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The Effect of Maintaining Cognition on Risk of Disability and Death

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Abstract

Objectives—To determine whether long-term maintenance of cognition is associated with health advantages such as lower mortality or incident disability in older adults.

Design—Longitudinal cohort study

Setting—Community clinics at two sites

Participants—Two thousand seven hundred thirty-three adults with a mean age of 74 at baseline and 80 at follow-up.

Measurements—Cognitive function was assessed with the Modified Mini-Mental State Examination (3MS), a test of global cognition, at least two times. Three cognitive groups were defined based on 4-year participant-specific slopes (“maintainers”: slopes of ≥ 0 ; “minor decliners”: slopes < 0 but no more than 1 standard deviation (SD) below the mean; “major decliners”: slopes > 1 SD below the mean). Whether the cognitive groups differed in mortality and incident disability during the subsequent 3 years was determined.

Results—Nine hundred eighty-four (36%) participants were maintainers, 1,314 (48%) were minor decliners, and 435 (16%) were major decliners. Maintainers had lower mortality (7% vs 14%, hazard ratio (HR)=0.48, 95% confidence interval (CI)=0.36–0.63) and incident disability (22% vs 29%, HR=0.74, 95% CI=0.62–0.89) than minor decliners. After adjustment for age, race, sex, education, apolipoprotein E $\epsilon 4$, depression, body mass index, stroke, hypertension, and diabetes mellitus, these differences remained. As expected, major decliners had greater mortality (20%) and incident disability (40%) than minor decliners.

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Conclusion—A substantial proportion of older adults maintain cognitive function in their eighth and ninth decades of life. These older adults demonstrate lower risk of death and functional decline than those with minor cognitive decline, supporting the concept of “successful” cognitive aging.

Keywords

Cognition; cognitive maintenance; mortality; disability

INTRODUCTION

Variability in cognitive function increases with age whereby some elders continue to perform as well as young adults and others perform substantially below the mean.^{1–3} Typically those with the most substantial declines have more concomitant disease and greater risk of death.^{4–6} Although many studies have identified various predictors and outcomes of cognitive decline in older adults, surprisingly few have sought to determine predictors and outcomes of maintaining cognitive function with age (i.e., experiencing no cognitive decline). It is unclear if these are similar (but opposite in direction) or different from those associated with cognitive decline, and if maintenance of cognitive function confers health advantages such as lower rates of mortality and disability.

Two recent studies have demonstrated that elders with maintained cognitive function have a distinct set of characteristics differentiating them from those with major cognitive decline; for example, healthy behaviors such as not smoking, weekly exercise, and moderate alcohol consumption.^{7, 8} Although several factors were identified that differentiated cognitive maintainers, from minor and major decliners, whether these groups experienced different outcomes, such as death and disability, was not evaluated. With the exponentially increasing number of elderly adults in the population, it is important to fully understand these outcomes in order to clearly describe the concept of “successful” cognitive aging.

The primary objectives of this study were to determine the proportion of elderly men and women in a biracial cohort who maintain or improve cognitive function over time and whether these maintainers differed from typical or major cognitive decliners in incident mobility limitation, disability and mortality. Until there is a full understanding of what the predictors, correlates and outcomes of cognitive maintenance are, there will be a lack of information necessary to clearly characterize “successful” cognitive aging. If differences in health outcomes can be demonstrated with cognitive maintenance, we will be one step closer to defining “successful” or “healthy” cognitive aging.

METHODS

Study Population

Participants were part of the Health, Aging and Body Composition (Health ABC) study, a prospective biracial cohort study of 3075 community-dwelling men and women living in Memphis, TN or Pittsburgh, PA and aged 70–79 years old in the year of recruitment (1997). To identify potential participants, a random sample of White and Black Medicare-eligible elders within designated zip code areas were contacted. To be eligible, participants had to report no difficulty with activities of daily living, walking a quarter of a mile, or climbing 10 steps without resting. They also had to be free of life-threatening cancer diagnoses and any intention of moving out of the study area for at least 3 years. All participants signed a written informed consent, approved by the institutional review boards at the clinical sites. We excluded the seven participants missing cognitive scores at baseline and the 335 with only one cognitive test score, leaving 2733 participants in our analytic cohort. This study

was approved by the institutional review boards of the coordinating center (University of California, San Francisco). Written informed consent was obtained from all patients participating in the study.

