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FROM THE ALZHEIMER'S ASSOCIATION INTERNATIONAL CONFERENCE 2016

FORMAL EDUCATION AND COMPLEX WORK MAY REDUCE THE NEGATIVE EFFECTS OF BAD DIET AND CEREBROVASCULAR DISEASE ON COGNITION

- Cognitive Training May Reduce New Cases of Cognitive Impairment and Dementia -
- Certain Genes May Lower Dementia/Alzheimer's Risk –
- Alzheimer's Resilience Factors May Vary Between Men and Women -

TORONTO, July 24, 2016 – Researchers from the Wisconsin Alzheimer's Disease Research Center and Wisconsin Alzheimer's Institute today presented new data that suggests that people whose work requires complex thinking and/or activities are better able to withstand the onset of Alzheimer's disease. Results — reported at the 2016 Alzheimer's Association International Conference (AAIC) in Toronto — suggest that working with people, rather than data or physical things, contributed the most to the protective effect.

Four additional studies also presented at AAIC 2016 add to the current body of evidence that modifiable risk factors can help build resilience to age-related cognitive decline. According to these reports, formal education, complex work and newly-identified genes may increase resilience to cognitive decline and dementia, even in people at high risk for the disease because of unhealthful diet or blood vessel problems in the brain. Additionally, resilience factors may vary between men and women at high genetic risk of Alzheimer's. Finally, a scientifically tailored cognitive training program led to a reduction in risk of developing cognitive decline or dementia over the 10-year course of a research study.

"These new data add to a growing body of research that suggests more stimulating lifestyles, including more complex work environments with other people, are associated with better cognitive outcomes in later life," said Maria C. Carrillo, PhD, Alzheimer's Association chief science officer.

"As each new study emerges, we further understand just how powerful cognitive reserve can be in protecting the brain from disease. As we've heard at AAIC this year, formal education and complex occupation could potentially do more than just slow cognitive decline – they may actually help compensate for the cognitive damage done by bad diet and small vessel disease in the brain. In metaphorical terms, we can see how cognitive reserve is taking on super power status," Carrillo said. "It is becoming increasingly clear that in addition to searching for pharmacological treatments, we need to address lifestyle factors to better treat and ultimately prevent Alzheimer's and other dementias."

> Note: "Cognitive reserve" describes the ability of the brain to withstand damage and maintain function. Resilience is generally evaluated behaviorally, while damage is evaluated through microscopic examination of cells and tissue. Childhood cognition, educational attainment, and adult occupation all contribute to cognitive reserve.

Cognitive Reserve May Moderate the Adverse Effects of Poor Diet on Cognition
The role of nutrition as a determinant of successful aging is a growing area of scientific exploration. Although the quality of one's diet and indicators of cognitive reserve have been associated with cognitive function in previous studies, there is little understanding of how the combination of these factors may influence cognitive function. In light of that, this study sought to understand whether indicators of cognitive reserve protected cognitive function against the impact of poor diet.

As reported at AAIC 2016, Matthew Parrott, PhD, of Baycrest Health Sciences, Toronto, Ontario, and colleagues measured adherence to a traditional "Western" dietary pattern (characterized by consumption of red and processed meats, white bread, potatoes, pre-packaged foods and sweets) in 351 independently living older adults. Alongside each participant's educational attainment, occupational complexity and social engagement, responses to a questionnaire on food consumption were analyzed and considered.

Over a three-year period, the researchers found that a "Western" diet is associated with more cognitive decline in older adults. However, individuals in the study eating a "Western" diet who also had a mentally stimulating lifestyle were protected from cognitive decline.

"Our results show the role higher educational attainment, mentally stimulating work and social engagement can play in protecting your brain from cognitive decline, counteracting some negative effects of an unhealthy diet," said Parrott. "This adds to the growing body of evidence showing how various lifestyle factors may combine to increase or protect against vulnerability to Alzheimer's disease."

Occupational Complexity, Cognitive Reserve, and White Matter Hyperintensities
It is well-established that white matter hyperintensities (WMHs) — white spots that appear on brain scans and indicate cerebrovascular disease — are commonly associated with Alzheimer's and may confer increased risk for cognitive decline.

