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Original Study

Predicting Cognitive and Functional Trajectories in People With Late-Onset Dementia: 2 Population-Based Studies

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A B S T R A C T

Objectives: Previous studies have shown large heterogeneity in the progression of dementia, both within and between patients. This heterogeneity offers an opportunity to limit the global and individual burden of dementia through the identification of factors associated with slow disease progression in dementia. We explored the heterogeneity in dementia progression to detect disease, patient, and social context factors related to slow progression.
Design: Two longitudinal population-based cohort studies with follow-up across 12 years.
Setting and Participants: 512 people with incident dementia from Stockholm (Sweden) contributed to the Kungsholmen Project and the Swedish National Study of Aging and Care in Kungsholmen.
Methods: We measured cognition using the Mini-Mental State Examination and daily functioning using the Katz Activities of Daily Living Scale. Latent classes of trajectories were identified using a bivariate growth mixture model. We then used bias-corrected logistic regression to identify predictors of slower progression.
Results: Two distinct groups of progression were identified; 76% (n = 394) of the people with dementia exhibited relatively slow progression on both cognition and daily functioning, whereas 24% (n = 118) demonstrated more rapid worsening on both outcomes. Predictors of slower disease progression were Alzheimer's disease (AD) dementia type [odds ratio (OR) 2.07, 95% confidence interval (CI) 1.15-3.71], lower age (OR 0.88, 95% CI 0.83-0.94), fewer comorbidities (OR 0.77, 95% CI 0.66-0.90), and a stronger social network (OR 1.72, 95% CI 1.01-2.93).
Conclusions/Implications: Lower age, AD dementia type, fewer comorbidities, and a good social network appear to be associated with slow cognitive and functional decline. These factors may help to improve the counseling of patients and caregivers and to optimize the planning of care in dementia.

As life expectancy increases, the worldwide burden of dementia will continue to increase as well.[1] With this increase, there is a growing need for detailed prognostic information for patients with dementia. Previous studies have shown large heterogeneity in the progression of dementia, both within and between patients.[2–6] This heterogeneity offers an opportunity to limit the global and individual burden of dementia through the identification of factors associated with slow disease progression. Identification of such factors is

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important, as the large variation in dementia progression speed limits the prognostic capacity of clinicians when counseling their patients. This limited ability to provide a personalized prognosis causes uncertainty regarding disease course and care needs. The uncertainty, in turn, can create additional emotional distress, including feelings of sorrow, anxiety, and despair for both patients and caregivers in a condition that is very stressful in itself already.[7] Remarkably, there are only a few studies aiming to disentangle the prognostic heterogeneity among patients diagnosed with dementia.[8] To enable anticipation of future care needs and to help physicians in counseling patients and their caregivers, we need to unravel the factors associated with slow disease progression in people with dementia and look beyond dementia-related characteristics.[9] Other characteristics of patients with dementia, such as their level of education,[10] comorbidity burden,[11] anticholinergic drug use,[12] and the social support they receive,[13] may also influence the rate of progression, but these factors have never been studied jointly in the context of dementia. Several studies have emphasized the need to examine impairments in daily functioning besides outcomes of cognitive decline when characterizing the course of this dementia.[14–16] Therefore, this study aims to identify (1) concurrent trajectories of cognition and daily functioning in community-dwelling older persons with incident dementia and (2) factors associated with slow progression rates.

Methods

Cohort Description

This study included data from 2 population-based studies conducted consecutively in the Kungsholmen parish of Stockholm: the Kungsholmen Project (KP) and the Swedish National Study of Aging and Care in Kungsholmen (SNAC-K). KP is a community-based longitudinal study of adults aged ≥75 years living at home or in institutions. Participants of KP were recruited among all 2368 inhabitants, of whom 1810 persons (76.4%) participated at baseline. The baseline assessment (wave 1) was carried out between 1987 and 1989 and was followed by 4 examinations spaced approximately 3 years apart (waves 2-5). The project reached a maximum follow-up period of 12 years. SNAC-K is an ongoing community-based longitudinal study of randomly selected adults aged ≥60 years living at home or in institutions. Of the original 4590 people invited to participate in SNAC-K, 3363 (73.3%) participated at baseline. The baseline assessment (wave 1) was carried out between 2001 and 2004. Since then, participants have been followed up regularly: every 6 years for the young-old cohorts (60-78 years) and every 3 years for the older cohorts (age ≥78 years). By the end of 2015, 4 study waves spaced 3 years apart (waves 1-4) were completed. Linkage to the Swedish inpatient and death registers provided additional information on medical events and survival. The Swedish inpatient register covers all diseases diagnosed in the hospital during a patient's life. Both cohort studies were approved by the regional ethical review board in Stockholm. Written informed consent was obtained from all participants or, in case of persons with cognitive impairment, from proxies (next of kin or guardians). Detailed information regarding study design and data collection for these cohorts can be found elsewhere.[17,18]

