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RESEARCH ARTICLE

Impact of cognitive training on claims-based diagnosed dementia over 20 years: evidence from the ACTIVE study

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Abstract

INTRODUCTION: The very long-term effect of cognitive training on the risk of Alzheimer's disease and related dementias (ADRD) is unknown.

METHODS: This study links data from the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) study (a four-arm randomized controlled trial of cognitive training in a large, diverse sample) to Medicare claims (1999 to 2019). Inclusion in the analyses required being enrolled in traditional Medicare at baseline (n = 2021). ADRD was measured with the Chronic Conditions Warehouse algorithm.

RESULTS: Participants randomized to the speed-training arm who completed one or more booster sessions had a significantly lower risk of diagnosed ADRD (hazard ratio [HR]: 0.75, 95% confidence interval [CI]: 0.59, 0.95), while speed-trained participants with no booster training did not have a lower risk of diagnosed ADRD (HR: 1.01, 95% CI: 0.81, 1.27). There was no main effect of memory or reasoning training on risk of ADRD.

CONCLUSIONS: Cognitive training involving speed of cognitive processing has the potential to delay the diagnosis of ADRD.

KEYWORDS
cognitive training, ADRD, medicare claims

Highlights

- The ACTIVE study (a four-arm randomized controlled trial of cognitive training in a large, representative sample) reports that the speed intervention arm of the study showed a reduced likelihood of being diagnosed with ADRD over a 20-year follow-up period.
- No prior cognitive training intervention has been shown to reduce risk of ADRD over a 20-year period.
- Cognitive training involving speeded, dual attention, adaptive tasks has the potential to delay the diagnosis of ADRD.

1 | BACKGROUND

There is considerable evidence that cognitive training has both short-term and long-term benefits for cognitive performance, as emphasized by a report from the National Academies.[1] This report highlighted key findings from the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) study, a four-arm randomized controlled trial that demonstrated improvements in domain-specific performance up to 10 years after the initial cognitive training intervention. Importantly, reductions in self-reported disability in instrumental Activities of Daily Living (IADLs) have also been reported 10 years following this domain-specific cognitive training, compared to a control group.[2–5] Some of the training arms appeared more efficacious than others. For example, immediately after training, reliable training improvement was shown for speed (87%), memory (26%), and reasoning (74%) training. The speed and reasoning training arms maintained this effect on domain-specific cognitive performance 10 years later.[5]

A 10-year follow-up for ACTIVE participants found a lower dementia risk among those in the speed-training arm compared to the controls, using an algorithmic definition of dementia, based on interview- and performance-based measures.[6] Moreover, each additional speed-training session (including the so-called booster sessions held at 11 and 35 months after baseline), resulted in a lower risk of dementia.

Although there is mounting evidence, above and beyond the ACTIVE study, that cognitive training interventions can improve cognitive function in healthy older adults,[7] there is ongoing debate regarding the efficacy of cognitive interventions to slow cognitive decline and reduce risk for Alzheimer's disease and related dementias (ADRD).[8–9] This question can only be adequately addressed by examining the long-term outcomes of a large, well-characterized sample followed into advanced old age.

The goal of this study was to determine the impact of the ACTIVE cognitive training interventions on the risk of diagnosed ADRD over a 20-year follow-up period, based on Medicare claims data. The use of Medicare claims data has several advantages, including that the outcome of diagnosed ADRD is independent of the study assessments and investigators, that the claims data are available even after participants might have dropped out of the ACTIVE study (thus mitigating some potential biases due to selective attrition), and the real-world importance of Medicare diagnoses, in terms of their influence on care options and treatment in daily life.

We examined whether the impact of cognitive training on the diagnosis of ADRD differed depending on the domain-specific training at baseline, whether the diagnosis of ADRD differed among the participants who had booster sessions (at 11 and 35 months) following baseline training, compared to those who did not, and whether the age of the participants at baseline training had a differential impact of the cognitive training on risk of diagnosed ADRD.

2 | METHODS

The ACTIVE study protocol, the power calculations for the targeted sample size, and the statistical analysis plan for the clinical trial have been described in detail elsewhere.[2] In brief, the ACTIVE study was a four-arm, multisite, single-blind, randomized controlled trial in a large ($N = 2802$), diverse (26% minority) sample, recruited from March 1998 to October 1999, in six metropolitan areas. Community-dwelling adults aged 65 years and older were eligible. Exclusion criteria included significant cognitive dysfunction (Mini-Mental State Examination [MMSE] score < 23),[10] functional impairment (dependency or regular assistance in Activities of Daily Living (ADLs) on the Minimum Dataset [MDS] Home Care),[11] self-reported diagnoses of Alzheimer's disease, stroke within the last 12 months, certain cancers, current chemotherapy or radiation therapy, or poor vision, hearing, or communicative ability that would have interfered with the training protocol. Participants were randomized after completing the baseline testing. A computer randomization system was used to assign participants to one of the four intervention arms. The staff members who administered the cognitive testing and questionnaires were blinded to the intervention

