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RESEARCH ARTICLE

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Cognitive and functional progression in Alzheimer disease: A prediction model of latent classes

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Objective: We sought to replicate a previously published prediction model for progression, developed in the Cache County Dementia Progression Study, using a clinical cohort from the National Alzheimer's Coordinating Center.

Methods: We included 1120 incident Alzheimer disease (AD) cases with at least one assessment after diagnosis, originating from 31 AD centres from the United States. Trajectories of the Mini-Mental State Examination (MMSE) and Clinical Dementia Rating sum of boxes (CDR-sb) were modelled jointly over time using parallel-process growth mixture models in order to identify latent classes of trajectories. Bias-corrected multinomial logistic regression was used to identify baseline predictors of class membership and compare these with the predictors found in the Cache County Dementia Progression Study.

Results: The best-fitting model contained 3 classes: Class 1 was the largest (63%) and showed the slowest progression on both MMSE and CDR-sb; classes 2 (22%) and 3 (15%) showed moderate and rapid worsening, respectively. Significant predictors of membership in classes 2 and 3, relative to class 1, were worse baseline MMSE and CDR-sb, higher education, and lack of hypertension. Combining all previously mentioned predictors yielded areas under the receiver operating characteristic curve of 0.70 and 0.75 for classes 2 and 3, respectively, relative to class 1.

Conclusions: Our replication study confirmed that it is possible to predict trajectories of progression in AD with relatively good accuracy. The class distribution was comparable with that of the original study, with most individuals being members of a class with stable or slow progression. This is important for informing newly diagnosed AD patients and their caregivers.

KEYWORDS

cognition, dementia, disease course, functioning, growth mixture model, trajectory

1 | INTRODUCTION

Alzheimer disease (AD) is a very heterogeneous condition, in terms of both its presentation and its progression.[1,2] Upon diagnosis, questions regarding future speed of decline may arise, which are difficult to answer owing to the large variation in disease course within and between patients. Moreover, different areas of functioning can be affected in AD patients: Whereas some develop mainly cognitive complaints, others show rapid decline in daily functioning as well.[3] As a consequence, patients, families, and physicians face considerable uncertainty regarding disease prognosis.

So far, only a limited number of studies have attempted to unravel the heterogeneity in AD progression.[4] Most of these studies looked at one health dimension at a time (eg, cognition), even though the importance of a multidomain approach in dementia has been repeatedly reinforced.[3,5,6] The few studies that have analysed multiple outcomes of AD simultaneously have shown correlation between rates of change in cognition and daily functioning.[2,7,8]

A literature review of factors associated with rapid cognitive decline in AD concluded that study results were heterogeneous and often contradictory. The review showed that studies are often limited in terms of sample size, duration of follow-up, or both. Moreover, the definition of rapid decline in AD varies across studies, and cut-offs are often arbitrarily chosen. Overall, younger patients with higher education and more cognitive impairment at baseline appear to decline more rapidly.[9] Other studies have shown AD progression is likely to be influenced by noncognitive factors, such as depressive symptoms and comorbid disease burden as well.[6,7] These findings suggest that combining disease-related characteristics with other information on the patient's profile may improve the prediction of AD progression. Such a prediction may not only provide valuable prognostic information for patients and caregivers but also help us to target patients who are most likely to benefit from interventions aimed at slowing disease progression.

In an attempt to increase our knowledge on the course of AD and its predictors, a prediction model based on data from the Cache County Dementia Progression Study (CCDPS) identified 4 different classes of cognitive and functional progression, with cognitive status at the moment of diagnosis being the strongest predictor of future decline.[8] Although replication is pivotal in prognostic factor research,[10] these findings have not been replicated yet. In the present study, we sought to replicate the prediction model from the CCDPS in a large clinical cohort from the National Alzheimer's Coordinating Center (NACC). The aims of this study are (1) to identify latent classes of trajectories of AD progression and (2) to predict class membership using AD-related and other characteristics of the patient.

