Terminal decline and practice effects in older adults without dementia

The MoVIES project

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ABSTRACT

Objective: To track cognitive change over time in dementia-free older adults and to examine terminal cognitive decline.

Methods: A total of 1,230 subjects who remained free from dementia over 14 years of follow-up were included in a population-based epidemiologic cohort study. First, we compared survivors and decedents on their trajectories of 5 cognitive functions (learning, memory, language, psychomotor speed, executive functions), dissociating practice effects which can mask clinically significant decline from age-associated cognitive decline. We used longitudinal mixed-effects models with penalized linear spline. Second, limiting the sample to 613 subjects who died during follow-up, we identified the inflection points at which the rate of cognitive decline accelerated, in relation to time of death, controlling for practice effects. We used mixed-effects model with a change point.

Results: Age-associated cognitive trajectories were similar between decedents and survivors without dementia. However, substantial differences were observed between the trajectories of practice effects of survivors and decedents, resembling those usually observed between normal and mildly cognitively impaired elderly. Executive and language functions showed the earliest terminal declines, more than 9 years prior to death, independent of practice effects.

Conclusions: Terminal cognitive decline in older adults without dementia may reflect presymptomatic disease which does not cross the clinical threshold during life. Alternatively, cognitive decline attributed to normal aging may itself represent underlying neurodegenerative or vascular pathology. Although we cannot conclude definitively from this study, the separation of practice effects from age-associated decline could help identify preclinical dementia. *Neurology*® 2011;77: 722-730

GLOSSARY

AD = Alzheimer disease; **CDR** = Clinical Dementia Rating; **CERAD** = Consortium to Establish a Registry for Alzheimer's Disease; **CI** = confidence interval; **DSM-III-R** = *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition, revised; **MCI** = mild cognitive impairment; **MMSE** = Mini-Mental State Examination; **MoVIES** = Monongahela Valley Independent Elders Survey.

Dementia is a well-known risk factor for mortality. However, even in the absence of clinically diagnosed dementia, and after accounting for other illnesses, declining cognitive function is also associated with mortality.¹⁻⁷ Therefore, cognitive decline could reflect biological aging independently of dementia. The concept of terminal cognitive decline refers to the relatively precipitous drop in cognitive function occurring in the years preceding death.⁸ Understanding terminal decline among older adults who remain free from dementia can potentially help distinguish normal cognitive aging from the cognitive decline associated with pathologic aging.

While previous studies have confirmed the existence of terminal decline,³⁻⁷ they have inadequately addressed practice or learning effects in cognitive test performance. Practice effects refer to the improvement in cognitive test scores over repeated administrations of cognitive tests.⁹⁻¹¹

Supplemental data at
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Supplemental Data

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Figure 1 Hypothetical cognitive trajectories with practice effects

Spurious acceleration or inflection points may be identified when practice effects wear off, usually by the third and fourth assessments. This situation is illustrated in figure 1 in a very simplified format, where the true time-to-death effects on cognitive functions could be those represented by scenarios I, II, or III. Ignoring practice effects could distort the assessment of event-associated cognitive trajectories.

Here, first, we tested the hypothesis that persons who died during follow-up had different age-associated rates of decline in cognitive functions, as well as different rates of practice effects, than those who survived. Next, limiting the sample to those who died during follow-up, we used a change point model^{6,12} to identify the inflection points at which the rates of decline accelerated, in relation to time of death.

METHODS Participants. The Monongahela Valley Independent Elders Survey (MoVIES) project was a population-based epidemiologic cohort study of cognitive impairment and dementia conducted from 1987 to 2002. As previously reported,^{13,14} the original cohort of 1,681 participants aged 65 and older comprised an age-stratified random sample of 1,422 older adults randomly drawn from voter registration lists (random sample) and 259 volunteers drawn from the same communities (volunteer sample) meeting the same inclusion criteria. All participants were community-dwelling at enrollment. The assessments were conducted primarily in participants' homes and were repeated approximately every 18 months for over 14 years. Average attrition not due to mortality was 2.8% between consecutive data collection waves with 627 subjects still actively participating when the study ended in 2002 (overall 15-year attrition including mortality: 62.7%). For the present analyses, we deleted 136

of the original 1,681 participants who were prevalent cases of dementia at baseline, 309 who became incident cases of dementia during follow-up, and 4 who completed no neuropsychological tests at baseline. We also removed 2 outliers (participants whose ages at death fell at 2.75 [age 99] and 3.97 [age 107] standard deviations above the mean). The analyses reported here are based on the remaining 1,230 participants.