RESEARCH IN CONTEXT

1. **Systematic review**: The authors searched the literature, using databases such as PubMed, through January 2024, to identify clinical trials involving cognitive training that examined the impact of training on the diagnosis of ADRD many years later. One study, using an algorithmic diagnosis of ADRD, was conducted approximately 10 years after the completion of a cognitive intervention clinical trial. No studies were found with a 20-year follow-up, or where the outcome was the diagnosis of ADRD, based on Medicare claims data.
2. **Interpretation**: This study examined the effect of cognitive training, as provided in the ACTIVE study (a four-arm randomized controlled trial of cognitive training in a large, representative sample) on the likelihood of being diagnosed with ADRD over a 20-year follow-up period, using Medicare claims data. Individuals in the speed-training arm who completed one or more booster sessions had a significantly lower risk of diagnosed ADRD. There was no main effect of memory or reasoning training on risk of ADRD.
3. **Future directions**: The speed intervention arm in this study involved a dual-attention, adaptive task, followed by booster sessions (11 to 35 months after baseline). Future work should examine the key features of this task that may have maximized the long-term cognitive benefit and impact on risk of ADRD.

arms to which the participants were assigned. There was no participant or public involvement in the design, conduct, and reporting of the trial. A Data Safety Monitoring Board, consisting of six experts in the field, was responsible for overseeing the study, including any adverse events, and found no significant harms to participants from their involvement in the clinical trial. The study was approved by the Institutional Review Boards at each study site. Preregistration for this study can be found at: AsPredicted.org #67523. Note that the description of study inadvertently omitted the inclusion of booster sessions in the analyses; these were an integral part of the study design from the beginning, as reflected in the Consort Diagram and previous publications from this study.[2–5] The Supplementary Materials (S5 to S8) include additional details of the clinical trial design.

Of the original 2802 ACTIVE participants, 2763 were matched to Medicare claims based on Acumen's matching algorithm.[12] These analyses excluded 725 participants enrolled in Medicare Advantage at baseline (26%), because Medicare Advantage does not have complete administrative claims data, raising concerns about the accuracy of our outcome measure. We further excluded eight participants who died in the same year as study enrollment, which did not allow sufficient time for a diagnosis of ADRD to occur, and nine participants who already had a diagnosis of ADRD upon entering ACTIVE. The final sample consisted of 2021 participants (72.1% of the original sample), approximately evenly distributed across the four arms (Figure 1).

2.1 | Cognitive training intervention

Participants in each of the three intervention arms received up to ten 60- to 75-min sessions of training in small groups over 5 to 6 weeks: (1) speed of processing training focused on visual search and the ability to process increasingly more complex information presented in successively shorter inspection times; (2) memory training focused on improving verbal episodic memory through instruction and practice in the use of mnemonic strategies; and (3) reasoning training focused on improving the ability to solve problems that contained a serial pattern. The fourth arm was a no-contact control group.

Individuals who completed at least eight out of 10 of these initial training sessions were randomized again to receive booster training sessions at 11 and 35 months after baseline (each consisting of up to four 75-min sessions). Booster sessions were central to the study design, as previous studies had shown that booster sessions improved the maintenance of training.[13,14]

2.2 | Medicare claims records

For these analyses, Medicare claims over a 20-year follow-up period (January 1, 1999 to December 31, 2019) were linked to the training data for 2763 of the original 2802 participants. The primary outcome was the diagnosis of ADRD appearing in Medicare claims, as defined by the Chronic Conditions Warehouse (CCW) algorithm.[15] Since adjudicated diagnoses are not possible using Medicare claims, these analyses used an International Classification of Diseases code-based algorithm for diagnosed ADRD. It is noteworthy that the CCW algorithm during the study period demonstrated 85% to 90% sensitivity and specificity for the diagnosis of ADRD.[16–18]

2.3 | Covariates

Several prespecified covariates were included: baseline age (categorical), sex, race (White vs non-White), years of education, marital status (married, separated/divorced, widowed, versus never married [reference category]). Because baseline health factors, particularly vascular risks, are associated with a higher likelihood of dementia,[19] analyses also controlled for cardiovascular risk factors (hypertension, diabetes, atrial fibrillation, acute myocardial infarction, ischemia or congestive heart failure as defined by the CCW),[20] smoking behavior at baseline[21] (current smoker, former smoker vs never smoker [reference category]), and baseline cognitive performance factor scores in the speed, memory, and reasoning domains (scaled to have a mean of 0 and variance of 1 at baseline for the entire ACTIVE study). Note that although ACTIVE is a randomized trial, previous studies showed that failure to adjust for

