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Latent Classes of Course in Alzheimer's Disease and Predictors: The Cache County Dementia Progression Study

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Abstract

Objective—Several longitudinal studies of Alzheimer Disease (AD) report heterogeneity in progression. We sought to identify groups (classes) of progression-trajectories in the population-based Cache County Dementia Progression Study (N=328), and to identify baseline predictors of membership for each group.

Methods—We used parallel-process growth mixture models (GMM) to identify latent classes of trajectories based on MMSE and CDR-sb scores over time. We then used bias-corrected multinomial logistic regression to model baseline predictors of latent class membership. We constructed ROC curves to demonstrate relative predictive utility of successive sets of predictors.

Results—We fit 4 latent classes; class 1 was the largest (72%), and had the slowest progression. Classes 2 (8%), 3 (11%), and 4 (8%) had more rapid worsening. In univariate analyses, longer dementia duration, presence of psychosis, and worse baseline MMSE and CDR-sb were associated with membership in class 2, relative to class 1. Lower education was associated with membership in class 3. In the multivariate model, only MMSE remained a statistically significant predictor of class membership. ROC AUCs were 0.98, 0.88, and 0.67, for classes 2,3, and 4 relative to class 1.

Conclusions—Heterogeneity in AD course can be usefully characterized using GMM. The majority belonged to a class characterized by slower decline than is typically reported in clinical

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samples. Class membership could be predicted using baseline covariates. Further study may advance our prediction of AD course at the population level, and in turn shed light on the pathophysiology of progression.

Search Terms

Alzheimer; growth mixture model; trajectory; disease course

Introduction

Alzheimer's disease (AD) is prevalent and costly (Wimo, Winblad, Jonsson, 2010; Alzheimer's Association, Thies, Bleiler, 2011). There is substantial heterogeneity in rates and patterns of progression in AD, with a substantial proportion (25–50%) experiencing relatively slow decline (Cortes *et al.*, 2008; Cortes *et al.*, 2008; Tschanz *et al.*, 2011). We aim to identify classes of patterns of progression, in a population-based cohort study of incident AD, and to determine which baseline characteristics are predictive of these patterns.

AD is characterized by cognitive and functional declines and the presence of neuropsychiatric symptoms, but there is considerable variability in rate of progression both between individuals, and during individual courses of illness (Folstein, Folstein, McHugh, 1975; Aguero-Torres, Fratiglioni, Winblad, 1998; Wilson *et al.*, 2000a; Cortes *et al.*, 2008; Tschanz *et al.*, 2011). In a review of clinic-based samples, average annual rate of decline on the Mini-Mental State Exam (MMSE) (Folstein, Folstein, McHugh, 1975), ranged from 2.7 to 4.3 points per year, but the standard deviations were comparatively large, ranging from 2.4 to 4.3 (Aguero-Torres, Fratiglioni, Winblad, 1998). In the REAL-FR study (Cortes *et al.*, 2008), in a large clinical sample, mean change over two years was 4.57 (0.23) MMSE points, and 4.17 (0.17) points on the Clinical Dementia Rating sum of boxes (CDR-sb) (Hughes *et al.*, 1982). In the Cache County Dementia Progression Study (DPS), mean annual rates of change were 1.53 (2.69) and 1.44 (1.82) points on the MMSE and CDR-sb, respectively (Tschanz *et al.*, 2011). In both of these samples, the authors noted distinct “profiles” or groups, which appeared to differ by rate and pattern of disease progression.

The rate of progression is not constant over the course of AD (Wild and Kaye, 1998; Xie *et al.*, 2009); typically decline is slower in the early stages of the disease. Individuals' changes in rates of progression over the course of AD are often modeled through the inclusion of a quadratic (time-squared) term (Wilson *et al.*, 2004; Camicioli and Kryscio, 2005; Tschanz *et al.*, 2011). This results in a fitted line which is curved; direction and magnitude of the curvature dictated by the sign and magnitude of the regression coefficient for the quadratic term. Trajectories are therefore characterized by the combination of intercept, slope, and quadratic terms with respect to time, rather than just the mean rate of progression. Growth mixture modeling (GMM), which estimates latent classes of trajectories, allows for the identification of subtypes of patterns of progression (Small and Backman, 2007). For example, it might identify a class of individuals with high baseline MMSE scores but sharply accelerating declines, and another class of individuals who start out with lower baseline but who experience a shallow and steady decline. Because AD is characterized by

both cognitive and functional decline, we will model class membership based on patterns of change in both of these domains, simultaneously.

