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ACTIVE Cognitive Training and Rates of Incident Dementia

Frederick W. Unverzagt[1], **Lin T. Guey**[2], **Richard N. Jones**[3], **Michael Marsiske**[4], **Jonathan W. King**[5], **Virginia G. Wadley**[6], **Michael Crowe**[7], **George W. Rebok**[8], and **Sharon L. Tennstedt**[2]

[1]Department of Psychiatry, Indiana University School of Medicine, Indianapolis, Indiana [2]New England Research Institutes, Watertown, Massachusetts [3]Institute for Aging Research, Hebrew Senior Life, Boston, Massachusetts [4]Department of Clinical and Health Psychology, University of Florida, Gainesville, Florida [5]Division of Behavioral and Social Research, National Institute on Aging, Bethesda, Maryland [6]Department of Medicine, University of Alabama at Birmingham, Birmingham, Alabama [7]Department of Psychology, University of Alabama at Birmingham, Birmingham, Alabama [8]Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland

Abstract

Systematic cognitive training produces long-term improvement in cognitive function and less difficulty in performing activities of daily living. We examined whether cognitive training was associated with reduced rate of incident dementia. Participants were from the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) study (n=2,802). Incident dementia was defined using a combination of interview- and performance-based methods. Survival analysis was used to determine if ACTIVE treatment affected the rate of incident dementia during 5 years of follow-up. A total of 189 participants met criteria for incident dementia. Baseline factors predictive of incident dementia were older age, male gender, African American race, fewer years of education, relationship other than married, no alcohol use, worse MMSE< worse SF-36 physical functioning, higher depressive symptomatology, diabetes, and stroke (all p<.05). A multivariable model with significant predictors of incident dementia and training group revealed that cognitive training was not associated with a lower rate of incident dementia. Cognitive training did not affect rates of incident dementia after 5 years of follow-up. Longer follow-up or enhanced training may be needed to fully explore the preventive capacity of cognitive training in forestalling onset of dementia.

Keywords

Cognitive training; Intervention; Aging; Dementia; Prevention; Cognition

INTRODUCTION

The prevalence of dementia in the United States is approximately 3.4 million individuals (Plassman et al., 2007). Because dementia is an age-related disorder and the older adult segment of the population is growing rapidly, the prevalence is expected to climb to 8–13 million individuals by 2050 (Sloane et al., 2002). At present, there are no disease modifying treatments for Alzheimer disease, the major cause of dementia. If a method of delaying disease onset by even 6 years were introduced, the overall projected number of people affected by 2050 would be reduced by 38 percent (Sloane et al., 2002). Thus, identification

Correspondence and reprint requests to: Frederick W. Unverzagt, Department of Psychiatry, Indiana University School of Medicine, 1111 W. 10th Street, Suite PB 218A, Indianapolis, IN 46202. funverza@iupui.edu.

of interventions with potential to delay onset of dementia is of enormous public health significance.

Epidemiological studies have consistently shown that mental engagement broadly considered, including increased education (Caamano-Isorna, Corral, Montes-Martinez, & Takkouche, 2006), cognitive stimulation in the form of reading, interpersonal interaction, and avocational activities (Scarmeas, Levy, Tang, Manly, & Stern, 2001; Verghese et al., 2003; Wilson, Bennett, et al., 2002), and increased occupational complexity (Stern et al., 1994) is associated with reduced risk of dementia. Environmental enrichment leads to reductions in brain proteins related to Alzheimer disease in transgenic mice (Lazarov et al., 2005), and a reduction in neuronal loss in the hippocampus of aged canines (Siwak-Tapp, Head, Muggenburg, Milgram,& Cotman, 2008). Systematic cognitive training in older adults produces long term improvements in cognitive function (Ball et al., 2002; Willis et al., 2006) and those so trained report less difficulty in the performance of instrumental activities of daily living after 5 years (Willis et al., 2006). These findings raise the question as to whether cognitive training in older age may be protective against Alzheimer disease and dementia.

We examined the relationship of exposure to cognitive training and incident dementia in the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) study, a randomized, controlled trial of the effectiveness of cognitive interventions (Memory, Reasoning, and Speed) in improving cognitive function and activities of daily living of community-dwelling, older adults. We hypothesized that exposure to the ACTIVE cognitive interventions would be associated with lower rates of incident dementia.