Key points

- Heterogeneity in Alzheimer disease (AD) progression causes uncertainty regarding prognosis for patients, families, and physicians.
- We identified 3 classes with distinct rates of cognitive and functional decline using growth mixture modelling.
- The majority of AD patients showed a slower progression as compared with the mean population trajectory, which is typically reported.
- Predictors of dementia course include education, hypertension, and cognitive and functional status at diagnosis.

2 | MATERIALS AND METHODS

2.1 | Sample description

Data from the NACC Uniform Data Set were used. This database consists of a referral/volunteer-based case series of AD patients from AD centres (ADCs) throughout the United States who are followed up yearly. We included 1120 incident AD cases with at least one assessment after diagnosis. Standardized criteria for the diagnosis of AD were used across the ADCs.[11] An AD incident case was defined as having a study visit at which the patient was deemed free of AD within 18 months prior to diagnosis and a global Clinical Dementia Rating (CDR) ≤ 1 at the moment of diagnosis. This analysis used data from 31 ADCs, with visit dates ranging from June 2006 through the December 2015 data freeze. A detailed description of the NACC data can be found elsewhere.[12]

2.2 | Measures of AD progression

We used the Mini-Mental State Examination (MMSE) score to assess cognition.[13] This is a global score of cognitive abilities ranging from 0 to 30, with higher scores indicating better cognitive performance. The CDR sum of boxes (CDR-sb) was used to assess daily functioning.[14] This scale measures global cognitive and functional abilities and ranges from 0 to 18, with higher scores indicating more severe impairment. To enhance comparability and interpretation of our model, CDR-sb scores were reverse-coded ranging up to 30, so higher scores indicated better performance (eg, a CDR-sb score of 1 was recoded as 29). Data across the first 3 years after diagnosis were used.

2.3 | Independent variables

The following variables were included as potential predictors of progression: age; gender; race (white vs other); education (years); time since first symptoms; MMSE[13] and CDR-sb[14] scores; and history of transient ischaemic attack (yes/no), history of hypertension (yes/no), Neuropsychiatric Inventory Questionnaire total score (range: 0-36, with higher values indicating more symptoms),[15] and its subdomains: psychosis (delusions or hallucinations: yes/no), depression or dysphoria (yes/no), and apathy or indifference (yes/no). We used information obtained at baseline, which corresponds to the moment of diagnosis in the present analysis.

2.4 | Statistical analyses

We used parallel-process growth mixture models (GMMs) to model trajectories of MMSE and CDR-sb jointly over time.[8] The GMMs allow for grouping of subjects into so-called latent classes, on the basis of similarities in their progression patterns over time.[16] This means an increasing number of curves is fit until an optimal balance between model fit

and model complexity is reached. The GMMs are a longitudinal form of latent class analysis, in which mixed models are used. A specific type of GMMs, termed parallel-process GMM, allowed us to model 2 outcomes simultaneously over time. We fit quadratic models with 1 to 5 classes and chose our final model on the basis of the Bayesian information criterion (BIC), Lo-Mendell-Rubin (LMR) likelihood ratio test, and class sizes.[17] The BIC is an indicator of model fit, with lower values indicating better model fit. The LMR test compares the improvement in model fit between 2 nested models. A significant LMR test denotes that the model with k classes fits better than did the same model with $k - 1$ classes.[18] Maximum likelihood estimation was used to obtain parameter estimates, with standard errors (SEs) that are robust to nonnormality. Observations were assumed to be spaced exactly 1 year apart. The variance of the quadratic slope was fixed to 0. The residual variances were allowed to vary over time and were assumed to be equal across classes. After the number of classes has been decided, multinomial logistic regression with the 3-step method was used to examine which factors predicted class membership in a multivariable model.[19] Continuous predictors were mean-centred. The area under the curve (AUC), a measure of classification utility, was subsequently calculated for sets of predictors via receiver operating characteristic (ROC) curves. The GMMs, including multinomial logistic regression models, were fit using Mplus version 8.[20] Further analyses, including ROCs and processing of results, were performed using R v. 3.2.4.[21]