GMM also allows for the modeling of predictors of class membership, and a number of correlates of progression have been identified in the literature. Female sex has been associated with faster decline (Tschanz *et al.*, 2011) but not in all studies (Martins *et al.*, 2005). Earlier age at symptom onset has been associated with faster decline (Jacobs *et al.*, 1994; Wilson *et al.*, 2004) as has higher education (Stern *et al.*, 1999; Andel *et al.*, 2006; Scarmeas *et al.*, 2006). Higher baseline cognitive function has been associated with slower decline (Atchison, Massman, Doody, 2007).

APOE genotype (4/4 homozygosity) has been associated with greater functional (Dal Forno *et al.*, 1996), and cognitive decline (Martins *et al.*, 2005), though these associations have not been found consistently (Growdon *et al.*, 1996; Murphy *et al.*, 1997; Aerssens *et al.*, 2001). Increased neuropsychiatric symptoms, including agitation and wandering (Miller *et al.*, 1993), hallucinations and delusions (Wilson *et al.*, 2000b), and depressive symptoms (Wilson *et al.*, 2002), have been associated with greater decline.

Concurrent, but not baseline, worsened general medical health has been associated with increased decline (Leoutsakos *et al.*, 2012b). Vascular risk factors, including atrial fibrillation, systolic hypertension, and angina have been associated with greater functional and cognitive declines (Mielke *et al.*, 2007), but not in all studies (Regan *et al.*, 2006).

If distinct subtypes of progression trajectories could be identified, and if it were possible to determine, at baseline, which subtype a given individual would express, there would be several important uses for those findings. First, it would improve the precision of forecasts of the burden of AD. Current models are based on mean times of progression from onset to need for skilled nursing care in clinical populations (Brookmeyer *et al.*, 2007). Better understanding of the types of courses and their prevalence would enable refinement of these projections. On an individual level, it could provide more information for long-term financial and caregiver planning. Identifying predictors of each subtype could provide clues to the underlying pathology governing decline. If any of these factors were modifiable, it could lead to advances in the treatment of AD. The goals of this work, therefore, are to identify discrete subtypes (latent classes) of AD progression; we hypothesize that one of these classes will be characterized by comparatively slow decline. Further, we will determine which baseline variable are useful in predicting class membership.

Methods

The Cache County Dementia Progression Study (DPS) is a prospective cohort study of all incident dementia cases identified as part of the Cache County Study on Memory in Aging (CCSMA) (Tschanz *et al.*, 2011). The CCSMA is a longitudinal, population-based cohort which began in 1995 and included 90% of county residents over 65. Nineteen incident AD cases were identified during wave 1, 108 during wave 2 (completed in 1999), 156 during wave 3 (completed in 2003) and 52 during wave 4 (completed in 2007). As part of the DPS, CCSMA participants with incident AD were followed prospectively, approximately every

six months, until death, loss-to-follow-up, or the close of the study. Institutional review boards at Utah State, Duke, and Johns Hopkins Universities reviewed and approved all study procedures, and all participants and their next-of-kin provided informed consent.

Details of the methods used in CCSMA and DPS are published elsewhere (Breitner *et al.*, 1999; Lyketsos *et al.*, 2000), but in brief, dementia cases were identified through a multi-stage procedure (Breitner *et al.*, 1999). This included screening with an adapted Modified Mini-Mental State Exam (MMSE) (Teng and Chui, 1987). Screen-positive individuals and a designated subsample were administered an informant-based telephone interview (Kawas *et al.*, 1994). The subsample and participants who still screened positive then underwent a clinical assessment (CA) by a trained nurse and neuropsychological technician which included a physical and neurological exam and a neuropsychological battery (Tschanz *et al.*, 2000). A study geriatric psychiatrist and a neuropsychologist then reviewed the available data and preliminary diagnoses were made using DSM-III-R criteria (American Psychiatric Association, 1987). Individuals with preliminary dementia diagnoses underwent MRI scans and standard laboratory studies for dementia. They were also examined in person by a geriatric psychiatrist or neurologist, and finally a panel with expertise in neurology, geriatric psychiatry, neuropsychology and cognitive neuroscience reviewed all data and assigned diagnoses of possible or probable AD as defined by NINCSD-ADRDA criteria (McKhann *et al.*, 1984).

