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RESEARCH ARTICLE

Cognitive and functional progression of dementia in two longitudinal studies

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Objectives: Previous studies have identified several subgroups (ie, latent trajectories) with distinct disease progression among people with dementia. However, the methods and results were not always consistent. This study aims to perform a coordinated analysis of latent trajectories of cognitive and functional progression in dementia across two datasets.

Methods: Included and analyzed using the same statistical approach were 1628 participants with dementia from the US National Alzheimer's Coordinating Center (NACC) and 331 participants with dementia from the Dutch Clinical Course of Cognition and Comorbidity study (4C-Study). Trajectories of cognition and instrumental activities of daily living (IADL) were modeled jointly in a parallel-process growth mixture model.

Results: Cognition and IADL tended to decline in unison across the two samples. Slow decline in both domains was observed in 26% of the US sample and 74% of the Dutch sample. Rapid decline in cognition and IADL was observed in 7% of the US sample and 26% of the Dutch sample. The majority (67%) of the US sample showed moderate cognitive decline and rapid IADL decline.

Conclusions: Trajectories of slow and rapid dementia progression were identified in both samples. Despite using the same statistical methods, the number of latent trajectories was not replicated and the relative class sizes differed considerably across

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datasets. These results call for careful consideration when comparing progression estimates in the literature. In addition, the observed discrepancy between cognitive and functional decline stresses the need to monitor dementia progression across multiple domains.

KEYWORDS

cognition, coordinated analysis, daily functioning, dementia progression, growth mixture model, trajectory

1 | INTRODUCTION

Considerable heterogeneity of dementia progression exists both between and within individuals.¹⁻⁵ Only considering the mean rate of progression in people with dementia is not precise enough to inform clinical practice. Instead, examining subgroups may improve our understanding of the disease course and unravel why some people show milder and slower decline than others. Furthermore, it may help patients and clinicians make treatment decisions.

Although cognitive decline is the cardinal sign of dementia,⁶ functional decline and neuropsychiatric symptoms are also important daily-life relating features. Including other outcomes alongside cognition would more accurately reflect the impact of dementia progression on the daily lives of people with dementia. To date, only a limited number of studies have worked on modeling trajectories of dementia progression in the first place, let alone studying multiple outcomes simultaneously.⁷

Some studies adopted a promising way to find patterns of decline using growth mixture modeling (GMM).⁸⁻¹¹ This method is particularly suitable for identifying homogeneous subgroups (ie, classes) within a larger heterogeneous population to increase our understanding of the individual variation in dementia disease course. For example, Leoutsakos et al¹⁰ identified four latent trajectories of cognitive and functional decline among people with clinically diagnosed Alzheimer disease (AD), using a population-based Cache County Dementia Progression Study (CCDPS) (N = 328). The two outcomes, Mini-Mental State Examination (MMSE) scores and Clinical Dementia Rating, were modelled jointly. Haaksma et al subsequently conducted a replication of Leoutsakos' study, using the same measurement scales in a sample

Key points

- We performed a coordinated analysis of trajectories in dementia progression across two samples in order to minimize the variation in results due to differences in statistical methods.
- Trajectories of relatively slow and rapid dementia progression were identified in both samples.
- Despite using the same statistical methods, the number of latent trajectories was not replicated and the sizes of classes with similarly shaped trajectories differed considerably across datasets.
- The discrepancy between the speed of decline in cognition and functioning in the majority of the NACC sample stresses the need to monitor dementia progression across multiple domains.

from the National Alzheimer's Coordinating Center (NACC) (N = 1120). This replication study yielded three latent trajectories.¹² A recent study based on a sample of incident dementia cases derived from two Swedish population-based cohorts identified two distinct trajectories of MMSE and activities of daily functioning.⁸ These observed disparities in trajectories across cohorts may have resulted from differences in study design of the cohorts. The NACC database consists of a referral-based/volunteer case series,¹³ while the CCDPS is a population-based cohort.¹⁴ And while the Swedish cohorts are

also population based, the study measurements are spaced much further apart (3 y), compared with those in the CCDPS (6 mo), and a different scale for daily functioning was used. Different model assumptions and analytical choices could also be an explanation for the inconsistent results across these studies. However, the details of the analytical choices and model assumptions are often difficult to ascertain based on the published work, complicating replication studies. Given these discrepancies between previously published GMMs, and given the danger of overextraction of classes,¹⁵ replication is vital to evidence the robustness of the results.¹⁶ Performing a coordinated analysis,¹⁷ ie, applying the same statistical approach to individual patient data from multiple studies, will rule out differences due to analytical choices and reveal whether consistent patterns of decline in dementia can be identified.