Sample Selection

In order to capture the entire trajectory of dementia progression, we limited our analysis to incident dementia cases. Incident dementia was defined as meeting the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III-R/DSM-IV) criteria[19] while not meeting them at the prior visit. Therefore, participants with a diagnosis of dementia at baseline (wave 1) were excluded. Dementia subtypes were defined as follows: AD according to NINCDS/ADRDA criteria, [20] Lewy body dementia according to McKeith criteria,[21] and vascular dementia according to NINDS-AIREN criteria.[22] A total of 520 incident dementia cases were identified (310 from KP and 210 from SNAC-K). After exclusion of 8 patients with schizophrenia, our final study sample consisted of 512 people with incident dementia (208, 34, 152, and 118 patients were diagnosed between waves 1-2, 1-3, 2-3, and 3-4, respectively). The 34 people diagnosed between waves 1 and 3 were part of the young-old cohort, and therefore they were followed up every 6 years up until wave 3; after that, they turned ≥78 years of age and were followed up every 3 years, as was the rest of the cohort.

Outcomes Measures

Cognitive progression was assessed using the Mini-Mental State Examination (MMSE) score, ranging from 0 to 30, with higher scores representing better cognitive functioning.[23] The sum score of the Katz Activities of Daily Living (ADL) scale was used to measure the progression of daily functioning.[24] The ADL score ranges from 0 to 12, with higher scores indicating more limitations in daily functioning. To enhance the interpretability of our model, ADL scores were reverse-coded, so higher scores indicated better performance (eg, an ADL score of 1 was recoded as 11). We used follow-up measurements of MMSE and ADL across a period of 12 years and derived latent classes of progression as described in the Statistical Analyses section below.

Independent Variables

We a priori selected 7 potential predictors of progression to include in our prediction model for classes of MMSE and ADL trajectories. These potential predictors included age, gender, education,[10] dementia nosology, comorbidity burden,[11] anticholinergic drug burden,[12] and social network.[13] We used 2 categories for education: elementary vs higher education. Dementia nosology was also divided into 2 categories: Alzheimer's disease (AD) and other dementia types. Comorbidity burden at the time of dementia diagnosis was operationalized as the number of chronic diseases, based on data retrieved from the Swedish National Patient Register.[25] The included disease categories are listed in Appendix 1. Diseases were classified using the International Classification of Diseases (ICD) classification, and further grouped according to disease categories published previously.[26] The ICD codes registered up to 5 years prior to study entry were included and, given the chronic nature of these conditions, we assumed that they were still present at subsequent follow-up examinations in individuals with any of the conditions at study baseline. Social network was operationalized at study baseline using a social network index based on 3 components: (1) being married and living with someone; (2) having children with daily to weekly satisfying contact; and (3) having relatives/friends with daily to weekly satisfying contact. The sample was subsequently divided into 2 categories: people with a poor/limited social network, who had either 1 or 0 of the social network components; and people with a moderate/extensive social network, who had either 2 or 3 of the social network components.[27] Anticholinergic drug burden at diagnosis was measured using the Anticholinergic Cognitive Burden (ACB) scale.[28] During the study visits, patients were asked to bring the drugs that they were currently using. Based on this information, we calculated a total ACB score. The drugs and their individual anticholinergic burden scores used are listed in Appendix 2.

Statistical Analyses

We used growth mixture models (GMMs) to model trajectories of MMSE and ADL jointly over time. GMMs allow for grouping of

Table 1
Sample Characteristics at the Study Visit of Diagnosis (T = 3)

Characteristic	Total Sample (n = 512, 100%)	Class 1: Slow Progression (n = 394, 77%)*	Class 2: Rapid Progression (n = 118, 23%)*
Age, y, mean (SD)	88.3 (5.3)	87.7 (4.8)	90.5 (6.2)
Gender, % (n)			
Female	78.3 (401)	78.9 (331)	76.3 (90)
Male	21.7 (111)	21.1 (83)	23.7 (28)
Education, % (n)			
Elementary school	42.9 (219)	43.5 (171)	41.0 (48)
High school or university	57.1 (291)	56.5 (222)	59.0 (69)
MMSE score, mean (SD)	17.4 (5.9)	18.9 (4.4)	11.2 (7.0)
ADL score			
Mean (SD)	8.6 (3.7)	10.3 (2.0)	2.9 (1.9)
% (n) with ≥1 ADL impairment	68.8 (352)	59.4 (234)	100.0 (118)
Comorbidity count			
Mean (SD)	1.8 (1.8)	1.5 (1.7)	2.6 (1.8)
% (n) with ≥2 comorbidities	47.5 (243)	40.6 (160)	70.3 (83)
ACB Scale, mean (SD)	1.0 (1.4)	0.9 (1.3)	1.4 (1.7)
Social network,† % (n)			
Poor/limited	31.8 (163)	28.7 (113)	42.4 (50)
Moderate/extensive	68.2 (349)	71.3 (281)	57.6 (68)
Dementia type, % (n)			
Alzheimer's disease	76.7 (393)	80.7 (318)	63.6 (75)
Mixed dementia	8.9 (45)	7.6 (30)	12.7 (15)
Vascular dementia	8.2 (42)	6.1 (24)	15.2 (18)
Other dementia type	5.6 (29)	5.3 (21)	6.8 (8)
Unspecified dementia type	0.6 (3)	0.3 (1)	1.7 (2)
Cohort, % (n)			
Kungsholmen Project	59.8 (306)	64.7 (255)	43.2 (51)
SNAC-K	40.2 (206)	35.3 (139)	56.8 (67)
Survival time after diagnosis, y, median (IQR)	2.8 (1.1-5.2)	3.4 (1.7-5.8)	1.1 (0.5-2.4)