At wave 1 of the CCSMA, demographics including years of education and sex were collected, as well as APOE genotype from buccal DNA. At each DPS follow-up visit, trained neuropsychological technicians administered the MMSE (Folstein, Folstein, McHugh, 1975), a measure of global cognitive functioning. A trained nurse administered the Clinical Dementia Rating (CDR) (Hughes *et al.*, 1982), a measure of functional ability in six domains on a scale from 0 (no impairment) to 5 (terminal), producing a summed score (CDR-sb) ranging from 0–30. The Neuropsychiatric Inventory (NPI) (Cummings *et al.*, 1994) was administered to caregivers, and measured the presence, frequency, and severity of 12 neuropsychiatric symptoms including delusions, hallucinations, agitation, depression, and apathy. Domain scores are calculated as the product of frequency and severity, range from 0–12, and are summed for the NPI total score.

Statistical Methods

The study sample included 328 subjects with complete data at baseline. Time was measured in years from dementia onset. Growth mixture models (GMMs) allow for the grouping of subjects based on similarities in their patterns of progression over time. Their use implies an assumption that each subject's scores over time arise from their membership in a latent (unobserved) trajectory class. In a typical mixed effects longitudinal regression model, coefficients for intercept, slope, and quadratic terms would be estimated, and would represent the expected trajectory for the entire sample. Random effects would be used to account for variability in intercept and slope among individuals. In GMM, separate intercept, slope, and quadratic terms are estimated for each latent class, and class membership is a function of all three terms (Muthen and Muthen, 2000; Jung and Wickrama, 2008).

Since AD involves both cognitive and functional declines, we chose to model class membership as a function of both MMSE and CDR trajectories, using parallel process growth mixture models (Gross and Rebok, 2011). Unlike MMSE, higher CDR-sb scores represent worse performance; for ease of interpretation and modeling, we reverse-coded all CDR-sb scores (e.g., a CDR-sb score of 1 was recoded as a 29). Since we expected declines in MMSE and CDR to be correlated, the random effects on intercept and slope for each outcome were allowed to be correlated to each other and with random effects on the other outcome. We fit models with 1–5 classes, and chose the model with the lowest BIC value (Nylund, Asparouhov, Muthen, 2007). Next, we tested our ability to predict membership in each latent class using baseline information, including age at AD onset, sex, education, duration of dementia, presence of 1 or more APOE e4 alleles, history of transient ischemic attack (TIA), history of hypertension, presence of either hallucinations or delusions as measured by the Neuropsychiatric Inventory, MMSE, and CDR-sb (reversed). Using the parallel process GMM parameter estimates, multinomial logistic regression was used to predict class membership in univariate models. For these regressions, age of onset was mean-centered at 84, education was centered at 12, MMSE was centered at mean-22, and CDR-sb (reversed) was mean-centered at 24. We then fit a multivariate model with any predictors that were significantly associated with class membership at $\alpha=0.10$ in the univariate analyses. It is well known that treatment of latent class membership as an observed variable in such regressions leads to downwardly-biased estimates of regression coefficients (Bolck, A., Croon, M.A., & Hagenaars, J.A., 2004). We used a 3-step bias correction procedure to address this issue (Asparouhov and Muthen, 2013).

