Progression of Cognitive, Functional, and Neuropsychiatric Symptom Domains in a Population Cohort With Alzheimer Dementia: The Cache County Dementia Progression Study

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Objectives: *Progression of Alzheimer dementia (AD) is highly variable. Most estimates derive from convenience samples from dementia clinics or research centers where there is substantial potential for survival bias and other distortions. In a population-based sample of incident AD cases, we examined progression of impairment in cognition, function, and neuropsychiatric symptoms, and the influence of selected variables on these domains.* **Design:** *Longitudinal, prospective cohort study.* **Setting:** *Cache County (Utah).* **Participants:** *Three hundred twenty-eight persons with a diagnosis of possible/probable AD.* **Measurements:** *Mini-Mental State Exam (MMSE), Clinical Dementia Rating sum-of-boxes (CDR-sb), and Neuropsychiatric Inventory (NPI).* **Results:** *Over a mean follow-up of 3.80 (range: 0.07–12.90) years, the mean (SD) annual rates of change were −1.53 (2.69) scale points on the MMSE, 1.44 (1.82) on the CDR-sb, and 2.55 (5.37) on the NPI. Among surviving participants, 30% to 58% progressed less than 1 point per year on these measures, even 5 to 7 years after dementia onset. Rates of change were correlated between MMSE and CDR-sb ($r = -0.62$, $df = 201$, $p < 0.001$) and between the CDR-sb and NPI ($r = 0.20$, $df = 206$,*

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$p < 0.004$). Female subjects (LR $\chi^2 = 8.7, df = 2, p = 0.013$) and those with younger onset (likelihood ratio [LR] $\chi^2 = 5.7, df = 2, p = 0.058$) declined faster on the MMSE. Although one or more apolipoprotein Eε4 alleles and ever use of FDA-approved antidementia medications were associated with initial MMSE scores, neither was related to the rate of progression in any domain. **Conclusions:** *A significant proportion of persons with AD progresses slowly. The results underscore differences between population-based versus clinic-based samples and suggest ongoing need to identify factors that may slow the progression of AD.* (Am J Geriatr Psychiatry 2011; 19:532–542)

Key Words: Alzheimer disease, Alzheimer dementia, cognition, decline, dementia, neuropsychiatric symptoms, progression

Alzheimer dementia (AD) is a significant cause of disability and mortality among the elderly. Some 26.6 million cases presently worldwide may increase to 106.2 million by 2050,[1] unless a means of prevention is identified. Without a cure, better understanding of the clinical course and course-modifying factors is needed.

AD causes impairment not only in cognition and function but also in behavior prompted by neuropsychiatric symptoms (NPS). Numerous studies report significant variability in the rate of cognitive and functional decline in AD. For example, a recent review reported that the mean annual rate of change (ARC) on the Mini-Mental State Exam (MMSE), a global measure of cognition, varied from 0.8 to 4.4 points.[2] Similar variability is seen in functional decline,[3] although comparisons across studies are impeded by differences in instrumentation. Neuropsychiatric symptoms in AD are marked both by increasing incidence over time and by an episodic course.[4]

These studies of the natural history of AD share several limitations. Most come from observations in clinics or clinical research centers. Clinic AD patients are up to 20 years younger, have higher educational and occupational attainment, are more often married and living with a spouse,[5] are more likely to be carriers of the apolipoprotein E (*APOE*) *ε4* allele,[6] and tend to suffer from fewer comorbid conditions than panels of AD cases ascertained from populations.[7] The few available population-based studies report lower ARCs in cognition or function.[3] Also, most studies of AD progression describe the course of prevalent cases. Rate of decline is known to vary by stage of dementia severity[8,9] so that survival bias may produce different estimates in prevalent versus incident samples.[10] Furthermore, few studies have examined cognition, function, and NPS simultaneously, so their descriptions of AD progression are incomplete. Finally, many studies encompass limited time of follow-up in their descriptions of dementia course.