METHOD

Design and Participants

ACTIVE is a multi-site, randomized, controlled clinical trial (see Ball et al., 2002; Jobe et al., 2001, for details). Recruitment occurred in six metropolitan areas using a variety of sampling strategies. Community-dwelling adults aged 65 years and older were eligible. Persons were excluded if they had significant cognitive dysfunction (score, 23 on the Mini-mental State Examination, MMSE; Folstein, Folstein, & McHugh, 1975); functional impairment (dependency or regular assistance in ADL on Minimum Data Set Home Care; Morris et al., 1997); self-reported diagnoses of Alzheimer disease, stroke within the last 12 months, or certain cancers; current chemotherapy or radiation therapy; or poor vision, hearing, or communicative ability that would have interfered with the interventions or outcome assessments. Enrollment resulted in a sample of 2,802 individuals (average age 74 years, average education 13 years, 74% white and 26% African American, and 76% women). Eligible participants were randomly assigned to one of three treatment arms (Memory, Reasoning, or Speed training) or a no-contact control group. Screening and baseline assessment took place before randomization. Outcome assessments were conducted immediately following and 1, 2, 3, and 5 years after the intervention. Study procedures were approved by the institutional review boards at the collaborating institutions, and all subjects gave informed consent to participate.

Interventions

ACTIVE training focused on memory, reasoning, and speed of processing because prior research indicated these abilities show early age-related decline and are related to activities of daily living. Interventions were conducted in small groups in ten 60- to 75-min sessions over 5 to 6 weeks. Memory training focused on improving verbal episodic memory through instruction and practice in strategy use. Reasoning training focused on improving the ability

to solve problems that contained a serial pattern. Speed training focused on visual search and the ability to process increasingly more information presented in successively shorter inspection times. Booster training (four 75-min sessions) was provided to a subset of participants in each intervention arm 11 and 35 months after training.

Procedures

Eligibility and demographic data (age, gender, race, education, and marital status) were gathered in telephone and in-person screening. Health history (self-report of diabetes, myocardial infarction, angina, heart failure, stroke, hypertension, high cholesterol, and current alcohol use [heavy drinkers defined as males who have 51 drinks a day or 3–4 drinks a day and drinks>3 times a week, females who have 31drinks a day or 1–2 drinks a day and drinks > 3 times a week; light drinkers defined as those who report drinking but do not meet criteria for heavy drinking; non-drinkers defined as subjects who never drink alcohol), physical status (Short-form 36; Ware & Sherbourne, 1992), functional status (MDS, see below), mental status (MMSE; Folstein et al., 1975) and cognitive measures (see below) were gathered via in-person examinations in individual and small-group formats at baseline. Depressive symptoms were measured with a 12-item version the Center for Epidemiologic Studies-Depression scale (Radloff, 1977) via self-report questionnaire at baseline.

Measures

Multiple measures of basic mental ability were gathered at each occasion of measurement (baseline, immediate posttest, 1-year, 2-year, 3-year, and 5-year follow-up). Memory ability was measured using the Hopkins Verbal Learning Test (total of the 3 learning trials; Brandt, 1991), Rey Auditory- Verbal Learning Test (total of the 5 learning trials; Rey, 1941), and Rivermead Behavioral Memory Test (immediate recall; Wilson, Cockburn, & Baddeley, 1985). Reasoning ability was measured using Letter Series (total correct; (Thurstone & Thurstone, 1949), Letter Sets (total correct; Ekstrom, French, Harman, & Derman, 1976), and Word Series (total correct; Gonda & Schaie, 1985). Speed of processing ability was measured using Useful Field of View (shortest presentation time needed to correctly perform the task 75% of the time; (Owsley et al., 1998). Semantic knowledge ability was measured using Vocabulary test (Ekstrom et al., 1976). Individual scales were normalized to the same metric with a Z-score transformation using the control group's baseline mean and standard deviation (each participant's test score subtracted from the control group mean score at baseline and the difference divided by the control group standard deviation at baseline resulting in a Z-score with mean of 0 and standard deviation of 1), and subsequently combined into domain-specific composites (average of the component Z-scores).