2.5 | Comparison with Cache County model

The model, which we aimed to replicate, was based on data from 328 incident AD patients of the population-based CCDPS.[8] It used the same diagnostic criteria, AD progression measures, independent variables, and statistical methods as described in the previous paragraphs. In contrast to the present study, however, the sample of the CCDPS was population-based. Four classes of quadratic trajectories were identified, with the majority of the sample (72%) belonging to class 1 with the slowest progression. Classes 2 to 4 each contained 8% to 11% of the sample and showed more rapid declines in both cognition and daily functioning. In the multivariable regression model, only MMSE score at diagnosis was identified as a significant predictor for class membership. Higher MMSE scores at diagnosis were associated with a decreased chance of being a member of more rapidly declining classes. The AUCs for the multivariate model were 0.98, 0.88, and 0.67, respectively, for classes 2 to 4 (with class 1 as the reference).

We aimed to replicate the latent classes from the CCDPS by modelling these 4 classes in our sample from the NACC, using the previously published parameter estimates. The goodness-of-fit of this model was subsequently compared with a 4-class model with unconstrained parameter estimates to determine whether a comparable model would be obtained in the absence of prior knowledge from the CCDPS. A chi-square difference test based on log-likelihood values and scaling correction factors was used for this comparison.

3 | RESULTS

3.1 | Sample characteristics

Baseline characteristics (from the moment of AD diagnosis) of our sample are summarized in Table 1. The mean age at diagnosis was

TABLE 1 Sample characteristics: mean (SD) or % [count]

Characteristics	Baseline	1st Follow-up	2nd Follow-up	3rd Follow-up
N	100 [1120]	100 [1120]	60.8 [681]	34.1 [382]
MMSE score	24.2 (3.2)	22.3 (4.5)	20.8 (5.1)	19.0 (6.2)
CDR-sb	3.8 (1.6)	5.6 (2.9)	7.0 (3.5)	8.5 (4.2)
Follow-up time, y	NA	1.2 (0.5)	2.2 (0.5)	3.3 (0.7)
Age at diagnosis	79.4 (8.7)			
Gender: female	52.1 [584]			
Race				
White	86.7 [968]			
Black or African American	9.5 [106]			
Asian	2.2 [24]			
Unspecified	1.6 [22]			
Time since first symptoms, y	5.5 (2.9)			
Education, y	15.4 (3.2)			
NPI-Q				
Severity score	3.6 (3.7)			
Psychosis	9.6 [104]			
Depression or dysphoria	37.4 [406]			
Apathy or indifference	36.3 [395]			
History of transient ischaemic attack	8.1 [90]			
History of hypertension	62.8 [703]			

Abbreviations: CDR-sb, Clinical Dementia Rating—sum of boxes (range, 0-18, higher = worse); MMSE, Mini-Mental State Examination (range, 0-30, higher = better); N, number of participants in whom at least 1 of 2 outcomes was measured; NA, not applicable; NPI-Q, Neuropsychiatric Inventory Questionnaire severity score (range, 0-36, higher = worse); SD, standard deviation.

79.4 years, with a range of 45.3 to 103.0. The majority of the sample was female (52.1%), and the mean follow-up time since diagnosis was 2.6 years. Three years after diagnosis, 103 patients had died (9.2%). The mean MMSE score at diagnosis was 24.2, and the mean CDR-sb was 3.8.

3.2 | Heterogeneity of progression

Quadratic curves for MMSE and CDR-sb progression were fit across the first 3 years after diagnosis. The observed individual trajectories of MMSE and CDR-sb and means of the entire sample are depicted in Figure 1A. The observed variation in the intercept and the slope was found to be significant, allowing for the identification of latent classes of progression, as described in the next paragraph. Trajectories of MMSE and CDR-sb were clearly related, as shown by the strong correlation between their random slopes (R = 0.92, P < .001).

3.3 | Latent classes of progression

When fitting models with increasing numbers of classes, the 3-class model provided the best fit according to the LMR test (3- vs 4-class model: −2LL(7) = 119.31, P = .565) and the class sizes. An overview of the model fit criteria is shown in Table 2. When increasing the number of classes beyond 3, the smallest class contained only 2% of our sample, indicating that a model with more than 3 classes derived from our sample is unlikely to be replicated. The difference in BIC between the 3-class model and the 4-class model is also rather small, indicating the model fit improvement caused by the 4th class was minimal.

