Empirically Defining Trajectories of Late-Life Cognitive and Functional Decline

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Abstract

Background: Alzheimer’s disease (AD) is associated with variable cognitive and functional decline, and it is difficult to predict who will develop the disease and how they will progress.

Objective: This exploratory study aimed to define latent classes from participants in the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database who had similar growth patterns of both cognitive and functional change using Growth Mixture Modeling (GMM), identify characteristics associated with those trajectories, and develop a decision tree using clinical predictors to determine which trajectory, as determined by GMM, individuals will most likely follow.

Methods: We used ADNI early mild cognitive impairment (EMCI), late MCI (LMCI), AD dementia, and healthy control (HC) participants with known amyloid-β status and follow-up assessments on the Alzheimer’s Disease Assessment Scale - Cognitive Subscale or the Functional Activities Questionnaire (FAQ) up to 24 months postbaseline. GMM defined trajectories. Classification and Regression Tree (CART) used certain baseline variables to predict likely trajectory path.

Results: GMM identified three trajectory classes (C): C1 (n = 162, 13.6%) highest baseline impairment and steepest pattern of cognitive/functional decline; C3 (n = 819, 68.7%) lowest baseline impairment and minimal change on both; C2 (n = 211, 17.7%) intermediate pattern, worsening on both, but less steep than C1. C3 had fewer amyloid- or apolipoprotein-E4 (APOE4) positive and more healthy controls (HC) or EMCI cases. CART analysis identified two decision nodes using the FAQ to predict likely class with 82.3% estimated accuracy.

Conclusions: Cognitive/functional change followed three trajectories with greater baseline impairment and amyloid and APOE4 positivity associated with greater progression. FAQ may predict trajectory class.

Keywords: Alzheimer’s disease, disease progression, amyloid, longitudinal studies, ADNI, function, cognition, MCI

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INTRODUCTION

Alzheimer’s disease (AD) is a progressive neurodegenerative disease typically characterized by slow cognitive and functional decline; however, considerable variability in rate of progression makes it hard to predict an individual’s future course. AD is a continuum beginning pathologically decades before symptoms appear (preclinical stage) [1]. Symptoms progress through an early to late phase of mild cognitive impairment (MCI) and then worsen to include a more pronounced functional impairment referred to as dementia. Clinicians would like to provide patients with a likelihood of progression and how fast it may occur. Early detection and intervention might delay cognitive deterioration and/or reduce costs, especially in someone who could progress quickly. It is also important to understand disease progression for future clinical trials.

While historically AD progression has been modeled as a linear process, we now know that progression is typically slower in early disease stages and then increases more rapidly as the patient progresses into dementia [2, 3]. Sona and colleagues reviewed 82 studies assessing the role that various factors may have on rapid cognitive decline in AD [4]. In the studies reviewed, disease progression was modeled using individuals’ mean cognitive scores that were regressed on covariates such as diagnosis, age, and education, to determine their impact on disease progression [4]. These approaches attempt to describe the relationships among variables with the goal of identifying significant predictors of outcome. The limitation of these types of analyses is that they do not allow for subpopulations with variable rates of progression and they assume that one trajectory is adequate to describe the whole study population.

Growth Mixture Modeling (GMM) is a modeling approach that looks for relationships among individuals’ trajectories with the goal of classifying groups based on similar growth patterns [5, 6]. This approach enables identification of unobserved subpopulations based on similarities in their growth patterns over time rather than assuming that one trajectory approximates the whole population. Additionally, GMM allows for non-linear (e.g., quadratic) progression curves. Several studies have used GMM to follow trajectories of change in cognition and/or functioning in subjects at various stages of AD. Small and Backman utilized GMM to follow longitudinal trajectories of cognitive change as assessed by decline in Mini-Mental State Examination (MMSE) scores in preclinical AD and reported that a two-group quadratic model (and not a linear model) of cognitive decline provided the best statistical fit to the observed data [7]. Others have used GMM to follow trajectories of cognitive decline in cognitively healthy older adults followed for up to 54 months [8], and in Caucasian subjects with possible or probable AD for up to 13.5 years [9]. Leoutsakos et al. used parallel-process GMM to model class membership jointly as a function of both cognitive and functional decline by assessing change in MMSE and Clinical Dementia Rating Sum of Boxes (CDR-SB) scores and reported four distinct latent classes [10].