Functional status was measured with an instrument based on the Minimum Data Set for Home Care (MDS) (Morris et al., 1997) which taps instrumental and basic activities of daily living (ADL). The instrumental activities covered by the MDS include 19 daily tasks spanning meal preparation, housework, finances, health care, telephone, shopping, and travel over the past 7 days. The basic activities covered by the MDS include need for assistance in dressing, personal hygiene, and bathing. The Performance subscale assesses the degree of independent completion of tasks. The Difficulty subscale assesses the perceived degree of difficulty in completing these subtasks. The MDS has high correlations with the Barthel measure of basic ADL (r=.74) and the Lawton measure of instrumental ADL (r=.81) (Landi et al., 2000).

Definition of Dementia

The ACTIVE study was not designed to be a primary prevention trial for dementia. It was designed to improve cognition and improve or maintain daily function over time for initially

well-functioning adults. The present study is a secondary analysis of the ACTIVE data set. For the purpose of this analysis, dementia was defined as the first occasion of measurement (immediate post-test, 1-year, 2-year, 3-year, and 5-year follow-up) in which a participant had any of these outcomes: (i) Memory composite 21.5 SD below the ACTIVE sample baseline mean; and Reasoning composite, Speed composite, or Vocabulary 21.5 SD below the mean; and functional impairment defined as MDS IADL Total Performance at or below the 10th percentile of the ACTIVE sample baseline; or, (ii) First visit in which MMSE<22 and all subsequent visits are MMSE<22 or are missing; or, (iii) Interval self- or proxy-report of diagnosis of dementia or Alzheimer disease during the follow-up; or, (iv) Interval self- or proxy-report of institutionalization during the follow-up; or, (v) Deactivation from the study due to the family refusing access to the subject.

These definitions recognize that dementia may have onset at any point in time during the ACTIVE study and subjects and families react differently to this event. For example, some subjects will develop dementia and continue to participate in the ACTIVE study. These individuals will be captured by Definition #1 which is based on our annual cognitive assessments. Other subjects will develop dementia and change the nature of their participation in ACTIVE perhaps requiring abbreviated batteries where more limited data like the MMSE are obtained (Definition #2). Some subjects and families seek medical evaluation when dementia symptoms appear and that subset may well receive a clinical diagnosis from a qualified health professional and report it to us (Definition #3). In other cases, subjects may proceed to institutionalization or families may restrict the subject's activities (Definitions #4 and 5). For these reasons, we actually needed several non-overlapping definitions of dementia to capture dementia in a reasonably complete way.

Statistical Analyses

Our aim was to determine whether subjects receiving ACTIVE training have lower rates of incident dementia than subjects who did not receive cognitive training during 5 years of follow-up.

Analyses were conducted using R version 2.12.0 (R Foundation for Statistical Computing, 2010). Descriptive statistics are presented as mean6standard deviation for continuous variables, and number of subjects (percentage) for categorical variables. Person years were calculated from the start of the ACTIVE study (time=0) to the last participation year or the midpoint of the interval in which incident dementia was observed. Survival curves between different training groups were similar (p..8); thus, training groups were collapsed into a single training variable (trained, not trained) in all analyses. Survival analysis using Cox proportional hazards models was used to determine if training group was associated with a lower rate of incident dementia relative to controls. The Kaplan-Meier method was used to plot cumulative survival functions by exposure to training. Unadjusted hazard ratios and their 95% confidence intervals (CI) were estimated for baseline characteristics to assess whether baseline characteristics, including training group, were predictive of incident dementia. The proportional hazards assumption was satisfied for all baseline characteristics. A multivariable Cox proportional hazards model of incident dementia was constructed with ACTIVE treatment and significant baseline characteristics ($p<.05$). Interactions between training group and significant predictors were additionally examined. Our current study has 80% power to detect a hazard ratio of 0.75 at a significance level of 0.05 assuming a 30% loss-to-follow-up rate.

Sensitivity analyses were conducted to evaluate the impact of different combinations of our definitions of dementia as follows: Definition #1, #2, #3, or #4; Definition #1, #2, or #3; Definition #1 or #3; and Definition #2 or #3.

RESULTS

A total of 189 cases of incident dementia were identified through the 5 years of follow-up. 152 subjects were defined as demented on the basis of meeting a single definition only, 29 cases met 2 of the definitions, 7 cases met 3 of the definitions, and 1 case met 4 of the definitions. A total of 16 subjects met one of the definitions at the baseline and are not included in the analyses. Thus, 2786 participants were included in the incident dementia analyses.

