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Effects of Sex and Education on Cognitive Change Over a 27-Year Period in Older Adults: The Rancho Bernardo Study

Emilie T. Reas, PhD[1], **Gail A. Laughlin, PhD**[2], **Jaclyn Bergstrom, MS**[2], **Donna Kritz-Silverstein, PhD**[2], **Elizabeth Barrett-Connor, PhD**[2], and **Linda K. McEvoy, PhD**[1,2]

[1]Department of Radiology, University of California, San Diego

[2]Department of Family Medicine and Public Health, University of California, San Diego

Abstract

Objective—This study investigated how cognitive function changes with age and whether rates of decline vary by sex or education in a large, homogenous longitudinal cohort characterized by high participation rates, long-duration of follow-up, and minimal loss to follow-up.

Design/Setting/Participants—Between 1988–2016, 2,225 community-dwelling participants of the Rancho Bernardo Study, aged 31–99 at their initial cognitive assessment, completed neuropsychological testing approximately every four years, over a maximum 27-year follow-up.

Measurements—Linear mixed effects regression models defined sex-specific cognitive trajectories, adjusting for education and retest effects.

Results—Significant decline across all cognitive domains began around age 65 and accelerated after age 80. Patterns of decline were generally similar between sexes, although men declined more rapidly than women on the global function test. Higher education was associated with slower decline on the tests of executive and global functions. After excluding 517 participants with evidence of cognitive impairment, accelerating decline with age remained for all tests, and women declined more rapidly than men on the executive function test.

Conclusions—Accelerating decline with advancing age occurs across multiple cognitive domains in community-dwelling older adults, with few differences in rates of decline between men and women. Higher education may provide some protection against executive and global function decline with age. These findings better characterize normal cognitive aging, a critical prerequisite for identifying individuals at risk for cognitive impairment, and lay the groundwork for future studies of health and behavioral factors that affect age-related decline in this cohort.

Address correspondence to Dr. Emilie T. Reas, Department of Radiology, Mail code 0841, UCSD, 9500 Gilman Dr., La Jolla, CA 92093-0841; ereas@ucsd.edu.

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Keywords

Cognitive aging; executive function; sex differences; education; cognitive decline

Objective

With the rapid aging of the population, there is need to better characterize the nature of cognitive changes that occur with normal aging. Such information is needed to improve policies, programs, and services aimed at older adults, and to better inform the public on the type and magnitude of cognitive changes that can be expected in typical aging (1).

While cross-sectional studies inform on cognitive abilities that differ by age, longitudinal studies are necessary to better understand change within individuals. Although few studies have followed older adults for prolonged periods (2–4), some large cohort studies have shown that typical aging is accompanied by declines in processing speed, executive function and memory, while semantic knowledge is relatively spared (2–6).

Longitudinal studies have not consistently accounted for performance improvements due to repeated exposure to the test, which may mask age-related decline (7), or for inclusion of individuals with incipient dementia. Because individuals with neurodegenerative diseases may experience accelerated cognitive decline preceding diagnosis (8, 9), including cognitively impaired individuals may inflate estimates of “normal” age-related change.

There is also controversy over whether men and women experience similar rates of cognitive decline with age. Some studies have reported that women decline more rapidly than men and may be more likely to suffer from dementia (3, 4, 10, 11), while others report greater risk of cognitive impairment and faster decline for men (12–15). It is also unclear whether higher educational attainment is associated with reduced rates of cognitive decline. Individuals with higher education demonstrate better cognitive function and are at lower risk for dementia (16, 17), but it remains uncertain how education alters decline in normal aging (4, 18–21).

We examined trajectories of cognitive aging in the Rancho Bernardo Study (RBS) of Healthy Aging—a large, well-characterized cohort of older adults with 27 years of cognitive function follow-up. High participation rates, minimal loss to follow-up, and homogeneity of ethnicity, socioeconomic status and access to healthcare enabled us to investigate effects of sex and education, while accounting for retest effects and assessing the influence of incipient dementia on age-related cognitive change.

Methods

Study Participants

The RBS is a population-based longitudinal cohort study established between 1972–1974 when 82% of adults aged 30 years or older living in the southern California community of Rancho Bernardo (N = 6,629) were enrolled in the NIH Lipid Research Clinics Prevalence Study of heart disease risk factors. Half the participants were age 60 and older, most were

married, of Northern European ancestry, and middle to upper-middle class; more than 80% had health insurance and at least a high school education.