IQR, interquartile range; SD, standard deviation.
ADL score range: 0-12, reverse-coded: higher = better; MMSE score range: 0-30, higher = better.
*Reported class counts and proportions are based on the most likely class membership; it should be noted that individuals are in fact assigned a probability of class membership.
†Social network was measured at study baseline.

participants into so-called latent classes, based on similarities in their progression patterns over time.[29] GMMs are a longitudinal form of latent class analysis, in which mixed models are used. A specific type of GMMs, termed parallel-process GMM (PP-GMM), allowed us to model our 2 outcomes simultaneously over time. Time was treated as time in years since the last assessment before dementia diagnosis. This means T = 3 indicates the study visit at which dementia was first diagnosed. However, it should be recognized that dementia manifested during the interval prior to this study visit, that is, between T = 0 and T = 3. All available MMSE and ADL scores between 3 years prior to T = 0 up until 9 years after this time point were used.

We fit quadratic models with 1 to 5 classes and chose our final model based on the bayesian information criterion (BIC), Lo-Mendell-Rubin (LMR) likelihood ratio test, and class sizes.[30] 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 indicates that the model with k classes fits better compared with the same model with $k - 1$ classes.[31] Maximum likelihood estimation was used to obtain parameter estimates, with standard errors that are robust to non-normality. To reduce computation time, observations were assumed to be spaced exactly 3 years apart (the resulting reduction in BIC was only marginal). The variance of the quadratic slope was fixed at zero. The residual variances were allowed to vary over time and were assumed to be equal across classes. Following the so-called 3-step method, logistic regression was used to examine which factors predicted class membership in a multivariable model.[32] The 3-step method comprised the following steps: (1) the latent class model was built, (2) participants were assigned to latent classes based on their posterior probabilities, and (3) the association between the assigned class membership and independent variables was investigated. Participants with missing values for independent variables (n = 3) were excluded from this

Table 2
Scores and Availability of Outcome Data Across Time

Variable	T = −3	T = 0	T = 3	T = 6	T = 9
MMSE score, mean (SD)	27.1 (1.9)	25.2 (2.6)	17.4 (5.9)	12.5 (7.3)	7.6 (7.7)
ADL score, mean (SD)	11.3 (1.3)	10.8 (2.0)	8.6 (3.7)	5.9 (4.2)	3.6 (3.5)
Follow-up time in years, mean (SD)	−3.2 (0.5)	0.0 (0.0)	3.1 (0.6)	6.0 (0.7)	8.8 (0.6)
Patients with data on MMSE, % (n)	55.3 (283)	91.0 (466)	87.7 (449)	35.4 (181)	12.3 (63)
Patients with data on ADL, % (n)	55.7 (285)	96.7 (495)	99.0 (507)	41.4 (212)	14.1 (72)
Deaths, % (n)	NA	NA	NA	50.4 (258)	18.0 (92)
Drop-outs,* % (n)	NA	NA	NA	6.6 (34)	<0.1 (2)

ADL score range: 0-12, reverse-coded: higher = better; MMSE score range: 0-30, higher = better. NA indicates not applicable given our study design; that is, participants had to be alive and not dropped out of the study in order to be diagnosed at T = 3. T = 3 indicates the study visit at which dementia was first diagnosed. However, it should be recognized that dementia likely manifested during interval prior to this study visit. Participants could refuse to take the MMSE or ADL questionnaire, which is why the number of participants with data on MMSE/ADL at a given time point does not completely add up to the total number of participants in the study at that time point.
*Reasons include refusal, no contact, or patient had moved away from Stockholm.