All baseline and demographic characteristics were similar by training arm (Table 1). Non-participation rates and reasons for non-participation did not differ by training arm (p..5). Baseline and demographic characteristics of the incident dementia and no dementia groups are presented in Table 2 along with their unadjusted hazard ratios. Compared to subjects without dementia, subjects with incident dementia were significantly older, more likely to be male, more likely to be African American, less likely to be married, more likely to be nondrinkers, had fewer years of education, had lower MMSE at baseline, had lower level of physical function, had more self-reported depressive symptoms, and higher rates of self-reported diabetes and stroke (all p's,.05).

Table 3 presents the event counts and dementia incidence rates per 1000 person years across intervention groups and collapsed across training groups versus controls. The dementia incidence rate was 17.1 cases per 1000 person years for the Memory-trained group, 18.9 cases for the Reasoning-trained group, 16.1 cases for the Speed-trained group, and 19.2 cases for the Control group. Across all three training groups combined, the dementia incidence rate was 17.4 cases per 1000 person years. Unadjusted hazard ratios for the Memory, Reasoning and Speed training groups were 0.89 (95% CI 0.59–1.32), 0.99 (95% CI 0.66–1.46), and 0.83 (95% CI 0.56–1.25) respectively and did not differ between training groups (p=.8).When all three training groups were combined, the unadjusted hazard ratio was 0.90 (95% CI 0.65–1.24).

A multivariable model was constructed with significant predictors of incident dementia (p<. 05) and training group (Table 4). Randomization to treatment group was non-significant in the multivariable model (HR=1.00; 95% CI 0.71–1.40). Age, gender, race, SF-36 physical function, MMSE, and diabetes remained significant in the multivariable model. Training group did not modify any of these risk factors (p..1). The Figure 1 shows Kaplan-Meier curves for training and controls groups and visually confirms the null associations shown in previous tables.

The results from sensitivity analyses examining the impact of different combinations of our definitions of dementia are shown in Table 5. The null results are highly consistent across all definitional permutations.

DISCUSSION

In a large sample of older adults screened for dementia and functional impairment at baseline, exposure to the systematic ACTIVE cognitive training interventions did not result in a reduction in the incidence of dementia over 5 years of follow-up. The hazard ratios in this study were in the protective direction (unadjusted HR from .83 to .99 for training arms separately to .90 for training groups combined) but nonsignificant. We have power to detect significant HR in the range of .75, a magnitude comparable to the effect of donepezil in delaying time to dementia among patients with mild cognitive impairment (Petersen et al., 2005). Larger samples or meta-analyses may be required to detect protective effects attributable to cognitive training. Theoretically, there are two mechanisms by which cognitive training could affect later development of dementia. First, training may increase

brain reserve capacity by enhancing the redundancy, capacity, or efficiency of the brain thus delaying the clinical expression of neurologic disease (Katzman, 1993; Satz, 1993). Second, training could have a direct trophic effect on neural tissue (Friedland, 1993) such that abnormal proteins associated with dementia like beta amyloid and hyperphosphorylated tau are less likely to be formed or become toxic. The brain reserve concept arose, in part, as a way to understand the protective effect of education on the display of clinical brain diseases in epidemiological studies. There is a correspondence, at some levels, between the type of training used in ACTIVE and the "mental exercise" associated with formal education that would favor reserve capacity as the operative mechanism for a beneficial effect of ACTIVE training on risk of dementia. To be sure, there are divergences as well including differences in the scope and duration of formal education and ACTIVE training and the time point in life when exposure occurred (childhood and young adulthood in one and old age in other) that could explain the lack of effect we see here.

Other cognitive interventions with well older adults have examined outcomes focused on mental ability and to a lesser extent on activities of daily living but follow-up intervals have been short and none have focused on dementia as an outcome (Acevedo & Loewenstein, 2007). The only treatment study to date to show even a small, positive (time-limited) effect on time-to-dementia looked at donepezil (vs. vitamin and placebo) in patients with mild cognitive impairment (Petersen et al., 2005). That sample was enriched with subjects likely to develop dementia and identified 212 cases of incident dementia during 3 years of follow-up. We identified 189 incident cases in 5 years of follow-up, a sizable number, and our analyses were able to detect known risk factors for incident dementia including age, education, diabetes, and depression, suggesting that any protective effect for this kind of cognitive training is of relatively small magnitude