Cognitive function testing was introduced in the 1988–1992 visit and included in all subsequent visits. The most recent visit occurred between 2014–2016, providing a maximum of seven visits at approximate four-year intervals over 27 years.

Exclusion criteria included being non-ambulatory or residing in a care facility. For inclusion in the current study, participants must have attended at least one visit in which cognitive function was assessed and have supplied information on educational attainment (N = 2,225; 59% women). At initial cognitive assessment participants ranged in age from 31–99 years (mean ± SD 70.9 ± 10.6); only 2% (N = 46) were <50 years old; 84% were 60 or older. Because not all participants attended every visit, their initial cognitive assessment could have occurred at any visit, except the most recent (the seventh visit), for which prior cognitive assessment was an inclusion criterion.

Study procedures were approved by the University of California, San Diego (UCSD) Human Research Protections Program Board, and all participants provided informed written consent prior to each visit.

Cognitive Assessment

A standardized cognitive test battery was administered by a trained interviewer, who used consistent administration and scoring procedures across visits. Tests were selected in conjunction with the UCSD Alzheimer's Disease Research Center in 1988 to incorporate those most likely to be sensitive to aging, and to assess multiple cognitive domains. The Mini-Mental State Exam (MMSE), the Trail Making Test, Part B ("Trails B") of the Halstead-Reitan Battery, and category fluency were administered at all visits. The MMSE assesses orientation, attention, language and memory and provides a measure of global cognition, with a maximum score of 30. Trails B evaluates visuomotor tracking, psychomotor processing speed and executive function, requiring participants to connect a sequence of alternating letters and numbers in ascending order. It is scored as seconds to complete with a maximum of 300 seconds. Category fluency, a test of verbal semantic fluency, requires participants to name as many unique animals as possible within 60 seconds. The Buschke-Fuld Selective Reminding test, a verbal episodic memory test, was administered at five visits. Participants are read a list of ten words and asked to recall as many as possible. They are reminded of omitted words and asked to recall all words again; this procedure is repeated six times. Total number of correctly recalled words across the six trials (maximum score of 60) was analyzed. Due to time constraints, this test was omitted from two visits, and an alternate word list was used in one visit.

Participant Characteristics

Education level was categorized into high school or less versus some college or more. Height and weight were measured and body mass index (BMI, kg/m^2) was calculated to estimate obesity. Information on smoking (never/past/current), exercise three or more times per week (no/yes), and alcohol consumption (average number of drinks per week), was obtained from standard questionnaires at each visit.

Statistical Analysis

Participant characteristics at the first cognitive assessment were compared between men and women using independent t-tests for continuous variables and chi-squared tests for categorical variables.

Sex-specific mixed-effects regression models were used to model rates of change with age for each test. Mixed effects models handle missing data and inconsistent measurement intervals within and across participants and account for within-subject correlation across repeated measures. Models included intercept and age as random effects, which allow individual subject baseline levels (intercept) and slopes to vary randomly about the mean trajectory described by the fixed effect terms. Models also included fixed effects of education and an age by education interaction term. Retest effects were evaluated by including a retest term. Based on prior findings, we assumed that the largest effect of retest would occur between the first and second assessments (22). Thus, the retest variable was defined as zero on the participant's first cognitive assessment and as one on subsequent assessments (23), and was retained in the final model only if it indicated significant improvement in performance for one or both sexes. Models included both linear and quadratic age terms. To determine whether trajectories of change differed significantly by sex, data from men and women were combined and mixed effects models included a sex term and an age by sex interaction term. Secondary models additionally adjusted for exercise, smoking and alcohol consumption as time-varying covariates.

To further explore quadratic effects of age on cognitive function, and to enable comparison of magnitudes of change over time across ages and cognitive domains, standardized change rates were computed for ages 50–100 and for the sub-ranges 50–64, 65–79 and 80–100 using predicted scores from the sex-specific mixed effects models. The difference in predicted scores between the youngest and oldest ages within each age range was divided by the sex-specific standard deviation of baseline scores for that test, and by number of decades per age interval, to yield an estimate of linear change over time, expressed as change per decade in standard deviations.