Classification utility for each covariate individually, and then for progressively larger sets of covariates, was assessed via ROC (Receiver Operating Characteristic) curves, which plot sensitivity of the linear predictor (from the previous multinomial logistic regression analyses) against 1-sensitivity. Area under the curve (AUC), a measure of classification utility, was calculated for each predictor and set of predictors, for each latent class (Obuchowski, 2003). Latent variable models, including the bias-corrected regression models, were fit using MPLUS v7.11 (Muthen and Muthen, 1998–2007). Further analyses, including ROCs and processing of results, was performed using R v. 2.13 (R Development Core Team, 2008). R code is available from the first author upon request.

Results

Demographics and other characteristics of the 328 subjects are shown in table 1. The majority were female (66%), and white (99%). The mean age at dementia onset was 84.3 (SD=6.4). Mean years of education was 13.2 (SD=3.0), and baseline MMSE, CDR, and NPI were 22.0 (SD=4.6), 5.9 (SD=3.4), and 4.6 (SD=9.3). The mean number of visits was 3.6 (SD=3.0) and the mean years of followup was 3.7 (SD=2.5); the respective medians were 2 visits and 3.1 years.

Parallel process growth mixture models were fit to MMSE and CDR scores measured at up to 7 timepoints. BIC statistics were 10679.827 (1-class model), 10550.432 (2-class model), 10200.264 (3-class model), 10184.256 (4-class model), and 10535.020 (5-class model). As such, a 4-class model was chosen. Parameter estimates from this 4-class parallel process

GMM are shown in table 2, and fitted and observed trajectories by class are shown in figure 1. Entropy, a measure of classification accuracy was 0.78. As expected, the random effects for each of the trajectories were highly correlated; the correlation between the intercepts for MMSE and CDR-sb was 0.56, and the correlation between the two slopes was 0.91. Class 1 included the majority (72%) of the sample, and was characterized by modest, but steady progression throughout the period of observation. Class 2 included 8% of the sample, and was characterized by poor MMSE and CDR-sb scores at the outset and rapid progression. Class 3 included 11% of the sample and was characterized by little progression in the first 1–2 years, followed by a precipitous change. Class 4 included 8% of the sample, and like class 2, was characterized by steep changes throughout, though these individuals started out with better MMSE and CDR-sb scores. In post-hoc bias-corrected analyses, mean number of visits (3.9, 1.7, 2.5, and 3.4 for classes 1–4, respectively) varied significantly by class ($\chi^2(3) = 73.3, p < 0.001$).

Table 3 shows bias-corrected results from univariate logistic regressions of each predictor on membership in each latent class versus class 1 (slow progressors). Tables 3 and 4 shows log odds ratios, rather than odds ratios, in order to facilitate risk calculations. Older age at baseline was associated with greater odds of membership in class 3 (OR: 1.19; 95% CI: 0.99–1.42; p-value=0.059). Greater education was associated with decreased odds of membership in class 3 (OR: 0.73; 95% CI: 0.58–0.92; p-value=0.007). Longer duration of dementia (OR: 1.61; 95% CI: 1.22–2.12; p-value<0.001) and presence of psychosis (OR: 5.19; 95% CI: 2.09–12.85; p-value<0.001) were associated with greater odds of membership in class 2. Higher MMSE was associated with decreased odds of membership in class 2 (OR: 0.31; 95% CI: 0.2–0.47; p-value<0.001) and class 3 (OR: 0.39; 95% CI: 0.27–0.56; p-value=0.001). Better CDR was associated with decreased odds of membership in class 2 (OR=0.29; 95% CI: 0.18–0.47; p-value<0.001).

Table 4 shows bias-corrected parameter estimates from a multivariate logistic regression model with age at onset, education, NPI psychosis, and MMSE. CDR-sb was omitted due to collinearity; dementia duration was omitted because the model including dementia duration failed to converge. In the multivariate model, only MMSE was a statistically significant predictor of class membership. Higher MMSE scores were associated with decreased odds of membership in class 2 (OR: 0.28; 95% CI: 0.14–0.58; p-value=0.001), and in class 3 (OR: 0.35; 95% CI: 0.17–0.73; p-value<0.001). Figure 2 shows sequential ROC curves for successively large sets of predictors in the multivariate model. AUCs for the multivariate model were 0.98, 0.88, and 0.67, respectively, for classes 2 through 4 (with class 1 as the reference).