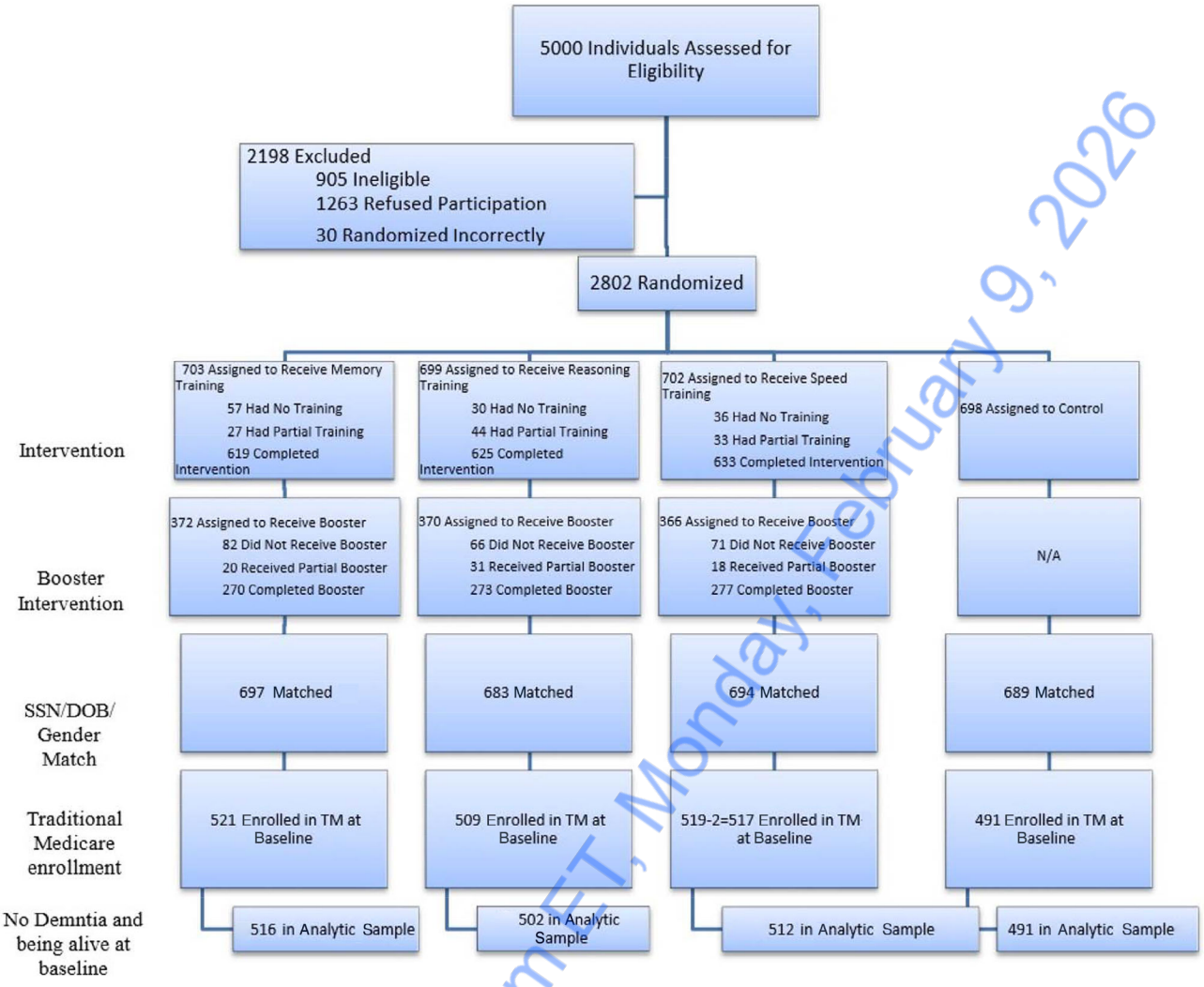

FIGURE 1 Graphical representation of Advanced Cognitive Training for Independent and Vital Elderly study design.

covariates associated with an outcome could result in lower power,[22] biased effect estimates, and incorrect conclusions.[23]

Covariate data, measured at baseline through ACTIVE or Medicare, were complete for all matched participants, except for marital status (missing = 2) and baseline processing speed factor score (missing = 16). We also controlled for basic study design features (fixed effects for site and waves of training and testing, i.e., replicate training waves), an aspect of the study design that enabled the participants to be recruited and trained over approximately 1.5 years.