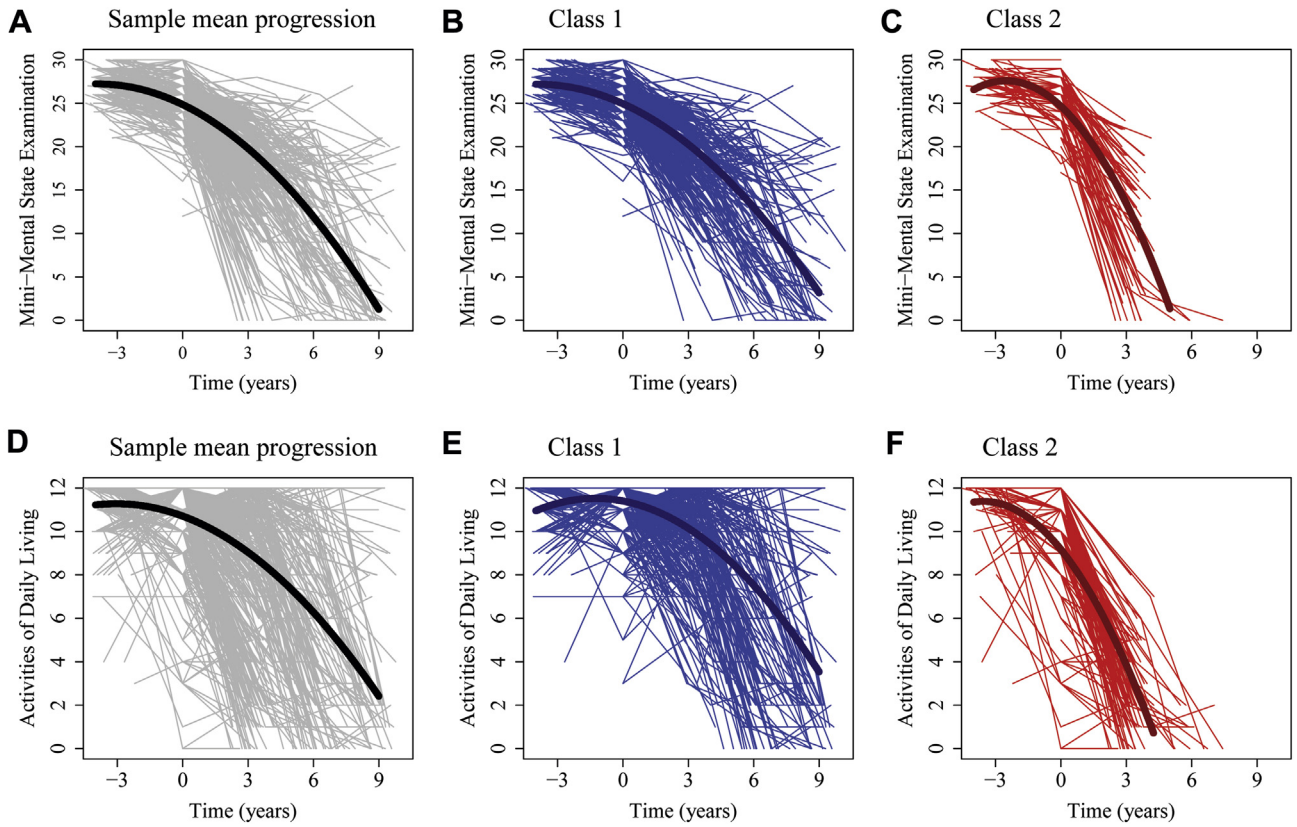

Fig. 1. Trajectories of Mini-Mental State Examination (A-C) and Activities of Daily Living scores (D-F) across the entire sample (N = 512; gray), class 1 (n = 394, blue), and class 2 (n = 118, red). The mean trajectories of each plot are shown in bold. ADL scores were reverse-coded, with higher scores indicating better daily functioning. For the purpose of plotting, individuals were assigned to classes based on their most likely class membership; it should be noted that individuals are in fact assigned a probability of class membership in the model.

analysis. The area under the curve was subsequently calculated for sets of predictors via receiver operating characteristic curves to assess the classification utility of our prediction model. The PP-GMM and logistic regression models were fit using Mplus, version 8.[33] Further analyses, including receiver operating characteristic curves and processing of results, were performed using R, version 3.2.4.[34]

Results

Sample Characteristics

Sample characteristics from the study visit at which dementia was first diagnosed (T = 3) are summarized in Table 1. The mean age at diagnosis was 88.3 years, with a range of 72.0 to 105.1 years. At T = 0, the mean MMSE score was 25.2 and the mean ADL score was 10.8. Scores and availability of outcome data across time, including reasons for drop-out, are reported in Table 2. At T = 6 years, 258 patients had died (50.4%), and at T = 9 years, only 162 (31.6%) were alive. The observed median (interquartile range) survival time in years after diagnosis was 2.8 (1.1-5.2).

Latent Classes of Progression

The observed individual trajectories of MMSE and ADL and means for the entire sample are depicted in the left panels of Figure 1. Trajectories of MMSE and ADL were clearly related, as shown by the strong correlation between their random slopes (1-class model; $R = 0.93$, $P < .001$). When fitting models with increasing numbers of classes, the 2-class model showed the best balance between model fit and model complexity. This was confirmed by the LMR test [2- vs 3-class model: −2 log likelihood (7) = 219.83, $P = .219$]. Moreover, the smallest class contained only 4% of our sample when increasing the number of classes beyond 2, indicating that a model with more than 2 classes derived from our sample is unlikely to be replicated. The difference in BIC between the 2-class model and the 3-class model is also rather small, indicating the model fit improvement caused by the third class was minimal. An overview of the model fit criteria is shown in Appendix 3.