Measurements

Cognitive tests—The Modified Mini-Mental State Examination (3MS) was administered to participants at baseline (Year 1) and after two and four years of follow-up (Year 3 and 5). The 3MS is a brief, general cognitive battery with components for orientation, concentration, language, praxis, and immediate and delayed memory.⁹ Possible scores range from 0 to 100, with higher scores indicating better cognitive function.

Baseline and follow-up characteristics—At baseline, participants reported their age, race, sex, education (categorized as less than high school, high school, or more than high school) and current smoking status. Self-rated health was reported as excellent, very good, good, fair, or poor. Medical conditions included diabetes mellitus, hypertension, myocardial infarct (MI) and history of stroke or transient ischemic attack (TIA), and were determined at baseline and each follow-up visit using self-report of physician diagnoses, clinic data, and medication use. Apolipoprotein E (APOE) genotype was determined using standard single nucleotide polymorphism analyses (Bioserve.com, Laurel, MD) and analyzed as presence or absence of e4 allele. Depressive symptoms were assessed at baseline with the 20-item Center for Epidemiologic Studies-Depression Scale (CES-D).¹⁰ Body mass index (BMI) (kg/m^2) was calculated from direct height and weight measurements at baseline.

Outcomes—We assessed mortality and incident physical disability after the Year 5 visit and through the Year 8 visit. Exact dates of death were ascertained by review of obituaries, family member reports, hospital records, and death certificates. Physical disability was ascertained by self-report at each annual visit, and was defined as having a lot of difficulty or being unable to walk a quarter mile and/or climb 10 steps, or having any difficulty with one or more of the following activities of daily living (ADL): transferring in and out of bed or chairs, bathing, dressing, or walking across a room. For this outcome, the date of onset was approximated by the date of the visit at which it was first reported. Participants who experienced the outcome from baseline through the year 5 visit were excluded from each analysis in order to study incident outcomes associated with trajectory.

Statistical Analyses

We defined three cognitive groups based on estimated rates of change in 3MS scores from baseline to the Year 5 visit. Only those participants with at least two of the three cognitive assessments were included. The participant-specific slopes were estimated by best linear unbiased predictions from a linear mixed model with random intercepts and slopes. In order to better predict these slopes, the model included fixed effects for age, sex, race, education, self-rated health, and time in years since the baseline cognitive measurement. Participants with predicted slopes of 0 or greater (indicating no change or improvement in cognitive scores over time) were classified as “maintainers”. Those with predicted slopes less than 0 (decline in cognitive score over time) but no more than one standard deviation (SD) below the mean of the slopes were classified as “minor decliners”. Those with predicted slopes more than 1 SD below the mean were classified as “major decliners”. These cutoffs were determined based on both face validity and consideration of previous cutoffs used in Health ABC and other studies for clinically significant decline.^{8, 11, 12} In addition, we conducted a sensitivity analyses using 1.5 SD below the mean for “major decliners.”

Baseline characteristics were compared across the three cognitive change groups using ANOVA for continuous variables and chi-square or Fisher’s exact tests for dichotomous

variables. Kaplan Meier curves and Cox proportional hazards models were used to compare mortality and incident disability among maintainers, minor decliners, and major decliners. The reference group for these analyses was the “minor decliner” group because we were interested in comparing risk of mortality and disability among those “maintainers” versus those with more “typical” decline and not with clinically significant decline. The Cox models were then adjusted for baseline characteristics that differed significantly ($p < 0.05$) across the groups as well as for baseline cognitive score. Proportional hazards assumptions were tested graphically and statistically and were met for all models. All analyses were conducted in Stata (Stata Corp, College Station, TX).