The objectives of this exploratory study were to define unobserved subgroups (latent classes) from participants in the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database who had similar growth patterns of both cognitive and functional change using GMM, and to identify characteristics associated with those trajectories. We then applied Classification and Regression Tree (CART) analysis [11] to develop a decision tree that uses clinical predictors that could be applied to individuals to determine which trajectory, as determined by GMM, they will most likely follow.

METHODS

Subjects

Data were obtained in August 2013 from the ADNI database (http://adni.loni.usc.edu). ADNI recruited cognitively normal older individuals (healthy control, HC), and persons with early or late MCI (EMCI, LMCI) and AD dementia across the U.S. and Canada. Baseline characteristics of the overall population can be found in Table 1. Written informed consent was obtained for participation and approved by the institutional review board at each participating center. Detailed diagnostic, inclusion and exclusion criteria are described on the ADNI website (http://www.adni-info.org/).

We included all HC, EMCI, LMCI, and AD dementia subjects from ADNI -1, ADNI-GO, and ADNI-2 who had at least one amyloid measurement using cerebrospinal fluid (CSF) amyloid β(1-42) (Aβ42), [11C] Pittsburgh compound B (PiB) positron emission tomography (PET) or [18F] florbetapir (FBP) PET, and at least one post-baseline assessment on the Alzheimer’s Disease Assessment Scale–Cognitive Subscale (ADAS-Cog13) or the Functional Activities Questionnaire (FAQ). Our study defined the baseline visit as the first amyloid measurement visit, for which we also used that associated clinical diagnosis.
of education: score range 9–11; 8–15 years: 5–9; 0–7 years: 1–4.

Logical Memory II (WMS-LMII) (EMCI: one paragraph from Wechsler Memory Scale-Revised using education adjusted scores on delayed recall of activities of daily living, and an absence of dementia.

Wechsler LM II 1.7 ± 1.2

EMCI subjects were required to have MMSE scores between 20–26 (inclusive), a subjectively healthy control, a MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; NPI-Q, Neuropsychiatric Inventory-Questionnaire.

Table 1

Baseline demographics and other clinical characteristics by latent class (mean ± SD unless otherwise specified)

| Class 1 | Class 2 | Class 3 | Total | p-value* |
|---------|---------|---------|-------|----------|
| Age (years) | 74.7 ± 8.3 | 74.4 ± 8.2 | 72.9 ± 7.6 | 73.4 ± 7.38 | 0.0021 |
| Female (%) | 59.3% | 62.1% | 54.8% | 56.7% | 0.1287 |
| Race (% Caucasian) | 97.5% | 96.2% | 93.7% | 97.7% | 0.0612 |
| Education (years) | 15.2 ± 8.3 | 113.7 ± 9.2 | 177.8 ± 24.0 | 136.6 ± 28.5 | 0.0001 |
| Amyloid Positive | 92.0% | 84.4% | 48.2% | 60.6% | <0.0001 |
| Diagnosis (%) | 69.1% | 64.0% | 38.3% | 47.1% | <0.0001 |
| Age (years) | 74.4 ± 8.3 | 74.1 ± 8.2 | 72.9 ± 7.6 | 73.4 ± 7.38 | 0.0021 |
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All EMCI and LMCI subjects were required to have MMSE scores between 24–30 (inclusive), a subjectively healthy control reported by subject, informant, or clinician, absence of significant levels of impairment in other cognitive domains, essentially preserved activities of daily living, and an absence of dementia.

