SUPPLEMENTARY MATERIAL

Examination of the clinico-pathological continuum of Alzheimer disease in the autopsy cohort of the National Alzheimer Coordinating Center.

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The association of demographic and neuropathological variables with ordered categories of CDR-SOB was examined with adjacent-categories logit models (22) including and excluding the CDR-SOB=0 group, using the VGAM package in R software (23). Given the six ordered categories of CDR-SOB (denoted by $Y = 0, 1, 2, 3, 4, 5$) and covariate X, the adjacent-categories logit models is of the form:

$$logit[P(Y = k \mid Y = k-1 \text{ or } k, X)] = log\left\{\frac{P(Y = k \mid X)}{P(Y = k-1 \mid X)}\right\} = \alpha_k + \beta_k X,$$

$$\text{where } k = \begin{cases} 1,2,3,4,5, & \text{if CDR-SOB=0 is included,} \\ 2,3,4,5, & \text{if CDR-SOB=0 is excluded,} \end{cases}$$

and $P(Y = k|X)$ denotes the probability of response category k given covariate X. Note that the regression coefficients β_k either can be equal for all $k = 1, 2, 3, 4, 5$, which implies the covariate X has same effect at each logit, or they can be different at some logits, which permits a separate effect of the covariate X for different adjacent categories of Y. This flexibility of the adjacent-categories logit models enables us to fit a parsimonious regression model for ordered categories of CDR-SOB without strong parametric assumptions on the relationship among ordered categories. With multiple demographic and neuropathological covariates, the assumption that a covariate having the same effect at each logit was checked for each covariate using likelihood ratio tests of nested models. Whenever the assumption was violated, nested sequences of weaker assumptions permitting separate effect of a covariate for some logits were considered and were checked using likelihood ratio tests, until the most parsimonious assumption allowing different effects for different logits was not rejected. All the covariates were then added to the model in a step-wise fashion to evaluate whether they independently contributed to the clinical outcome (CDR-SOB).

The interpretation of the regression coefficient β_{kx} is the log odds ratio of having CDR-SOB in category k versus category k-1 with covariate value X+1 relative to covariate value X if X is continuous, and relative to the reference category of X if X is categorical. More examples of interpretation are found in the footnote of Table 4.

Supplementary Table 1. Summary of results of the adjacent-categories multivariable regression model with inverse probability weighting.

	Model 1 (only demographics)		**Model 2** (Model 1 + neuritic plaques+NFTs)		**Model 3** (Model 2 + concurrent pathologies)	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Sex (female as ref.)						
at *k=1,2,3,4*	1.11 (1.04, 1.19)	0.003	1.13 (1.03, 1.24)	0.010	1.15 (1.02, 1.29)	0.022
at *k=5*	0.53 (0.41, 0.68)	<0.001	0.51 (0.39, 0.66)	<0.001	0.56 (0.40, 0.77)	<0.001
Age of death (in 5-year units)	0.89 (0.88, 0.91)	<0.001	0.90 (0.88, 0.92)	<0.001	0.87 (0.85, 0.90)	<0.001
Education (in 4-year units)	0.91 (0.88, 0.94)	<0.001	0.85 (0.81, 0.89)	<0.001	0.84 (0.79, 0.89)	<0.001
CERAD (neuritic plaques) (none/sparse as ref.)						
moderate			1.44 (1.29, 1.61)	<0.001	1.39 (1.20, 1.60)	<0.001
frequent			1.78 (1.58, 2.00)	<0.001	1.83 (1.56, 2.13)	<0.001
NFTs (Braak) (none/I/II as ref.)						
Stage III/IV						
at *k=1*			4.82 (3.46, 6.73)	<0.001	7.09 (4.71, 10.67)	<0.001
at *k=2,3,4,5*			1.02 (0.87, 1.21)	0.794	0.86 (0.70, 1.06)	0.147
Stage V/VI						
at *k=1*			8.16 (4.74, 14.04)	<0.001	10.72 (5.60, 20.53)	<0.001
at *k=2,3,4,5*			2.22 (1.87, 2.63)	<0.001	1.85 (1.50, 2.28)	<0.001
CAA (none as ref.)						
mild					1.14 (1.02, 1.28)	0.017
moderate					1.42 (1.25, 1.62)	<0.001
severe					1.55 (1.29, 1.86)	<0.001
Lewy bodies (present vs. absent)					1.06 (0.96, 1.19)	0.250
Arteriosclerosis (none as ref.)						
mild					0.85 (0.75, 0.97)	0.013
moderate					1.11 (0.97, 1.27)	0.132
severe					1.47 (1.22, 1.78)	<0.001
Hippocampal sclerosis (present vs. absent)					1.51 (1.21, 1.88)	<0.001

Six ordinal levels of the response variable CDR-SOB, i.e., 0, [0.5, 3], [3.5, 6], [6.5, 12], [12.5, 17.5], 18, are represented by k=0,1,2,3,4,5. Inverse probability weighting method was used to adjust for potential sampling bias for autopsy sample, where the probability of receiving autopsy is estimated based on a logistic regression model for those who died, receiving or not receiving autopsy with covariates age at death, sex, education, and CDR-SOB. Interpretation of the odds ratios is similar to those in Table 4.