All analyses were repeated after excluding individuals with evidence of cognitive impairment, as defined by an MMSE score greater than two standard deviations below sex-, age-, and education-adjusted means at either first or last cognitive assessment, based on normative data from the National Alzheimer's Coordinating Center Uniform Data Set (24).

No adjustment was made for multiple comparisons. *P*-values for two-sided tests are shown; $p < 0.05$ was considered statistically significant. Data were analyzed using SAS v9.3 (SAS Institute, Cary, NC).

Results

Participant Characteristics

Participant characteristics and age- and education-adjusted cognitive test scores at first cognitive assessment are shown in Table 1. Men and women did not differ in age (mean 71

years). More men than women were college-educated, former smokers, and reported regular exercise. Men also had higher BMIs and consumed more alcohol than women.

At first cognitive assessment, men performed better than women on the Trails B and category fluency tests, whereas women scored higher than men on the MMSE and Buschke total recall.

On average, participants completed three cognitive assessments (20% completed five or more, 27% three or four, 20% two, and 32% one). Of those who completed more than one assessment, the average number of assessments was 3.7 and the average follow-up period was 11 years (maximum 27 years). There was no significant difference in number of assessments ($t(2223) = 0.60$; $p = 0.55$), or follow-up time ($t(2223) = 0.20$; $p = 0.84$) between men and women. Age at baseline negatively correlated with total follow-up ($t(2223) = -0.49$; $p < 0.001$); those who participated longer were younger at entry. Individuals with at least some college completed more assessments than those who did not ($t(2223) = 3.22$; $p = 0.001$). After adjusting for age and education, individuals who participated in fewer assessments performed more poorly at baseline on all cognitive tests (Supplemental Table 1). The most common reasons for non-participation were death (67% mortality to date) or no longer dwelling locally. Average age at last assessment was 78 years and did not differ between men and women. At final cognitive assessment, 48% of participants were between 80–100 years.

Effects of Sex on Cognitive Change

Figure 1A shows modeled sex-specific trajectories of performance with age for each test (raw data from a subsample of participants are shown in Supplemental Figure 1). Parameter estimates of mixed effects models displayed in Figure 1A are presented in Table 2. For both sexes, performance on all tests showed significant decline with age, which accelerated with advancing age. Significant positive retest effects were observed for the MMSE and Trails B tests (Table 2); therefore, the retest term was retained in the models for these tests.

Trajectories of cognitive performance appear qualitatively similar for men and women. However, when men and women were included in the same model, there was a significant age by sex interaction ($t(3943) = 2.95$; $p = 0.003$) for the MMSE. There was a significant main effect of sex for Buschke total recall ($t(2082) = 6.58$; $p < 0.001$), with women performing better than men across the age span, but no sex difference in the rate of change. There were no significant main effects of sex or age by sex interactions for Trails B or category fluency.

Figure 1B shows modeled sex-specific trajectories of cognitive function with age after excluding 517 individuals (222 women) with cognitive impairment; parameter estimates are presented in Table 2. Of the excluded participants, 324 (121 women) met criteria for cognitive impairment at initial assessment, and 193 (101 women) developed cognitive impairment by their final assessment. Compared to individuals without cognitive impairment, those with cognitive impairment were older at their initial visit (69.1 ± 10.5 versus 76.7 ± 8.8 years, $t(2223) = 14.98$; $p < 0.001$) and more likely to be men (32% of men versus 17% of women were impaired, $x^2(1) = 69.80$; $p < 0.001$).

After exclusion of impaired individuals, significant decline remained for all tests, although rates of decline were slower (Figure 1B and Table 2), and there was no longer a significant age by sex interaction for the MMSE. However, the age by sex interaction attained significance for Trails B ($t(3202) = 2.58$; $p = 0.01$), with women demonstrating more rapid decline than men. Women continued to out-perform men on Buschke total recall ($t(1598) = 6.05$; $p < 0.001$), with no difference in rates of change ($t(1753) = 0.72$; $p = 0.47$). When models additionally adjusted for exercise, smoking and alcohol consumption, the age by sex interaction for Trails B ($t(3180) = 2.62$; $p < 0.009$) and the main effect of sex for Buschke total recall ($t(1597) = 6.11$; $p < 0.001$) were unchanged. No other effects of sex or age by sex interactions were significant among cognitively intact participants.