Elizabeth Boots, research specialist, and colleagues at the Wisconsin Alzheimer's Disease Research Center and Wisconsin Alzheimer's Institute, evaluated WMHs in brain scans of 284 late-middle-aged healthy individuals at risk for Alzheimer's and then compared that data with the participants' cognitive function and the types of work they do. They explored three different kinds of complex work situations – work with data, people and things – to determine which are most effective at building cognitive reserve in people at risk for Alzheimer's.

The scientists, led by Ozioma Okonkwo, PhD, found that people with increased white matter injury who worked primarily with other people, rather than things or data, were able to tolerate brain damage indicated by WMHs better than their peers, and better maintain cognitive function.

"These findings indicate that participants with higher occupational complexity are able to withstand pathology associated with Alzheimer's and cerebrovascular disease and perform at a similar cognitive level as their peers. This association is primarily driven by work with people, rather than data or things," said Boots. "These analyses underscore the importance of social engagement in the work setting for building resilience to Alzheimer's disease."

Memory Resilience in Carriers of Alzheimer's Genetic Risk Varies in Women and Men
At AAIC 2016, Kirstie McDermott and colleagues from the University of Alberta, Edmonton, reported results from the Victoria Longitudinal Study, a long-term, large-scale, and multi-faceted investigation of human aging in western Canada. They looked at how memory resilience varies in men and women who are genetically susceptible to Alzheimer's disease.

The researchers investigated whether memory resilience to established genetic risk factors Apolipoprotein E (*APOE*) ε4 and Clusterin (*CLU*) C alleles is predicted by modifiable factors that are sex-specific and genetically robust. They followed 642 non-demented older adult participants aged 53-95 for up to nine years and assessed their individual episodic memory performance and trajectory.

Researchers classified participants as resilient if they sustained higher levels of memory over time despite their Alzheimer's genetic risk. They examined predictors of resilience from four Alzheimer's risk domains: (1) demographic (e.g., education), (2) functional (e.g., pulse pressure), (3) health (e.g., mobility), and (4) lifestyle (e.g., cognitive activity). All analyses were stratified by sex.

They found that, over the course of the study, memory level and stability was maintained in 67.6 percent of female participants vs. 52.8 percent of male participants. Memory resilience was reliably predicted by younger age, higher educational level, greater muscle tone, and participation in challenging, everyday cognitive activity (such as playing bridge or doing taxes) across sex for both genetic variants.

However, selectively for women, memory resilience was also predicted by:
• Force of expiration (a measure of lung function).
• Pulse pressure (a measure of cardiovascular health).
• Mobility factors, such as walking speed.
• Social activities, such as volunteering and visiting family and friends.

For men, one additional functional factor – less depressive symptoms – was an important predictor.

"Our results broadly show that while some predictors of memory resilience to Alzheimer's genetic risk are the same for men and women, there are also a number of modifiable predictors unique to gender," McDermott said. "The more we know about both common and gender-specific factors that may protect against Alzheimer's risk, the better we can create tailored and appropriate interventions that promote functional maintenance and delay cognitive decline."

Linkage and Whole Genome Sequence Analysis of AD Resilience and Risk
At AAIC 2016, researchers from Brigham Young University, Utah State University, the University of Utah and the Washington University School of Medicine presented an approach that incorporated linkage analysis, whole genome sequencing (WGS), validation and biological follow-up to identify candidate protective gene variants for Alzheimer's. Gene variants that cause a loss of function, and those that protect from disease, may be drug targets.

The study examined people over the age 75 who have been able to remain cognitively normal even in the face of genetic risk for Alzheimer's disease. Using data from the Cache County Study on Memory Health and Aging and the Utah Population Database, this study identified families with several individuals that fit this definition and looked for shared genetic factors that may explain their resilience against Alzheimer's symptoms.

Findings detected suggestive linkage in two pedigrees. Significant association in the protective direction was found for variants rs142787485 (p=0.018, OR=0.58) and rs7653 (p=0.0049, OR=0.35). RAB10 overexpression resulted in a significant increase in the Aβ42/Aβ40 ratio (p=0.017) and RAB10 silencing resulted in a significant decrease in the Aβ42/Aβ40 ratio (p=0.048).