Standard protocol approvals, registrations, and patient consents. Written informed consent was obtained from all participants and the University of Pittsburgh Institutional Review Board approved the study.

Cognitive measures. The MoVIES cognitive test battery incorporated the neuropsychological panel established by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD).¹⁵ Tests included the Mini-Mental State Examination (MMSE),¹⁶ Trail Making Tests A and B,¹⁷ CERAD 10-word Word List Learning and Delayed Recall,¹⁵ Story Immediate Retell and Delayed Recall,¹⁸ Initial Letter Fluency (P and S) and Category Fluency (Fruits and Animals),¹⁹ 15-item CERAD version of the Boston Naming Test,²⁰ CERAD Constructional Praxis,²¹ and Clock Drawing.²² The MMSE, CERAD Constructional Praxis, and Clock Drawing were excluded from the current analysis due to their highly skewed distributions. For the remaining tests, composite scores were created to represent specific cognitive domains, with groupings based on conceptual grounds and factor analysis.²³ Individual test scores were first z-transformed based on their distribution at baseline, combined as shown below, and averaged to create composite scores: 1) learning: Word List Learning Test (total of 3 trials) and Story, Immediate Retell; 2) memory: Word List Delayed Recall and Story Delayed Recall; 3) language: Verbal Fluency for Categories and Boston Naming Test; 4) psychomotor speed: Trail Making Test A (correct connections per second); and 5) executive function: Verbal Fluency for Initial Letters and Trail Making Test B (correct connections per second).

Diagnosis of dementia. At each wave, participants with operationally defined cognitive impairment or decline, and a randomly selected comparison group of individuals with normal cognitive scores, were selected to undergo a clinical assessment for dementia.¹³ Diagnosis of dementia was based on the criteria of the *DSM-III-R*²⁴ and severity or stage of dementia was based on the Clinical Dementia Rating scale (CDR).²⁵ Details of the diagnostic procedures are described elsewhere.^{13,14} For current analyses, we excluded both prevalent and incident cases of dementia including very mild dementia defined as CDR = 0.5.

Other covariates and mortality. Demographic characteristics (age, sex, and education [high school education or higher vs less than high school education]) and recruitment status (volunteers vs random sample) were included in all models. Complete ascertainment of mortality was obtained from baseline (enrollment between 1987 and 1989) until death (or censored by end of the study, December 31, 2001). Date of death was obtained from obituaries and confirmed by obtaining death certificate information. Our study protocol to confirm death certificate is described in detail elsewhere.²⁶

Analysis. Characteristics at baseline were compared between those who died during follow-up (decedents) and those who survived (survivors), using the *t* test for continuous variables and Pearson χ^2 test for categorical variables. Longitudinal mixed-effects models with penalized linear spline²⁷ estimated the patterns of change over time in each of 5 cognitive domains,