TABLE 2 Overview of class enumeration

No. Classes	No. Parameters[a]	BIC	Entropy	LMR P Value	Smallest Class Size, %
1	24	29 173.68	…	…	…
2	31	28 877.56	0.919	.000	9
3	38	28 732.35	0.748	.007	10
4	45	28 662.18	0.772	.565	2
5	52	28 609.51	0.778	.014	2

Abbreviations: BIC, Bayesian information criterion (lower values imply better model fit); Entropy, higher values imply better classification quality; LMR, Lo-Mendell-Rubin likelihood ratio test.

[a]The process of class enumeration was based on models with class-invariant random intercept and random slope.

The best-fitting model included class-specific intercept variances and class-specific slope variances. The parameter estimates of this 3-class model are shown in Table 3, and the trajectories are depicted in Figure 1B-D. Class 1 was the largest (63%) and showed the best cognitive and functional abilities at diagnosis, as well as the slowest decline. Class 2 was the second largest class (22%), showing somewhat decreased cognitive and functional abilities at diagnosis, as well as a quadratic decrease of abilities over time. Class 3 was the smallest (15%), showing somewhat decreased cognitive and functional abilities at diagnosis, as well as dramatic worsening over time.

3.4 | Predictors of class membership

All potential predictors of class membership listed in Table 1 were examined using multivariable logistic regression, with predicted class