> *Note: Plasma levels of amyloid β protein (Aβ40 and Aβ42), and the ratio between them, may be useful for identifying people at increased risk for mild cognitive impairment and Alzheimer's disease.*

"These findings implicate RAB10 as a potential Alzheimer's resilience gene and suggest that reduced expression of RAB10 may result in resilience to Alzheimer's via reduced Aβ42 throughout life," said Keoni Kauwe, PhD, of Brigham Young University. "RAB10 plays a role in regulating the production of amyloid beta, and RAB10 is less active in people resistant to Alzheimer's, therefore we see RAB10 as a potential therapeutic target for the prevention of Alzheimer's."

Brain Training May Protect Against Cognitive Impairment and Dementia: the ACTIVE Study
Cognitive training for the maintenance of brain health is a growing area of interest, particularly as it may offer a complement or alternative to drug therapies in delaying the onset of cognitive decline. At AAIC 2016, researchers presented 10-year results from the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) study, which examined the impact of several types of brain training on cognitively healthy older adults (average age 73.6).

The study examined the effects of cognitive training programs on 2,785 participants at six trial sites in the U.S., who were divided into three intervention groups – classroom-based memory strategies, classroom-based reasoning strategies, and computerized speed-of-processing training – and a control group. The participants had 10 60-minute training sessions conducted over five weeks; some participants received "booster" sessions (an additional four sessions about one year after the original training, and four more sessions about three years after the original training). The researchers measured cognitive and functional changes immediately following the training sessions and at one, two, three, five and 10 years after the training.

After 10 years, only the speed-of-processing training group showed a statistically significant impact on cognition. The researchers detected a 33 percent reduction (p=0.012) in risk of developing cognitive decline or dementia over those 10 years in those assigned to the speed training group. Participants who did the booster sessions – those who participated in 11 or more sessions of the computerized training – showed a 48 percent reduction in risk of developing cognitive decline or dementia over time. There was no significant difference in the other two training groups.

Over the 10 years of the study, 73 people in the speed of processing training group (n=698) developed cognitive decline or dementia, compared with 97 people in the control group (n=695).

Participants in the speed-of-processing group were trained on a specific task designed to improve the speed and accuracy of visual attention. The user identifies an object (i.e., a truck) at the center of his/her gaze while

at the same time identifying a target in the periphery (i.e., a car). As the user gets the answers correct, the speed of presentation becomes progressively briefer, while the targets become more similar. In the more difficult training tasks, the target in the periphery is obscured by distracting objects.

"We believe this is the first time a cognitive training intervention has been shown to protect against cognitive impairment or dementia in a large, randomized, controlled trial," said University of South Florida associate professor Jerri Edwards, PhD, first author of the AAIC 2016 scientific abstract. "Next, we'd like to get a better grasp on what exactly is the right amount of cognitive training to get the optimal benefits."

"The Alzheimer's Association believes there is sufficiently strong evidence to conclude that lifelong learning and certain types of cognitive training may reduce the risk of cognitive decline," Carrillo said. "These new 10-year findings are evidence that it may hold true for dementia as well as cognitive decline."

> Baumgart, et al. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: A population-based perspective. Alzheimer's & Dementia, Volume 11, Issue 6, June 2015, Pages 718–726.

About Alzheimer's Association International Conference (AAIC)
The Alzheimer's Association International Conference (AAIC) is the world's largest gathering of researchers from around the world focused on Alzheimer's and other dementias. As a part of the Alzheimer's Association's research program, AAIC serves as a catalyst for generating new knowledge about dementia and fostering a vital, collegial research community.
AAIC 2016 home page: www.alz.org/aaic/
AAIC 2016 newsroom: www.alz.org/aaic/press.asp

About the Alzheimer's Association
The Alzheimer's Association is the leading voluntary health organization in Alzheimer's care, support and research. Our mission is to eliminate Alzheimer's disease through the advancement of research, to provide and enhance care and support for all affected, and to reduce the risk of dementia through the promotion of brain health. Our vision is a world without Alzheimer's. Visit alz.org or call 800.272.3900.