The best-fitting 2-class model included a class-invariant random intercept and no random slope. Posterior probabilities (which measure classification accuracy) were high (>0.9) for both classes, indicating good model fit. The parameter estimates of this 2-class model are shown in Table 3, and the trajectories of both classes are depicted in the center and right panels of Figure 1. Class 1 was the largest, comprising 77% (n = 394) of our sample, and showed the slowest decline. Class 2 comprised 23% (n = 118) of our sample and showed much more rapid cognitive and functional decline, despite similar cognitive and functional abilities at diagnosis. From here on, classes 1 and 2 will be referred to as the slowly declining group and rapidly declining group, respectively. Patients in the rapidly declining group had a significantly shorter survival time as compared to those in the slowly declining group. Although patients in the slowly declining group showed a median survival time of 3.4 years after diagnosis, the median survival time in the rapidly declining group was only 1.1 years (P log-rank < .001). In the course of the interval during which dementia clinically manifested (ie, between T = 0 and T = 3), the estimated average decline in our total sample was −5.1 points for MMSE and −1.7 points for ADL (Figure 1; left panels). Over the same time period, patients in the slowly declining group declined with −4.7 points for MMSE and −1.3 points for ADL (Figure 1; center panels),

Table 3
Parameter Estimates for MMSE and ADL Trajectories by Latent Class

	Class 1: Slow Progression	Class 2: Rapid Progression
Prevalence, % (n)*	76.95 (394)	23.05 (118)
Fixed effects, mean (SE)		
Intercept (T = 0)		
MMSE	24.84 (0.14)	24.93 (0.33)
ADL	11.37 (0.09)	9.16 (0.31)
Linear annual rate of decline		
MMSE	−1.16 (0.04)	−2.41 (0.18)
ADL	−0.19 (0.03)	−1.28 (0.06)
Quadratic annual rate of decline		
MMSE	−0.13 (0.01)	−0.57 (0.07)
ADL	−0.08 (0.01)	−0.20 (0.04)
Random effects, mean (SE)		
Intercept variance		
MMSE	2.29 (0.38)	2.29 (0.38)
ADL	0.63 (0.18)	0.63 (0.18)
Residual variance at T = −3		
MMSE	1.52 (0.30)	1.52 (0.30)
ADL	1.12 (0.31)	1.12 (0.31)
Residual variance at T = 0		
MMSE	4.26 (0.51)	4.26 (0.51)
ADL	2.72 (0.44)	2.72 (0.44)
Residual variance at T = 3		
MMSE	24.25 (2.47)	24.25 (2.47)
ADL	3.77 (0.58)	3.77 (0.58)
Residual variance at T = 6		
MMSE	49.31 (4.40)	49.31 (4.40)
ADL	18.68 (1.52)	18.68 (1.52)
Residual variance at T = 9		
MMSE	70.56 (12.63)	70.56 (12.63)
ADL	11.00 (1.76)	11.00 (1.76)

N, number of individuals; SE, standard error.
The best-fitting 2-class model included class-invariant intercept variance and no random slope.
*Reported class counts and proportions are based on the most likely class membership; it should be noted that individuals are in fact assigned a probability of class membership. MMSE score range: 0-30, higher = better; ADL score range: 0-12, reverse-coded: higher = better.

whereas patients in the rapidly declining group declined with −12.4 points for MMSE and −5.6 points for ADL (Figure 1; right panels) on average.

Predictors of Disease Progression

All potential predictors of disease progression listed in Table 1 were examined using multivariable logistic regression, with predicted class membership in our final 2-class model as the dependent variable. The results of this regression analysis are summarized in Table 4. This analysis was based on 509 patients; 3 patients (<0.1%) were excluded because of missing values for covariates. Missing explanatory variables were education (n = 2) and ACB score (n = 1). Factors associated with slow disease progression in the multivariable model were lower age, AD dementia type, fewer comorbidities at diagnosis, and a more extensive social network. For example, 1 additional chronic disease at diagnosis decreased the likelihood of being a part of the slowly declining group by 23% (OR 0.77, 95% CI 0.66-0.90, $P = .001$). Combining the 4 significant predictors of dementia disease course yielded an area under the curve of 0.75. Appendix 4 depicts receiver operating characteristic curves for successively larger sets of predictors, showing the discriminative ability of our model increases with each additional predictor.