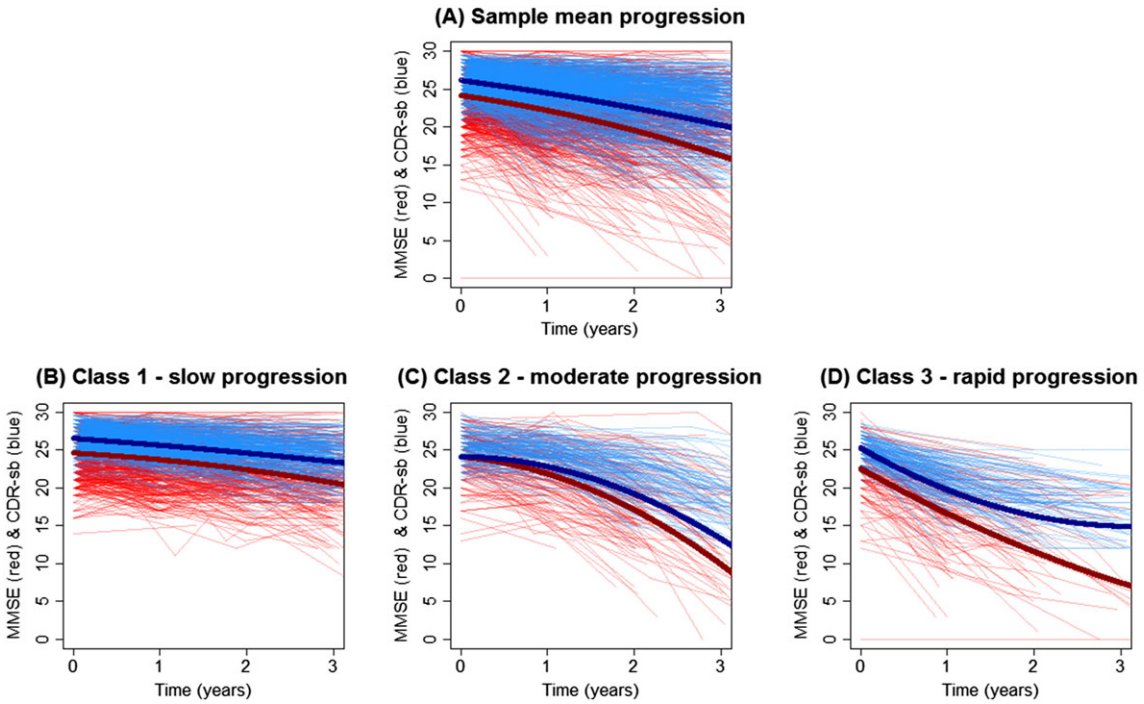

FIGURE 1 Fitted and observed MMSE and CDR-sb trajectories. MMSE trajectories are shown in red. CDR-sb trajectories are shown in blue. CDR-sb scores were reverse-coded ranging up to 30 (higher = better). A, The trajectories of the entire sample (N = 1120). The identified latent classes are presented in bottom row of the figure. B, The slowly progressing class 1 (N = 778). C, Class 2 (N = 169) with moderate progression speed. D, The rapidly progressing class 3 (N = 173). The mean trajectories of each plot are shown in bold. Individuals were assigned to classes on the basis of their most likely class membership, causing the class counts to slightly differ from those in the text and Table 3, which were based on the probability of class membership. CDR-sb indicates Clinical Dementia Rating—sum of boxes; MMSE, Mini-Mental State Examination score [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Parameter estimates for MMSE and CDR-sb trajectories by latent class

		Class 1 Slow Progression	Class 2 Moderate Progression	Class 3 Rapid Progression
Prevalence (% [N][a])		63 [702]	22 [243]	15 [175]
		Mean (SE)	Mean (SE)	Mean (SE)
Fixed effects				
Intercept	MMSE	24.60 (0.18)[b]	24.13 (0.53)[b]	22.53 (0.39)[b]
	CDR-sb[c]	26.52 (0.07)[b]	25.78 (0.19)[b]	25.24 (0.14)[b]
Linear annual rate of decline	MMSE	−0.67 (0.18)[b]	−1.06 (0.57)	−6.37 (0.93)[b]
	CDR-sb[c]	−0.84 (0.09)[b]	−0.17 (0.54)	−6.55 (0.57)[b]
Quadratic annual rate of decline	MMSE	−0.21 (0.06)[b]	−1.22 (0.29)[b]	0.45 (0.43)
	CDR-sb[c]	−0.06 (0.04)	−1.15 (0.26)[b]	1.04 (0.19)[b]
Random effects				
Intercept variance	MMSE	5.18 (0.67)[b]	5.73 (1.69)[b]	12.02 (3.45)[b]
	CDR-sb[c]	1.71 (0.17)[d]	2.09 (0.34)[b]	1.54 (0.28)[b]
Linear slope variance	MMSE	0.54 (0.25)[b]	2.54 (0.48)[b]	9.82 (2.75)[b]
	CDR-sb[c]	0.44 (0.14)[b]	0.99 (0.25)[b]	4.51 (0.92)[b]
Residual variance at baseline	MMSE	3.67 (0.46)[b]	3.67 (0.46)[b]	3.67 (0.46)[b]
	CDR-sb[c]	0.56 (0.14)[b]	0.56 (0.14)[b]	0.56 (0.14)[b]
Residual variance at 1st follow-up	MMSE	4.22 (0.39)[b]	4.22 (0.39)[b]	4.22 (0.39)[b]
	CDR-sb[c]	1.16 (0.14)[b]	1.16 (0.14)[b]	1.16 (0.14)[b]
Residual variance at 2nd follow-up	MMSE	4.72 (0.62)[b]	4.72 (0.62)[b]	4.72 (0.62)[b]
	CDR-sb[c]	2.23 (0.28)[b]	2.23 (0.28)[b]	2.23 (0.28)[b]
Residual variance at 3rd follow-up	MMSE	6.76 (1.21)[b]	6.76 (1.21)[b]	6.76 (1.21)[b]
	CDR-sb[c]	1.95 (0.64)[d]	1.95 (0.64)[d]	1.95 (0.64)[d]

Abbreviations: CDR-sb, Clinical Dementia Rating—sum of boxes; MMSE, Mini-Mental State Examination score; SE, standard error.

[a]N was based on the final class counts of the estimated model. Note that individuals are in fact assigned a probability of class membership.

[b]$P < .001$.

[c]CDR-sb scores were reverse-coded, ranging up to 30 (higher = better).