One can use the coefficients in table 4 to calculate the model-based log odds of class membership for an individual, and from that probability of membership in given class based on a set of baseline variables. For example, consider an individual with dementia onset at age 75, with 12 years of education, no NPI psychosis, and a baseline MMSE of 25. They would have a 99% chance of being a member of class 1, a 1% of being in class 4, and near-zero chances of being in classes 2 or 3. By contrast, that same individual, but with a baseline MMSE of 15, would have a 3% chance of being in class 1, an 80% chance of being in class

2, a 17% chance of being in class 3, and a near-zero chance of being in class 4. A spreadsheet to perform these calculations is available from the first author on request.

Discussion

Growth mixture modeling has been used to model cognitive decline among older adults (Small and Backman, 2007; Leoutsakos et al., 2012a), but to our knowledge this is its first application in incident AD. We demonstrated substantial heterogeneity in course in both cognition and function. It is noteworthy that the majority of people with incident AD belonged to a class characterized by relatively slow progression (0.62, 1.63, and 7.05 expected loss of MMSE points, and 0.33, 1.01, and 5.20 expected CDR-sb points, respectively, at 1, 2, and 5 years). In previously published analyses from DPS, random effects models fit across all participants yielded expected MMSE and CDR-sb losses at 5 years of 8.8 and 6.5, respectively (Tschanz et al., 2011). To paraphrase Stephen Jay Gould, *the mean is not the message* (Gould, 1985), since most individuals actually declined considerably less.

The progression observed in DPS, even as a whole, is much slower than is typically reported in clinical based samples. For example, a meta-analysis of research clinic samples reported a pooled mean annual rate of loss on the MMSE of 3.3 points (Han et al., 2000). The Kungsholmen project reported mean annual MMSE losses of 2.75 (first three years) and 3.03 (3–7 years). Given that the rate of progression in AD varies over the course of the disease (Camicoli and Kryscio, 2005), it may be better to move away from discussions of annual rates of change (e.g. slopes), and towards predictions of expected loss at set intervals (1,2, and 5 years, for example). This more flexible convention would allow for the communication of the meaning behind non-linear terms, such as quadratic terms, that are now being used more frequently.

We found that it was possible, using a set of baseline predictors, to classify individuals with good accuracy (AUCs ranging from 0.74 to 0.99). Predictably, baseline MMSE and CDR-sb were the most potent predictors. Though baseline total NPI score was not predictive of decline when the sample was analyzed together (Tschanz *et al.*, 2011), presence of psychosis as measured by the NPI delusions and hallucinations domains was predictive of membership in class 2 (a class characterized by steep declines) in univariate models. Canavelli and colleagues looked at clusters of NPI symptoms as predictors of decline in the large ICTUS sample, and found no relationship between these clusters and rate of decline (Canavelli et al., 2013). Presence of neuropsychiatric symptoms has been shown to be predictive of conversion to dementia among those with MCI (Chan et al., 2011; Peters et al., 2013). Male sex was not predictive of class membership in our analyses. This finding is not consistent with other reports that females with AD decline more rapidly (Aguero-Torres et al., 1998; Tschanz et al., 2011). Education was associated with increased odds of membership in class 3 in the univariate analysis; this is consistent with other reports (Stern et al., 1999; Andel et al., 2006; Scarmeas et al., 2006).

We are not aware of any published risk calculators for rate of decline in AD, but a function to predict mortality using data from the PAQUID study has been developed. It uses age at

diagnosis, sex, and number of impaired ADLs at baseline, and had an AUC of 0.75. Neither subjective health nor education were predictive in their model (Delva et al., 2013).

There are a number of limitations to our findings which should be noted. First, the use of single, relatively crude measures of cognition (MMSE) and functional decline (CDR-sb) may not have fully captured the nature of participants' declines. Though population-based, the sample is from a single county in northern Utah whose residents are almost universally of northern or western European descent, who are almost all members of the Church of Jesus Christ of Latter Day Saints. Findings from DPS may not generalize to other populations.