RESULTS

Of the 2733 elders (1303 (48%) men and 1430 (52%) women), 984 (36%) were maintainers, 1314 (48%) minor decliners, and 435 (16%) major decliners. For each group, the predicted mean change over 4 years on the 3MS was 0.6 points for the maintainers, -1.1 points for minor decliners and -4.5 points for major decliners (Figure 1). Compared to both groups of decliners, maintainers were younger, less likely to be female, to be Black, to have fair/poor self-rated health, and were better educated (all $p < 0.001$, Table 1). Minor decliners had slightly higher average BMI than the other two groups ($p = 0.008$). Maintainers were less likely to be depressed than decliners ($p = 0.002$), to report a history of stroke/TIA ($p = 0.005$), hypertension, diabetes, or be APOE e4 carriers (all $p < 0.001$). The three groups were similar in terms of self-reported history of MI.

We constructed Kaplan-Meier curves for death among 2592 participants who were alive and followed after the Year 5 visit (Figure 2a). We excluded 91 participants who were no longer alive in Year 5 and an additional 50 for whom we did not have vital status information. These excluded participants were more likely to be Black and to have had lower baseline cognitive scores ($p < 0.05$) but did not differ in terms of gender, age or education. There were a greater proportion of major decliners that were lost to follow-up on outcome data compared to minor decliners or maintainers (6% vs. 5% and 2% respectively, $p = 0.001$). The mean follow-up time was 2.9 years and ranged from two weeks to 3.5 years. Kaplan-Meier estimates of death were lowest in the maintainer group (7% died by the Year 8 visit), intermediate among minor decliners (14% died), and highest among major decliners (20% died, Table 2). In the unadjusted Cox model, maintainers had an estimated 52% lower hazard of mortality (Hazard Ratio (HR) = 0.48; 95% Confidence Interval (CI) = 0.36–0.63), whereas major decliners had a 48% increased hazard (HR = 1.48; 95% CI = 1.14–1.92) compared to minor decliners. These hazard ratios were slightly stronger and remained statistically significant after adjustment for age, gender, race, education, APOE e4, depression, baseline cognitive score, BMI, stroke/TIA, and time-dependent hypertension and diabetes (maintainers HR = 0.46; 95% CI = 0.34–0.64 and major decliners HR = 1.58; 95% CI = 1.16–2.16).

We constructed Kaplan-Meier curves for disability among the 1837 participants with no reported disability through the Year 5 visit (Figure 2b). We excluded 91 participants who were no longer alive, 743 who reported disability at the Year 5 visit, and 62 for whom we did not have disability information during follow-up. The mean follow-up time was 2.6 years and ranged from 8 months to 3.7 years. As expected, incidence is clustered at the Year 6, Year 7, and Year 8 visits. Kaplan-Meier estimates of incident disability were lowest in the maintainer group (22% were disabled by the Year 8 visit), intermediate among minor decliners (29% were disabled), and highest among major decliners (40% were disabled). In the unadjusted Cox model, the hazard of incident disability was 26% lower among maintainers (HR = 0.74; 95% CI = 0.62–0.89), and 49% higher among major decliners (HR = 1.49; 95% CI = 1.19–1.86) compared to minor decliners. The magnitude of the association

diminished slightly after adjustment for age, gender, race, education, APOE e4, depression, baseline cognitive score, BMI, stroke/TIA, and time-dependent hypertension and diabetes, but was still significant at a trend level (maintainers HR=0.84; 95% CI=0.69–1.04 and major decliners HR=1.37; 95% CI=1.06–1.78).

In order to determine if our results were robust to the cut-off points for major decline, we repeated our analyses using a cut-off for major decline of 1.5 standard deviations from the mean and found similar results. In addition, we determined if there were interactions of race or gender on cognitive trajectory group and risk of incident mortality or disability and did not find any statistically significant interaction.