Here, we describe results from the Cache County Dementia Progression Study (DPS), an ongoing population-based study of AD that characterizes the course of symptoms in the domains of cognition, function, and NPS from a point near the onset of dementia. We also assess the influence of several variables reported to affect progression, including age of onset, gender, education, and *APOE* genotype.[11,12]

METHODS

The DPS was derived from the longitudinal, population-based Cache County Study on Memory in Aging (CCSMA), which has examined the prevalence, incidence, and risk factors for dementia in a U.S. county recognized for its residents' longevity.[13] In its first wave, CCSMA enrolled 90% of the 5,677 county residents who were 65 years or older. Three subsequent triennial waves of case detection have been completed. As described later, most individuals with incident dementia have been followed prospectively by the DPS. Those with diagnoses of possible or probable AD were included in the present analyses.

Participants and Dementia Diagnoses

The multistage case identification procedures of the CCSMA have been reported elsewhere.[13] Briefly, participants were screened for cognitive disorders

by the modified MMSE,[14] as adapted for epidemiologic studies.[15] Those who screened positive, as well as members of a weighted, stratified population subsample (irrespective of screening results), were studied further using an informant-based telephone interview. This interview queried cognitive and functional impairments typical in dementia.[16] Participants whose interviews were suggestive of dementia or its prodrome, and those of the population subsample, were invited to undergo a clinical assessment (CA) by a trained research nurse and a psychometric technician. The CA included a structured physical and neurologic examination and a battery of neuropsychological tests.[17] A knowledgeable informant provided information regarding the participant's history of cognitive or functional impairment, medical history, and psychiatric symptoms.

A study geropsychiatric psychiatrist and neuropsychologist next reviewed data from the CA and assigned preliminary diagnoses of dementia according to *Diagnostic and Statistical Manual of Mental Disorders, Third Edition Revised* (*DSM-III-R*) criteria.[18] The age of onset was estimated as the age when the participant unambiguously met *DSM-III-R* criteria for dementia. Dementia severity was rated using the Clinical Dementia Rating (CDR,[19] see later) and health status as assessed with the General Medical Health Rating.[20] Participants with suspected dementia were asked to undergo neuroimaging and laboratory studies as well as a geropsychiatric physician's examination to provide differential diagnoses of dementia. Participants were also recruited for a postmortem brain autopsy program. A panel of experts in neurology, geropsychiatry, neuropsychology, and cognitive neuroscience reviewed all available clinical and neuropathologic data and assigned diagnoses of AD and other forms of dementia according to standard protocols (e.g., National Institute of Neurological and Communicative Disorders and Stroke–AD and Related Disorders Association research criteria for AD).[21] All participants with suspected dementia or a dementia prodrome were invited for an 18-month follow-up CA, the results of which were reviewed by the expert panel who rendered final diagnoses. Participants with dementia newly diagnosed at Waves 2 to 4 were invited to join the DPS (Figure 1). All study procedures were approved by the institutional review boards of Utah State University, Duke University, and the Johns Hopkins University.

