwise)	1.53 (0.84, 2.78)	.16	1.60 (0.83, 3.11)	.16
Education (yrs)	1.02 (0.97, 1.07)	.39	1.02 (0.97, 1.08)	.36
Duration of Symptoms (yrs)	.95 (0.89, 1.03)	.27	.94 (0.87,1.02)	.16
Baseline MMSE Severity (1=moderate or severe, 0=mild)	1.46 (1.06, 2.01)	.02	1.62 (1.14, 2.32)	<.01
Baseline Raw AMNART (1-point increments)	1.01 (0.99,1.02)	.22	1.01 (0.99, 1.03)	.30

[a] Examination of Schoenfeld residuals indicated that the proportional hazards assumption was not violated.

Conclusions

- A measure of pre-morbid IQ is preferable as a predictor of cognitive performance and rate of cognitive decline than education in persons diagnosed with probable AD
- Neither pre-morbid IQ nor education is associated with overall survival after a diagnosis of probable AD

Implications

- Baseline differences in cognitive performance and global function associated with pre-morbid IQ are preserved over long-term follow-up
- The difference in the slope of decline associated with higher pre-morbid IQ is relatively small, and the practical impact on outcomes such as nursing home placement and/or caregiver burden needs further study
- A measure of pre-morbid IQ is preferable to education as a predictor of AD outcomes