Rates of Change in Middle and Late Life

To further explore the significant quadratic effects of age, Table 3 shows standardized change rates on each test for the age range 50–100 years and for the sub-intervals 50–64, 65–79 and 80–100 years. All tests demonstrated accelerated decline with age, with the greatest overall change on Trails B, followed by Buschke total recall. Decline on all tests was minimal before age 65 and most rapid after age 80.

Effects of Education on Cognitive Change

Figure 2 shows performance trajectories as a function of education in the full cohort. For both sexes, higher education was associated with slower rates of decline on the MMSE and Trails B (Table 2). There were no significant age by education interactions for either sex for category fluency or Buschke total recall. After excluding individuals with cognitive impairment, the age by education interaction remained significant on Trails B for both men and women.

Conclusions

This study characterized trajectories of cognitive performance from middle to older age on a range of cognitive domains within a large, relatively homogeneous sample of community-dwelling adults followed for nearly three decades. We observed significant age-related decline, and acceleration of decline with age, on tests of global cognitive function (MMSE), executive function (Trails B), verbal fluency (category fluency) and verbal episodic memory (Buschke total recall). More men than women met criteria for cognitive impairment. After excluding cognitively impaired individuals, age-related decline on all tests remained significant and a sex difference in executive function emerged, with women declining more rapidly than men. Higher education was associated with slower decline in global and executive functions for both sexes.

These findings add to a growing body of literature indicating that typical aging is associated with decline in numerous cognitive abilities (2, 5, 6), with decline emerging around age 65 (25) and accelerating with age (4, 5, 7). Because risk of neurodegenerative disorders increases with age, it is often unclear whether cognitive decline in older age reflects typical aging or latent neurodegenerative disease (26). Although participants in our study were not evaluated for dementia, we attempted to control for effects of incipient dementia by

performing a sensitivity analysis after excluding individuals with cognitive impairment. This attenuated rates of decline but performance on all tests continued to show significant, accelerating decline with age.

Steepest decline was observed on Trails B, an executive function test that stresses psychomotor processing speed and mental flexibility, functions particularly vulnerable to aging (6, 27). Episodic memory, assessed with the Buschke total recall test, showed the next highest rate of decline, even after excluding cognitively impaired individuals. This is consistent with reports that episodic memory ability decreases with age even among cognitively unimpaired older adults (2, 5). Decreases in memory thus appear to be part of typical aging, and not necessarily indicative of dementia.

Performance on the MMSE, a test of global cognitive function, also showed accelerating decline with age. Consistent with the known elevated risk of cognitive impairment with age, participants who met MMSE-based criteria for cognitive impairment were older than those who remained cognitively normal. Exclusion of these individuals attenuated but did not eliminate significant age effects on the MMSE; thus decline in global cognitive function also appears to characterize typical aging.

In our sample, men were more likely to be cognitively impaired than women. The literature on sex differences in cognitive impairment and dementia risk is mixed; some studies reported no clear sex differences (28), while others found greater risk for women (29) or for men (12, 13). Differences in longevity may contribute to some prior findings, because women live longer and thus, are at greater risk for age-related diseases. However, in our study, men and women were of similar age at first and last cognitive assessment, and did not differ in length of follow-up. Thus, the sex differences observed here are less likely to have been influenced by survival bias.

When individuals with cognitive impairment were excluded, women showed steeper executive function decline than men, but rates of decline did not differ between sexes for any other test. Although several prior longitudinal studies (30–33) reported no sex difference in rates of change on a variety of cognitive tests, those studies had smaller sample sizes and shorter follow-up periods. Longitudinal studies with large samples sizes and relatively long follow-up periods have reported sex differences, but the domains affected and direction of effects differ across studies. For example, some studies have found no sex differences in change in episodic memory or executive function, but more rapid decline for men than women on general intelligence and global cognitive function (14, 15). Yet others observed steeper decline for women than men in global cognitive function and psychomotor speed (3, 4). For one of these studies (3), the sex difference emerged only after adjustment for smoking rates, which differed greatly between sexes. Adjustment for smoking, alcohol, and exercise, which differed between men and women, did not change our results.