2.4 | Statistical analysis

A modified intention-to-treat[24] analysis was performed, estimating a cause-specific Cox proportional hazard model, a natural extension of the standard Cox model, where a proportional hazard model is applied to each cause-specific hazard, in this case ADRD diagnosis and death. The cause-specific hazard reported is the rate, or chance, of a diagnosis of ADRD. The time scale was time since initial intervention. We used scaled Schoenfeld residuals to test proportional hazard assumptions; when violated, we included interaction terms with covariates and time. Participants were censored if they enrolled in Medicare Advantage or reached the end of the study period (December 31, 2019) without developing the end point of interest.

To promote scientific rigor, we report both the cause-specific hazard models (described above) and the Fine–Gray hazard models.[25] The Fine–Gray model[26] estimates the relative effect of the intervention on the cumulative incidence of the outcome (in this instance, the diagnosis of ADRD) in the presence of a competing risk (death).[27] The hazard ratios (HRs), using the Fine–Gray model, are presented in the Supplemental Materials.

2.5 | Impact of each cognitive training intervention

To examine the effect of each of the training arms, we compared the three intervention arms to the no-contact control arm (i.e., three comparisons). Missing data among the covariates were handled with

multiple imputation (10 iterations). Standard errors were adjusted for the variability introduced by multiple imputation according to Rubin's rules.[28]

To study the effect of the booster sessions, each of the intervention arms was divided into two groups, since the booster sessions were randomized to a subset of the total sample (i.e., individuals who completed at least eight out of 10 initial training sessions [$n = 1370$]). In the subsample of those eligible for booster sessions, the total number of sessions ranged from eight to 18. HRs for these booster training groups measure the difference in the hazard of diagnosed ADRD between each booster group compared to the control group (for a total of three comparisons). To address potential differences between those who participated in the booster sessions and those who did not, we tested for differences between those randomized to receive booster training and those not randomized, among the booster-eligible subsample within each training arm (speed $N = 449$; memory $N = 456$; reasoning $N = 465$), by including an indicator for booster assignment. These HRs measure the difference between those randomized to booster training versus those who were eligible, but not randomly assigned within each intervention arm (for a total of three comparisons).

To study the effect of age at baseline, we included interaction terms for age groups (65 to 69 years, 70 to 74 years, 75 to 79 years, >79 years) and intervention arm (three groups).

All tests were two-sided, and a p value of < 0.05 was considered statistically significant. Data were analyzed using SAS Enterprise Guide 7.15 in the Centers for Medicare & Medicaid Services (CMS) Virtual Research Data Computing environment.

3 | RESULTS

3.1 | Study sample

The characteristics of the study sample ($N = 2021$) are shown in Table 1. The average age was 73.6 years at enrollment (range: 65 to 94), with 76% female and 70% White. Average schooling was 13.7 years. The sample had several vascular risk factors at baseline (Table 1), including hypertension (66%), ischemia (40%), congestive heart failure (20%), atrial fibrillation (8%), acute myocardial infarction (3%), and diabetes (21%).

Seven percent were current smokers at baseline; 38% were former smokers. The sample experienced 77% mortality during the 20-year follow-up period. The average age at death was 83.9 years.

Demographics and health characteristics at baseline were balanced across the four arms, with very few exceptions (Table 1). No qualitative or statistical differences were found for the primary variables between the final Medicare-matched sample and the original sample, except for intervention site (Table S1). There were no qualitative and no statistical differences between the covariates in the intervention arms compared to the control arm, except for baseline age (Table S2).

3.2 | Impact of baseline training on risk of ADRD

A total of 239 out of 491 participants (48.7%) in the control arm were diagnosed with ADRD within the 20-year follow-up period (Table 2). Comparison of each intervention arm to the control group revealed that participants in each training arm tended to have a lower risk of being diagnosed with ADRD, but these differences were not statistically significant. Results were similar when computing the unadjusted HRs comparing each intervention group with the control group (Table 2; Column 2). Adjusting for baseline covariates had minimal impact on the estimated effects of the training interventions (Table 2; Column 3).

3.3 | Impact of baseline training combined with booster sessions on risk of ADRD

Individuals in the speed-training arm who were randomized to receive booster sessions had a statistically lower hazard of diagnosed ADRD in the unadjusted and adjusted models (adjusted HR: 0.74, 95% CI: 0.59 to 0.93), compared to the control arm. Notably, individuals in the speed-training arm who were randomized to receive booster sessions also had a lower hazard of diagnosed ADRD (adjusted HR: 0.81, 95% CI: 0.66 to 1.0) compared to those in speed training randomized not to receive booster training. Neither memory nor reasoning training effects were significantly different with booster training versus no booster training.