The use of growth mixture modeling, while novel, increases the complexity of the analysis by estimating model parameters for each latent class. Joint modeling of functional and cognitive decline adds a second layer of complexity. This complexity is the likely cause of the convergence failure we experienced for the multivariate model that included dementia duration. Further, because the classes are latent, it is impossible to know with certainty of what class an individual is a member. By modeling predictors of class membership rather than trajectories themselves, our findings are not directly comparable with findings from other observational studies which look at modifiers of a single mean trajectory across all individuals.

The strengths of the study include the population-based sample which includes individuals observed prior to the onset of dementia and throughout the course of their illness. The use of growth mixture modeling is novel and allows for characterization of heterogeneity in dementia course. Jointly modeling both cognition and function acknowledges the inter-relatedness of these two domains.

In conclusion, we demonstrated that heterogeneity in AD course can be modeled as classes of trajectory types, and that most individuals in our sample were members of a class with rates of decline which were less precipitous than the overall mean trajectory previously reported from the DPS study. Subjects could be accurately classified using baseline variables. Few (if any) population-based longitudinal studies of AD are comparable to DPS, making replication of our findings difficult, though such replication is essential. If similar patterns of decline and predictors of those patterns are reported using independent samples, it will be important to use this information to revise current projections of the global burden of AD (Brookmeyer et al., 2007). We note that comparison of predictors of class membership across samples would only be possible if the latent classes of decline themselves were similar. Finally, further study of predictors of class membership could shed light on the underlying neuropathological processes of AD.

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Key Points

1. There is significant variability in rate of progression both within and between individuals over the course of AD.
2. We use growth mixture modelling to identify 4 latent classes of progression trajectories
3. The majority of the cohort were members of a class characterized by slow progression
4. Predictors of course include age, education, presence of psychosis at baseline, and MMSE and CDR-sb scores at baseline.