Table 1 Participant characteristics at study baseline

	Survivors (n = 617)	Decedents (n = 613)
Age, y, mean $\pm$ SD (range)	70.30 $\pm$ 3.81 (64.95-85.63)	74.30 $\pm$ 5.97 (64.88-95.63)
Sex, % women	65.48	50.24
Education, % with high school or greater education	68.40	54.32
Recruitment status, % from volunteer sample	23.82	9.95
Follow-up duration, y, mean $\pm$ SD (range)	9.59 $\pm$ 3.67 (0.10-13.79)	6.79 $\pm$ 3.96 (0.21-14.84)
Cognitive test scores		
Learning, mean (SD)		
z-Transformed score ^a	0.37 (0.76)	0.01 (0.83)
Word List Learning (total of 3 trials)	20.39 (3.41)	18.96 (3.63)
Story Immediate Retell	6.91 (2.86)	5.94 (2.97)
Memory, mean (SD)		
z-Transformed score ^a	0.40 (0.76)	0.01 (0.83)
Word List Delayed Recall	6.87 (1.74)	6.12 (1.89)
Story Delayed Recall	6.29 (2.86)	5.15 (2.95)
Language, mean (SD)		
z-Transformed score ^a	0.37 (0.68)	0.01 (0.81)
Verbal Fluency Categories	28.50 (5.39)	25.95 (5.89)
Boston Naming	14.45 (0.90)	14.10 (1.16)
Psychomotor speed, mean (SD)		
z-Transformed score ^a	0.56 (1.06)	0.01 (0.99)
Trail Making A (connections/s)	0.61 (0.19)	0.51 (0.17)
Executive, mean (SD)		
z-Transformed score ^a	0.47 (0.81)	0.02 (0.81)
Trail-Making B (connections/s)	0.26 (0.09)	0.20 (0.09)
Verbal Fluency for Initial Letters	23.37 (7.45)	21.36 (7.40)

^a z-Transformed score using distributions of test scores among entire Monongahela Valley Independent Elders Survey (MoVIES) cohort (n = 1,681) at baseline.

comparing those who died vs those who survived. This model has the flexibility to estimate nonparametric trajectories (see appendix for further explanation). Five dummy variables indicating the number of cognitive assessments (second, third, fourth, fifth, and sixth), with the baseline assessment as the reference group, were included in all models, allowing us to decompose the cognitive trajectories into age-associated decline and practice effects. Normality of distribution of outcomes (cognitive scores) was confirmed by examining normal probability plots.

Next, limiting the data to those who died during follow-up, a longitudinal mixed-effects model with a change point¹² was used to examine whether the annual rate of decline in each cognitive domain changed (accelerated) at some point relative to

death, and estimate the magnitude of change. The inclusion of a change point in the mixed-effects model allows the rates of change to differ before and after the change point. The point of change in the coefficients is relative to the time of death (years before death), as opposed to age (years after birth). Five dummy variables were included to indicate the number of assessments and to capture practice effects. We fit models with and without these dummy variables.

The location of the change point relative to death was estimated by maximum likelihood using the SAS procedure NLMIXED (SAS Institute, Cary, NC) and was treated as a fixed effect as opposed to a random effect. Separate mixed-effects models were fit with the change point at fixed 1-month intervals up to 14 years before death. The model with the highest likelihood was used to summarize the results. We tested whether there was an acceleration in the rate of change in outcomes relative to death by calculating a 95% confidence interval (CI) around the parameter on the change point term, using a likelihood ratio approach.¹² The significance of the other terms in the mixed-effects model was determined using a Wald test statistic.²⁸ Standard errors for the parameter estimates were calculated using the conditional variance as proposed previously.¹² Statistical significance was taken as $p = 0.05$. We used statistical software *R* (version 2.11) and SAS (version 9.2, Cary, NC).

RESULTS Participant characteristics. Participant details are shown in table 1. Among 1,230 participants free from dementia throughout the follow-up period, 613 (48.6%) subjects died during follow-up; they had a mean (SD) follow-up duration of 6.7 (3.9) years. The 617 subjects who survived had a mean (SD) follow-up duration of 9.5 (3.6) years. The 2 groups differed ($p < 0.001$) on all baseline characteristics examined here. As expected, those who died were older, had shorter duration of follow-up, had lower cognitive test performance at baseline in all domains, a smaller proportion had high school or greater educational attainment, were more likely to be men, and were less likely to be from the volunteer subsample than those who survived.