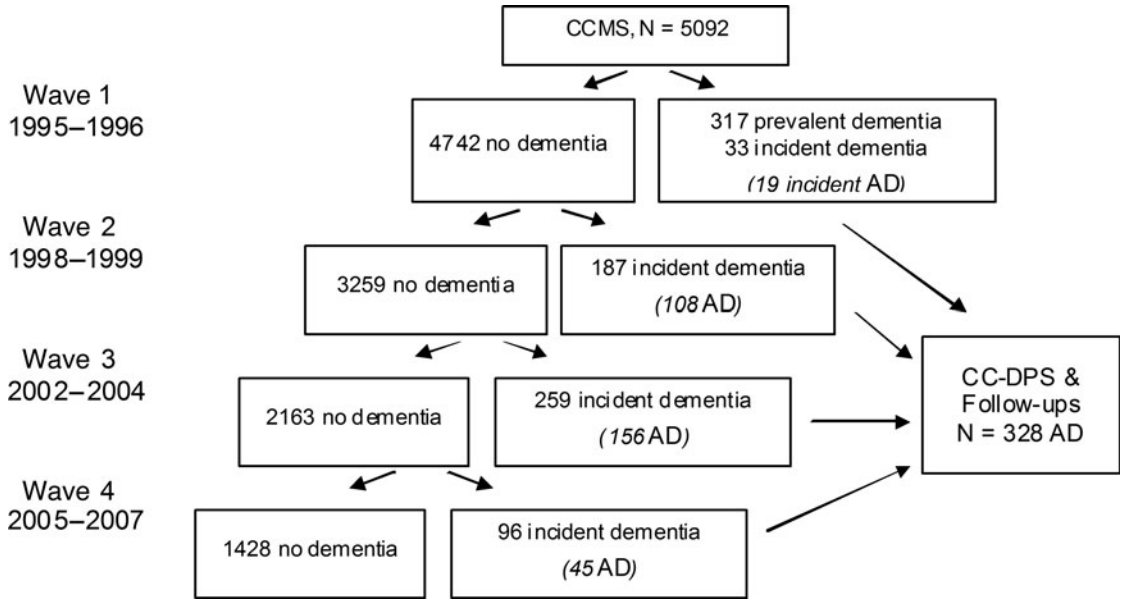
Measures of Dementia Progression

The MMSE, a measure of global cognitive functioning,[22] was administered by trained neuropsychological technicians. A study neuropsychologist trained these individuals and periodically reviewed audio-taped test sessions to ensure consistent techniques of standardized administration. As in the CCSMA,[13] we calculated an adjusted MMSE score by discarding items missed because of sensory or motor impairment (e.g., severe vision or hearing loss, motor weakness, tremor), noting the percentage correct and rescaling the final score on a 30-point scale. Participants whose sensory or motor impairments affected more than 3 points were excluded from the analyses (n = 30, 9%).

The CDR[19] is a measure of functional ability in six areas: memory, orientation, judgment/problem solving, community affairs, participation in home/hobbies, and personal care. An ordinal scale is used to reflect degree of impairment: 0 = no impairment; 0.5 = questionable impairment; 1 = mild impairment; 2 = moderate impairment; 3 = severe impairment; 4 = profound impairment; and 5 = terminal. The CDR was scored by a trained research nurse at each visit, considering the caregiver's report of symptoms and the participant's neuropsychological test performance. A geriatric psychiatrist conducted the initial training and performed periodic reviews of the RN ratings. For analyses, the ratings in each category were summed (Clinical Dementia Rating sum-of-boxes [CDR-sb]).

The Neuropsychiatric Inventory (NPI) assesses NPS that commonly occur in dementia including delusions, hallucinations, agitation–aggression, depression–dysphoria, apathy–indifference, elation–euphoria, anxiety, disinhibition, irritability–lability, and aberrant motor behavior. A trained research nurse administered the NPI[23] to the caregiver. The instrument screens for the presence of each symptom and follows positive responses with a series of standardized questions to characterize the symptom, its frequency, severity, and degree of change from premorbid characteristics. The NPI frequency and severity ratings were multiplied to yield a summary score

FIGURE 1. Individuals identified with dementia from the Cache County Study (CCMS) to the present. Not shown are the CCMS subjects lost to follow-up between study waves. CC-DPS, Cache County Dementia Progression Study



for each symptom and then summed across all 10 symptom types (range: 0–120).

Predictor Variables

Variables available from the CCSMA included age of dementia onset, gender, education, and the presence of one or two *APOE ε4* alleles, determined from buccal DNA.[24]

Analyses

To illustrate an individual participant's course of decline in cognition, function, and NPS, we calculated an ARC or linear slope for each outcome for those with at least two measurements. Subjects were categorized into groups on the basis of whether their slopes were above or below the group median on the MMSE. Participants' trajectories of scores on the MMSE, CDR-sb, and NPI were plotted, with blue lines representing subjects whose MMSE slopes were above the median and red lines representing subjects below the median.

To model nonlinear effects, we examined average change from dementia onset for each outcome, using mixed effects models, treating subject-specific intercepts and linear change with time as random effects. This approach allowed us to account for the dependence between within-subject repeated measures and for *nonlinear* change with respect to time by incorporating time-squared effects. We then calculated the average change in MMSE, CDR-sb, and NPI from dementia onset to specific time points over the course of dementia, providing means and standard errors of estimated change for each measure for selected time points. To estimate the proportion of individuals with a slowly progressive course, we used a threshold of less than 1 point per year decline on the MMSE or similar magnitude increase on the CDR-sb or NPI.