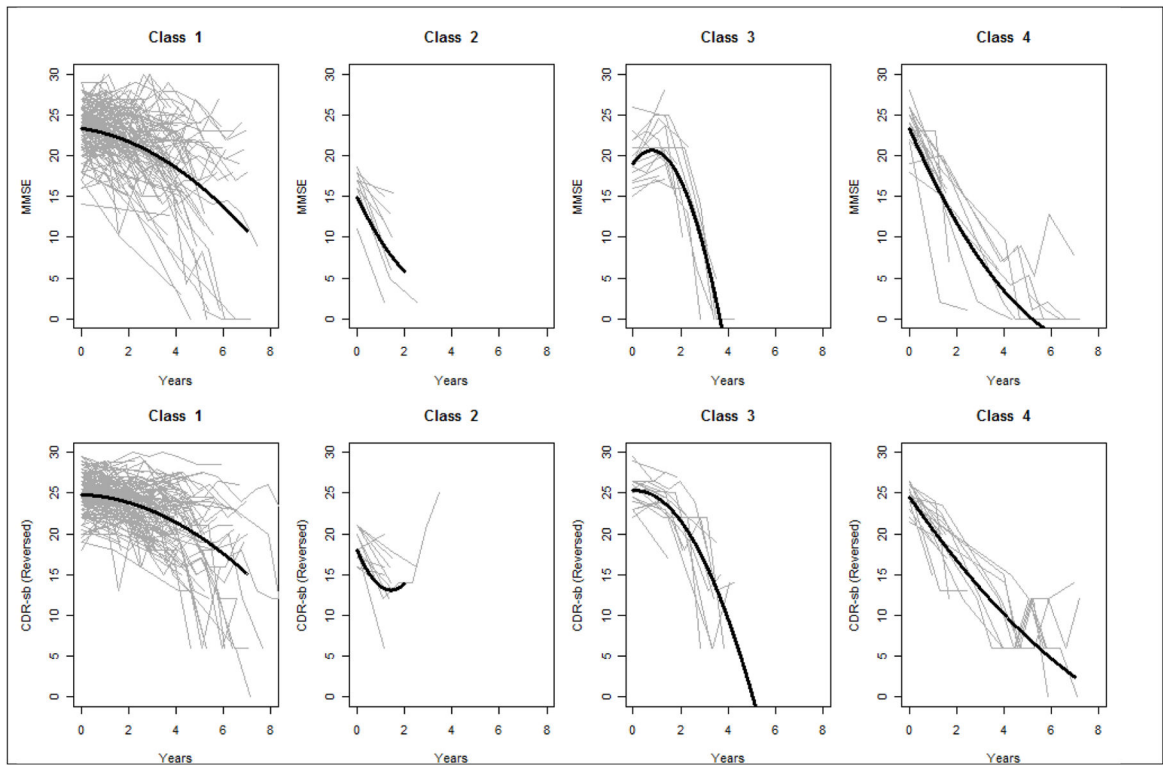


Figure 1.
 Fitted and Observed MMSE and CDR-sb¹ Trajectories By Class
¹CDR-sb has been reverse coded, such that higher scores represent less progression.

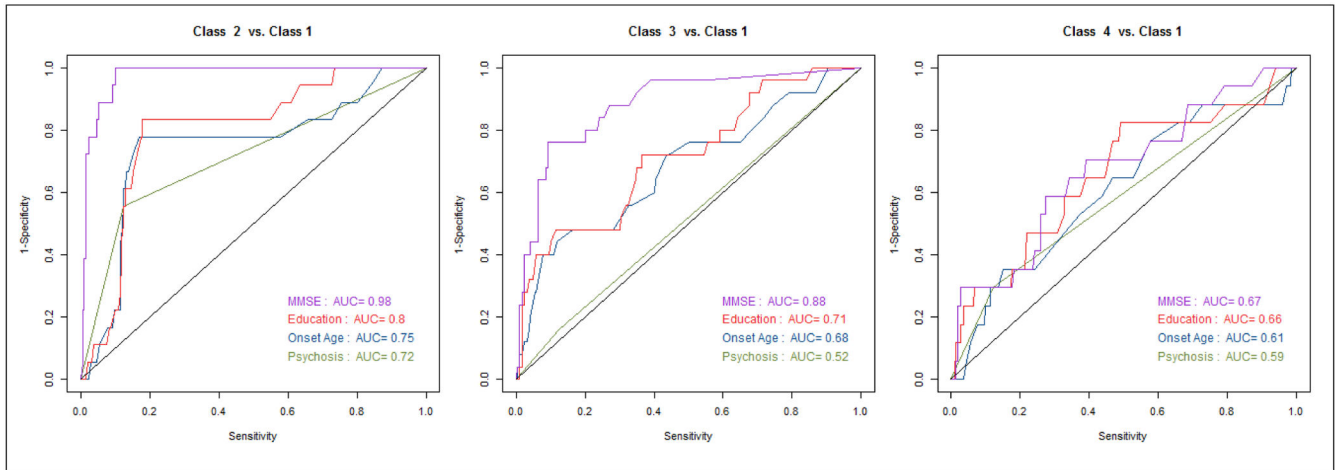


Figure 2.
ROC Curves for Successive Sets of Predictors of Latent Class Membership

Table 1

Sample Characteristics

Age at Onset (yrs)	84.3 (6.3) ¹
Male (yes/no)	35 (114) ²
Education (yrs)	13.2 (3.0)
Dementia Duration (yrs)	1.64 (1.2)
White (yes/no)	99 (326)
APOE (yes/no)	3/4 or 4/4 40 (131)
Transient Ischemic Attack (yes/no)	18 (57)
Hypertension (yes/no)	54 (172)
NPI (Total)	4.4 (9.0)
NPI Psychosis (yes/no)	17 (55)
NPI Depression (yes/no)	23 (75)
NPI Apathy (yes/no)	16 (52)
MMSE	22.4 (3.8)
CDR-sb	5.7 (2.8)
Visits	3.6 (3.0)
Length of Followup (yrs)	3.8 (2.5)

¹ Mean (SD) are displayed for all continuous variables

² Percent (count) are displayed for all dichotomous variables (denoted as yes/no)