3.4 | Impact of age at training on risk of ADRD

There was no significant effect of age at training on risk of diagnosed ADRD over 20 years of follow-up for participants in any of the three intervention arms (Table 3). There was a trending, but not statistically significant, association of age for the memory-trained group, such that those who started the memory intervention at younger ages experienced a lower risk of ADRD (age 65 to 69: HR 0.69: 95% CI: 0.46 to 1.02; age 70 to 74: HR: 0.73: 95% CI: 0.51 to 1.05) compared to the controls. Full results are shown in Table S3.

These results are comparable to the estimates based on the Fine–Gray model, as shown in Table S4.

4 | DISCUSSION

In this randomized controlled trial of cognitive training, individuals who were randomized to the speed group and received booster training 11 and 35 months after the baseline intervention showed a statistically significant lower risk of diagnosed ADRD over 20 years of follow-up. Importantly, individuals in the speed group who did not complete the initial speed training, or any of the booster sessions, did not show a significantly lower risk of diagnosed ADRD over the follow-up period.

TABLE 1 Descriptive statistics for matched Advanced Cognitive Training for Independent and Vital Elderly participants enrolled in traditional Medicare in 2000: ACTIVE study[a] (*N* = 2021).

	Training intervention arm							
	Memory		Speed		Reasoning		Control	
Number of participants	**516**		**512**		**502**		**491**	
Baseline demographics								
Age Mean (SD)	73.74	(5.95)	73.37	(5.70)	73.46	(5.81)	74.00	(5.99)
65 to 69 years	0.31	(0.46)	0.31	(0.46)	0.28	(0.45)	0.27	(0.44)
70 to 74 years	0.26	(0.44)	0.32	(0.47)	0.32	(0.47)	0.31	(0.46)
75 to 79 years	0.22	(0.41)	0.21	(0.41)	0.23	(0.42)	0.23	(0.42)
>79 years	0.21	(0.41)	0.16	(0.37)	0.16	(0.37)	0.19	(0.39)
Proportion female, *N* (%)	0.76	(0.43)	0.77	(0.42)	0.76	(0.43)	0.74	(0.44)
Proportion White, *N* (%)	0.72	(0.45)	0.71	(0.45)	0.68	(0.47)	0.68	(0.47)
Years of education, mean (SD)	13.59	(2.73)	13.85	(2.67)	13.70	(2.74)	13.57	(2.81)
Marital status *N* (%)								
Proportion married	0.38	(0.48)	0.35	(0.48)	0.38	(0.49)	0.36	(0.48)
Proportion separated/divorced	0.16	(0.36)	0.15	(0.36)	0.15	(0.35)	0.13	(0.33)
Proportion widowed	0.42	(0.49)	0.41	(0.49)	0.39	(0.49)	0.45	(0.50)
Proportion single	0.05	(0.22)	0.08	(0.28)	0.08	(0.27)	0.06	(0.23)
Health behaviors at baseline *N* (%)								
Current smoker	0.09	(0.29)	0.07	(0.26)	0.06	(0.24)	0.07	(0.26)
Former smoker	0.36	(0.48)	0.40	(0.49)	0.39	(0.49)	0.37	(0.48)
Personal health characteristics at baseline *N* (%)								
Ischemia	0.42	(0.49)	0.38	(0.49)	0.42	(0.49)	0.38	(0.49)
Acute myocardial infarction	0.03	(0.18)	0.03	(0.17)	0.03	(0.16)	0.03	(0.16)
Atrial fibrillation	0.06	(0.24)	0.09	(0.28)	0.10	(0.30)	0.08	(0.27)
Congestive heart failure	0.19	(0.39)	0.19	(0.40)	0.21	(0.41)	0.20	(0.40)
Diabetes	0.22	(0.42)	0.21	(0.41)	0.23	(0.42)	0.18	(0.39)
Hypertension	0.69	(0.46)	0.65	(0.48)	0.66	(0.47)	0.64	(0.48)
Memory factor score	0.00	(0.85)	0.05	(0.83)	0.03	(0.81)	−0.03	(0.88)
Speed factor score	−0.05	(0.89)	0.00	(0.90)	−0.03	(0.90)	0.05	(0.88)
Reasoning factor score	0.04	(0.92)	0.06	(0.90)	0.02	(0.90)	−0.06	(0.88)
Study design characteristics *N* (%)								
Site								
Pennsylvania State University	0.14	(0.34)	0.15	(0.36)	0.14	(0.35)	0.12	(0.32)
Indiana University	0.20	(0.40)	0.20	(0.40)	0.19	(0.39)	0.20	(0.40)
Hebrew Rehabilitation Center for the Aged	0.13	(0.33)	0.13	(0.33)	0.12	(0.33)	0.13	(0.34)
Johns Hopkins University	0.20	(0.40)	0.20	(0.40)	0.18	(0.39)	0.20	(0.40)
Wayne State University	0.20	(0.40)	0.20	(0.40)	0.21	(0.41)	0.21	(0.41)
University of Alabama	0.14	(0.35)	0.13	(0.34)	0.16	(0.36)	0.14	(0.35)
Competing risks and censoring events								
Mortality	0.76	(0.43)	0.76	(0.43)	0.79	(0.41)	0.77	(0.42)
Age at death, if died before December 31, 2019, mean (SD)	84.21	(6.69)	83.70	(6.88)	83.83	(6.77)	84.07	(6.60)
Enrolled in Medicare Advantage prior to death, *N* (%)	0.21	(0.41)	0.18	(0.39)	0.20	(0.40)	0.17	(0.38)