We used five criteria to characterize participant dementia status. Two were performance-based and completed on subjects who attended in-person assessments, and three were report-based. Our algorithm using the three cognitive domain scores and the functional marker map directly onto clinical diagnostic criteria for dementia (American Psychiatric Association, 1994) which support its use. Our other performance-based criterion was MMSE<22. One recent meta-analysis found that the MMSE has 83% sensitivity and 87% specificity to a clinical diagnosis of dementia in non-specialist and community settings (Mitchell, 2009). The cut-score we used was below the typical cut score of,24 and as such would tend to be slightly less sensitive but more specific and thus a definition with reasonable fidelity to dementia. Most clinicians would agree that the MMSE-based definition (#2, MMSE<22), while not useful for differential diagnosis of dementia subtype (i.e., cause), is consistent with severe cognitive impairment and not normal cognitive aging or even MCI. For subjects who were unable to attend assessments, self- or proxy-report of dementia diagnosis, proxy-report of institutionalization, and deactivation from study due to family refusing access were all counted as denoting dementia. Self-report of chronic medical conditions has good correspondence to medical record diagnoses (Okura, Urban, Mahoney, Jacobsen, & Rodeheffer, 2004) and is often used in prevalence and risk factor studies (Colditz et al., 1986; O'Mahony, Dobson, Rodgers, James, & Thomson, 1995) but may be less sensitive for incident disease (Oksanen et al., 2010). Report of institutionalization is unlikely to be wrong and one study found that the dementia alone or in combination accounted for 64% of all nursing home placements (McCallum, Simons, Simons, & Friedlander, 2007). Definition #5 (family refuses access) is admittedly the most speculative. On a logical basis, it seems likely that this type of family behavior would be a typical response to protect an impaired relative but the causes are likely broader than just severe cognitive impairment and might include severe physical illness or non-illness related motivations altogether. The expanded sensitivity analyses produced consistently null results across all permutations, suggesting that our pattern of findings is not related to variations in dementia case definition.

The observed dementia incidence rate in our study is comparable with that reported in a large national sample for persons aged 72–79 years that used a full clinical assessment and expert consensus panel for diagnosis (Plassman et al., 2011) suggesting that our definition was reasonable. In addition, the associations we found for age (Ganguli, Dodge, Chen, Belle, & DeKosky, 2000; Gao, Hendrie, Hall, & Hui, 1998; Launer et al., 1999; Lindsay et al., 2002; Plassman et al., 2011), race (Tang et al., 2001), education (Ganguli et al., 2000; Launer et al., 1999; Lindsay et al., 2002; Plassman et al., 2011), depression (Saczynski et al., 2010; Wilson, Barnes, et al., 2002), and diabetes (Arvanitakis, Wilson, Bienias, Evans, & Bennett, 2004) are in the direction of prior epidemiological work in incident dementia. Gender is weak risk factor with one meta-analysis indicating no effect of gender (Gao et al., 1998) but at least one study showing higher risk for males (Ganguli et al., 2000). The fact that the rate of incident dementia and the pattern of risk factors in the ACTIVE cohort are comparable to those reported in large epidemiological studies suggests that our case definition of dementia was a reasonable approximation of those used in the epidemiological studies.

This study has strengths including a large, diverse sample that was cognitively normal at the baseline, using interventions shown to produce cognitive improvements, and long follow-up interval. One important limitation is the absence of a clinical diagnosis of dementia. While our rates of dementia and the identified risk factors are consistent with epidemiological studies, a clinical diagnosis of dementia may be more sensitive and may have returned different results. Another limitation related to attrition over the follow-up interval. ACTIVE's 67% retention rate is partly a function of the older age at enrollment (mean age at baseline of 73.6 years) and the relatively long follow-up (5 years). ACTIVE is comparable to observational studies of cognitive aging in older, community- dwelling adults where retention rates of 60–71% are reported (Evans et al., 2003; Hendrie et al., 2001; Tang et al., 2001). The ACTIVE retention rate is notable in comparison as it occurred in the context of significantly greater respondent burden (training activities and more frequent and longer cognitive assessments) which might be expected to depress participation rates. It is important to note that differential attrition by training group assignment did not occur. To the extent that less cognitively able subjects were overrepresented among the drop-outs, a likely situation (Euser, Schram, Hofman, Westendorp, & Breteler, 2008), our findings would underestimate the dementia incidence rates and possibly underestimate the relation between cognitive training and incidence of dementia.