EMCI and LMCI were distinguished from each other using education adjusted scores on delayed recall of one paragraph from Wechsler Memory Scale-Revised (WMS-LMII) (EMCI: ≥16 years of education: score range 9–11; 8–15 years: 5–9; 0–7 years: 3–6; LMCI: ≥16 years: ≤8; 8–15 years: ≤4; 0–7 years: ≤2). For some subjects the first amyloid measurement (our study baseline) occurred after initial enrollment in ADNI, and those who converted to MCI were not designated as EMCI and LMCI at post-entry follow-up visits. For those MCI subjects, we applied the WMS-LMII education-adjusted score ranges from the ADNI-2 protocol to separate them into EMCI and LMCI groups. Inclusion criteria for AD subjects were MMSE scores between 20–26 (inclusive), a global Clinical Dementia Rating Scale score of 0.5

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or 1.0, and meeting National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS/ADRDA) criteria for probable AD. A specific functional scale was not mandated as part of the clinical diagnosis.

Amyloid positive status was defined according to either PiB-PET composite standard uptake value ratio (SUVR) mean across five regions of interest (ROI) (anterior cingulate, frontal, lateral temporal, precuneus, and parietal cortices) of $\geq 1.6$ normalized to the cerebellar cortex [12], FBP-PET composite SUVR of $\geq 1.1$ mean across six ROIs (anterior and posterior cingulate, precuneus, frontal, temporal, and parietal cortices) using the whole cerebellum reference region [13], or CSF Ab$_{42}$ $\leq 195$ pg/ml [14]. When a subject had more than one amyloid measure at baseline, the amyloid status was considered to be positive if at least one measure was positive.

The ADAS-Cog$_{13}$, a 13-item cognitive test (score range 0 [normal] to 85 [impaired]), and the FAQ, an informant-rated, 10-item functional scale (score range 0 [no impairment] to 30 [dependent]), were assessed at baseline, 6-, 12-, and 24-month visits.

Demographic data, apolipoprotein E $e4$ (APOE4) status (presence or not of at least one $e4$ allele), FAQ, MMSE, Montreal Cognitive Assessment (MoCA), WMS-LMI, CDR-SB, Trail Making Test (TMT) Parts A and B, Geriatric Depression Scale (GDS) short form, and Neuropsychiatric Inventory (NPI)-Q scores were also documented from our study baseline visit.

Statistical analyses

GMM jointly modeled ADAS-Cog$_{13}$ and FAQ scores to identify unobserved subpopulations based on similarity in trajectories, regardless of diagnosis or other clinical characteristics [5, 6]. The optimal number of subpopulations was determined by evaluating $k$ (starting from 2) classes versus $k-1$ classes sequentially, until adding an additional class no longer statistically significantly improved fit through Lo-Mendell-Rubin-Adjusted Likelihood Ratio test. The mean structure (i.e., linear, quadratic, cubic, etc.) in GMM was determined by selecting the best-fitting model as defined by the largest Entropy and lowest Bayesian information criterion value.

Baseline characteristics were compared among the latent classes, including diagnosis, demographics, comorbidities, other clinical and cognitive measures, and amyloid and APOE4 status, with a likelihood ratio test in multinomial logit model for categorical characteristics, and analysis of variance for continuous measures. Uncertain class assignment was taken into consideration, using the three-step approach proposed in Asparouhov and Muthen [15].

CART [11] evaluated baseline variables to determine those that best predicted GMM most likely class membership. The model included gender, amyloid status, history of alcohol, smoking, cardiovascular disease, endocrine disease, education, age, as well as animal category fluency, FAQ, MMSE, MoCA, and NPI-Q scores. We built the classification tree using all data. Prediction accuracy was obtained through 10-fold cross-validation.

GMM was done in Mplus 7.1. CART was implemented using rpart package in R 15.3. And SAS 9.2 was used for all other analyses. Significance level of 0.05 was used when applicable.

RESULTS

The total dataset included 325 HC, 279 EMCI, 372 LMCI, and 216 AD dementia subjects. The average length of follow-up for the FAQ was 16.3 months (SD $\pm 7.1$) and for the ADAS-Cog$_{13}$ was 16.2 (SD $\pm 7.1$).