This study aims to coordinate the identification of latent trajectories of cognition and daily functioning among people with dementia across two datasets.¹⁷ We hypothesize that, when using the same statistical models and model assumptions, the relative class distribution can be replicated across different datasets.

2 | MATERIALS AND METHODS

2.1 | Sample description

We included participants from the NACC and the Clinical Course of Cognition and Comorbidity study (4C-Study).

Participants from the NACC were derived from the NACC Uniform Data Set (December 2017 data freeze) and originated from 32 Alzheimer Disease Centers (ADCs) across the United States. Each ADC enrolls its participants according to its own protocol. Participants may come from clinician referral, self-referral by patients or family members, active recruitment through community organizations, and volunteers who wish to contribute to research on various types of dementia. After enrollment, participants undergo regular evaluations, spaced approximately 1 year apart until either dropout or death.¹³ Dementia was diagnosed using either the 1984¹⁸ or the 2011 McKhann criteria.¹⁹

Participants from the 4C-Study were recruited from three Dutch Alzheimer Centers upon dementia diagnosis and underwent a maximum of three annual follow-up assessments after baseline.²⁰ The 4C sample hence comprises a clinical cohort. Dementia was diagnosed based on the DSM-IV criteria.²¹

2.2 | Inclusion criteria

Participants from the NACC and the 4C study were included when they met the following criteria:

1. Participants had incident dementia (ie, dementia was newly diagnosed).
2. Participants were clinically diagnosed with either AD, Lewy body disease, progressive supranuclear palsy, corticobasal degeneration,

frontotemporal lobar degeneration, vascular brain injury, vascular dementia, or another (unspecified) type of dementia.

3. Participants had at least one postdiagnosis assessment of cognition or daily functioning.

These criteria were fulfilled by all 331 participants of the 4C-Study at baseline, as a new diagnosis of dementia was a requirement for inclusion in this cohort. For participants from the NACC (which also included people with normal cognition at baseline), we defined incident dementia as follows: The interval between the assessment at which participants were deemed free of dementia, and the latter assessment at which the participants had been diagnosed with dementia, had to be less than 18 months. The interval of 18 months was chosen to allow for outcome examination from diagnosis onwards. These criteria resulted in the inclusion of 1628 participants from the NACC.

2.3 | Outcomes assessment

In the NACC dataset, cognition was measured using the MMSE.⁴ The scores range from 0 to 30, and lower scores indicate lower cognitive levels.²² Daily functioning was evaluated using the Functional Activities Questionnaire (FAQ), a standardized assessment of instrumental activities of daily living (IADL).²³ The scores range from 0 to 30. In our study, lower scores indicate less independence as all the FAQ scores were reverse coded to enhance comparability with trajectories of cognition.

In the 4C dataset, cognition was also measured with the MMSE. Daily functioning was measured by the Disability Assessment for Dementia (DAD). The scores of the DAD are expressed as a percentage, with a lower percentage indicating poorer functioning.²⁴ Unlike the FAQ, the DAD contains both IADL items and activities of daily living (ADL) items.²⁴ In order to compare the functional trajectories across the two datasets, we only used the 22 IADL items from the DAD in the 4C dataset. The sum scores of IADL items were rescaled from 0 to 30, with lower scores indicating less independence, in order to obtain a uniform range of scores across both datasets.