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- Matthew Parrott, PhD, et al. Indicators of Cognitive Reserve Moderate the Adverse Relationship Between Poor Diet Quality and Cognitive Decline in Independent Older Adults: The Nuage Study. (Funders: Canadian Consortium on Neurodegeneration in Aging; Canadian Institutes of Health Research; Fonds de recherche de Québec-Santé)
- Elizabeth Boots, BS, and Ozioma Okonkwo, PhD, et al. Occupational Complexity, Cognitive Reserve, and White Matter Hyperintensities: Findings from the Wisconsin Registry for Alzheimer's Prevention. (Funders: National Institutes of Health; Alzheimer's Association)
- Kirstie McDermott, BSc, et al. Memory Resilience in Carriers of Alzheimer's Genetic Risk: Predictors Vary for Female and Male Older Adults. (Funders: National Institutes of Health; Canadian Consortium on Neurodegeneration in Aging (CNNA))
- Keoni Kauwe, PhD, et al. Linkage and Whole Genome Sequence Analysis of AD Resilience and Risk. (Funders: National Institutes of Health; Brigham Young University; Donors Cure Foundation - Charleston Conference on Alzheimer's Disease)
- Jerri Edwards, PhD, et al. The ACTIVE Study: What We Have Learned and What Is Next? (Funders: National Institute of Nursing Research; National Institute on Aging; Indiana Alzheimer Disease Center; Cognitive and Aerobic Resilience for the Brain Trial)

Proposal ID: 10770
Posters presentation: Monday, July 25, 2016, 9:30 am
Theme selection: Epidemiology

Indicators of Cognitive Reserve Moderate the Adverse Relationship between Poor Diet Quality and Cognitive Decline in Independent Older Adults: The Nuage Study

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Background: Although diet quality and indicators of cognitive reserve (CR) have been associated with cognitive function in separate studies, there is little understanding of how the combination of these factors may influence cognitive function. A mentally stimulating environment has been shown to abolish the adverse impact of poor diet quality on memory in laboratory animals. Therefore, our primary objective was to determine whether the relationship between diet quality and cognitive function was dependent on an individual's level of CR in community-dwelling older adults.

Methods: Poor diet quality was defined at baseline as adherence to a 'Western' dietary pattern identified by principal component analysis of food frequency questionnaire responses from 351 independently living older adults followed over 3 years. CR was defined as a binary composite score which considered an individual's educational attainment, occupational complexity, and social engagement. Statistical interactions between diet quality and CR were specified in multiple-adjusted mixed models to test possible interdependent effects on cognitive function (Modified Mini-Mental State Examination; 3MS).

Results: Adherence to the Western pattern was characterized by consumption of red and processed meats, white bread, potatoes, pre-packaged foods and sweets. In basic models, high adherence to the Western pattern was associated with accelerated cognitive decline (P=0.011) after adjusting for sex, age, physical activity, smoking, and CR. Possible dependency between CR and diet quality was indicated by a marginally significant interaction (P=0.073). After stratification it was found that the adverse relationship between Western pattern adherence and cognitive decline was present in individuals with low CR (P=0.003; n=182), but was absent in individuals in the upper category of CR (P=0.546; n=169).

Conclusions: We found that the adverse relationship between poor diet quality and cognitive decline was restricted to individuals with low indications of CR. A similarly poor diet was not associated with cognitive decline in those with high indications of CR. These results suggest that educated older adults with a history of mentally stimulating work and who remain socially engaged may be spared from the adverse effect of a Western diet on age-related cognitive decline.

Proposal ID: O3-05-01
Oral session: Tuesday, July 26, 2016: 2:00-3:30 PM
Theme: Prevention (non-pharmacological)
Topic: Non-Pharmacological Interventions and Meaningfulness of Risk Factors

Occupational Complexity, Cognitive Reserve, and White Matter Hyperintensities: Findings from the Wisconsin Registry for Alzheimer's Prevention

Presenting author: Elizabeth Boots, BS
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Background: White matter hyperintensities (WMHs) - markers of cerebrovascular disease - are commonly associated with Alzheimer's disease (AD) and may confer increased risk for cognitive decline. Cognitive reserve (CR), measured by occupational complexity (OCC), may protect against this increased risk; however, little is known of the relationship between CR and WMHs. The objective of this study was to determine whether greater OCC was associated with increased WMHs given comparable cognitive function in a late-middle-aged cohort at risk for AD.