Overall, 60% subjects were considered amyloid positive with amyloid positivity increasing with advanced disease stage (HC 35.1%, EMCI 51.3%, LMCI 71.8%, AD 91.7%). There were 31 cases that had discrepant amyloid results between CSF and FBP-PET (20 of the 31 discrepant cases were CSF positive but FBP-PET negative, and the opposite was true for the remaining 11 cases).

Table 2 shows a number of GMM models from which the final model was selected. The final model identified three quadratic trajectories across all subjects for cognitive/functional change as measured by the ADAS-Cog$_{13}$ and FAQ bivariate analysis. While the graphs in Fig. 1 illustrate trajectories using mean values of individuals assigned to each class for each scale separately, GMM took both cognition and function into consideration when determining the classes. Additionally, Fig. 2 illustrates spaghetti plots of individuals’ trajectories in each class, overlayed with the fitted mean trajectory of that class.

Class 1 ($n = 462, 13.6\%$) had the highest baseline FAQ and ADAS-Cog$_{13}$ scores and steepest pattern of cognitive and functional worsening of all classes. In contrast, Class 3 ($n = 819, 68.7\%$) had the lowest baseline FAQ and ADAS-Cog$_{13}$ scores and minimal change on both over time. Class 2 ($n = 211, 17.7\%$) had an intermediate pattern with baseline FAQ and ADAS-Cog$_{13}$ scores that were more impaired than Class 3 but...
Table 2
GMM adjustment indices for 2 to 4 classes

| Number of Classes | Growth Structure | AIC    | BIC    | p-Value LMR-LRT | Entropy | n (%) of smallest class |
|-------------------|------------------|--------|--------|-----------------|---------|-------------------------|
| 2                 | Linear           | 43178.7 | 43321.0 | <0.0001        | 0.943   | 217 (18.2%)             |
|                   | Quadratic        | 43181.7 | 43369.8 | <0.0001        | 0.946   | 219 (18.4%)             |
| 3                 | Linear           | 42868.6 | 43041.5 | 0.0081         | 0.912   | 162 (13.6%)             |
|                   | Quadratic        | 42802.1 | 43030.8 | 0.0329         | 0.917   | 162 (13.6%)             |
| 4                 | Linear           | 42794.9 | 42977.9 | 0.3796         | 0.928   | 79 (6.6%)               |
|                   | Quadratic        | 42495.6 | 42765.1 | 0.0819         | 0.944   | 64 (5.4%)               |

AIC, Akaike Information Criteria; BIC, Bayesian Information Criteria; LMR-LRT, Lo-Mendell-Rubin - Likelihood Ratio Test.

Fig. 1. Three trajectories (latent classes) are graphed for the FAQ (left) and ADAS-Cog13 (right) when jointly modeled by GMM.

Table 1 shows baseline demographics by latent class. Significant differences were observed among the three classes across most variables including age (p = 0.0021), APOE4 status (p < 0.0001), amyloid status (p < 0.0001), diagnosis (p < 0.0001), alcohol abuse (p = 0.0474), and all clinical and cognitive measures (p < 0.0001 except GDS p = 0.0007). No significant differences were observed for gender, education, or comorbidities of smoking, cardiovascular disease, or endocrine disease. On average, Class 1 subjects were older and more likely amyloid (92%) or APOE4 (69.1%) positive. The majority of Class 1 was diagnosed with AD dementia (79%) or LMCI (17.9%). This group showed the greatest amount of impairment across measures of cognition and function and the greatest neuropsychiatric symptom severity.

In contrast, Class 3 subjects were younger and less likely to be amyloid (48.2%) or APOE4 (38.3%) positive. Class 3 included HCs (39%) or were diagnosed with EMCI (29.9%) or LMCI (29.1%), and showed the least amount of impairment across all measures of cognition and function, and the lowest neuropsychiatric symptom severity.