Together, these discrepant findings do not support a strong effect of sex on trajectories of cognitive aging. Men and women differ in numerous cultural, behavioral, and health factors that are likely to influence cognitive change (10), and differences in these factors may underlie the incongruent reports across studies.

Education is one factor that differs between men and women historically and culturally, and that may influence cognitive decline. Low education level is a risk factor for dementia (17) but effects of education on cognitive decline in typical aging are less clear. Despite a consistent positive association between educational attainment and performance on a range of cognitive tests, reports on effects of education on rates of change are mixed (18–21, 34). Here, higher education was associated with better baseline performance on all cognitive tests, and with slower rates of decline in global and executive function for both men and women. If higher education and engagement in cognitively stimulating activities increase resilience to cognitive decline with age (18, 19), it is possible that the sex differences observed here in rates of executive function decline may reflect lifetime differences in exposure to cognitively demanding experiences that could arise from education-related factors such as occupational differences. Women in RBS had lower levels of employment and lower occupational status than men.

This study has several strengths and some limitations. It has one of the longest cognitive follow-up periods and includes a broad age range from middle to old age, including a large number of assessments into very late age. The homogeneity of this population, which comprised mainly white, middle-class Americans, may limit generalizability but allows assessment of sex and education effects while minimizing confounding due to socioeconomic status, ethnicity, and access to healthcare. As with all studies of aging, survivor bias or selective attrition of individuals in poorer physical or cognitive health may have attenuated estimates of decline (2, 35), but our long follow-up and continued high participation rates minimize this concern. Although our cognitive battery assessed several domains, it was by necessity brief. Multiple tests within a domain provide better sensitivity and specificity for detecting change. While the MMSE is highly sensitive to dementia, it is not sensitive to mild cognitive impairment (MCI), and thus individuals with MCI may have been included in our sub-analyses of cognitively intact individuals. Our age-based rather than time-based analytic approach, while theoretically justified given our interest in age effects on cognitive function, may inflate estimates of within-person change due to lack of convergence of cross-sectional and longitudinal age effects (36, 37). Finally, we intentionally used minimally-adjusted models to describe typical cognitive aging, and thus cannot speculate on other factors that may influence rates of decline. We previously found that cardiovascular disease risk and metabolic syndrome influence rates of decline in subsets of this cohort (38, 39), and we plan to further explore how cognitive trajectories differ by health and behavioral factors.

In summary, this study characterized trajectories of cognitive change from middle to older age in a large cohort of community-dwelling adults while considering the influence of cognitive impairment. Global cognitive function, executive function, verbal fluency and episodic memory declined with age beginning around age 65 and accelerating after age 80. Men and women showed generally similar patterns of change, and education was associated with slower global and executive function decline. These findings help to characterize cognitive aging over the latter half of the lifespan, and may support clinicians in distinguishing normal from pathological cognitive transitions with age while minimizing unwarranted concern over cognitive changes inherent to normal aging. They also point to a need for support among those of advanced age to assess when declining executive function