Methods: 284 cognitively–healthy participants (age=60.38 ± 6.42 years) enrolled in the Wisconsin Registry for Alzheimer's Prevention underwent work history assessment, T2FLAIR structural MRI scanning, and cognitive assessment. Three OCC ratings (work with people, data, things) were obtained from O*NET classifications, averaged across up to three reported jobs, weighted by years on each job, and summed to create a composite OCC measure. Total WMHs were quantified using Lesion Segmentation Toolbox and log-transformed. The mean of four cognitive factors — Verbal Learning & Memory, Speed & Flexibility, Working Memory, and Immediate Memory — was used as a measure of global cognition.

Results: Regression analyses revealed that greater composite OCC was associated with increased WMHs while sequentially adjusting for (1) intracranial volume, global cognition, and demographics, (2) AD risk, (3) vascular risk, (4) mental health, and (5) socioeconomic status (p's≤.041). Using the fully adjusted models, analyses of OCC component ratings revealed that increased work with people was associated with greater WMHs (p=.042), but work with data or things were not associated with WMHs (p's≥.363).

Conclusions: In a cohort at risk for AD, higher OCC is associated with increased WMHs given comparable cognitive function, indicating that participants with higher OCC are able to withstand pathology associated with AD and cerebrovascular disease and perform at a similar cognitive level as their peers. Analysis of OCC components revealed this association was driven by work with people, not by work with data or things. These findings suggest that OCC may provide CR by preserving cognitive function in the face of underlying ischemic lesions, but further investigation is required. Additionally, complex social interaction involved in work with people may play an important role in CR.

Proposal ID: 8458
Poster presentation: Sunday, July 26, 2016, 9:30 am
Theme selection: Diagnosis and Prognosis

Memory Resilience in Carriers of Alzheimer's Genetic Risk: Predictors Vary for Female and Male Older Adults

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Background: Apolipoprotein E (APOE) ε4 and Clusterin (CLU) C alleles are established genetic risk factors for both Alzheimer's disease (AD) and non-demented episodic memory (EM) decline. We investigated whether memory resilience to AD genetic risk (i.e., APOE ε4 and CLU CC) is predicted by modifiable factors that are sex-specific and genetically robust.

Methods: The data included non-demented older adults in the Victoria Longitudinal Study (n=642 eligible cases, aged 53-95; 3 waves, 9 years). All analyses were stratified by sex. We used growth mixture emonstr to analyze 9-year latent variable memory level and trajectories. Participants with higher (level) and sustained (slope) EM performance were differentiated from those with lower and declining EM performance. We classified participants as memory resilient if they (1) had the APOE or CLUAD risk allele(s) and (2) were included in the higher and sustained memory performance group. We examined resilience group differences for a set of factors derived from four documented AD risk domains: (1) demographic (e.g., education), (2) functional (e.g., pulse pressure), (3) health (e.g., mobility), and (4) lifestyle (e.g., cognitive activity). We used random forest analysis to test the relative predictive importance of these factors for memory resilience.

Results: Memory level and stability over nine years was maintained in 67.6 percent of female participants (slope=0.00±0.01, intercept=0.60±0.61) and 52.8 percent of male participants (slope=0.00±0.01, intercept=0.10±0.59). Memory resilience was reliably predicted by younger age, higher educational level, and lifestyle-related cognitive activity across sex for both genetic variants. Selectively for females, memory resilience was also predicted by selected functional, health, and social factors. For males, an additional functional factor (muscle tone) was an important predictor. Prediction patterns of memory resilience were robust across these two genetic variants.

Conclusions: Long-term memory resilience in non-demented aging is predicted by risk and protective factors that are both common and unique to females and males. To the extent these factors are modifiable, the greater number and breadth identified for females may enhance opportunities for sex-specific multi-factorial interventions to promote functional maintenance and delay cognitive decline. Identifying factors that promote cognitive resilience is especially crucial for aging adults with AD genetic risk.

Proposal ID: 10970
Posters presentation: Monday, July 25, 2016, 9:30 am
Theme selection: Diagnosis and Prognosis

Linkage and Whole Genome Sequence Analysis of AD Resilience and Risk

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Background: Rare variants that cause a loss of function and protect from disease may represent tractable drug targets (e.g., PCSK9). We have used an approach, which incorporates linkage analysis, whole genome sequencing (WGS), validation, and biological follow-up to identify candidate protective variants for AD.