To examine the association between predictor variables and change in each outcome, we built upon the base mixed model by adding each predictor followed by its interaction with time and time squared. A predictor was retained in the model if the individual term had an associated Wald statistic with $p < 0.05$ or if the likelihood ratio (LR) χ^2 test of models with and without the new terms yielded a $p < 0.05$. To consider the effects of incomplete follow-up or dementia duration before diagnosis, we repeated these analyses for participants with at least two follow-up visits whose dementia diagnoses were made within 3 years after onset. Finally, in secondary analyses, we examined whether differences in rate of change

could be attributable to use of Federal Drug Administration–approved medications for AD at any time in the course of the illness following two approaches: (1) we added a term for medication use, contrasting those who were ever or never treated with antidementia medications; and (2) we repeated analyses excluding those ever treated with these medications. Analyses were completed using SAS, Version 9.1 (SAS Institute Inc., Cary, NC).

RESULTS

The CCSMA identified 328 individuals with incident AD. The majority of the participants were female (66%) and White (99%). Table 1 displays sample characteristics at the diagnosis visit. Participants were observed at times between 0.07 and 12.9 years after onset. Sixty-three percent died while being followed, and 4% either refused further participation or moved out of the area. The remaining 33% were active participants at the time of analysis. The mean (SD) duration of dementia from onset to the last observation was 3.80 (2.58) years. Individuals who lacked any follow-up numbered 112 (34%), in most instances because of death (n = 88, 79%). These 112 individuals were significantly older (t = 3.59, df = 326, p < 0.0001) and scored lower on the MMSE at diagnosis (t = 3.09, df = 295, p = 0.002) than those with follow-up data. However, years of education and proportion of men/women did not differ between these groups.

TABLE 1. Demographic and Baseline Characteristics

Male, N (%)	112 (34)
Female, N (%)	216 (66)
Age, *M* (SD)	85.92 (6.34)
Years of education, *M* (SD)	13.20 (3.01)
Caucasian, N (%)	325 (99)
APOE ε4 carrier, N (%)	147 (45)
Dementia duration, *M* (SD)	1.71 (1.26)
Residence: assisted living, N (%)	41 (12)
Residence: nursing home, N (%)	22 (7)
Ever use of antidementia medications, N (%)	73 (22)
MMSE, *M* (SD)	21.92 (4.60)
CDR, global, *M* (SD)	1.06 (0.59)
NPI, any behavior, N (%)	165 (50)
NPI, total, *M* (SD)	4.30 (8.30)
General health	
Excellent, N (%)	39 (12)
Good, N (%)	178 (54)
Fair/poor, N (%)	109 (34)
Number follow-ups, *M* (SD)	1.97 (2.09)
Duration follow-ups, *M* (SD)	3.80 (2.58)

Course of Dementia

Over time, the severity of cognitive, functional, and behavioral symptoms increased (MMSE LR χ^2 = 128.7, df = 2, p < 0.0001; CDR-sb LR χ^2 = 137.6, df = 2, p < 0.0001; NPI LR χ^2 = 77.1, df = 2, p < 0.0001). The mean (SD), measure-specific ARCs were −1.53 (2.69) for the MMSE, +1.44 (1.82) for the CDR-sb, and +2.55 (5.37) for the NPI. Fifty percent of participants experienced NPS at baseline, most commonly depression (26%), irritability (17%), or apathy (17%). Most NPI symptoms increased over time such that 89% of survivors were experiencing symptoms by the final visit. However, for hallucinations, anxiety, and irritability, the percentage of those affected declined at the final visit, possibly reflecting the fluctuating nature of NPS (Figure 2), differential survival of those without symptoms, or other factors that diminished the occurrence of symptoms over time. The pattern of NPS also shifted over time, as apathy became the most commonly reported symptom by Visit 4. Table 2 displays the 1-month prevalence of NPS at each visit.

Person-specific longitudinal scores on the MMSE, CDR-sb, and NPI are plotted in Panels A–C of Figure 2. Inspection of the plots shows a substantial number of individuals declining slowly. There was a strong association between slopes on the MMSE and CDR-sb (r = −0.62, df = 201, p < 0.001), none between the MMSE and NPI (r = 0.052, df = 195, p = 0.469), and only a weak association between the CDR-sb and NPI (r = 0.20, df = 206, p = 0.004).

Mixed-effects models revealed a significant nonlinear component in trajectories for MMSE and CDR-sb (MMSE LR χ^2 = 17.5, df = 1, p < 0.0001 for quadratic time; CDR LR χ^2 = 12.3, df = 1, p = 0.0005), suggesting acceleration in the rate of change over time. Nonlinearity of change was slight on the NPI (LR χ^2 = 1.82, df = 1, p = 0.18). Table 3 displays the estimated mean (SE) annual change at selected time points for each measure. Some 30% to 58% of the survivors (5%–10% of the entire cohort) declined slowly (less than 1 point per year), even at 5 to 7 years after onset. Table 4 displays the percentages of those with a slow course in each of the three domains.