and memory compromise quality of life. Future studies on this cohort will examine how cognitive changes with age are influenced by health and behavior.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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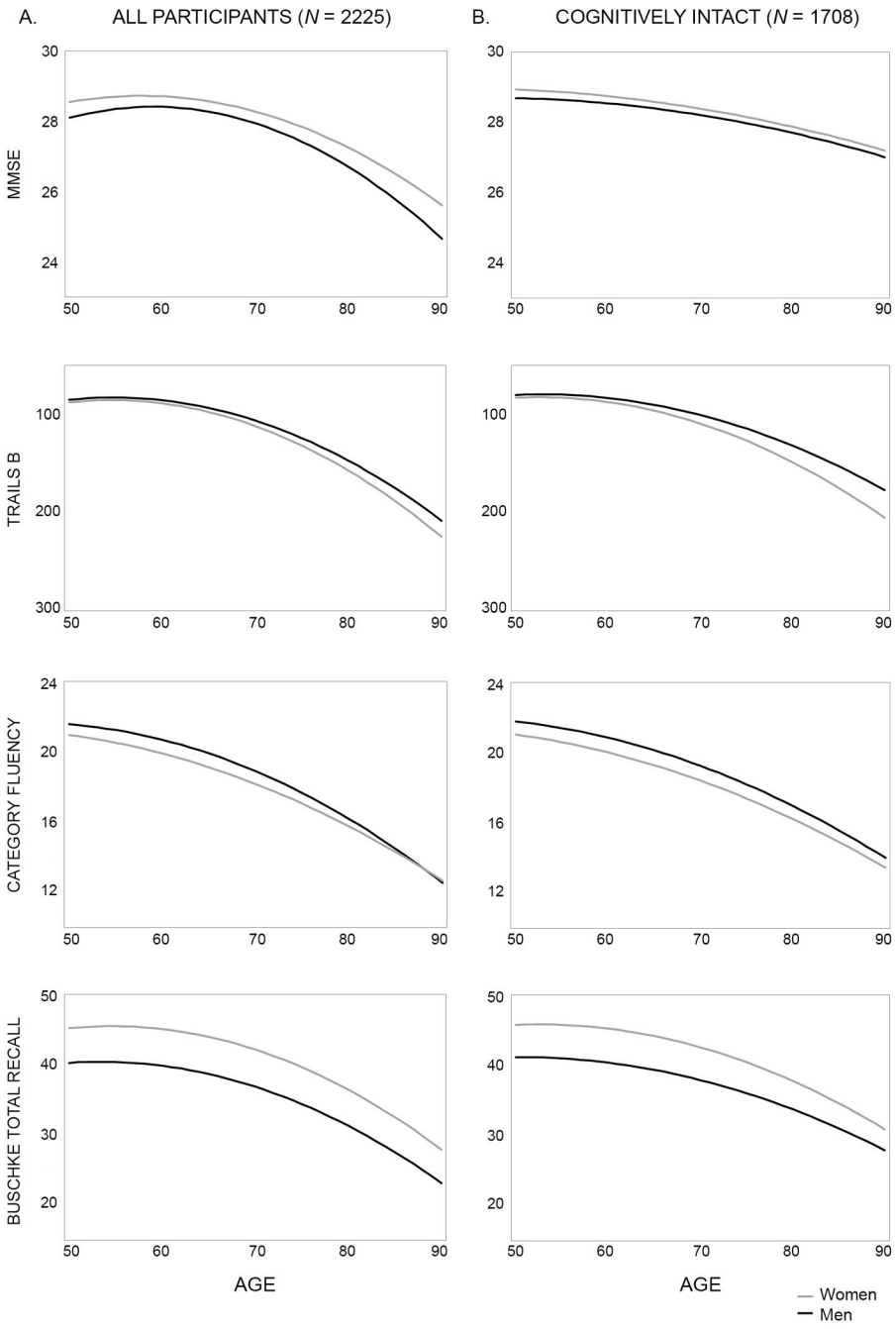

Figure 1. Cognitive trajectories by sex

Modeled trajectories for scores on each cognitive test as a function of age for men (black line) and women (gray line). Trajectories are plotted for the entire cohort (A) and for individuals without cognitive impairment (B). The y-axis for Trails B is inverted because lower scores indicate better performance.