[d]$P < .01$.

membership in our final 3-class model as dependent variable. Table 4 shows the significant predictors of class membership, corrected for age, gender, and time since first symptoms. This analysis was based on 1008 patients; 112 patients (10%) were excluded owing to missing values for covariates. Significant predictors of membership in class 2, relative to class 1, were worse baseline CDR-sb, higher education, and lack of hypertension. Significant predictors of membership in class 3, relative to class 1, were worse MMSE and CDR-sb at diagnosis. For example, a 1-point higher MMSE score (reflecting better cognitive functioning) at diagnosis reduces the risk of membership in the rapidly declining class 3 by 15%, relative to class 1 (OR = 0.85, 95% CI, 0.79-0.92, $P < .001$).

Combining all significant predictors of class membership yielded AUCs of 0.70 and 0.75 for classes 2 and 3, relative to class 1. Figure 2 shows ROC curves for successively larger sets of predictors. The AUC increased when more predictors were added.

3.5 | Replication of the Cache County model

When comparing the previously published 4-class model (using the parameter estimates from the CCDPS as constraints) with an unconstrained 4-class model in our sample from the NACC, the chi-square test indicated that the unconstrained model fit the data better ($\chi^2(24) = 706.70$, $P < .001$). When constraining the model parameters to be equal to those from the 4-class Cache County model, 2 of 4 classes contained very few patients (class prevalence < 0.02). These

TABLE 4 Odds ratios (ORs) from multivariate prediction of class membership (N = 1008)[a]

	Class 2: Moderate Progression		Class 3: Rapid Progression	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age	0.98 (0.95-1.02)	.353	1.03 (1.00-1.06)	.088
Gender: male	0.69 (0.34-1.43)	.320	0.71 (0.42-1.19)	.193
Time since first symptoms	1.00 (0.87-1.13)	.942	0.94 (0.84-1.05)	.269
MMSE score	0.98 (0.90-1.11)	.969	**0.85 (0.79-0.92)**	**<.001**
CDR-sb[b]	**0.40 (0.28-0.58)**	**<.001**	**0.51 (0.42-0.62)**	**<.001**
Education	**1.19 (1.11-1.28)**	**.015**	1.05 (0.97-1.14)	.190
History of hypertension	**0.41 (0.21-0.82)**	**<.001**	0.66 (0.40-1.10)	.113

[a]Bold estimates are significant at $P < .05$. Reference is class 1.

[b]CDR-sb scores were reverse-coded (higher = better).

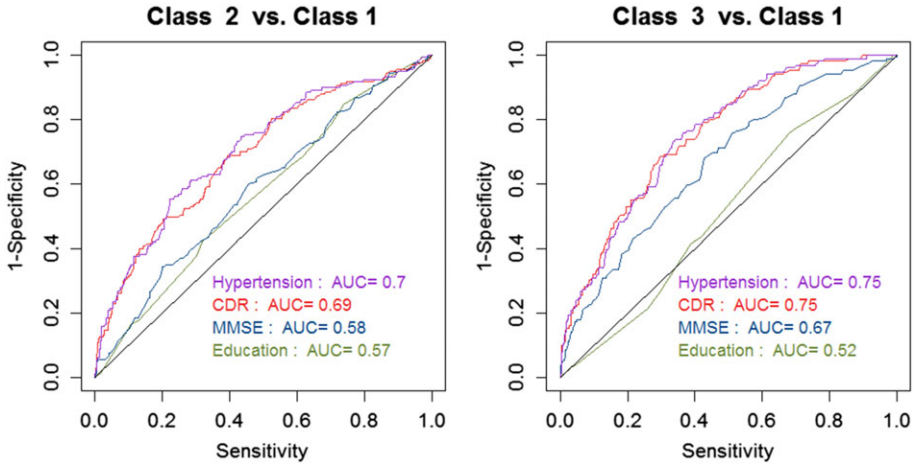

FIGURE 2 Receiver operating characteristic curves for successive sets of predictors of latent class membership. Green = education. Blue = education and MMSE. Red = education, MMSE, and CDR-sb. Purple = education, MMSE, CDR-sb, and hypertension. AUC indicates area under the curve; CDR, Clinical Dementia Rating; MMSE, Mini-Mental State Examination score [Colour figure can be viewed at wileyonlinelibrary.com]

results show we were unable to replicate the exact class structure identified in the CCDPS.