FIGURE 2. The trajectories of cognitive (A), functional (B), and NPS (C) domains of dementia. Trajectories in *blue* represent those whose MMSE slopes fall above the median and *red* are those that fall below the median. Filled black circles represent individuals with no follow-up. Note the individual in Panel A whose slope falls above the median, but their MMSE score is stable at 0. This reflects the relative insensitivity of the MMSE to change in very severe dementia. Inspection of the plots suggests a significant number of individuals decline slowly, with MMSE values at 20 or above at the final observation. The plots also suggest an association between cognitive and functional domains but little-to-no association between cognitive and NPS domains.

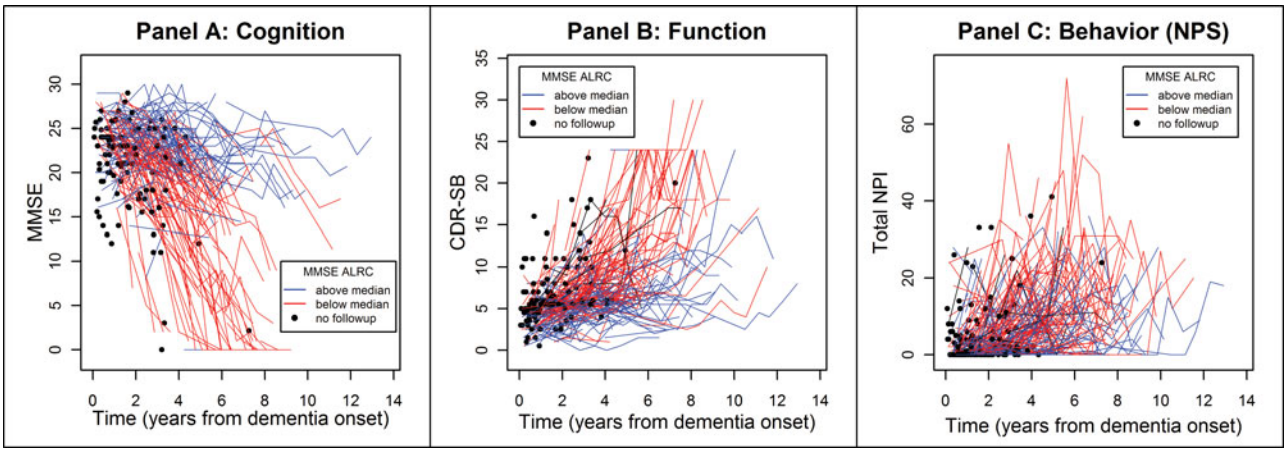


TABLE 2. One-Month Prevalence of NPS by Visits

	Visits						
	Dx V	**FV 1**	**FV 2**	**FV 3**	**FV 4**	**FV 5**	**FV 6**
N	328	216	140	110	84	60	35
Years from dementia onset, *M* (SD)	1.71 (1.26)	3.28 (1.47)	4.47 (1.92)	5.20 (1.89)	5.64 (1.83)	6.55 (1.95)	7.72 (2.24)
Any behavior, %	50	73	78	82	85	93%	89%
Delusions, %	15	26	36	33	41%	35	39
Hallucinations, %	5	10	15	18	24	25	12
Agitation, %	10	17	27	23	30	37	46
Depression, %	**26**	**36**	38	41	41	37	37
Apathy, %	17	32	**45**	**47**	**57**	**63**	**63**
Elation, %	0.6	1	0.7	2	2	7	3
Anxiety, %	13	24	30	27	29	37	17
Disinhibition, %	7	14	16	18	24	23	31
Irritability, %	17	26	25	18	25	32	23
Aberrant motor behavior, %	8	19	21	24	26	30	33

Notes: Dx V: diagnosis visit; FV: follow-up visit. Figures in bold represent the most common symptom at any given follow-up visit.