Note: Values in parentheses are standard deviations.

[a]Percentages may not total 100 because of rounding.

TABLE 2 Primary specifications cause-specific hazard model: Advanced Cognitive Training for Independent and Vital Elderly study (*N* = 2021).

Group	Intervention	Ever diagnosed dementia	Unadjusted analysis Hazard ratio (95%)	Adjusted analysis[g] Hazard ratio (95% CI)	Within-treatment difference with booster training[h] Hazard ratio (95% CI)
Full sample[a]		*No. of events/total no. (%)*			
Control arm		239/491 (48.68)			
Treatment group					
	Memory	231/516 (44.77)	0.86 (0.72,1.03)	0.85 (0.70,1.02)	
	Speed	223/512 (43.55)	0.85 (0.70,1.01)	0.87 (0.72,1.05)	
	Reasoning	223/502 (44.42)	0.86 (0.72,1.04)	0.88 (0.73,1.07)	
Booster-ineligible subgroup[b]		83/160 (51.9)			
	Memory	29/60 (48.33)			
	Speed	26/47 (55.32)			
	Reasoning	28/53 (52.83)			
Booster-eligible subgroup[c]		594/1370 (43.40)			
	Memory + Booster	123/271 (45.39)	0.87 (0.70,1.08)	0.86 (0.68,1.07)	0.95 (0.78,1.15)[d]
	Memory without booster	79/185 (42.7)	0.85 (0.68,1.07)	0.84 (0.66,1.06)	
	Speed + Booster	105/264 (39.77)	0.74 (0.59,0.93)	0.75 (0.59,0.95)	0.81 (0.66,1.00)[e]
	Speed without booster	92/201 (45.77)	0.97 (0.78,1.21)	1.01 (0.81,1.27)	
	Reasoning + Booster	119/264 (45.08)	0.79 (0.63,0.98)	0.83(0.66,1.04)	0.91 (0.75,1.11)[f]
	Reasoning without booster	76/185 (41.08)	0.97 (0.77,1.23)	0.96 (0.76,1.21)	

[a]Full sample is 2021 participants. The outcome is diagnosed dementia that classifies subjects with ADRD based on the Chronic Conditions Warehouse (CCW) algorithm.
[b]Subsample of 160 participants randomized to a treatment group but did not complete at least eight of 10 initial training sessions.
[c]Subsample of 1861 participants: 491 controls and 1370 participants in a training arm who completed at least eight of the original 10 training sessions and thus were eligible for randomization to the booster training.
[d]Subsample of 456 memory-trained participants that completed at least eight of the original 10 training sessions.
[e]Subsample of 465 speed-trained participants that completed at least eight of the original 10 training sessions.
[f]Subsample of 449 reasoning-trained participants that completed at least eight of the original 10 training sessions.
[g]Adjusted analysis: *N* = 2021 person-year observations with Alabama site, control group, and Replicate Code 6 as reference groups. Participants are censored when they enroll in Medicare Advantage or reach the end of the sample (December 31, 2019) without an event. Adjusted analysis include covariates (all measured at baseline) memory factor score, reasoning factor score, speed factor scores, age, race, sex, self-reported health, years of education, ischemia, heart attack, atrial fibrillation, congestive heart failure, diabetes, hypertension, marital status, smoking status, site and replicate code.
[h]Difference with booster column presents the results of three separate regressions testing the difference between the sample randomized to receive the booster training compared to those randomized to not receive the booster, within each intervention arm, adjusted for covariates.

TABLE 3 Effect modification based on age at baseline intervention from cause-specific hazard model: Advanced Cognitive Training for Independent and Vital Elderly study (*N* = 2021).