4 | DISCUSSION

This study identified 3 latent classes of progression in AD, with the majority (63%) of the patients being members of a class with steady and slow progression, expecting to lose 3.9 MMSE points and 3.1 CDR-sb points during the 3 years following diagnosis. At diagnosis, an individual's class membership could be predicted with relatively good accuracy (AUC = 0.70-0.75) on the basis of their MMSE, CDR-sb, education, and history of hypertension. The difference between the rates of change in the classes of our GMM (Figures 1B-D) and the population mean rate of change (Figure 1A) is substantial. According to the population mean, patients are expected to lose 7.9 MMSE points and 5.9 CDR-sb points during the 3 years following diagnosis. The fact that most patients (63%) decline considerably less indicates the need to look beyond the population mean and underlines the importance of acknowledging subpopulations when clinicians try to make prognoses for their AD patients. Similarly, researchers should take into account the possibility of subgroups when studying decline in AD. Inferences based on the mean trajectory of a population may lead to serious overestimations of progression speed, as most patients declined considerably less than average. It is therefore crucial for future research to take into account subgroups of patients when analysing the course of AD, which can, for example, be done by using a GMM. Previous studies have already shown how the GMM approach can aid the identification of preclinical AD patients in a cohort of cognitively normal older adults.[22-24] The present study shows the GMM approach can also provide valuable insight into AD progression after diagnosis, a topic that is studied far less often.

In our study, worse MMSE and CDR-sb scores at diagnosis appeared predictive of more rapid AD progression, as did higher education. The latter may be caused by a delay in diagnosis due to cognitive reserve, leading to more rapid decline after diagnosis as a consequence of a more advanced disease stage.[25] Having a history of hypertension was associated with a reduced progression rate, ie, a reduced likelihood of being a member in class 2, relative to class 1, OR (95% CI) = 0.41 (0.21-0.82). This may be counterintuitive, however, having a history of hypertension is likely to coincide with antihypertensive use, which was previously found to be associated with decreased rate of decline in AD and may offer a possible explanation.[26]

Although the identified classes in the present study are different from those identified in the CCDPS, the finding that the majority of the patients is a member of the class with relatively slow disease progression is consistent across cohorts.[8] According to the Cache County model, 72% of the patients had an expected loss of 3.7 MMSE points and 2.0 CDR-sb points at 3 years after diagnosis, which resembles our findings. The fourth class identified in the CCDPS also strongly resembles the third class of our model, with an expected loss of 15.1 and 16.2 MMSE points, and 10.3 and 11.3 CDR-sb points at 3 years, and a class prevalence of 15% and 8% in NACC and CCDPS, respectively. Furthermore, a strong correlation between cognitive and functional decline was observed in both cohorts (R = 0.92 in NACC and R = 0.91 in CCDPS), and this is consistent with other studies as well.[7,27-29] A study investigating the temporal ordering of cognitive and functional decline in 2 different cohorts showed that cognitive decline appears to precede and predict functional decline in AD.[30] These findings indicate that while cognitive complaints worsen, patients also experience more limitations in their daily functioning. In both the NACC and the CCDPS, the MMSE score at diagnosis was a strong predictor of future progression. Differences in the identified classes in the NACC and the CCDPS are likely due to differences in study population. Whereas the CCDPS is a population-based study from a single county in northern Utah, the NACC cohort is a clinical cohort, consisting of referral/volunteer-based case series from multiple ADCs across the United States. Moreover, the CDR-sb was measured on a 5-point scale in CCDPS, while the NACC used a 3-point scale, and patients in the CCDPS were followed up every 6 months, while NACC participants were followed up yearly. These differences may have caused small changes in progression to remain undetected in the NACC cohort. Interestingly, a recent study of cognitive and functional

trajectories in a sample of 331 Dutch dementia patients also found 3 classes of progression, with similar patterns of decline.[29]