2.4 | Statistical method

Cognition and daily functioning in the first 3 years after dementia diagnosis were modeled jointly by parallel-process GMM. GMM can capture individual variation around the group mean curves.²⁵ Parallel-process GMM allows analysis of multiple outcome trajectories simultaneously.²⁶ In order to improve comparability of the results across the two datasets, the intercept and the slope of the models were corrected for age during the class enumeration process. We centered the age of all subjects at 65 years. We fitted models from one class through four classes with random intercepts and random slopes in both datasets. The best model was chosen based on Lo-Mendell-Rubin (LMR) likelihood ratio test between two nested models.²⁵ Significant results of LMR likelihood ratio test indicate that k -class model fits the data better than $(k-1)$ -class model. Bayesian information criterion (BIC) of different models were compared as well (a smaller BIC indicates a better model fit). We also examined the model's entropy, a measure of class separation. An entropy value approaching 1

indicates a clear delineation of classes.²⁷ Models with one or more small-sized classes (with less than 5% of all the participants) were excluded because classes with such few individuals are unlikely to provide trustworthy generalization.²⁸ Study visits were assumed to be spaced exactly 1 year apart with baseline (time zero) defined as the first postdiagnosis visit. Only assessments after diagnosis were included. The residual variances were assumed to be constant across classes but were allowed to vary over time. Based on the model selection criteria above, we selected the most suitable model structure for each of the datasets. We calculated the correlation between the variance in the linear slopes of MMSE and daily functioning across the entire sample of each dataset. GMM was carried out using Mplus version 8. Data management and plot making were performed in R version 3.4.0.

3 | RESULTS

3.1 | Sample characteristics

Among the NACC participants, 83.8% were diagnosed with AD, while the 4C dataset consisted of 65.3% AD participants. Participants in the

TABLE 1 Sample characteristics

	1st Postdiagnosis Visit	2nd Postdiagnosis Visit	3rd Postdiagnosis Visit	4th Postdiagnosis Visit
NACC (N = 1628)				
Age, mean (SD)	78.6 (9.2)			
Gender				
Male, N (%)	818 (50.2)	809 (50.2)	519 (51.5)	318 (53.0)
Female, N (%)	810 (49.8)	804 (49.8)	489 (48.5)	282 (47.0)
Education years, mean (SD)	15.5 (3.2)	15.5 (3.2)	15.6 (3.1)	15.7 (3.0)
Dementia type				
AD, N (%)	1364 (83.8)	1354 (83.9)	869 (86.2)	517 (86.2)
Other types, N (%)	264 (16.2)	259 (16.1)	139 (13.8)	83 (13.8)
MMSE, mean (SD)	24.0 (3.8)	22.1 (4.9)	20.6 (5.3)	19.2 (6.3)
FAQ, mean (SD)	17.4 (7.7)	12.3 (8.4)	9.3 (7.9)	6.8 (7.2)
Follow-up time, mean (SD)	0 (0)	1.2 (0.6)	2.3 (0.6)	3.3 (0.7)
4C (N = 331)				
Age, mean (SD)	74.9 (10.2)			
Gender				
Male, N (%)	150 (45.3)	115 (46.6)	87 (47.5)	70 (49.6)
Female, N (%)	181 (54.7)	132 (53.4)	96 (52.5)	71 (50.4)
Education years, mean (SD)	10.5 (3.5)	10.8 (3.4)	10.8 (3.5)	10.7 (3.5)
Dementia type				
AD, N (%)	216 (65.3)	164 (66.3)	129 (70.5)	100 (70.9)
Other types, N (%)	115 (34.7)	83 (33.6)	54 (29.5)	41 (29.1)
MMSE, mean (SD)	21.9 (3.7)	21.0 (5.1)	19.1 (5.8)	18.3 (5.9)
IADL, mean (SD)	17.6 (8.7)	16.5 (8.9)	13.3 (9.1)	10.6 (8.1)
Follow-up time, mean (SD)	0 (0)	1.1 (0.1)	2.1 (0.1)	3.1 (0.2)

Abbreviations: FAQ, Functional Activities Questionnaire (range: 0 to 30, reverse-coded, a higher recoded FAQ score means a better functional level); IADL, instrumental activities of daily living of Disability Assessment for Dementia (range: 0 to 30, recoded, a higher IADL score means a better functional level); MMSE, Mini-Mental State Examination (range: 0 to 30, a higher MMSE means a better cognitive level); SD, standard deviation.