Class 2 subjects were HCs (0.9%) or diagnosed with EMCI (13.7%), LMCI (49.8%), or AD dementia (35.5%). Subjects were close in age to Class 1, and a higher percentage than Class 3 was amyloid (84.4%) or APOE4 (64%) positive but slightly less than Class 1. Baseline scores on cognitive, functional, and neuropsychiatric scales were intermediate between Classes 1 and 3.

Figure 3 shows FAQ or ADAS-Cog13 mean scores by diagnostic group graphed adjacent to each class’s trajectory line. As expected, the arrays for mean score...
lines were ordered according to level of impairment of each diagnostic group and either above or below the latent class line.

CART analysis identified the FAQ as the input variable most predictive of latent classes found in GMM with two decision nodes that separated subjects into their most likely class at an estimated prediction accuracy of 82.3% (SD 1.11%) (Fig. 4). The first node partitioned Class 3 if the FAQ score was <5. The remaining subjects were split at the second node into Class 2 if the FAQ was <14, and into Class 1 if the FAQ was ≥14.

DISCUSSION

We approached the topic of clinical trajectories by using a person-centered modeling approach (GMM) in contrast to most other reports that use variable-centered approaches [4]. This enabled us to discern unobserved subpopulations based on similarities in their growth patterns over time rather than to assume that one trajectory approximates the whole population or to specify subgroups based on one or more variables. We found that the combination of cognitive and functional change over a 24-month period followed three distinct trajectories, represented by one class with the lowest baseline cognitive and functional impairment and virtually no change (Class 3) and two classes that both progressed but were separated by their degree of baseline impairment. Additionally, there were some clinical characteristics that differed across the classes, such as diagnosis, APOE4, and amyloid status. Our study included cases ranging from HC through AD dementia as diagnosed in the ADNI cohort, while other studies may not have addressed this whole spectrum. Further, we only selected ADNI cases where amyloid status was known, whereas most prior reports do not have the benefit of knowing amyloid status.
Fig. 3. Trajectories are graphed to reveal diagnostic subgroups for Classes 1, 2, and 3 for the FAQ (top) and the ADAS-Cog13 (bottom) when jointly modeled by GMM. Class trajectories (from Fig. 1) are shown in color.

Finally, GMM allowed quadratic in addition to linear trajectories.

Our study found three trajectories of cognitive and functional change. Class 1 had the highest baseline FAQ and ADAS-Cog13 scores and the steepest pattern of cognitive and functional worsening. In contrast, Class 3, the largest group, had the lowest baseline FAQ and ADAS-Cog13 scores and minimal change on both scales. Not surprisingly, its constituents had diagnoses suggesting earlier stages of disease.
classes. Class 1 was the largest (72%) and had the CDR-SB scores, those authors identified four latent group [10]. Using bivariate GMM based on MMSE and to identify baseline predictors of membership for each Progression Study in up to 8 years of follow-up, and identify classes of progression trajectories in incident dementia followed for up to 13.5 years. The concomi-
tion and function (like ours) have the shortest follow-up trajectory for Class 2 would eventually look like that for Class 1 as patients become more impaired. It is important to note that we did not look at the relation-
ship between cognitive and functional decline because GMM was a bivariate analysis, nor do we know how the scales perform relative to each other in a psychometric fashion.

Previous studies have described trajectories of change in cognition and behavior in subjects with MCI or AD dementia. Xie and colleagues [16] used group-based trajectory analysis to identify distinct cognitive change patterns among a cohort of 187 MCI patients from two geriatric outpatient clinics over a course of up to 3.5 years. Five trajectories were identified and labeled based on their baseline MMSE score. Their two least cognitively impaired groups (MMSE of 27 and 29) had a stable course, which is consistent with our findings for Class 3.