Group	Intervention	Age 65 to 69	Age 70 to 74	Age 75 to 79	Age 80+
Full Sample[a]					
Control arm					
Treatment					
	Memory	0.688 (0.464,1.021)	0.728 (0.507,1.047)	0.973 (0.669,1.413)	0.998 (0.664,1.499)
	Speed of processing	0.826 (0.557,1.226)	0.890 (0.633,1.251)	0.864 (0.594,1.257)	0.907 (0.599,1.375)
	Reasoning	0.770 (0.517,1.145)	0.896 (0.635,1.263)	0.862 (0.591,1.257)	0.934 (0.611,1.428)

[a]Adjusted analysis: *N* = 2021 person-year observations with Alabama site, control group, and Replicate Code 6 as reference groups. Participants are censored when they enroll in Medicare Advantage or reach the end of the sample (December 31, 2019) without an event. Adjusted analysis included covariates (all measured at baseline) memory factor score, reasoning factor score, speed factor scores, age, race, sex, self-reported health, years of education, ischemia, heart attack, atrial fibrillation, congestive heart failure, diabetes, hypertension, marital status, smoking status, site, and replicate code.

There was no statistically significant benefit of memory or reasoning training on subsequent diagnosis of ADRD.

The benefit of the booster sessions for the speed-training arm is notable. The usefulness of repetitive task training in neurorehabilitation is well established in other neurological conditions such as stroke.[29] There are at least two potential reasons for this effect: (1) a dose effect, simply more training leads to better outcomes, or (2) that the boosters strengthen the training by adapting to the improving abilities of the participant, as the task difficulty increases. The latter hypothesis is consistent with a meta-analysis showing that speed-training effects are larger for tasks that are adaptive than ones that are not.[30] This may suggest that cognitive training needs to be repeated over time in a specific manner to reduce ADRD risk by facilitating the neuroplastic activation of neuronal connectivity.[31]

The differential benefits of the speed-training arm reflected in these findings are consistent with earlier results from the ACTIVE study which showed that participants in the speed-training arm outperformed individuals in the other groups.[3–6] It is noteworthy that the speed training focused on improving both visual processing and attention, particularly divided attention. Moreover, the speed training differed from the memory and reasoning training in that it was administered on a computer in an adaptive manner, with increasing task difficulty based on the individual's performance. It is possible that this led to broader brain activation, contributing to the differential findings between the intervention arms. In addition, discussion sessions among the participants in the intervention groups emphasized the potential impact of the training on daily activities. In the speed-training group, some of the discussion focused on how improved divided attention might show benefits on tasks such as driving. Notably, participation in speed training was associated with lower at-fault collisions 6 years after baseline, and the number of speed-training booster sessions was associated with maintenance of driving frequency.[32] It is important to note that other types of training, in addition to speed training, have demonstrated an impact on maintenance of driving; however, speed training tended to show greater benefits.[33]

The fact that the memory or reasoning trainings did not show statistical significance in any of the analyses presented here was somewhat surprising. Prior findings in ACTIVE showed that reasoning training was associated with fewer Instrumental Activities of Daily Living impairments 10 years after baseline.[8] Reasoning training in the Seattle Longitudinal Study has been associated with a lower likelihood of a dementia rating.[34] We would note, however, that both the memory and reasoning trainings primarily provided strategies for improving performance, whereas the speed training did not but rather adaptively increased in difficulty with improved performance. Thus, the memory and reasoning training utilized "declarative memory" as it provided explicit strategies for how to improve performance, whereas the speed training involved "procedural memory," as no explicit strategies were provided about how to improve performance, and response times were extremely brief.[35] Additionally, cognitive aging has been associated with changes in controlled processes,[36] whereas associative memory problems are generally the first symptoms of prodromal Alzheimer's disease. Since almost all the ACTIVE participants were cognitively unimpaired at baseline, it seems reasonable that programs targeting controlled processes may have been more effective in delaying the onset of ADRD. Further studies are needed to elucidate the underlying reasons for this outcome.

Although single-domain cognitive-training interventions like ACTIVE may slow cognitive decline, there is increasing interest in multidomain interventions targeting multiple modifiable risk factors through lifestyle modifications. These lifestyle-change interventions combine various approaches, such as exercise, cardiovascular health monitoring, and cognitive training. The study designs are based on the notion that the causes of cognitive decline are multifactorial and that a combined intervention may act synergistically to slow cognitive decline.

Both the FINGER (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability) Study[37] and the US POINTER Study (Study to Protect Brain Health Through Lifestyle Intervention to Reduce Risk)[38] reported cognitive benefits in the intervention group versus the controls measured over 2 years. However, neither trial was designed to assess the impact on the subsequent diagnosis of dementia or the impact of the separate intervention components during the initial phase. Consequently, it is not possible to determine whether one of the intervention components was more effective than the others, or whether they operated synergistically. The longer-term sustainability of the cognitive benefits of these and other multidomain interventions,[39–40] as well as the potential impact on dementia incidence, remains to be demonstrated.