Methods: We identified pedigrees with a significant excess of AD mortality from the Utah Population Database that included at least 4 samples deemed AD resilient (cognitively normal, APOE e4 carriers, >75 years of age) and at least 4 clinically diagnosed Alzheimer's disease cases. Linkage analysis, considering the "resilient" samples as "affected" was conducted using SNP array data in MCLINK. WGS was acquired from key samples in each pedigree and analyzed using commercial variant analysis pipelines. Validation was conducted in four independent case/control series (WES series: 405 AD cases and 801 controls; Cache County Study: 544 cases and 3605 controls; Mayo series: 3776 cases and 4907 controls; ADNI WGS: 132 cases, 359 controls). The impact of the key genes identified in the analysis was evaluated for the effects on amyloid beta secretion in neuroblastoma cells.

Results: We detected suggestive linkage in two pedigrees. We used WGS data to prioritize variants in each linkage region (rs142787485 RAB10; rs7653 SAR1A). Analysis in WES series yielded significant association in the predicted protective direction for both variants (rs142787485 p=0.018, OR=0.58; rs7653 p=0.0049, OR=0.35). We failed to detect significant association with rs7653 in our subsequent validation analyses. Rs142787485 was significantly associated with reduced risk for AD in the Cache County Study (p=0.028, OR=0.69) and in gene-based association using SKAT-O in WGS from ADNI (p=0.0001). While the OR for both markers was in the protective direction (OR=0.94), we failed to detect significant association in the Mayo Series. Overexpression or silencing of SAR1A in N2A-APP695 cells failed to alter secreted $A\beta$ levels. RAB10 overexpression resulted in a significant increase in the $A\beta42/A\beta40$ ratio (p=0.017) and RAB10 silencing resulted in a significant decrease in the $A\beta42/A\beta40$ ratio (p=0.048).

Conclusions: Our findings implicate RAB10 as a potential AD resilience locus and suggest that reduced expression of RAB10 may result in resilience to AD via reduced $A\beta42$ throughout life.

Proposal ID: S2-01-02
Symposium: Computerized Cognitive Training: What Works, With Whom and How?
Monday, July 25, 2016: 8:00 AM - 9:30 AM, Metro Toronto Convention Centre, 105

The ACTIVE Study: What We Have Learned and What Is Next? Cognitive Training Reduces Incident Dementia Across Ten Years

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Objective: To examine the effects of three different cognitive training techniques on time to incident dementia.

Methods: The Advanced Cognitive Training in Vital Elderly study (ACTIVE) was a multisite, randomized controlled trial examining the efficacy of three cognitive training programs relative to a no-contact control condition among community dwelling older adults. Eligible participants (N=2,832; average age 73.6 years) completed baseline assessments of cognitive (i.e., memory, reasoning, and speed of processing) and functional abilities (i.e., self-report and performance-based measures of everyday function) and were randomized to one of four conditions: strategy-based memory or reasoning training, computerized, process-based speed of processing training, or no-contact controls. Participants in the training conditions completed up to 10 sessions of training over a 5-week period. All participants were reassessed immediately post-training, and at 1, 2, 3, 5 and 10 years. Participants were offered additional training sessions prior to years 1 and 3. The outcome of interest was years from the start of the ACTIVE study to the incidence of dementia. Dementia was defined using previously published criteria based upon interview- and performance- data characterizing cognitive and functional status. Intent-to-treat analysis examined whether participants randomized to reasoning, memory, or speed training had different risk of incident dementia. Given that training transfer varies by dose, we further examined dose effects of training, indicated by the number of training sessions completed.

Results: 2,785 participants were included in analyses, of which 331 met the criteria for dementia. Participants randomized to speed of processing training were 33% less likely than controls to develop dementia over 10 years (HR 0.67, 95%CI 0.49-0.91, p=.012). Significant effects of speed training sessions remained after adjustment for age, sex, race, mental status, physical function, depressive symptoms, and diabetes (HR=0.92, 95%CI 0.87-0.98, p=.013). Among participants in the control condition, dementia incidence was 14%. Dementia incidence was 12.1% among those completing 10 or fewer sessions of speed of processing training, while only 8.2% among those who completed 11-14 speed of processing training sessions, a reduction of 48% risk relative to controls (HR=0.52, 95%CI=0.33-0.82, p=.005).

Conclusions: Specific forms and doses of cognitive training may offer a means to delay dementia onset and thereby improve public health.

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