Trajectories of decedents vs survivors. Age-associated trajectories and practice effects for the 2 groups (decedents vs survivors) were examined for each cognitive domain based on all 1,230 participants (figure 2). The spline curves show that the rates of age-associated decline were relatively similar between the 2 groups, but striking differences were found in practice curves between the groups. As for executive functions, decedents experienced virtually no practice effects, in sharp contrast to the upward curves observed among the survivors. Overall we observed practice effects in learning, memory, and language functions (first block of rows in table 2, indicated under practice effects). However, decedents had smaller practice effects than survivors, and the difference tended to diverge as the number of assessments increased, especially in learning and executive functions (figure 2 and second block of rows in table 2

Figure 2 Age-associated cognitive trajectories and practice effects: Survivors and decedents

indicated under interaction of death and practice effects). For example, the practice effect was lower among decedents compared with the survivors at the sixth assessment by 0.24 SD points ($p = 0.04$) in learning and 0.26 SD points ($p = 0.03$) in executive functions (interaction of death and sixth assessment).

As a post hoc analysis, we also included interactions of age at first interview with number of assessments, hypothesizing that those who joined the study at younger ages could have experienced larger practice effects than those who joined at older ages. Additionally we controlled duration of follow-up and included its interactions with number of assessments, hypothesizing that those who participated for longer durations were healthier in general than those with shorter durations of follow-up, leading to different learning effects. The main results remained un-

changed and similar differences as reported in table 2 were found in practice effects between survivors and decedents (results of the additional analyses can be found in table e-1 on the *Neurology*[®] Web site at www.neurology.org).

Next, we examined change point models limiting the sample to decedents (table 3). Model 1 and 2 presents results with and without controlling for practice effects, respectively. After controlling for practice effects, terminal cognitive decline was first observed in language function (9.7 years before death, CI 8.2–unknown) and executive function (9.7 years, CI 8.0–unknown), followed, in order, by speed (9.4 years, CI 5.7–13.0), memory (7.5 years, CI 5.2–9.9), and learning (7.4 years, CI 5.4–8.9). The upper limit of the CIs for executive and language functions could not be observed in our current

Table 2 Results of mixed-effects models with penalized linear spline (n = 1,230)

Outcome ^a (domain-specific cognitive functions)	Learning coefficient (SE)	Memory coefficient (SE)	Language coefficient (SE)	Psychomotor speed coefficient (SE)	Executive functions coefficient (SE)
Practice effects					
1st assessment	(reference)	(reference)	(reference)	(reference)	(reference)
2nd assessment (n = 989)	0.135 ^b (0.029) (p < 0.001)	0.194 ^b (0.030) (p < 0.001)	0.027 (0.028) (p = 0.35)	0.103 ^c (0.042) (p = 0.02)	0.006 (0.028) (p = 0.85)
3rd assessment (n = 830)	0.287 ^b (0.039) (p < 0.001)	0.299 ^b (0.040) (p < 0.001)	0.085 ^c (0.038) (p = 0.03)	0.013 (0.054) (p = 0.81)	0.066 (0.039) (p = 0.10)
4th assessment (n = 709)	0.443 ^b (0.051) (p < 0.001)	0.384 ^b (0.052) (p < 0.001)	0.107 ^c (0.050) (p = 0.04)	0.033 (0.068) (p = 0.63)	0.093 (0.052) (p = 0.08)
5th assessment (n = 584)	0.501 ^b (0.063) (p < 0.001)	0.488 ^b (0.065) (p < 0.001)	0.132 ^c (0.063) (p = 0.04)	0.060 (0.084) (p = 0.48)	0.092 (0.066) (p = 0.17)
6th assessment (n = 454)	0.559 ^b (0.077) (p < 0.001)	0.471 ^b (0.079) (p < 0.001)	0.097 (0.077) (p = 0.21)	−0.076 (0.101) (p = 0.45)	0.022 (0.081) (p = 0.79)
Interaction of death and practice effects					
1st assessment	10.851 ^{c,d} (p = 0.05)	5.345 ^d (p = 0.38)	7.872 ^d (p = 0.16)	3.451 ^d (p = 0.63)	13.096 ^{c,d} (p = 0.02)
2nd assessment	(reference)	(reference)	(reference)	(reference)	(reference)
3rd assessment	−0.061 (0.042) (p = 0.15)	−0.054 (0.043) (p = 0.21)	−0.000 (0.041) (p = 0.99)	−0.092 (0.061) (p = 0.14)	−0.031 (0.041) (p = 0.45)
4th assessment	−0.170 ^b (0.055) (p < 0.01)	−0.086 (0.056) (p = 0.12)	−0.094 (0.053) (p = 0.08)	−0.076 (0.077) (p = 0.32)	−0.126 ^c (0.055) (p = 0.02)
5th assessment	−0.171 ^c (0.070) (p = 0.02)	−0.086 (0.071) (p = 0.23)	−0.069 (0.068) (p = 0.32)	−0.090 (0.096) (p = 0.35)	−0.173 ^c (0.071) (p = 0.02)
6th assessment	−0.240 ^b (0.088) (p < 0.01)	−0.194 ^c (0.090) (p = 0.03)	−0.042 (0.087) (p = 0.63)	−0.168 (0.121) (p = 0.17)	−0.306 ^b (0.091) (p < 0.001)
Education: high school or more vs less than high school (reference group)	−0.236 ^c (0.116) (p = 0.04)	−0.130 (0.118) (p = 0.28)	−0.201 (0.114) (p = 0.08)	−0.112 (0.158) (p = 0.48)	−0.256 ^c (0.119) (p = 0.03)
Sex: female	0.430 ^b (0.038) (p < 0.001)	0.406 ^b (0.040) (p < 0.001)	0.362 ^b (0.039) (p < 0.001)	0.425 ^b (0.049) (p < 0.001)	0.517 ^b (0.042) (p < 0.001)
Recruitment status: volunteer	0.463 ^b (0.038) (p < 0.001)	0.412 ^b (0.039) (p < 0.001)	−0.028 (0.038) (p = 0.47)	0.134 ^b (0.048) (p < 0.01)	0.104 ^c (0.041) (p = 0.01)
	0.127 ^b (0.048) (p = 0.01)	0.168 ^b (0.050) (p < 0.001)	0.152 ^b (0.050) (p < 0.01)	0.252 ^b (0.062) (p < 0.001)	0.187 ^b (0.053) (p < 0.001)