DISCUSSION

In a longitudinal study of over 2700 initially well-functioning men and women followed for up to 8 years free of cognitive impairment at baseline, 36% maintained their cognitive function, about half had minor decline and 16% experienced an accelerated rate of cognitive loss. Maintenance of cognitive function over the first four years of follow-up was associated with a lower risk of mortality and incident disability over the subsequent 3 years of follow-up. As expected, experiencing accelerated clinically significant cognitive decline was associated with increased risk of mortality and physical disability.^{13–15}

In a recent study of elderly women followed for 15 years, 9% experienced maintenance of optimal cognition while 58% experienced minor cognitive decline and 33% experienced substantial cognitive decline.⁷ In the current study using a biracial cohort of well-functioning men and women, a greater proportion of participants maintained cognitive function and a lower proportion experienced major cognitive decline. This is most likely because all of the subjects were higher functioning at baseline, the follow-up period was shorter (4 versus 15 years), and a slightly different definition was used for the major decline group. We found that many of the same baseline factors predicted maintenance of cognitive function such as white race, younger age, more education, low depressive symptoms and lack of comorbidities such as diabetes and hypertension.^{7, 8}

The landmark article by Rowe and Kahn distinguished “successful” from “usual” aging, emphasizing that the physiologic, psychological and adaptive changes that promote chronic disease, disability and death are not the inevitable consequences of aging.¹⁶ The current study builds upon this prior work by demonstrating that successful cognitive aging is associated with health advantages including survival and less incident disability compared to those with more typical cognitive decline. Our results are supported by those from a longitudinal study in which trajectories of cognitive decline were associated with poorer functional outcomes.¹⁷ Interestingly, a Veteran’s Affairs Normative Aging Study (NAS) on successful aging has suggested that genetic factors may contribute to successful aging.¹⁸ This finding, along with those demonstrating different factors associated with cognitive maintenance versus cognitive decline^{7, 8}, suggest that cognitive maintainers compose a discernible group that is not just the opposite of cognitive decliners. It also suggests that maintenance of cognitive function has far greater implications for independence and longevity over time than previously considered.

What may underlie the ability of some elders to maintain cognitive function over time? Clinicopathological studies have demonstrated a wide range of neuropathological changes consistent with dementing diseases in elders with normal cognitive function whereby some elders have little pathology in the setting of a clinical dementia and others have substantial pathology without clinical symptoms.¹⁹ Indeed, at autopsy, cognitively normal older adults with and without Alzheimer disease-type neuropathology had similar prior cognitive

trajectories.²⁰ It is also possible that those who maintain cognitive function have a different genetic or epigenetic profile. Although we found large differences in the proportion of elders with APOE e4 across cognitive groups, almost 25% of the maintainers carried an e4 allele suggesting that other genetic mechanisms are more likely. It is also likely that “successful” cognitive aging individuals display adaptive qualities. These could be at the cellular level such as neuronal changes seen in aging with strengthened synaptic connectivity or encoding.^{21, 22} These could also be at a more psychosocial or behavioral level such as experiencing less stress, having more positive motivational forces or having greater health related behaviors (i.e. more physical activity or not smoking) in those with optimal cognitive aging.^{23, 24} Most likely, “successful” cognitive aging represents an interplay between these factors. Finally, we cannot say for certain that maintaining cognitive function is causally related to less disability and death. Although we adjusted for many covariates which differed by cognitive slope group, there are most likely unmeasured confounders that could be associated with both cognitive aging and adverse outcomes. In any event, we have identified a phenotype of elders who maintain cognitive function, and that is linked to better aging related outcomes.