Unfortunately, studies investigating trajectories of multiple dementia domains simultaneously are rare; however, there are several studies that have identified classes of trajectories on the basis of a single outcome. For example, a study by Wilkosz et al, focussing solely on MMSE trajectories in a sample of 201 AD patients from Pittsburgh (United States), found a strong relationship between psychosis at baseline and more rapid cognitive decline.[31] We did not find a similar association, possibly owing to the low prevalence of psychosis (9.6%) in our sample. Across a period of 13.5 years, 6 classes of progression were identified by Wilkosz et al, some of which did not appear to differ clinically.[31] This may be the result of using the BIC as the only criterion for class enumeration. For this reason, we based our model on the agreement of at least 2 model fit criteria (the LMR likelihood ratio test and class size). On the basis of a large cohort (N = 3441) derived from UK electronic health records, Baker et al. identified 6 different trajectories of MMSE progression as well.[32] Unfortunately, this study did not stratify patients on the basis of their moment of dementia onset or diagnosis. Consequently, the observed heterogeneity may be largely attributable to differences in disease stage at baseline, hampering inferences about the progression of AD and its predictors. Our results agree, in part, with a recent longitudinal study from Norway by Eldholm et al.[33] Similar to our finding that the majority of AD patients progresses relatively slowly, this study showed that approximately half of their sample consisted of slow progressors, defined as showing less than 1 point worsening in CDR-sb per year. As in our study, the slow progressors from the Norwegian cohort scored better on cognitive tests and the CDR-sb at diagnosis, than did the more rapid progressors. In contrast to our findings, the intermediate and rapid progressors in this study had fewer years of education than had the slow progressors. It should be noted that the study by Eldholm et al included only a single follow-up measurement after a mean follow-up time of 2 years, and its sample consisted of both AD and MCI patients.[33]

The strengths of the present study include its large sample of patients with a clinical diagnosis of AD and the inclusion of both cognitive and functional measures of AD progression, reflecting the multidimensional impact of AD. In addition, the use of GMMs allowed us to compare non-linear change rates across subpopulations, without using an arbitrary cut-off for rapid decline. It has been shown that linear progression cannot simply be assumed in AD.[34] The GMMs thus enabled us to better assess correlations between progression measures and their rates of change, as compared with studies using correlations between linear rates of change.[35]

Limitations of our study include the use of single, relatively crude measures of cognition (MMSE) and functioning (CDR-sb), which may not have captured subtle changes in progression. To correct for more subtle differences in cognitive ability, we also included educational attainment in our model. It should be noted that the CDR-sb also contains questions relating to cognition, which may, in part, have driven the correlation with MMSE. Yet the CDR-sb does provide an extra dimension to our operationalization of AD, as compared with looking merely at MMSE. As the exact moment of AD onset is often unknown, one could wonder to what extent differences in baseline MMSE and CDR-sb scores across our classes reflect differences in disease stage. The difficulty of synchronization of AD onset is widely recognized in AD trajectory studies.[36,37] To minimize the differences in disease stage in our sample, we used a strict definition of AD incidence in which patients had to be deemed free of AD within 18 months prior to diagnosis and had a global CDR ≤ 1 at the moment of diagnosis. In addition, we corrected for time since first symptoms in our multinomial logistic regression model. Despite these efforts to correct for possible differences in disease stage, it is possible that patients in the slowly declining class, as compared with those in the other 2 classes, presented at the clinic in an earlier stage of their disease, which may partly explain the observed heterogeneity of decline. Another drawback is the lack of additional relevant determinants of progression in the NACC data, such as a patient's social network and co-morbidity burden.

To our knowledge, this study is the first multidomain trajectory analysis including over 1000 incident AD patients. In accordance with previous studies,[8,29] the majority of patients in our study showed stable and slow disease progression, considerably more optimistic than the population mean trajectory. Moreover, we confirmed that it is possible to predict trajectories of progression in AD with acceptable accuracy. These findings are important for informing newly diagnosed patients and their caregivers about the course of AD, especially given the large uncertainty regarding prognosis, which they are currently facing. These results are also important for informing clinical trials intended to slow AD progression. Targeting those patients who are specifically prone to decline rapidly will increase the chance to detect statistically significant effects of beneficial interventions.[38] Future research should focus on identifying additional modifiable determinants of AD progression in order to better characterize the large patient group with a relatively mild disease course.

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CONFLICT OF INTEREST

None declared.

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