Other studies with longer patient follow-up periods (up to 13.5 years) [9, 10] found that cognitive func-
tion, as measured by the MMSE, eventually declined to very low levels in almost all of the trajectories. In contrast, studies that delineate a group with a stable cognitive trajectory [2] or “nonprogression” in cogni-
tion and function (like ours) have the shortest follow-up periods (2 to 3.5 years). Wilkosz and colleagues [9] used latent class modeling and found six trajectories of cognitive and behavioral decline in a cohort of 201 Caucasian subjects with possible or probable AD dementia followed for up to 13.5 years. The concomi-
tant variables included in the best latent class trajectory model were initial MMSE and age. Also, two of our co-authors (JSL and CGL) completed an analysis to identify classes of progression trajectories in incident AD dementia cases from the Cache County Dementia Progression Study in up to 8 years of follow-up, and to identify baseline predictors of membership for each group [10]. Using bivariate GMM based on MMSE and CDR-SB scores, those authors identified four latent classes. Class 1 was the largest (72%) and had the slowest progression as compared to the other three classes with more rapid worsening. In a multivari-
ate model, only MMSE was a statistically significant predictor of likely class membership. However, these two studies only included subjects with dementia. Our study also included HC and EMCI subjects who progress more gradually over many years [17]. Overall, our findings are consistent with reports that the course of cognitive impairment in clinically diagnosed AD is variable, starts slow and progressively increases over time [2, 17].

A recent review of 82 studies that reported at least one factor associated with rate of progression for an AD patient population considered an extensive list of potential factors such as age, gender, edu-
cation, family history of dementia, MMSE and CDR scale baseline scores, comorbidities, APOE genotype, and cholinesterase inhibitor use [4]. Study results were often contradictory, and no reliable conclusions regarding factors possibly associated with rapid cognitive decline could be made; however, a trend was found for younger, more educated and/or more impaired patients. The more rapid decline in the higher educated is consis-
tent with the hypothesis that higher cognitive reserve protects from early clinical manifestation of AD, but later patients deteriorate more rapidly as the disease progresses.

We found that class membership was associated with baseline age, APOE4 and amyloid status, diagno-
sis, and all cognitive, functional, and neuropsychiatric scores. Subjects that progressed were more often APOE4 or amyloid positive, older in age, and later in their disease stage. A number of studies, but not all [18], report that younger subjects have a more rapid decline in cognition compared to older subjects, as reviewed by Sona et al. [4]. However, we found an opposite association for age with class membership where subjects in Class 1 with the steepest progression were older than in Class 3, though we did not control for time from disease onset or disease severity, and AD and HC groups were age-matched, while EMCI and LMCI groups were younger on average. This find-
ing may be driven by the fact that amyloid portends poorer outcome, especially when combined with other pathologies that increase with aging. Our findings are consistent with a number, but not all, of other studies that report greater cognitive decline in subjects with worse baseline cognitive impairment [3, 4, 19, 20]. APOE4 positivity is associated with a greater decline in function [21] and cognition [22, 23], although this rela-
tionship has not been observed consistently [24–27]. Possible explanations have focused on linear versus
ADAS-Cog13 because it is utilized in research and the original GMM classes, we chose to exclude the ADAS-Cog13 and FAQ results jointly defined projects most likely belong to the GMM classes. While nodes, both based on FAQ results, to predict which sub-

cate individuals to a particular class when applying the tree with a series of if-then scenarios to best allo-

non-linear statistical models [22], or different AD clinical populations [23]. Our study results are consistent

additional, a faster decline in cognition is reportedly associated with increased neuropsychiatric symptom severity including agitation and wandering [34], hallucinations and delusions [35], and depressive symptoms [36]. Our results showed a higher NPI-Q score was associated with faster pro-

We did not find class membership to be associated with gender, education, or comorbidities of smoking, cardiovascular disease, or endocrine disease, although there is other evidence that vascular risk factors are associated with greater functional and cog-

We included HCs in the analyses as some are still at risk population may limit generalizability of these results. In the current study, education did not differ among the three classes, though most subjects in the ADNI cohort have a high level of education, limiting the ability to study this factor.