4C dataset were on average 3.7 years younger and showed a worse cognitive performance at diagnosis with an average 2.1 point lower MMSE compared with participants from the NACC. The mean length of education was remarkably less (5 years) in our 4C sample as compared with our NACC sample. Daily functioning was measured differently in the two datasets. In the NACC dataset, the mean FAQ score at diagnosis was 17.4 (SD: 7.7), and in the 4C dataset, the mean IADL score derived from DAD at diagnosis was 17.6 (SD: 8.7). Sample characteristics were further summarized in Table 1.

3.2 | Trajectories of cognitive and functional decline

In the NACC dataset, the quadratic three-class model with a random intercept and a random slope was found to be the optimal model. Although the BIC decreased with each additional class from the one-class model through the four-class model, the decrease became smaller with every additional class. The LMR *P* value of the four-class model was not significant anymore, indicating the four-class model did not fit significantly better than the three-class model. Moreover, the three-class model had a higher entropy value (.773) than the four-class

model (.720), its average latent class probability was good (.899), and classes of the three-class model met our minimal class size requirement (greater than 5% of the sample in each class).

In the 4C dataset, the quadratic two-class model with a random intercept and a random slope was found to be the optimal model. The BIC of the two-class model was the smallest of those from the one- through the four-class models. The LMR *P* value of the three-class model was not significant anymore, indicating that the three-class model did not fit significantly better than the two-class model. Moreover, the two-class model had a higher entropy value (.628) than the three-class model (.530), its average latent class probability was good (.884), and classes of the two-class model met our minimal class size requirement.

An overview of the model fit criteria of the models with one through four classes fitted in both samples is depicted in Appendix S1. The parameter estimates of the best models are shown in Appendix S2, and the trajectories of the overall sample and each class are shown in Figure 1 (NACC) and Figure 2 (4C). The availability of outcome data across time is summarized in Appendix S3.

In the NACC model, class 1 contained 26% (*n* = 430) of participants and showed slow cognitive and functional decline. In the first year, the average decline was 1.06 point on the MMSE and 1.12 point on the FAQ. The decline accelerated in the second and third year after diagnosis. The majority of participants (67%, *n* = 1092) was a member of class 2. Those participants had poor daily functioning at diagnosis and a more rapid decline compared with class 1. The cognitive status

at diagnosis of participants in class 2 was better compared with their daily functioning. Class 3 contained 7% (*n* = 106) of participants who showed poor cognitive and daily functioning at diagnosis, as well as a rapid decline in both outcomes.

In the 4C model, 74% of participants (*n* = 245) showing slow cognitive and functional decline constituted class 1. The remainder of participants was a member of class 2 (26%; *n* = 86) and showed rapid decline in both cognition and daily functioning. Notably, when examining the (not optimal) quadratic three-class model in the 4C dataset, remarkably similar patterns of decline were observed as compared with the three-class NACC model (Appendix S4).

The correlation between random slopes of MMSE and FAQ across the NACC sample was .61 (*P* value < .001). Similarly, the random slopes of MMSE and IADL in the 4C sample were correlated (*r* = .79, *P* value < .001).

3.3 | Patient characteristics across latent trajectories

Table 2 shows the patient characteristics of members of each class in the NACC dataset and the 4C dataset. In the NACC dataset, the proportion of AD cases in classes 1 and 2 was similar to that of the total sample (around 85%). However, the proportion of AD cases in class 3 was only 60%. In the 4C dataset, the proportion of AD cases was relatively constant across all classes (around 65%). The gender proportion in every class of each dataset was comparable (around 50%