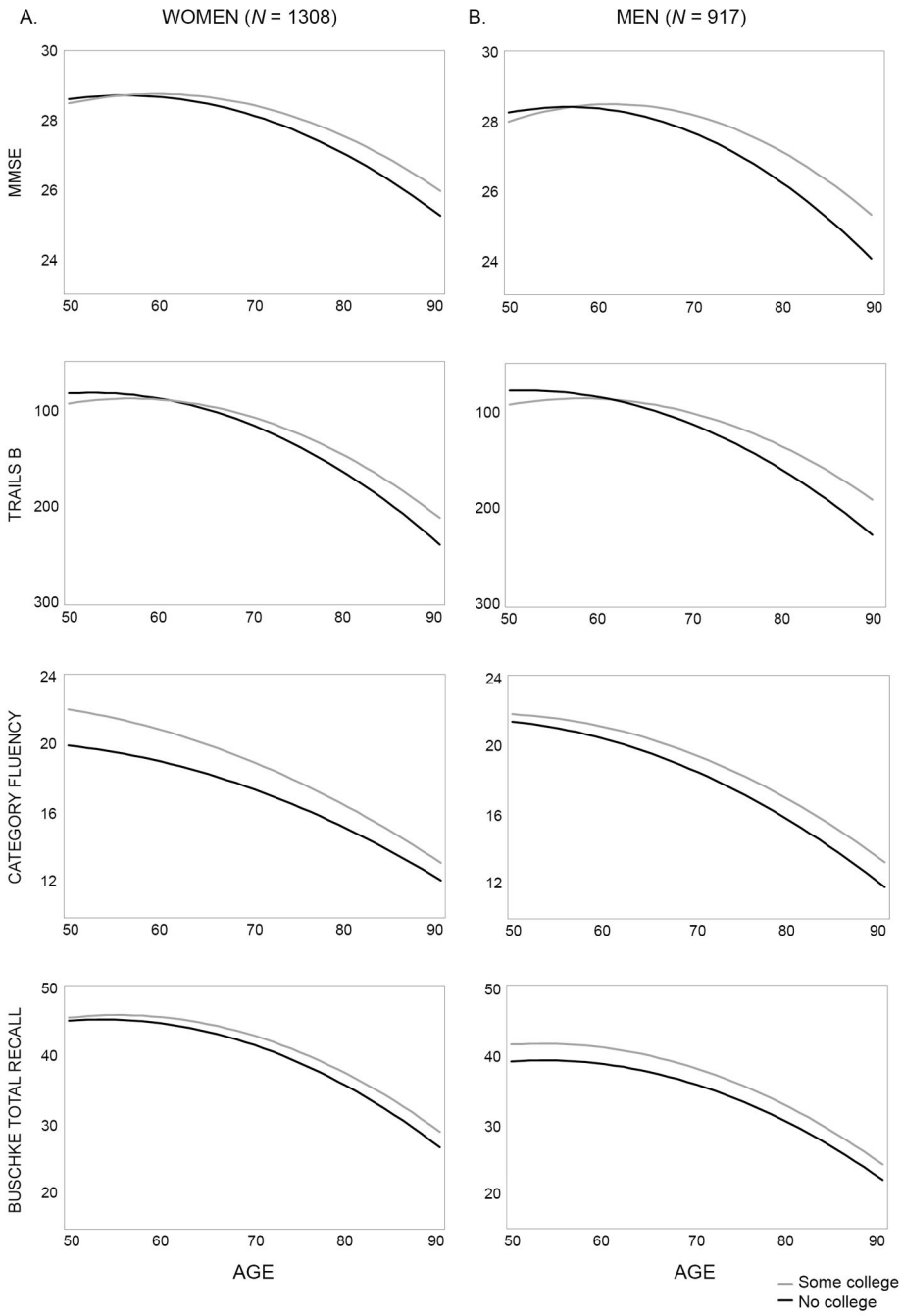

Figure 2. Cognitive trajectories by education level

Modeled trajectories for scores on each cognitive test as a function of age. Sex-specific trajectories are plotted separately for individuals with at least some college education versus those without college. The y-axis for Trails B is inverted because lower scores indicate better performance.

Table 1

Participant characteristics and cognitive test scores at first cognitive assessment [a].

	All Participants (*N* = 2225)	Women (*N* = 1308)	Men (*N*= 917)	Statistical Comparison of Sex
Age (yrs)	70.9 ± 10.6	70.6 ± 10.7	71.2 ± 10.4	$F(1, 2223) = 1.38$; $p = 0.24$
Some college education (%)	71	64	80	$x^2(1) = 68.10$; $p < 0.001$
Smoking (% former/current)	46/9	39/10	57/8	$x^2(2) = 68.00$; $p < 0.001$
Exercise (% 3+ times/week)	69	65	75	$x^2(1) = 21.92$; $p < 0.001$
BMI (kg/m^2)	25.5 ± 4.1	24.9 ± 4.3	26.4 ± 3.6	$F(1, 2223) = 75.12$; $p < 0.001$
Alcohol (drinks/week)	5.4 ± 7.2	4.2 ± 5.9	7.0 ± 8.5	$F(1, 2213) = 81.59$; $p < 0.001$
MMSE [b]	27.5 ± 2.1	27.6 ± 1.9	27.2 ± 2.3	$F(1, 2167) = 37.68$; $p < 0.001$
Trails B [b]	124.7 ± 64.4	127.6 ± 66.4	120.4 ± 61.0	$F(1, 2174)= 8.93$; $p = 0.003$
Category Fluency [b]	18.3 ± 5.2	18.1 ± 5.0	18.5 ± 5.3	$F(1, 2212)= 5.40$; $p = 0.02$
Buschke Total Recall [b]	38.6 ± 9.6	40.8 ± 9.0	35.4 ± 9.7	$F(1, 1969)= 194.98$; $p < 0.001$