^a z-Transformed score using the overall sample of Monongahela Valley Independent Elders Survey (MoVIES) cohort at baseline.^b p < 0.01.^c p < 0.05.^d Likelihood ratio test for a group of variables based on the maximum likelihood estimations.

Table 3 The change point model for decedents (n = 613)

	Learning ^a		Memory ^a	
	Model 1 (95% CI)	Model 2 (95% CI)	Model 1 (95% CI)	Model 2 (95% CI)
Change point: years before death	5.25 (1.25, 8.25)	7.41 (5.41, 8.91)	5.08 (1.29, 7.98)	7.58 (5.25, 9.91)
Age slope	−0.011 ^b (−0.019, −0.004)	−0.031 ^b (−0.041, −0.022)	−0.014 ^b (−0.020, −0.006)	−0.035 ^b (−0.045, −0.026)
Additional decline in slope after the change point	−0.021 ^c (−0.039, −0.002)	−0.047 ^b (−0.064, −0.031)	−0.018 ^c (−0.037, 0.001)	−0.041 ^b (−0.058, −0.025)
Assessment				
1st assessment		(reference)		(reference)
2nd assessment		0.106 ^b (0.045, 0.167)		0.170 ^b (0.107, 0.232)
3rd assessment		0.200 ^b (0.119, 0.281)		0.291 ^b (0.208, 0.373)
4th assessment		0.419 ^b (0.309, 0.528)		0.434 ^b (0.322, 0.545)
5th assessment		0.477 ^b (0.331, 0.623)		0.491 ^b (0.342, 0.640)
6th assessment		0.597 ^b (0.396, 0.798)		0.588 ^b (0.383, 0.793)
Education: high school or more (vs less than high school as a reference group)	0.475 ^b (0.363, 0.588)	0.430 ^b (0.320, 0.541)	0.468 ^b (0.353, 0.584)	0.415 ^b (0.302, 0.528)
Sex: female	0.359 ^b (0.247, 0.471)	0.358 ^b (0.249, 0.468)	0.312 ^b (0.197, 0.428)	0.314 ^b (0.202, 0.427)
Recruitment status: volunteer	0.228 ^c (0.046, 0.410)	0.216 ^c (0.039, 0.393)	0.242 ^b (0.054, 0.429)	0.227 ^b (0.046, 0.408)

—Continued

Abbreviations: CI = confidence interval; UK = unknown due to left censoring.