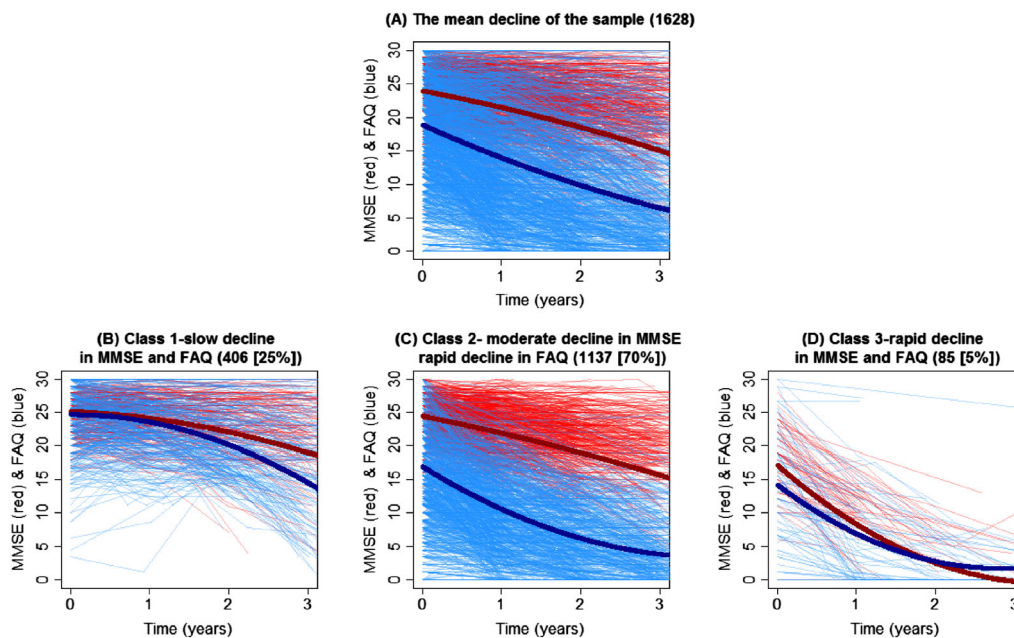


FIGURE 1 Fitted and observed Mini-Mental State Examination (MMSE) and Functional Activities Questionnaire (FAQ) trajectories in the National Alzheimer's Coordinating Center (NACC) dataset. MMSE and FAQ trajectories are shown in red and blue respectively. FAQ was reverse coded with higher scores indicating better daily functioning. A, The mean decline of the sample (*N* = 1628). B, Class 1—slow decline in MMSE and FAQ (*N* = 406 [25%]). C, Class 2—moderate decline in MMSE and rapid decline in FAQ (*N* = 1137 [70%]). D, Class 3—rapid decline in MMSE and FAQ (*N* = 85 [5%]). The trajectories of individual participants are shown in thin lines. The average trajectories of the whole sample and the mean trajectories of each class are shown in bold lines. Note that individuals were assigned to each class based on their most likely class membership. Therefore, the numbers of participants in each class are slightly different from those in the manuscript text and Appendix S2 [Colour figure can be viewed at wileyonlinelibrary.com]