Association Between Predictors and Rate of Change

Mini-Mental State Exam. On average, males (LR $\chi^2 = 14.1$, df = 1, p = 0.002), *APOE ε4* carriers (LR $\chi^2 = 4.5$, df = 1, p = 0.035), and those with older onset ages (LR $\chi^2 = 20.9$, df = 1, p < 0.0001) and fewer years of education (LR $\chi^2 = 21.2$, df = 1, p < 0.0001) scored worse at dementia onset. Females declined more rapidly than males (LR $\chi^2 = 8.7$, df = 2, p = 0.013), with an average additional decline of 2.9 points over 3 years, 3.8 points over 5 years, and 4.1 points over 7 years. Those with younger onset ages also declined faster (LR $\chi^2 = 5.7$, df = 2, p = 0.058). Notably, neither *APOE* genotype nor education influenced the *rate of decline.* There were no appreciable differences in results in analyses restricted to those with more complete follow-up and whose dementia was diagnosed within 3 years of onset (results not shown).

Clinical Dementia Rating sum-of-boxes. On average, older onset age (LR $\chi^2 = 6.8$, df = 1, p = 0.0096) and female gender (LR $\chi^2 = 7.9$, df = 1, p = 0.0053) were

associated with greater impairment at onset. For each added year of age, there was a 0.06 (SE = 0.02) point higher score, and females scored 0.80 points higher on average than males. Neither education nor *APOE* genotype was associated with rate of change. There were no appreciable differences in results in analyses restricted to those with more complete follow-up and whose dementia was diagnosed within 3 years of onset (results not shown).

Total NPI. On average, individuals with younger onset ages had higher total NPI scores (LR $\chi^2 = 3.6$, df = 1, p = 0.060). In separate models considering the time elapsed between dementia onset and diagnoses, participants with older onset ages had higher total NPI scores but only among those diagnosed within 3 years of onset (LR $\chi^2 = 3.2$, df = 1, p = 0.076). *APOE* genotype, gender, and education were not associated with NPI. Table 5 displays the results of the multivariable models for the MMSE, CDR-sb, and NPI.

TABLE 3. Summary of Estimated Annual Rate of Change in Three Dementia Trajectories From Mixed Effects Models

	Cognitive ΔMMSE (SE)[a]	Functional ΔCDR-sb (SE)[a]	Behavioral ΔNPI Total (SE)[a]
All subjects, N	203	214	209
One year postonset	−1.50 (0.14)	1.00 (0.10)	2.20 (0.23)
Three years postonset	−1.60 (0.12)	1.13 (0.09)	1.93 (0.17)
Five years postonset	−1.76 (0.12)	1.30 (0.09)	1.70 (0.14)
Seven years postonset	−1.90 (0.13)	1.44 (0.10)	1.47 (0.16)

Notes: The values given are estimated average annual rate of change for each measure from a series of linear mixed effects models. The increase in absolute values over time reflects the slight acceleration in decline (MMSE) or impairment (CDR-sb) estimated by mixed effects models incorporating terms for time and time.[2] The estimates of annual change for the subsample participants with a diagnosis of AD within 3 years of their dementia onset were similar to the displayed values and therefore are not provided.
[a]Standard error (SE) represents the standard deviation of the estimated rate of change computed from the fitted model.

Effect of Antidementia Medications

Twenty-two percent of participants had used antidementia medications at some point over the course of dementia. Such medication use was associated with higher MMSE scores at onset (LR $\chi^2 = 3.83$, df = 1, p = 0.051) but did not significantly influence *rate of decline* in the MMSE, CDR-sb, or NPI. However, analyses that excluded those treated with antidementia medications no longer showed association of younger onset age with more rapid decline in MMSE.

DISCUSSION

This study of a population-based, incident cohort of persons with AD found the following observations: first, that 30% to 58% *of those who survived* 5 to 7 years after dementia onset declined slowly; second, that AD progressed faster in women than in men; third, that number and severity of NPS increased over time but the course was variable and episodic; and fourth, that rate of change in NPS was correlated weakly, if at all, with rate of change in cognition or function.

Several studies have noted a contrast between "fast" and "slow" progressors in AD,[25,26] but studies of incident cases from populations are lacking. Approximately, one-third to one-half of persons in

TABLE 4.