^a z-Transformed score using the overall sample at baseline. Model 1: controlling for sex, education, and sampling group (volunteer vs random). Model 2: controlling for sex, education, sampling group (volunteer vs random), and 5 dummy variables indicating the number of assessments.^b $p < 0.01$.^c $p < 0.05$.

data; potentially, if the cohort had been followed longer, earlier change points might have been observed. Without controlling for practice effects, the inflection points occurred closer to death for learning, memory, and language functions.

DISCUSSION Although practice effects have been studied intensively in the psychological literature,^{11,29–31} their influence on terminal declines has not been established. Among older adults remaining free from dementia during 14 years of observation, we found the rate of age-associated decline in all examined cognitive domains was relatively similar between those who survived and those who died during follow-up. However, we observed substantial differences in the trajectories of practice effects between the 2 groups. Decedents showed smaller practice effects compared with survivors in learning and executive functions.

Previous studies have shown that the amount of practice effect is different between individuals with mild cognitive impairment (MCI) and those who are cognitively intact,³² as well as between individuals who go on to develop MCI and those who remain cognitively intact.^{9,10} Although the endpoint in our analysis is death, rather than the incidence of MCI or dementia, the biological aging process leading to death could be accompanied by a similar pathologic burden as that in dementing diseases, suppressing practice effects at their earliest stage. In fact, in the

Religious Orders Study,⁴ age-related decline in cognitive function was mainly attributable to the same neurodegenerative pathology traditionally associated with dementia. Neurofibrillary tangles, cerebral infarction, and neocortical Lewy bodies all contributed to gradual age-related cognitive decline, while little age-related decline was observed in the absence of these lesions. That is, either “normal” cognitive aging (pathology-free cognitive decline) might not exist, or, what we consider normal cognitive aging may itself be a reflection of degenerative or vascular burden. Terminal decline may reflect presymptomatic disease which did not cross the threshold into dementia before the individual died.

We observed differences in practice effects between survivors and decedents mainly in learning and executive functions, but not in memory. It is likely that practice effects are dependent on implicit or procedural abilities reflected by global brain dysfunction, rather than explicit or declarative memory, which is dependent on medial temporal lobe structures such as the hippocampus. Possibly, global brain dysfunction indicated by deficits in practice effects is the outcome of the early stages of Alzheimer disease (AD)- or vascular-related pathology.³³

Limiting the sample to those who died during follow-up, we found language and executive functions had inflection points almost 10 years before death, followed closely by psychomotor speed at

Table 3 Continued

Psychomotor speed ^a		Executive ^a		Language ^a	
Model 1 (95% CI)	Model 2 (95% CI)	Model 1 (95% CI)	Model 2 (95% CI)	Model 1 (95% CI)	Model 2 (95% CI)
8.58 (4.58, 12.75)	9.41 (5.75, 13.08)	9.75 (8.08 – UK)	9.75 (8.08 – UK)	6.08 (2.91, 10.7)	9.75 (8.25 – UK)
–0.048 ^b (–0.058, –0.038)	–0.052 ^b (–0.064, –0.041)	–0.029 ^b (–0.038, –0.021)	–0.032 ^b (–0.041, –0.022)	–0.030 ^b (–0.037, –0.022)	–0.037 ^b (–0.047, –0.027)
–0.038 ^b (–0.054, –0.022)	–0.045 ^b (–0.064, –0.026)	–0.033 ^b (–0.044, –0.022)	–0.038 ^b (–0.053, –0.022)	–0.037 ^b (–0.053, –0.021)	–0.048 ^b (–0.063, –0.032)
	(reference)		(reference)		(reference)
	0.061 (–0.022, 0.145)		0.021 (–0.037, 0.079)		0.086 ^b (0.026, 0.146)
	0.055 (–0.055, 0.165)		0.050 (–0.032, 0.133)		0.129 ^b (0.045, 0.213)
	0.136 (–0.011, 0.284)		0.098 (–0.017, 0.214)		0.258 ^b (0.142, 0.374)
	0.154 (–0.042, 0.351)		0.028 (–0.126, 0.182)		0.380 ^b (0.226, 0.535)
	0.138 (–0.130, 0.406)		0.069 (–0.138, 0.277)		0.245 ^c (0.037, 0.453)
0.428 ^b (0.296, 0.506)	0.418 ^b (0.285, 0.551)	0.477 ^b (0.364, 0.590)	0.470 ^b (0.357, 0.583)	0.408 ^b (0.293, 0.523)	0.388 ^b (0.273, 0.503)
0.117 (–0.014, 0.249)	0.113 (–0.018, 0.245)	0.045 (–0.066, 0.158)	0.042 (–0.069, 0.155)	–0.129 ^c (–0.244, –0.013)	–0.140 ^c (–0.254, –0.026)
0.315 ^b (0.579, 0.630)	0.310 ^b (0.098, 0.522)	0.368 ^b (0.187, 0.549)	0.366 ^b (0.185, 0.547)	0.319 ^b (0.131, 0.507)	0.306 ^b (0.120, 0.492)