Lastly, we would note that while the prevalence of dementia in the controls was high (i.e., 48.7%), it was close to recent estimates of lifetime risk of dementia based on the ARIC Cohort (i.e., 42%).[41] It is noteworthy that both studies included a substantial number of minorities (i.e., 30% and 27%, respectively), and, as demonstrated in the ARIC cohort and many others, the prevalence of dementia is higher in minority populations.

Despite many strengths, the ACTIVE study has limitations. Although the intervention arms are balanced in observable characteristics, the potential for post-randomization selection bias remains. The study sample represented approximately 73% of the ACTIVE sample (excluded were individuals who did not match the Medicare claims [$N = 39$] or through being enrolled in Medicare Advantage at baseline [$N = 725$], being previously diagnosed [$N = 9$], or having died soon after entering ACTIVE [$N = 8$]). Individuals enrolled in Medicare Advantage were intentionally excluded because of limitations in the claims data available; however, these participants tend to be healthier as a group, and this could have biased our results toward the null. The match with Medicare claims data mitigates some concerns about study attrition and point-in-time measures of dementia status by capturing cumulative measures of diagnosed ADRD. However, there is still the potential for selection bias in who matches to Medicare claims or who received a diagnosis for ADRD. Individuals who are able to access the healthcare system, who have family members who notice cognitive decline, and individuals with a higher education are more likely to receive dementia diagnoses.[42] However, the strength of capturing cumulative incidence of dementia over a 20-year period from an independently collected

source would appear to outweigh these limitations. A further limitation is that booster training was offered to a random subset of participants in training groups who completed at least eight initial training sessions at baseline; however, this was mitigated by comparing those randomized to booster to those eligible, but not randomized to booster. Additionally, we acknowledge that, given the large number of publications generated from the ACTIVE study, there is the potential for a Type I error, but since this is the first analysis from the ACTIVE Study using Medicare claims data, we believe this risk is low.

In summary, the findings presented here underscore the potential benefits of cognitive training involving speeded, dual-attention, adaptive tasks for delaying the diagnosis of ADRD. Future studies should examine why the reasoning and memory training in this study did not translate into long-term dementia risk reduction.

AUTHOR CONTRIBUTIONS

Concept and design: Coe, Felix, Marsiske, Rebok, Willis. *Acquisition, analysis, or interpretation of the data*: Coe, Felix, Gross, Jones, Marsiske, Miller, Rebok, Sun, Taggert, Willis. *Drafting of the manuscript*: Coe, Felix, Marsiske. *Critical revision of the manuscript for important intellectual content*: Albert, Ball, Coe, Felix, Gross, Jones, Marsiske, Rebok, Willis. *Statistical analysis*: Coe, Gross, Jones, Marsiske, Miller, Sun, Taggert. *Obtained funding*: Coe, Rebok, Willis. *Administrative, technical or material support*: Miller, Sun, Taggert. *Supervision*: Coe, Rebok, Willis. Katherine Miller and Chuxuan Sun had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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The funder had no role in the design and conduct of the study; collection management, analysis, or interpretation of the data, preparation; review or approval of the manuscript; or decision to submit the manuscript for publication. The opinions expressed here are those of the authors and do not necessarily reflect those of the funding agencies, the academic, research, governmental institutions, or corporations involved.

CONFLICT OF INTEREST STATEMENT

Norma Coe has no disclosures to report. Katherine Miller has no disclosures to report. Chuxuan Sun has no disclosures to report. Elizabeth Taggert has no disclosures to report. Alden Gross has no disclosures to report. Richard Jones has no disclosures to report. Cynthia Felix has no disclosures to report. Marilyn Albert has no disclosures to report. George Rebok has no disclosures to report. Michael Marsiske has no disclosures to report. Karlene Ball serves as a consultant and owns stock in Posit Science Inc. Posit Science acquired and markets the Useful Field of View Test and speed of processing training software, which was initially developed by the Visual Awareness Research Group, Inc. and was used in the ACTIVE clinical trial. Dr. Ball continues to collaborate on the design and testing of these assessment and training programs as a member of the Posit Science Scientific Advisory Board. Sherry Willis has no disclosures to report. Author disclosures are available in the Supporting Information.

DATA AVAILABILITY STATEMENT

Deidentified participation data and data dictionary are available from NACDA. The ACTIVE-CMS linked data are available to researchers through the National Institute on Aging LINKAGES program.

CONSENT STATEMENT

All participants provided informed consent prior to the initiation of the procedures associated with the study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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