		Survivors With Slow Course (%)			Entire Sample (N = 328) With Slow Course (%)		
Onset to	No. Surviving	Cognitive (MMSE)	Functional (CDR-sb)	NPS (NPI-Total)	Cognitive (MMSE)	Functional (CDR-sb)	NPS (NPI-total)
1 year	282	37.9	46.1	34.8	32.6	39.6	29.9
3 years	185	36.2	55.1	36.2	20.4	31.1	20.4
5 years	98	30.0	58.2	36.7	8.8	17.4	11.0
7 years	46	34.8	41.3	45.7	4.9	5.8	6.4

Notes: The percentages of persons with possible/probable AD with a slow course from age of dementia onset to time points 1, 3, 5, and 7 years postonset are displayed. Slow course is defined as an average annual decline of no more than 1 point on MMSE (or average annual increase of no more than 1 point for CDR-sb and NPI-total). The numbers and percentages of survivors represent those who survived up to each time point whereas those of the total represent the entire sample of 328 persons with AD. A small number of subjects who scored 0 (floor) at their first observation were excluded from the analyses on the MMSE.

TABLE 5. Parameter Estimates From Mixed-Effects Models

Effect	Estimate	Standard Error	*t*-Statistic	p
MMSE trajectory				
Intercept	40.3284	4.5858	8.79	<0.0001
Time	−7.4168	2.6980	−2.75	0.0065
Time^2	0.6064	0.2970	2.04	0.0419
Age of onset	−0.2467	0.05397	−4.57	<0.0001
Male gender	−2.4857	0.6619	−3.76	0.0002
APOE ε4 present	−0.8584	0.4045	−2.12	0.0345
Education	0.3092	0.06720	4.60	<0.0001
Time* onset age	0.07266	0.03261	2.23	0.0264
Time^2* onset age	−0.00834	0.003686	−2.26	0.0243
Time* male gender	1.2689	0.4354	2.91	0.0038
Time^2* male gender	−0.09864	0.05310	−1.86	0.0640
CDR-sb trajectory				
Intercept	−0.5369	2.1333	−0.25	0.8015
Time	0.8317	0.1601	5.20	<0.0001
Time^2	0.06423	0.01866	3.44	0.0006
Age of onset	0.06135	0.02357	2.60	0.0096
Male gender	−0.8024	0.2864	−2.80	0.0053
APOE ε4 present	−0.09872	0.2862	0.34	0.7303
Education	−0.03024	0.04748	−0.64	0.5244
NPS trajectory				
Intercept	14.4520	5.7428	2.52	0.0123
Time	1.2848	0.4187	3.07	0.0024
Time^2	0.07639	0.04918	1.55	0.1211
Age of onset	−0.1191	0.06318	−1.89	0.0601
Male gender	−0.5906	0.7772	−0.76	0.4478
APOE ε4 present	0.07593	0.7758	−0.10	0.9221
Education	−0.1277	0.1280	−1.00	0.3191

Notes: The results of mixed effects models in the three dementia domain trajectories are shown. Parameter estimates, standard errors, *t*-statistics (assuming a t distribution), and their associated p values are provided. Not shown are the results of mixed effects models of the subset of individuals diagnosed within 3 years of dementia onset and with more than two follow-up visits. The results of analyses did not differ except in the NPS trajectory where a shorter duration between dementia onset and diagnosis was associated with a lower NPI score. Among those diagnosed within 3 years of onset, older individuals had higher average NPI scores.

the Cache County DPS fell into the slow progression category. In contrast, the multicenter French Network on Alzheimer Disease (REAL-FR) consisting of a volunteer sample of 686 individuals reported that 23% of their sample could be characterized as "slow" progressors.[27] The French study also reported that 89% of their participants were receiving treatment for AD (cf. 22% of DPS participants). The lower figure in DPS is similar to estimates (26%) reported among Medicare beneficiaries with dementia.[28] Nonetheless, our analyses suggest that slow dementia progression is not attributable to treatment with antidementia medications.