We have shown that a systematic but brief exposure to cognitive training in late life did not reduce the likelihood of developing dementia over 5 years. While this secondary analysis looking at the role of mental training in reducing risk of incident dementia and time to dementia returned negative results, it is still possible cognitive training could have a salutary effect on dementia. The hazard ratio went in the protective direction but was non-significant. Given power limitations in this analysis, there is a possibility that subtle but real risk reduction due to training is possible. Clearly a primary prevention trial focused on this issue would be definitive and the outlines of such an effort are suggested by this experience. Sampling approaches that make it more likely to observe cases in the follow-up would have improved power to detect small and medium effects. This suggests enrollment of subjects with older age given the well-known association between dementia and older age (Gao et al., 1998) (perhaps age 70 years and older as opposed to age 65 years and older as here). A longer follow-up interval would also produce more cases and in this respect follow-up beyond 5 years may be needed. Enriching the sample with subjects possessing one or two copies of the ApoE e4 allele, the major susceptibility gene for sporadic Alzheimer disease that shifts the age at onset downward, would also improve power to detect subtle risk reduction.

At the same time, there may be modifications to the nature and type of cognitive training that could increase its potency. ACTIVE looked at unitary approaches to improving mental ability. It is possible that combinatorial approaches, e.g., ones that target multiple cognitive domains simultaneously, might have a larger impact. Along those same lines, longer duration interventions might be expected to produce more robust results, although there is likely an asymptote in that relationship. A recent systematic review of cognitive training trials found that around 20 sessions were optimal in balancing treatment effects and subject retention (Jean, Bergeron, Thivierge, & Simard, 2010) but that number could change based on the degree that the exercise is engaging to the participant, the time spent in a given session, and participant characteristics. The ACTIVE intervention lasted just over 2 months. To see the education-like effects on dementia risk reduction reported in epidemiological studies, it may be necessary to have much longer cognitive training exposures or types of training that result in persistent behavior change even after the offset of treatment.

This is a rich area for further exploration and investigation of primary prevention programs for dementia, including ones focused on cognitive interventions, should be a national research priority (Daviglus et al., 2010).

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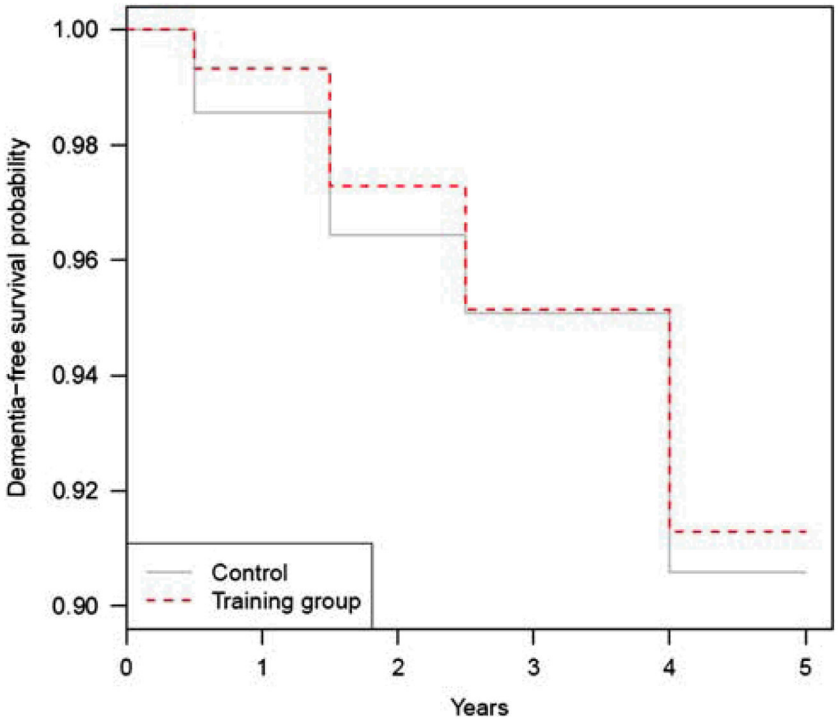