Table 2

Parameter Estimates By Latent Trajectory Class

	Class 1	Class 2	Class 3	Class 4
Prevalence	0.72	0.08	0.11	0.08
Baseline	MMSE 23,350 (0.368) ¹	14,919 (0.820)	19,098 (1.043)	23,395 (1.361)
	CDR ² 24,838 (0.180)	17,947 (0.708)	25,289 (0.650)	24,574 (0.672)
Rate of decline ³	MMSE -0.419 (0.259)	-6.234 (2.014)	3.964 (0.984)	-6.595 (1.212)
	CDR -0.149 (0.137)	-6.853 (1.705)	0.232 (0.742)	-4.194 (1.554)
Change in rate of decline ⁴	MMSE -0.198 (0.041)	0.836 (0.994)	-2.511 (0.316)	0.401 (0.130)
	CDR -0.178 (0.029)	2.416 (0.636)	-1.040 (0.309)	0.147 (0.243)

¹ Parameter estimate (SE)

² CDR scores were reverse coded

³ Slope parameter

⁴ Quadratic, or "time squared", parameter

Table 3
Parameter Estimates and AUC from Univariate Prediction of Latent Class Membership

	Class 2 ¹		Class 3 ¹		Class 4 ¹	
	Log Odds Ratio ²	AUC	Log Odds Ratio	AUC	Log Odds Ratio	AUC
Age at Onset	0.051 (0.048)	0.57	0.171 (0.091) 0.059	0.63	0.037 (0.087)	0.54
Male	-0.010 (0.437)	0.50	-0.625 (0.924)	0.54	-1.606 (2.753)	0.56
Education	-0.168 (0.104)	0.60	-0.316 (0.116) 0.007	0.66	0.187 (0.136)	0.57
Dementia Duration	0.474 (0.142) 0.001	0.68	-0.432 (0.366)	0.57	-0.497 (0.296) 0.093	0.58
APOE	-0.166 (0.442)	0.52	0.342 (0.727)	0.52	-1.318 (2.003)	0.55
TIA	0.086 (0.553)	0.51	0.661 (0.790)	0.53	-0.459 (1.872)	0.51
HTN	-0.057 (0.427)	0.51	0.538 (0.813)	0.53	0.167 (1.095)	0.51
NPI Psychosis	1.608 (0.465) 0.001	0.72	0.951 (0.847)	0.52	1.272 (1.043)	0.59
NPI Depression	0.665 (0.461)	0.56	0.405 (0.864)	0.51	2.316 (1.477)	0.62
NPI Apathy	0.777 (0.475)	0.57	-1.322 (2.545)	0.53	-3.635 (30.897)	0.53
MMSE	-1.187 (0.219) <0.001	0.97	-0.949 (0.189) <0.001	0.88	0.163 (0.181)	0.56
CDR-sb (reversed)	-1.488 (0.243) <0.001	0.99	0.363 (0.310)	0.57	-0.071 (0.107)	0.54

¹ Log odds ratios with Class 1 as the reference class.

² Bias-Corrected Beta (SE) *p-value*; *P*-values are shown where *p*<0.10. Estimates can be translated to odds ratios by exponentiation; 95% confidence intervals for odds ratios can be obtained by constructing the interval for the log odds ratios and the exponentiating the upper and lower bounds.

Table 4

Logs Odds Ratios from Multivariate Prediction of Class Membership

	Class 2	Class 3	Class 4
Intercept	-5.801 (1.169) <0.001 ¹	-4.304 (1.010) <0.001	-4.572 (1.073) <0.001
Age at Onset	-0.030 (0.069)	0.110 (0.059) 0.063	0.009 (0.087)
Education	-0.166 (0.137)	-0.258 (0.120) 0.099	0.265 (0.139) 0.057
NPI Psychosis	-0.225 (1.251)	-1.305 (1.473)	1.957 (1.111) 0.078
MMSE	-1.259 (0.366) 0.001	-1.056 (0.375) 0.005	0.141 (0.174)

¹Bias-Corrected Beta (SE) *p-value*; P-values shown where $p < 0.10$. Estimates can be translated to odds ratios by exponentiation; 95% confidence intervals for odds ratios can be obtained by constructing the interval for the log odds ratios and then exponentiating the upper and lower bounds.

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