[a] Values are mean ± SD unless otherwise indicated

[b] Means are adjusted for age and education

Table 2

Intercept and slope parameters (β-estimates) for each cognitive test from the sex-specific linear mixed effects regression models; *p*-values shown are from the t-tests for fixed effects.

All Participants (N = 2225)	**MMSE**		**TRAILS B**		**CATEGORY FLUENCY**		**BUSCHKE TOTAL RECALL**	
	Women	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**
Intercept	28.33	27.96	85.82	78.32	19.91	21.34	44.97	39.05
Age	0.36 **	0.51 **	−5.42	−3.29	−0.58 *	−0.54	1.05	0.90
Age²	−0.30 ***	−0.39 ***	11.06 ***	10.09 ***	−0.34 ***	−0.46 ***	−1.40 ***	−1.29 ***
Education	−0.12	−0.26	10.22 *	14.19 **	2.09 ***	0.44	0.44	2.42
Retest	0.56 ***	0.55 ***	−6.41 ***	−0.82	-	-	-	-
Age x Education	0.21 **	−0.38 **	−9.36 ***	−12.69 ***	−0.27	0.25	0.45	0.05
Cognitively Intact (N = 1708)								
Intercept	28.61	28.32	81.21	77.18	19.99	21.62	45.56	39.69
Age	−0.15 *	−0.04	0.34	0.80	−0.58 *	−0.67	0.29	0.05
Age²	−0.08 ***	−0.09 ***	8.72 ***	7.01 ***	−0.29 ***	−0.34 ***	−1.06 ***	−0.84 ***
Education	0.14	0.33	9.71 *	8.54	2.10 ***	0.33	0.37	2.92
Retest	0.53 ***	0.42 ***	−6.26 ***	−2.98	-	-	-	-
Age x Education	0.07	0.04	−9.33 ***	−9.17 ***	−0.31	0.17	0.46	−0.01

* $p < 0.05$,

** $p < 0.01$,

*** $p < 0.001$.

The intercept shows the modeled score of a 50 year old with less than a college education; the age term is the modeled change in score per ten year increase in age over age 50. Degrees of freedom for each test statistic are provided in Supplemental Table 2.

Table 3

Standardized change rates (SD per decade) for each cognitive test, stratified by age group. Sex-specific raw baseline means and standard deviations, used to compute the standardized change rate for each test, are shown at the top of each column.

	MMSE		TRAILS B [a]		CATEGORY FLUENCY		TOTAL RECALL	
All Subjects	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**
Baseline Mean (SD)	27.7 (1.9)	27.3 (2.2)	128.7 (64.9)	120.3 (60.9)	17.8 (5.0)	18.6 (5.3)	40.4 (9.0)	35.6 (9.7)
Age (yrs)								
50–100	−0.56	−0.56	0.70	0.67	−0.49	−0.52	−0.63	−0.58
50–64	0.02	0.07	0.08	0.07	−0.24	−0.20	−0.08	−0.10
65–79	−0.46	−0.46	0.59	0.57	−0.45	−0.46	−0.54	−0.50
80–100	−1.04	−1.09	1.21	1.17	−0.69	−0.78	−1.10	−0.98
Cognitively Intact								
Age (yrs)								
50–100	−0.28	−0.23	0.61	0.51	−0.44	−0.43	−0.53	−0.43
50–64	−0.12	−0.08	0.12	0.10	−0.23	−0.20	−0.11	−0.12
65–79	−0.25	−0.20	0.52	0.44	−0.41	−0.40	−0.46	−0.38
80–100	−0.41	−0.35	1.01	0.86	−0.62	−0.63	−0.88	−0.69

[a] Positive values for Trails B indicate decline, since lower scores indicate better performance.