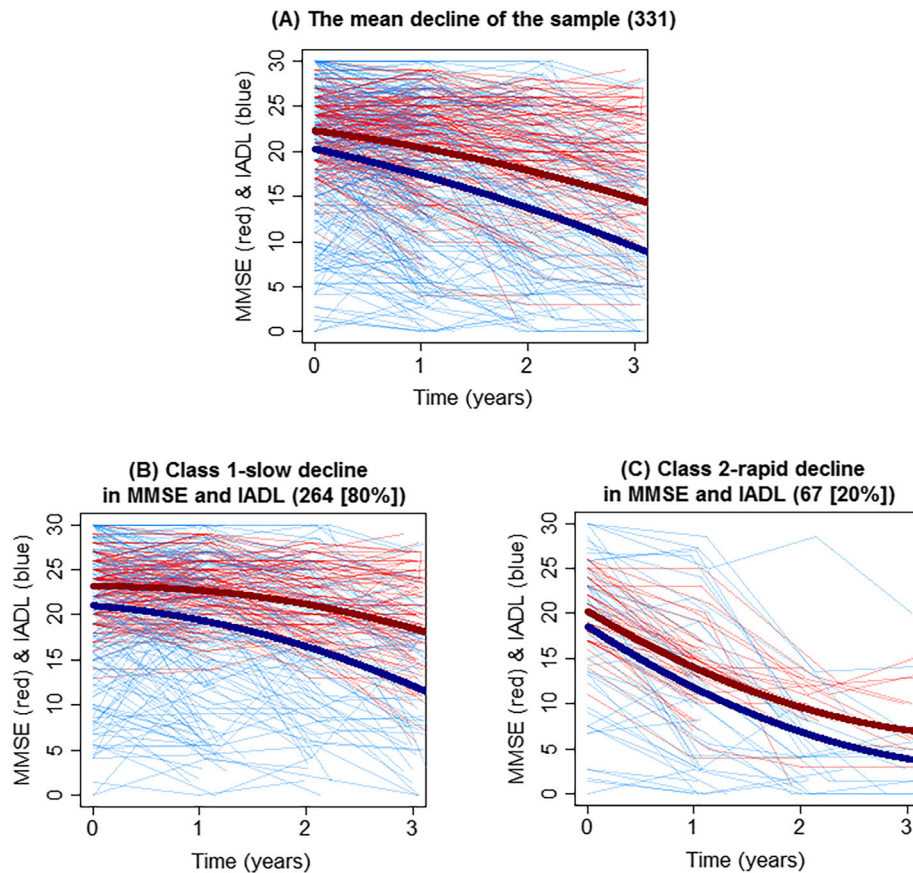


FIGURE 2 Fitted and observed Mini-Mental State Examination (MMSE) and instrumental activities of daily living (IADL) trajectories in the 4C dataset. MMSE and IADL trajectories are shown in red and blue, respectively. IADL was recoded with a scale of 0 to 30. A, The mean decline of the sample ($N = 331$). B, Class 1—slow decline in MMSE and IADL ($N = 264$ [80%]). C, Class 2—rapid decline in MMSE and IADL ($N = 67$ [20%]). The trajectories of individual participants are shown in thin lines. The average trajectories of the whole sample and the mean trajectories of each class are shown in bold lines. Note that individuals were assigned to each class based on their most likely class membership. Therefore, the numbers of participants in each class are slightly different from those in the manuscript text and Appendix S2 [Colour figure can be viewed at wileyonlinelibrary.com]

males), except class 2 in the 4C dataset, which contained more females (68.8%).

4 | DISCUSSION

4.1 | Results and clinical relevance

We identified distinct patterns of latent trajectories for cognition and daily functioning across a Dutch and a US dataset, using a coordinated analysis approach.¹⁷ In both samples, participants in the slowly declining class 1 showed above-average cognitive status and daily functioning at diagnosis, with slow decline in both outcomes. In addition, both classes contained a class with below-average cognitive status and daily functioning at diagnosis, followed by a rapid decline in both outcomes (4C class 2; NACC class 3). Although latent trajectories of relatively slow and rapid dementia progression were identified in both samples, the sizes of these comparable classes differed considerably across datasets. In the NACC dataset, only a 7% of participants (NACC class 3) showed a rapid decline on both outcomes,

whereas in the 4C dataset, 26% of participants declined rapidly (4C class 2). Moreover, the number of latent trajectories identified was different across our two samples. Given our coordinated analysis approach, these differences are unlikely the result of variation in analysis methods but are rather the result of differences in study design and study population between the two datasets (further discussed under limitations).

While the majority of participants in both datasets showed a slow to moderate cognitive decline across the first 3 years after dementia diagnosis, the majority of the NACC sample also showed rapid decline in daily functioning (class 2). This discrepancy between cognition and IADL trajectories emphasizes the importance of considering both domains when examining the disease progression of people with dementia.