Table 4
ORs and 95% CIs for Membership in Slowly Progressing Class 1 (Reference: Rapidly Declining Class 2)

Characteristic	Univariable OR (95% CI)	Multivariable OR* (95% CI)
Age	**0.89 (0.84-0.94)**	**0.88 (0.83-0.94)**
Male gender	0.85 (0.50-1.44)	0.69 (0.37-1.30)
Higher vs elementary education	0.89 (0.57-1.41)	1.44 (0.67-1.92)
Comorbidity count	**0.72 (0.63-0.81)**	**0.77 (0.66-0.90)**
Moderate/extensive vs poor/limited social network	**1.93 (1.21-3.06)**	**1.72 (1.01-2.93)**
AD vs non-AD dementia	**2.58 (1.58-4.22)**	**2.07 (1.15-3.71)**
ACB scale	**0.78 (0.67-0.90)**	0.87 (0.73-1.05)

AD, Alzheimer's disease; CI, confidence interval; OR, odds ratio.
*n = 509. Bold estimates are significant at $P < .05$.

Discussion

In the present study we identified 2 groups of dementia progression, with the majority of our sample (class 1; 77%) showing relatively mild progression rates and a smaller group of patients (class 2; 23%) showing more rapid decline in cognition and daily functioning. We were able to assign patients to either the slowly or the rapidly declining group with fair accuracy (area under the curve = 0.75) based on their age, type of dementia (AD vs non-AD), social network, and comorbidity count. These factors may contribute to an individualized prognosis for people with dementia.

The observed average rate of change in MMSE in our study is comparable to the previously reported rates from the Cache County Dementia Progression study, a population-based study from Utah.[4] The high correlation between the trajectories of cognition and daily functioning observed in our study is consistent with previous studies as well.[4–6,15,35] This indicates that cognitive and functional complaints tend to occur in unison. Furthermore, the majority of our sample showed relatively slow disease progression, which is consistent with previously published GMMs of cognitive and functional decline in dementia.[5,6]

Few studies possess the necessary data to allow for prognostic modeling of multiple dementia domains with demographic, medical, and social predictors simultaneously. However, the predictors examined in this study have been reviewed individually in previous studies. For example, low educational attainment has been associated with increased risk of incident dementia[36,37] and cognitive decline[38] in previous studies. However, no predictive effect of education on dementia progression was found in the present study. Consistent with our current findings, a recent systematic review also found an association between comorbidity burden and more rapid progression in cognition and daily functioning in people with dementia.[11] A meta-analysis including 19 longitudinal cohort studies concluded that poor social relationships are associated with cognitive decline in the general population.[39] Moreover, an active and socially integrated lifestyle appears to be associated with a decreased risk of developing dementia.[40,41] Our study adds to this by showing that a good social network also appears to be protective of rapid cognitive and functional decline in people with dementia. This indicates that social network not only influences the development of dementia, but seems to play an important role across the whole cognitive dysfunction continuum. Although anticholinergic drug load was previously shown to be associated with decreased cognitive abilities,[12,42] it was not a significant predictor of disease course in our multivariable model. We did find AD dementia type to be associated with less rapid cognitive and functional decline as compared to non-AD dementia. Differences between rates of cognitive and functional decline in AD vs non-AD have not been studied extensively and have mostly focused on small groups of vascular dementia patients. These studies reported contradictory findings, with some studies showing slower decline[43–45] and 1 showing more rapid decline[46] in non-AD as compared to AD patients. Longitudinal studies examining rates of decline in large, representative groups of people with non-AD dementia are currently lacking.

Strengths of our study include the long follow-up period, both before and after the clinical manifestation of dementia (across a total time frame of 12 years), as well as our exceptionally large sample of incident dementia cases from population-based cohorts. In addition, the in-depth information on disease and patient characteristics available in SNAC-K and KP allowed us to examine potential predictors that have rarely been examined in the context of dementia progression, such as a patient's social network. Linkage to registries allowed for complete follow-up of comorbidity status, medication use, and mortality. Moreover, the population-based nature of the examined cohorts increases the generalizability of our findings to the overall population of patients with dementia, as compared to GMMs based on clinical data.[6,47] Furthermore, GMMs can detect important associations, which may be missed by conventional models using a single mean trajectory to describe progression, as those look only for effects that are consistent across groups.[48]

A limitation of our study is the relatively long measurement intervals of 3 years, which prevents us from examining yearly changes in cognition and daily functioning. These 3-year intervals, in combination with the insidious onset of dementia, also prevent us from pinpointing the exact moment of dementia diagnosis. This means that the heterogeneity observed in our study may, in part, be explained by variation in timing of dementia diagnosis. Another drawback is the short median survival time of our sample, which is probably due to the high age of the included individuals (mean age of 88.3 years at the visit of diagnosis). This relatively high age is the result of the fact that we sampled incident cases from a cohort of older adults. It should also be noted that people living in the Kungsholmen parish of Stockholm have a relatively high socioeconomic status and educational attainment. These factors may reduce the generalizability of our observed patterns of decline. Furthermore, the ACB score used in our study was calculated at the moment of dementia diagnosis, which may have led to an underestimation of the effect of anticholinergic burden on dementia progression, given that several antipsychotics with high anticholinergic burden may have been prescribed later, during the course of the disease. As the ACB score largely overlapped with the use of antipsychotic medications, we did not include antipsychotic medication use as a separate variable in this study, nor did we include behavioral symptoms. It should also be noted that alterations in diagnostic thinking over the past 4 decades, which have, for example, changed practices regarding the diagnosis of vascular and mixed dementia, limit the generalizability of the dementia subtype distribution reported here. However, the diagnostic criteria for dementia, on which these analyses are primarily based, have changed little during that period.