In the DPS sample, the mean ARC on the MMSE was considerably lower than was found in clinical or other convenience samples. For example, a mean ARC of −3.9 (SD = 3.7) has been reported from the multicenter Consortium to Establish a Registry in AD[8] and rates of −2.97 (SD = 4.26) for possible AD and −3.05 (SD = 3.86) for probable AD in patients at California AD centers.[29] A meta-analysis of studies primarily from clinical/university research centers or hospitals reported a pooled ARC on the MMSE of −3.3 (95% confidence interval: −2.9 to −3.7).[30] To our knowledge, the Kungsholmen Project is the only population-based study that has reported an ARC on the MMSE. This was somewhat greater than that in the DPS (−2.75 at the study's first 3-year follow-up and −3.03 at the second follow-up after 3–7 more years).[31] We speculate that the Kungsholmen cases may not have entered the longitudinal analysis as shortly after diagnosis as the DPS cases and that their case cohorts may therefore show some of the same phenomena (survival bias, entry into study when MMSE decline was more rapid) as is likely in convenience samples.

Functional change in DPS participants was also quite variable. The REAL-FR study reported a mean change in CDR-sb of 4.17 over 2 years (2.09 per year),[27] an approximately 0.65-point faster rate of progression than was observed in DPS. However, differences in CDR versions used between studies make comparisons problematic.

In the behavioral domain, we observed increasing occurrence, rate, and overall severity of NPS over time, consistent with other studies (reviewed in Chung and Cummings[4]). Change in severity of symptoms in the DPS was higher than that reported in REAL-FR. However, again, comparisons between studies are hampered due to differences in the NPI versions and baseline differences in NPI scores (mean: 4.30 in DPS versus 15.11 in REAL-FR). In the DPS, rate of change in NPS was marginally associated with change in CDR-sb but not with change in MMSE. Although the lack of correspondence between dementia domains is consistent with other reports,[32] these results may also reflect the crude measurements of change employed here. Alternate methods that characterize the nonlinear nature of progression in each domain may reveal stronger associations.[33] We also note that the occurrence of NPS varies with severity of dementia,[34] creating problems for cross-study comparisons, and that symptoms tend to be correlated.[35] Hence, a

global summary score may not be optimal for examining associations between NPS and other clinical features of AD.

Among the variables examined, there was no consistent set of factors that influenced change across domains. In cognition, carriers of the *APOE ε4* allele performed worse at baseline than noncarriers, but *APOE* status did not affect rate of decline. Studies examining the effect of *APOE* after dementia onset have found inconsistent results. Our findings are consistent with recent work suggesting that *APOE ε4* exerts deleterious effects early in the disease course.[12] In DPS, education was associated with higher MMSE scores at onset but not with decline on any of the outcomes. This finding contrasts with studies reporting more rapid decline among those with more years of education[36] but is consistent with higher education, conferring advantages early in the disease course.[37] Differences in results may also reflect sample differences in years of education and the timing of observations along the course of dementia.

Older age was associated with worse cognition and function at baseline, while women declined more rapidly (in cognition) than men. More rapid decline among women with AD has been reported in some[31] but not all studies.[38] The reasons for gender differences on rates of decline in AD are unclear and warrant further study.

Among the study limitations are the use of single measures of cognition, function, and NPS. Some measures (e.g., MMSE) have been criticized both for differential performance in classifying the cognitive status of individuals from different ages and educational backgrounds and for significant floor effects when studying persons with severe dementia (reviewed in Tombaugh and McIntyre[39]). We do not believe that these issues substantially affected the results, as a somewhat more sensitive measure, the 3MS, was employed in dementia screening in the Cache County population, and dementia diagnoses were based on rigorous clinical examination. In addition, because we followed individuals with incident dementia, the majority (89%) of our participants did not reach the floor of this measure over the period of observation.

Other limitations included the missing MMSE scores at baseline and/or follow-up owing to sensory/motor impairments among 9% of the sample, the lack of follow-up among 29% of the sample (mostly due to death),[40] and our cursory examination of the effects of antidementia medications on dementia progression. Here, we did not consider duration or consistency of medication use; a thorough examination of the effects of antidementia medications will be the topic of a subsequent paper on dementia treatments. Finally, the Cache County population is primarily White, and of northern European descent. Thus, the results obtained here may not generalize to populations with different ethnic representation.

The study strengths include its population base, its focus on incident cases, the characterization of course in the three domains of dementia, the extended follow-up after dementia onset, and the high participation rates observed in dementia ascertainment and over the period of observation.

In conclusion, a significant proportion of individuals with AD exhibit a slowly progressive course. The present results in general suggest important differences between population-based versus clinic-based samples. As the DPS continues to accrue additional observations, we will focus our efforts on identifying factors that moderate dementia progression, in addition to those we have described earlier.[41–44]

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