Fig. 1.
Kaplan-Meier curves for training and control groups

Table 1

Baseline and demographic characteristics by training arm

	Memory (*n* = 700)	Reasoning (/1 = 693)	Speed (*n* = 700)	Control (/1 = 693)
Female	534 (76.3%)	534 (77.1 %)	537 (76.7%)	510 (73.6%)
Race				
Black/other	179 (25.6%)	194 (28%)	178 (25.4%)	193 (27.8%)
White	521 (74.4%)	499 (72%)	522 (74.6%)	500 (72.2%)
Years of education	13.6 ± 2.7	13.5 ± 2.7	13.7 ± 2.7	13.4 ± 2.7
Married	256 (36.6%)	246 (35.5%)	241 (34.5%)	258 (37.2%)
AJcoholconsumption				
Nondrinker	297 (42.7%)	299 (43.3%)	293 (42.0%)	348 (50.6%)
Light drinker	339 (48.7%)	345 (50.0%)	362 (51.9%)	311 (45.2%)
Heavy drinker	60 (8.6%)	46 (6.7%)	42 (6.0%)	29 (4.2%)
MMSE	27.3 ± 2.0	27.3 ± 2.0	27.4 ± 2.0	27.3 ± 2.0
SF-36 physical function score	69.2 ± 23.5	67.5 ± 24.1	69.8 ± 24.1	69.2 ± 24.4
CES-D (range 0–36)	5.1 ± 5.3	5.5 ± 5.3	5.2 ± 5	5.1 ±4.9
Disease history				
Number of health conditions	2.2 ± 1.4	2.3 ± 1.5	2.2 ± 1.4	2.1 ± 1.4
Diabetes	95 (13.6%)	98 (14.2%)	86 (12.3%)	75 (10.8%)
Myocardial infarction	79 (11.4%)	77 (11.2%)	76 (10.9%)	75 (10.8%)
Angina	108 (15.5%)	115 (16.8%)	94 (13.6%)	100 (14.6%)
Heart failure	30 (4.3%)	44 (6.4%)	27 (3.9%)	36 (5.3%)
Stroke or TlA	46 (6.6%)	54 (7.9%)	50 (7.2%)	44 (6.4%)
Hypertension	371 (53.2%)	366 (53.1 %)	349 (50.1 %)	334 (48.6%)
High cholesterol	307 (44.5%)	315 (46.5%)	305 (44.4%)	292 (42.8%)
Participated at 5-year	470 (67.1%)	467 (67.4%)	483 (69.0%)	450 (64.9%)
Non-participation reason				
Death	50(7.1%)	61 (8.8%)	67 (9.6%)	62 (8.9%)
Subject’s decision to withdraw	115 (16.4%)	111 (16.0%)	98 (14.0%)	123 (17.7%)
Site’s decision to withdraw	62 (8.9%)	47 (6.8%)	45 (6.4%)	54 (7.8%)
Family refuses access	3 (0.4%)	7(1.0%)	7(1.0%)	4 (0.6%)

Note. Sixteen subjects who met dementia criterion #1 (low cognitive and functioning scores) at baseline were excluded. Of the 16 excluded subjects, 3 were in Memory, 6 were in Reason, 2 were in Speed, and 5 were in the Control group. MMSE = Mini-Mental State Examination score; SF 36 = Short Form 36 Health Survey, range 0–100, higher scores indicate better function; CES-D = Center for Epidemiologic Studies Depression scale, higher score indicates more depressive symptoms; TIA = transient ischemic attack.

Table 2

Baseline and demographic characteristics by incident dementia

	No dementia (*N* = 2597)	Incident dementia (*N* = 189)	Hazard ratios (95% CI)	*p* value
Training group	1954 (75.2%)	139 (73.5%)	0.90 (0.65–1.24)	0.52
Age*	73.3 ± 5.7	77.7 ± 6.5	2.03 (1.78–2.32)	<0.001
Female	1986 (76.5%)	129 (68.3%)	0.66 (0.49--0.90)	0.01
Race				
Black/other	674 (26.0%)	70 (37.0%)	1.00 (reference)	
White	1923 (74.0%)	119 (63.0%)	0.52 (0.39--0.70)	<0.001
Years of education"	13.6±2.7	12.8 ± 2.7	0.69 (0.59--0.80)	<0.001
Married	948 (36.5%)	53 (28.2%)	0.65 (0.47--0.89)	0.007
Alcohol consumption				
Nondrinker	1135 (43.9%)	102 (54.5%)	1.00 (reference)	
Light drinker	1281 (49.6%)	76 (40.6%)	0.65 (0.48--0.87)	0.004
Heavy drinker	168 (6.5%)	9 (4.8%)	0.63 (0.32–1.25)	0.19
MMSE*	27.4 ± 2.0	26 ± 2.0	0.47 (0.41–0.54)	<0.001
SF-36 physical function score"	69.6 ± 23.8	59 ± 25.7	0.65 (0.57--0.74)	<0.001
CES-D (range 0–36)*	5.1±5.1	6.7 ±5	1.34 (1.19–1.50)	<0.001
Disease history				
Number health conditions	2.2 ± 1.4	2.3 ± 1.5	1.07 (0.97–1.18)	0.19
Diabetes	320 (12.3%)	34 (18.2%)	1.64 (1.13–2.38)	0.009
Myocardial infarction	284 (1–1%)	23 (12.2%)	1.18 (0.76--1.82)	0.47
Angina	384 (14.9%)	33 (17.6%)	1.21 (0.83–1.76)	0.33
Heart failure	124 (4.8%)	13 (7.0%)	1.75 (0.99–3.07)	0.052
Stroke or TlA	173 (6.7%)	21 (11.2%)	1.72 (1.09–2.70)	0.02
Hypertension	1328 (51.4%)	92 (48.9%)	0.92 (0.69–1 .23)	0.59
High cholesterol	1138 (44.6%)	81 (43.3%)	0.92 (0.69–1.23)	0.57