around 9 years before death. Accelerations in decline in memory and learning occurred somewhat later, around 7 years before death. Intriguingly, when practice effects were not controlled for, the inflection points were found to occur closer to death for learning, memory, and language functions. This finding suggests that practice effects could be masking true declines. A Swedish population-based study, which examined dementia-free elderly in the Göteborg cohort followed for over 20 years,³ showed that onset of terminal decline was detectable 6.6 years prior to death for verbal ability measured by the Synonyms test, 7.8 years for spatial ability by the Block Design test, and 14.8 years for perceptual speed by the Figure Identification test. Results are difficult to compare between that study and ours because of differences in the neuropsychological tests used as well as in other variables controlled in the models. However, both studies, with their relatively long follow-up periods, suggest that terminal decline occurs even a decade or more before death in some domains, with most inflection points occurring earlier than 6 years before death.

Neuropsychological tests that are more sensitive than others to subtle declines in cognition might also show earlier inflection points in relation to death. In the population-based longitudinal Kungsholmen project,⁷ the impending death group had a faster rate of decline in Word Recognition and Category Fluency during the 3 years before death, compared with the survivors, even after excluding preclinical cases of

dementia. In our study, language function, which included a Category Fluency test, showed the earliest inflection point along with executive function measured by Trails B, after controlling for practice effects. Interestingly, Category Fluency test was found useful in identifying preclinical dementia in several studies,^{10,34,35} and Trails B has also been found to predict subsequent onset of dementia.³⁶ Thus, these 2 tests seem to be able to identify subtle changes associated either with terminal decline or preclinical dementia. This finding also adds weight to the speculation that AD-related pathology might have been present among our deceased participants even though they did not develop dementia or cognitive impairment during life. Since degenerative pathology can be present even a decade or more before the clinical symptoms of AD appear,^{37–39} it is likely that our dementia-free cohort included individuals with presymptomatic disease.

Advantages of this study include a relatively large cohort followed for up to 14 years, with a low rate of attrition from causes other than mortality. However, an even larger sample followed for even longer would have allowed us to estimate the upper confidence bounds for terminal decline in executive and language functions. Our use of standardized, validated neuropsychological measures is also a strength, although tests more sensitive to subtle impairments might have detected even earlier inflection points. A methodologic innovation is our use of mixed-effects models with penalized linear spline to decompose

longitudinal trajectories of cognitive functions into practice effect and age-associated decline, and controlling for practice effects in change point models. Limitations include lack of autopsy data to support our speculations. It is possible that we misclassified some very mild cases of dementia as normal. Statistical significance at the population level does not necessarily reflect clinical significance at the individual level. Change points and their associated accelerations in slopes identified in our data require further steps to translate these findings into a potential prognostic indicator among dementia-free older adults. We suggest, but cannot conclude definitively, that the separation of practice effects from age-associated decline can help identify preclinical dementia.