Care should be taken when interpreting the meaning of the identified classes of dementia progression. Latent trajectories represent a data-driven breakdown of a heterogeneous data mass. Hence, the latent trajectories do not represent specific subtypes of dementia.²⁹ Yet these latent trajectories provide information that would have remained unnoticed had we only studied the mean decline across each

TABLE 2 Characteristics of the three classes

NACC (N = 1628)	Class 1 slow decline (N = 406)	Class 2 moderate cognitive and rapid functional decline (N = 1137)	Class 3 rapid decline (N = 85)
Age at 1st postdiagnosis visit, mean (SD)	77.9 (8.0)	79.0 (9.5)	75.9 (11.1)
Dementia type			
AD, N (%)	361 (88.9)	952 (83.7)	51 (60.0)
Other types, N (%)	45 (11.1)	185 (16.3)	34 (40.0)
Gender			
Male, N (%)	223 (54.9)	552 (48.5)	43 (50.6)
Female, N (%)	183 (45.1)	585 (51.5)	42 (49.4)
Education (y), mean (SD)	15.6 (3.1)	15.5 (3.2)	15.2 (3.2)
MMSE at diagnosis, mean (SD)	25.0 (3.1)	24.2 (3.1)	16.6 (6.0)
FAQ at diagnosis, mean (SD)	23.9 (4.9)	15.4 (7.1)	13.3 (8.2)
4C (N = 331)	Class 1 slow decline (N = 264)		Class 2 rapid decline (N = 67)
Age at 1st postdiagnosis visit, mean (SD)	75.6 (9.9)		71.9 (10.8)
Dementia type			
AD, N (%)	173 (65.5)		43 (64.2)
Other types, N (%)	91 (34.5)		24 (35.8)
Gender			
Male, N (%)	126 (47.7)		24 (35.8)
Female N (%)	138 (52.3)		43 (64.2)
Education (y), mean (SD)	10.5 (3.4)		10.7 (3.7)
MMSE at diagnosis, (mean (SD)	22.6 (3.2)		19.1 (4.2)
IADL's at diagnosis, mean (SD)	18.0 (8.5)		16.2 (9.3)

Abbreviations: FAQ, Functional Activities Questionnaire (range: 0 to 30, reverse-coded, a higher recoded FAQ score means a better functional level); IADL, instrumental activities of daily living of Disability Assessment for Dementia (range: 0 to 30, recoded, a higher IADL score means a better functional level); MMSE, Mini-Mental State Examination (range: 0 to 30, a higher MMSE means a better cognitive level); SD, standard deviation.

sample. For example, we observed that most people with dementia in our study were able to maintain a reasonable cognitive status across the first 3 years after diagnosis. This is relevant knowledge for newly diagnosed patients and their caregivers. Therefore, both clinicians and researchers should consider the heterogeneity in dementia progression and realize that referring to the average progression rate means little to the individuals and may lead to wrong conclusions.³⁰

4.2 | Comparison with other studies and potential mechanisms

In accordance with previous studies, we observed great heterogeneity in the longitudinal course of dementia.^{10,12,31} In both our samples, a clear correlation was observed between MMSE and IADL trajectories (NACC: $r = .61$, $P < .001$; 4C: $r = .79$, $P < .001$). This indicates that those declining more quickly than other participants on one outcome measure tend to decline more quickly on the other outcome as well. Previous studies have observed an even higher correlation between cognition and daily functioning.^{9,12,32-34} For example, studies by Leoutsakos et al and Haaksma et al identified a high overall

correlation between the slopes of cognition and daily functioning ($r = .91$ and $r = .92$, respectively).^{10,12} However, the use of different outcome measures may explain the lower correlation in our study. The two previous studies used the Clinical Dementia Rating scale sum-of-boxes,³⁵ which also contains some cognitive components, and the MMSE. In contrast, we used IADL items, which solely measure daily functioning in instrumental activities. The finding that non-AD dementia types are most common in the rapidly progressing class of the NACC sample is consistent with other studies reporting that non-AD dementia types tend to progress more rapidly.^{8,36} Another potential explanation for differences in rates of cognitive decline across classes may lie in the theory of "cognitive reserve,"³⁷ stating that more education is associated with faster cognitive decline. Higher-educated people might be better able to cope with the initial signs of the disease and maintain their daily functioning, up until a certain threshold, after which they exhibit a sudden and steep decline.³⁷ However, we did not observe any differences in duration of education across the identified classes within each dataset (Table 2). Importantly, persons with dementia may change over the course of the dementia: They may or may not develop additional comorbidity or frailty, and these intercurrent exposures may result in more variable disease courses.³⁸