There are several limitations that may affect the interpretation of our findings. First, the Health ABC study enrolled only well-functioning elders at baseline; therefore, it is likely that we may have found an even greater effect of maintaining cognitive function on mortality and disability if the participants had had a wider range of functioning at baseline. We also did not determine maintenance in all cognitive function domains but used a sensitive measure of global cognitive function as we felt this was most representative of the definition of maintaining cognition. It would be of interest to replicate these findings with measures specific for delayed memory and for executive function. As in any longitudinal study, there was some attrition. We sought to minimize this effect by using survival models in which participants contribute data until they develop the outcome or are censored, and by controlling for determinants of attrition, which makes informative censoring less likely. In addition, we excluded participants with prevalent disability at Year 5 in order to determine how belonging to one of the three cognitive trajectory groups impacted upon subsequent incident disability.

In summary, we have demonstrated that a substantial proportion of elders maintain cognitive function in late-life. These elders demonstrate lower risk of death and functional decline than those with minor cognitive decline supporting the concept of successful cognitive aging. We believe these results, in conjunction with prior studies,^{7, 8, 18} suggest that cognitive maintainers are a separate group of aging adults, experiencing different risk factors and outcomes than cognitive decliners. Future studies should continue to investigate differences between these groups including risk factors, outcomes, and genetics. Fully understanding what distinguishes successful cognitive aging from more typical cognitive aging and cognitive decline is an important step in preventing negative cognitive outcomes in older adults.

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Figure 1.
Cognitive Slopes over Time for the Three Cognitive Groups

Figure 2a.

Figure 2b.

Figure 2.

- a. Kaplan-Meier Curves for Death According to Cognitive Group.
- b. Kaplan-Meier Curves for Incident Disability According to Cognitive Group.

Table 1

Baseline Characteristics by Cognitive Group.

Characteristic	Maintainers (N=984)	Minor Decliners (N=1314)	Major Decliners (N=435)	P-Value [*]
Age (mean, sd)	72.7 (2.6)	73.7 (2.8)	75.2 (2.8)	<0.001
Female (%)	37	56	75	<0.001
Black (%)	20	46	66	<0.001
Fair/poor self-rated health (%)	4	15	37	<0.001
Education	9	31	60	<0.001
<high school (%)	26	36	38	
high school (%)	51	28	22	
>high school (%)	27.2 (4.4)	27.7 (4.9)	27.1 (5.4)	0.008
Body mass index (mean, sd)	3	4	7	0.002
Depression score ≥ 16 (%)	6	8	10	0.005
Stroke/TIA (%)	57	64	70	<0.001
Hypertension (%)	18	25	29	<0.001
Diabetes (%)	11	12	11	0.62
Myocardial infarction (%)	24	30	36	<0.001
ApolipoproteinE e4 (%)	0.6 (0.5)	-1.1 (0.9)	-4.5 (2.2)	<0.001
Change in 3MS score (mean, sd)				

* P-value by ANOVA for continuous variables or χ^2 for categorical variables.

Table 2

The Association between Cognitive Group and Risk of Death and Incident Disability.

Cognitive Group (Years 1 – 5)	% Dead or Disabled (Years 5 – 8)*	Hazard Ratio (95% Confidence Interval)	Adjusted Hazard Ratio (95% Confidence Interval)
Risk of Death [†]			
Maintainers (N=955)	7	0.48 (0.36–0.63)	0.46 (0.34–0.64)
Minor Decliners (N=1,237)	14	1.0 (ref.)	1.0 (ref.)
Major Decliners (N=400)	20	1.48 (1.14–1.92)	1.58 (1.16–2.16)
Incident Disability [‡]			
Maintainers (N=763)	22	0.74 (0.62–0.89)	1.37 (1.06–1.78)
Minor Decliners (N=857)	29	1.0 (ref.)	1.0 (ref.)
Major Decliners (N=217)	40	1.49 (1.19–1.86)	1.37 (1.06–1.78)

* Kaplan-Meier estimate

[†] Adjusted for baseline 3MS score, age, age squared, race, gender, education, ApoE e4, depression, BMI, stroke, and time-dependent hypertension and diabetes.[‡] Adjusted for baseline 3MS score, age, race, gender, education, ApoE e4, depression, BMI, stroke, and time-dependent hypertension and diabetes