Longitudinal cognitive trajectories are combinations of age-associated declines (which may partly reflect presymptomatic disease), practice effects, and the duration of survival and follow-up. Careful considerations of each component are required in studying trajectories of cognitive functions. Further studies to examine normal vs pathologic cognitive trajectories could aid in identifying early signs of presymptomatic dementia.

AUTHOR CONTRIBUTIONS

Dr. Dodge: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, statistical analysis, study supervision, obtaining funding. C.-N. Wang: analysis or interpretation of data, statistical analysis. Dr. Chang: analysis or interpretation of data, statistical analysis. Dr. Ganguli: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, obtaining funding.

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DISCLOSURE

Dr. Dodge serves on the statistical advisory board for *International Psychogeriatrics* and receives research support from the NIH/NIA. C.-N. Wang reports no disclosures. Dr. Chang serves on the statistical advisory board for *International Psychogeriatrics*. Dr. Ganguli serves as an Associate Editor for the *Journal of the American Geriatrics Society* and *International Psychogeriatrics* and receives research support from the NIH/NIA.

APPENDIX

This appendix provides the mathematical form of the model used to determine the trajectories of the cognitive test scores. Mean cognitive scores do not necessarily decline in a linear fashion, and may not be captured by a simple polynomial model. A penalized linear spline model is often used. Essentially, this model divides the time axis into a series of segments and treats the trend over time as though it comprises piecewise linear trends, having different slopes within each segment but joined or tied together at fixed times.^{27,40} To estimate and compare the age-associated trajectories between the survivors and the decedents, we used mixed-effect models with penalized linear spline, which had the following form:

$$Z_{ij} = f_{\text{Decedent}}(\text{Age}_{ij}) + \beta_{\text{assessment}} \times \text{Assessment}_{ij} + \beta_{\text{assessment_dead}} \times \{\text{Dead}_i \times \text{Assessment}_{ij}\} \\ + \beta_{\text{female}} \times \text{Female}_i + \beta_{\text{edu}} \times \text{Education}_i + \beta_{\text{vol}} \times \text{Volunteer}_i + U_i + \epsilon_{ij} \quad (1)$$

where

$$f_{\text{Decedent}}(\text{Age}_{ij}) = \beta_0 + \beta_1 \times \text{Age}_{ij} + \mu_1 \times (\text{Age}_{ij} - \kappa_1)_+ + \mu_2 \times (\text{Age}_{ij} - \kappa_2)_+ + \dots + \mu_K \times (\text{Age}_{ij} - \kappa_K)_+ + \text{Dead}_i \times \{\gamma_0 + \gamma_1 \times \text{Age}_{ij} + \omega_1 \times (\text{Age}_{ij} - \kappa_1)_+ + \omega_2 \times (\text{Age}_{ij} - \kappa_2)_+ + \dots + \omega_K \times (\text{Age}_{ij} - \kappa_K)_+\}, \\ U_i \sim N(0, \sigma^2_U), \epsilon_{ij} \sim N(0, \sigma^2_\epsilon), \mu_k \sim N(0, \sigma^2_\mu), \omega_k \sim N(0, \sigma^2_\omega) \\ \text{and } (x)_+ = \max(0, x).$$

Z_{ij} = domain-specific Z-normalized cognitive test scores at the j-th interview for a subject i; Age_{ij} = age at the j-th interview for a subject i; Assessment_{ij} = 5 dummy variables indicating 2nd, 3rd, 4th, 5th, 6th assessment for a subject i; Female_i = female is coded as 1, male as 0; Education_i = those with high school or higher education coded as 1, 0 otherwise; Volunteer_i = coming from volunteer sample is coded as 1, 0 from random sample; Dead_i is coded as 1 if died during the follow-up, 0 survived. f is a smooth function which reflects the age effect on cognitive test. K is the number of knot. κ_k is the locations for the k-th knot and these locations are selected so that these K knots are equally distributed across the whole observed age range. In this model, we allow the function f is different for the decedent and the survivor by including interaction terms of death indicator and spline functions.

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