Note.

*Continuous measures standardized in Cox proportional hazards model such that the hazard ratios represent the hazard for a I standard deviation increase in the continuous variable. CI = confidence interval; MMSE = Mini-mental State Examination; SF 36 = Short Form 36 Health Survey, range 0–100, higher scores indicate better function; CES-D = Center for Epidemiologic Studies Depression scale, higher score indicates more depressive symptoms; TIA = transient ischemic attack.

Table 3

Dementia event rate by intervention arm and collapsed across intervention arms

	Memory	Reasoning	Speed	All Interventions combined	Control
Total N	700	693	700	2093	693
Event	46	49	44	139	50
Event rate	0.066	0.071	0.063	0.066	0.072
Incidence	17.1	18.9	16.1	17.4	
rate/1000 person years (95% CI)	(12.2,22.1)	(13.6,24.2)	(11.4,20.9)	(14.5,20.2)	19.2 (13.9,24.6)
Prevalent cases of dementia[a]	3	6	2	11	5

[a]Not included in any analyses or in incidence rates. CI = confidence interval.

Table 4

Multivariable model of incident dementia

	Hazard ratio (95% CI)	*p* value
Training group	1.00 (0.71–1.40)	0.98
Age*	1.88 (1.61–2.19)	<0.0001
Female	0.46 (0.32–0.66)	<0.0001
White vs. Black/Other	0.49 (0.35–0.68)	<0.0001
Years of education*	0.85 (0.72–1.01)	0.06
Married	0.89 (0.61–1.31)	0.57
Alcohol consumption		
Nondrinker	1.00 (reference)	
Light drinker	0.86 (0.62–1.19)	0.37
Heavy drinker	1.10 (0.55–2.19)	0.79
Mini-Mental State Examination*	0.56 (0.48–0.66)	<0.0001
Short-Form 36 physical function score*	0.85 (0.73–0.99)	0.04
CES-D*	1.13 (0.98–1.30)	0.1
Diabetes	1.60 (1.08–2.38)	0.02
Stroke or TIA	1.23 (0.76–2.00)	0.4

Note.

*Continuous measures standardized in Cox proportional hazards model such that the hazard ratios represent the hazard for a 1 standard deviation increase in the continuous variable. CI=confidence interval; CES-D=Center for Epidemiologic Studies Depression scale; TIA=transient ischemic attack

Table 5

Sensitivity analysis examining the impact of different definitions of dementia (unadjusted models)

Dementia definition	$N_{dementia}$	Hazard ratio (95% CI)	*p* value
(1), (2), (3), (4), (5) [primary analysis]	189	0.90 (0.65–1.24)	0.52
(1), (2), (3), (4)	177	0.87 (0.62–1.21)	0.41
(1), (2), (3)	150	0.86 (0.60–1.23)	0.42
(1), (3)	86	0.84 (0.52–1.34)	0.46
(2), (3)	117	1.04 (0.68–1.59)	0.87

Definitions: (1) = Low cognitive test scores and low daily function scores; (2) = MMSE,22; (3) = Self- or proxy-report of dementia or Alzheimer disease diagnosis; (4) = Institutionalization; (5) = Deactivation due to family refusal; CI = confidence interval.