4.3 | Strengths and limitations

In this coordinated analysis, we used the same methodology across two datasets. By using IADL items to operationalize daily functioning in both datasets, we made the outcome measures as comparable as possible. So far, this is unique in dementia research, given it requires access to individual patient data from multiple datasets with sufficient follow-ups after the dementia diagnosis, which is scarce. We used parallel-process GMM to look beyond the mean progression rates and identify different classes of dementia progression based on parallel trajectories of cognition and daily functioning. The merit of using parallel-process modeling lies in the fact that it can address the association between the changes in two variables over time.³⁹ Moreover, we used multiple statistical criteria to assess model fit, which provides strong support for our final models.

Although allowing for individual variation was considered a strength of this study, GMM also brought a limitation, as, within each class, there is still considerable variation in progression speed (Figures 1B-D and 2B,C). The relatively small sample size of the 4C dataset is also a limitation, especially considering the decrease in data availability over time. Three years post diagnosis, the data availability had dropped to approximately 30% across both samples, and the data availability was lowest in the rapidly declining classes (Appendix S3). This indicates that the rapidly declining classes may, in part, have been driven by attrition. Another limitation is the use of MMSE, which is a single and relatively crude measure and might not capture subtle changes in progression. The main limitation of our study is the fact that the participants from the NACC and the 4C datasets were not fully comparable, due to differences in study design. Although we adjusted the trajectories for age in both datasets, several differences between the datasets remain, such as differences regarding the level of education, gender composition, dementia types, and the method of enrollment of participants. In the NACC database, participants came from clinician- or self-referral, active recruitment through community organizations and volunteers.¹³ In contrast, the 4C study is a clinical cohort enrolling participants who were newly diagnosed with dementia.²⁰ As dementia has an insidious onset, the exact time of onset is difficult to pinpoint in dementia progression studies. As participants were enrolled in the 4C-Study after they were newly diagnosed with dementia, their exact cognitive status prior to diagnosis was unknown, and though we confirmed the participants from the NACC were free of dementia at least 18 months before their diagnosis, the exact time of dementia onset was still unknown (as in all other dementia studies). This may have caused additional heterogeneity, because the timing of diagnosis and disease onset may not systematically align in the same way for all individuals in our datasets.

5 | CONCLUSION

This study included two datasets with a total of 1959 participants with incident dementia, who were followed yearly after diagnosis for approximately 3 years. Using a coordinated analysis approach, our

study identified similar trajectories of slow and rapid dementia progression in both samples. However, the number of latent trajectories was not replicated and the sizes of classes with similarly shaped trajectories differed considerably across datasets, despite using the same statistical methods. These results call for careful consideration when comparing progression estimates in the literature. Moreover, the considerable heterogeneity in dementia progression, observed both within and between samples in our study, stresses the importance of looking beyond the mean progression rates when studying the course of dementia over time. Although cognition and daily functioning generally tend to decline in unison, we observed a discrepancy between trajectories of cognition and IADL in the majority of the NACC participants. Most people with dementia in our study were able to maintain a reasonable cognitive status over time, whereas their IADL functioning declined more rapidly. This is relevant knowledge as it stresses that average dementia trajectory—certainly if based on cognitive functioning alone—means little to patients, caregivers, clinicians, and researchers. Furthermore, these results suggest that both clinical practice and future research would benefit from repeatedly measuring cognition as well as daily functioning over time.

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CONFLICT OF INTEREST

None declared.

DATA ACCESSIBILITY STATEMENT

The 4C research group actively encourages and welcomes external collaborations. Data are available for researchers with a specific research question. Interested and potential collaborators are invited to contact the study coordinators (Dr. René Melis rene.melis@radboudumc.nl or Dr. Inez Ramakers i.ramakers@maastrichtuniversity.nl). Data from the NACC can be requested by researchers with a specific research question from www.alz.washington.edu

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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