CART analysis can uncover complex interactions among predictors of trajectory class membership which could be difficult to identify using traditional multivariate techniques [11]. The result is a decision tree with a series of if-then scenarios to best allo-

For AD and could be transitional toward impairment [34]. CART uses most likely class membership, and cannot accommodate the fact that a subject could be in another class with smaller probability. Although our sample size of 1,192 was relatively large, the follow-

There are some limitations to this study that should be taken into consideration. When determining amy-

Our findings make a unique contribution to the litera-

ture on longitudinal change in older persons, including those clinically diagnosed with MCI and AD demen-
tia and may help inform clinicians and patients when amyloid biomarker testing is not available. Moreover, patients with MCI were further subdivided into EMCI and LMCI to better capture how those categorical des-

perhaps the FAQ cutoff values of 5 and 14, as identified through CART analysis, can facilitate identification of who will progress in other patient populations. These findings may extend the initial report suggesting a cut point of ≥9 ("dependent" or a score of 3 in three or more activities) to indicate impaired function consis-
tent with dementia [40]. However, CART analyses are exploratory for generating hypotheses that need further testing.

population may limit generalizability of these results. In the current study, education did not differ among the three classes, though most subjects in the ADNI cohort have a high level of education, limiting the ability to study this factor.

CART analysis can uncover complex interactions among predictors of trajectory class membership which could be difficult to identify using traditional multivariate techniques [11]. The result is a decision tree with a series of if-then scenarios to best allo-

computer individuals to a particular class when applying the variable cutoff values that produced the best fit. This provides a straightforward approach to apply clinical predictors. The CART analysis identified two decision nodes, both based on FAQ results, to predict which sub-

jects most likely belong to the GMM classes. While the ADAS-Cog11 and FAQ results jointly defined the original GMM classes, we chose to exclude the ADAS-Cog11 because it is utilized in research and not available to a clinician. However, we ran a sep-

arate CART analysis that included the ADAS-Cog and the FAQ remained the main differentiator. It is note-

worthy that baseline cognitive variables or amyloid status were not better predictors of GMM member-

ship. The FAQ is a functional measure that includes instrumental activities of daily living, such as prepar-

Here, we did not find class membership to be asso-

iated with gender, education, or comorbidities of smoking, cardiovascular disease, or endocrine disease, although there is other evidence that vascular risk factors are associated with greater functional and cog-

nitive decline [26, 37, 38]. Regan and colleagues [39] note though these risk factors may contribute to AD initially, they are not part of the underlying disease process. Alcohol abuse showed a significant difference among the trajectory classes in our analysis, but the percentage of patients reporting alcohol abuse was rel-

atively low among the groups (range: 3.3% to 8%), making this finding less reliable. Those with higher cognitive reserve (more years of education) diagnosed with AD show an initial delay in symptom expression, which could be difficult to identify using traditional methods. In another class with smaller probability. Although our sample size of 1,192 was relatively large, the follow-

up period of up to two years (mean about 16 months) may not be long enough to see progression, especially earlier in the disease spectrum. In addition, the relatively low incidence of comorbidities, limited racial representation and high years of education in the ADNI population may limit generalizability of these results.

We included HCs in the analyses as some are still at risk for AD and could be transitional toward impairment and indeed, some were amyloid positive (35%).

Our findings make a unique contribution to the litera-

ture on longitudinal change in older persons, including those clinically diagnosed with MCI and AD demen-
tia and may help inform clinicians and patients when amyloid biomarker testing is not available. Moreover, patients with MCI were further subdivided into EMCI and LMCI to better capture how those categorical des-

ignations populated the three latent classes. Our sample was larger than most prior reports and the amyloid
status of patients was known. Third, we looked at changes in both cognition and function. Lastly, we used CART analysis to develop a decision tree, and identified two decision nodes based on the FAQ that separated patients along the three latent classes. These decision nodes may further the understanding of the FAQ scale cutoff values in relation to severity of impairment.

In summary, the combination of cognitive and functional change over a 24-month period followed three distinct trajectories where positive APOE4 and amyloid status were more associated with a subpopulation that had greater decline over time (64%–69% and 84%–92%, respectively). The FAQ score may help to predict trajectory. This type of information could be shared by the physician to help patients and families plan for the future. However, our results are exploratory and should be confirmed in other populations with longer term follow-up.

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