Conclusions and Implications

This study is the first multidomain trajectory analysis based on a population-based cohort of more than 500 people with incident dementia. We showed that a significant proportion of patients progressed along a trajectory that was substantially different from the population mean progression. Lower age, AD dementia type, fewer comorbidities, and a good social network appeared to be protective of rapid cognitive and functional decline. These results call for an increased focus on non-AD dementia in research, diagnosis, and treatment planning, as data on the progression speed of non-AD dementia types is scarce. Although the potential causality of our observed prognostic associations requires replication and further study, our results raise the hypothesis that maintaining a strong social network and reducing the number of comorbidities may be important in slowing cognitive and functional decline in dementia. The prognostic factors identified in this study may improve the counseling of patients and caregivers and optimize the planning of care in dementia.

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Supplementary Data

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.jamda.2019.03.025.

References

1. Satizabal CL, Beiser AS, Chouraki V, et al. Incidence of dementia over three decades in the Framingham Heart Study. N Engl J Med 2016;374:523–532.
2. Proust C, Jacqmin-Gadda H. Estimation of linear mixed models with a mixture of distribution for the random effects. Comput Methods Programs Biomed 2005;78:165–173.
3. Cortes F, Nourhashemi F, Guerin O, et al. Prognosis of Alzheimer's disease today: A two-year prospective study in 686 patients from the REAL-FR Study. Alzheimers Dementia 2008;4:22–29.
4. Tschanz JT, Corcoran CD, Schwartz S, et al. Progression of cognitive, functional, and neuropsychiatric symptom domains in a population cohort with Alzheimer dementia: The Cache County Dementia Progression Study. Am J Geriatr Psychiatry 2011;19:532–542.
5. Leoutsakos JM, Forrester SN, Corcoran CD, et al. Latent classes of course in Alzheimer's disease and predictors: The Cache County Dementia Progression Study. Int J Geriatr Psychiatry 2015;30:824–832.
6. Haaksma ML, Calderón-Larrañaga A, Olde Rikkert MGM, et al. Cognitive and functional progression in Alzheimer disease: A prediction model of latent classes. Int J Geriatr Psychiatry 2018;33:1057–1064.
7. Aminzadeh F, Byszewski A, Molnar FJ, et al. Emotional impact of dementia diagnosis: Exploring persons with dementia and caregivers' perspectives. Aging Ment Health 2007;11:281–290.
8. Schmidt C, Wolff M, Weitz M, et al. Rapidly progressive Alzheimer disease. Arch Neurol 2011;68:1124–1130.
9. Fotuhi M, Hachinski V, Whitehouse PJ. Changing perspectives regarding late-life dementia. Nat Rev Neurol 2009;5:649–658.
10. Amieva H, Mokri H, Le Goff M, et al. Compensatory mechanisms in higher-educated subjects with Alzheimer's disease: A study of 20 years of cognitive decline. Brain 2014;137:1167–1175.
11. Haaksma ML, Vilela LR, Marengoni A, et al. Comorbidity and progression of late onset Alzheimer's disease: A systematic review. PLoS One 2017;12:e0177044.
12. Pfistermeister B, Tümena T, Gaßmann K-G, et al. Anticholinergic burden and cognitive function in a large German cohort of hospitalized geriatric patients. PLoS One 2017;12:e0171353.
13. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. Lancet 2017;390:2673–2734.
14. Green C, Zhang S. Predicting the progression of Alzheimer's disease dementia: A multidomain health policy model. Alzheimers Dementia 2016;12:776–785.
15. Haaksma ML, Leoutsakos JMS, Bremer JA, et al. The clinical course and interrelations of dementia related symptoms. Int Psychogeriatr 2018;30:859–866.
16. Tractenberg RE, Aisen PS, Weiner MF, et al. Independent contributions of neural and "higher-order" deficits to symptoms in Alzheimer's disease: A latent variable modeling approach. Alzheimers Dementia 2006;2:303–313.
17. Lagergren M, Fratiglioni L, Hallberg IR, et al. A longitudinal study integrating population, care and social services data. The Swedish National study on Aging and Care (SNAC). Aging Clin Exp Res 2004;16:158–168.
18. Fratiglioni L, Viitanen M, Backman L, et al. Occurrence of dementia in advanced age: The study design of the Kungsholmen Project. Neuroepidemiology 1992;11:29–36.
19. American Psychiatric Association. revised (DSM-III-R). In: Diagnostic and Statistical Manual of Mental Disorders. 3rd ed. Washington, DC: American Psychiatric Association; 1987.
20. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939–944.
21. McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): Report of the consortium on DLB international workshop. Neurology 1996;47:1113–1124.
22. Román GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: Diagnostic criteria for research studies: Report of the NINDS-AIREN International Workshop. Neurology 1993;43:250.
23. Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.
24. Katz S, Ford AB, Moskowitz RW, et al. Studies of illness in the aged: The Index of ADL: A standardized measure of biological and psychosocial function. JAMA 1963;185:914–919.

25. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. BMC Public Health 2011;11:450.
26. Calderón-Larrañaga A, Vetrano DL, Onder G, et al. Assessing and measuring chronic multimorbidity in the older population: A proposal for its operationalization. J Gerontol A Biol Sci Med Sci 2017;72:1417–1423.
27. Wang HX, Karp A, Winblad B, et al. Late-life engagement in social and leisure activities is associated with a decreased risk of dementia: A longitudinal study from the Kungsholmen project. Am J Epidemiol 2002;155:1081–1087.
28. Boustani M, Campbell N, Munger S, et al. Impact of anticholinergics on the aging brain: A review and practical application. Aging Health 2008;4:311–320.
29. Jung T, Wickrama KAS. An Introduction to latent class growth analysis and growth mixture modeling. Soc Personal Psychol Compass 2008;2:302–317.
30. Muthén B, Muthén LK. Integrating person-centered and variable-centered analyses: Growth mixture modeling with latent trajectory classes. Alcohol Clin Exp Res 2000;24:882–891.
31. Nylund KL, Asparouhov T, Muthén BO. Deciding on the number of classes in latent class analysis and growth mixture modeling: A Monte Carlo simulation study. Struct Eq Model 2007;14:535–569.
32. Vermunt JK. Latent class modeling with covariates: Two improved three-step approaches. Polit Anal 2010;18:450–469.
33. Muthén LK, Muthén BO. Mplus User's Guide. 8th ed. Los Angeles, CA: Muthén & Muthén; 1998-2017.
34. R Development Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2008.
35. Zahodne LB, Devanand DP, Stern Y. Coupled cognitive and functional change in Alzheimer's disease and the influence of depressive symptoms. J Alzheimers Dis 2013;34:851–860.
36. Beydoun MA, Beydoun HA, Gamaldo AA, et al. Epidemiologic studies of modifiable factors associated with cognition and dementia: Systematic review and meta-analysis. BMC Public Health 2014;14:643.
37. Fratiglioni L, Wang HX. Brain reserve hypothesis in dementia. J Alzheimers Dis 2007;12:11–22.
38. Lenehan ME, Summers MJ, Saunders NL, et al. Relationship between education and age-related cognitive decline: A review of recent research. Psychogeriatrics 2015;15:154–162.
39. Kuiper JS, Zuidersma M, Zuidema SU, et al. Social relationships and cognitive decline: A systematic review and meta-analysis of longitudinal cohort studies. Int J Epidemiol 2016;45:1169–1206.
40. Kuiper JS, Zuidersma M, Oude Voshaar RC, et al. Social relationships and risk of dementia: A systematic review and meta-analysis of longitudinal cohort studies. Ageing Res Rev 2015;22:39–57.
41. Fratiglioni L, Paillard-Borg S, Winblad B. An active and socially integrated lifestyle in late life might protect against dementia. Lancet Neurol 2004;3:343–353.
42. Papenberg G, Backman L, Fratiglioni L, et al. Anticholinergic drug use is associated with episodic memory decline in older adults without dementia. Neurobiol Aging 2017;55:27–32.
43. Pilon MH, Poulin S, Fortin MP, et al. Differences in rate of cognitive decline and caregiver burden between Alzheimer's disease and vascular dementia: A retrospective study. Neurology (ECronicon) 2016;2:278–286.
44. Smits LL, van Harten AC, Pijnenburg YA, et al. Trajectories of cognitive decline in different types of dementia. Psychol Med 2015;45:1051–1059.
45. Gill DP, Hubbard RA, Koepsell TD, et al. Differences in rate of functional decline across three dementia types. Alzheimers Dementia 2013;9:S63–S71.
46. Tolea MI, Morris JC, Galvin JE. Trajectory of mobility decline by type of dementia. Alzheimer Dis Assoc Disord 2016;30:60–66.
47. Haaksma ML, Leoutsakos J-MS, Larrañaga AC, et al. Latent classes of dementia course show an optimistic prognosis for the majority of patients. Alzheimers Dementia 2017;13:P1314–P1315.
48. Terrera GM, Brayne C, Matthews F. One size fits all? Why we need more sophisticated analytical methods in the explanation of trajectories of cognition in older age and their potential risk factors. Int Psychogeriatr 2010;22:291–299.