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## **GOING BEYOND RISK REDUCTION: PHYSICAL EXERCISE MAY BE AN EFFECTIVE TREATMENT FOR ALZHEIMER'S DISEASE AND VASCULAR DEMENTIA**

*Results of Three New Trials Reported at the Alzheimer's Association International Conference 2015 May Help People Live Better with Alzheimer's and Vascular Dementia*

**WASHINGTON, DC, July 23, 2015** – Positive results of three new randomized controlled trials of aerobic exercise in Alzheimer's disease, vascular cognitive impairment (VCI) and mild cognitive impairment (MCI) were reported today at the Alzheimer's Association International Conference® 2015 (AAIC® 2015) in Washington, D.C. They provide hope there may soon be a tool that people with dementia can use to prolong their independence and improve their quality of life.

There is a convincing body of evidence that regular physical activity can reduce the risk of cognitive decline, and possibly reduce the risk of Alzheimer's disease and other dementias. In healthy older people, studies suggest physical exercise can improve cognition. However, until now, whether physical exercise could improve symptoms in people with Alzheimer's, or beneficially impact the physical changes in the brain caused by the disease, was unknown.

“Based on the results we heard reported today at AAIC 2015, exercise or regular physical activity might play a role in both protecting your brain from Alzheimer's disease and other dementias, and also living better with the disease if you have it,” said Maria Carrillo, PhD, Alzheimer's Association Chief Science Officer.

“These findings also highlight the potential value of non-drug therapies for Alzheimer's disease and other dementias, and remind us that research ought to adamantly pursue combination and multi-modal approaches to Alzheimer's therapy and prevention,” Carrillo said.

The evidence presented today at AAIC 2015 supports the guidance from the Alzheimer's Association that highlights regular physical activity as one of several proactive steps people can take to reduce their risk of cognitive decline. There is a growing body of evidence that certain lifestyle choices, such as staying mentally active, eating a heart-healthy diet and staying socially engaged, can slow cognitive decline as people age. The Alzheimer's Association now offers *10 Ways to Love Your Brain* – recommendations on how to reduce the risk of cognitive decline.

### **Physical Exercise Reduces Psychiatric Symptoms of Alzheimer's in Four-Month Study**

At AAIC 2015, Steen Hasselbalch, MD, and colleagues from the Danish Dementia Research Centre (DDRC), Copenhagen, Denmark reported results from the Danish ADEX Study, the first large, controlled trial of moderate to high intensity exercise in people with mild to moderate Alzheimer's in Denmark.

In the ADEX study, 200 people with Alzheimer's age 50-90 (average age 70.9 years) were randomly assigned to either a supervised aerobic exercise program (60-minute exercise sessions three times a week for 16 weeks supervised by experienced physiotherapists) or a control group (standard care, no extra exercise). In the exercise group, after 4 weeks of adaptation exercise, participants performed aerobic exercise at a target intensity of 70-80% of maximum heart rate for the remaining 12 weeks.

The researchers studied the effects of exercise on a range of factors related to Alzheimer's disease. The primary outcome measure was change from baseline to 16 weeks in cognitive performance estimated by Symbol-Digit Modalities test (SDMT). Secondary outcomes were neuropsychiatric and depressive symptoms, activities of daily living, quality of life and other cognitive measures. No significant difference was found between the intervention and control group on the primary outcome, but there was a significant difference in neuropsychiatric symptoms in favor of the intervention group ( $p=0.002$ ).

At AAIC 2015, the researchers reported that:

- People who participated in the exercise program had far fewer neuropsychiatric symptoms (such as anxiety, irritability, and depression). Those in the control group had deteriorated on measures of psychiatric symptoms, while the intervention group improved slightly. This led to a statistically significant difference between the two groups.
- People in a subgroup of the exercise group who attended more than 80% of the classes and exercised vigorously (raising their heart rate to more than 70% of their maximal rate) had statistically significant ( $p=0.03$ ) improvements on mental speed and attention, as measured by the SDMT.
- In addition, people who participated in the exercise program improved in physical fitness, physical function, dual-task performance and exercise self-efficacy.

"Symptoms such as anxiety, irritability, and depression that often occur in Alzheimer's disease are the cause of great distress in both caregivers and people with the disease," Hasselbalch said. "While our results need to be verified in larger and more diverse groups, the positive effects of exercise on these symptoms that we saw in our study may prove to be an effective complement or combination with antedementia drugs. This calls for further study of multimodal treatment strategies, including lifestyle and drug therapies."

The Danish ADEX study was a collaboration between the DDRC, eight memory clinics in Denmark, and the Musculoskeletal Rehabilitation Research Unit, Bispebjerg & Frederiksberg Hospitals, University of Copenhagen.

### **Aerobic Exercise Reduces Tau Protein in Older Adults with Mild Cognitive Impairment**

One of the hallmarks of Alzheimer's is a brain lesion known as a tau tangle. Normally, tau functions to stabilize the structure of cells in the brain. When it becomes abnormal, tau initiates a variety of biological changes that can result in brain cells dying. Higher levels of tau in the brain are associated with faster rates of decline to Alzheimer's dementia. Therapies to prevent cognitive decline and dementia are now beginning to focus on reducing tau.

Researchers Laura Baker, PhD and colleagues from Wake Forest School of Medicine, Winston Salem NC, USA had previously shown that in older adults with mild cognitive impairment (MCI), regular moderate-to-high intensity aerobic exercise has benefits for cognition and plasma levels of amyloid protein, the primary component of the other Alzheimer's hallmark lesion, known as plaques. At AAIC 2015, they reported results of a 6-month randomized controlled trial of moderate-to-high intensity aerobic exercise in 65 sedentary adults 55-89 years old with MCI to test whether aerobic exercise might also lower tau levels in the brain.

Participants in the study were randomly assigned to either supervised aerobic training or a stretching group for 45–60 minutes four times per week for six months, using community facilities. The aerobic group exercised at 70–80% of their maximum heart rate, while the stretching group exercised at below 35 percent. The researchers tested participant’s cognitive skills (verbal recall, tests of executive function) and examined blood and cerebrospinal fluid (CSF) samples at the beginning and end of the study. Forty participants also received MRI brain scans. Participants completed their assigned exercise activities 92 percent of the time.

The researchers found that:

- Participants who completed aerobic exercise (most commonly using a treadmill) saw a statistically significant ( $p < 0.05$ ) reduction in tau levels in CSF. The effect was most pronounced in adults over the age of 70.
- Aerobic exercise significantly ( $p < 0.05$ ) increased blood flow in the memory and processing centers of participant’s brains, with a corresponding improvement in attention, planning, and organizing abilities referred to as “executive function” ( $p < 0.05$ ).

“These findings are important because they strongly suggest a potent lifestyle intervention such as aerobic exercise can impact Alzheimer’s-related changes in the brain,” Baker said. “No currently approved medication can rival these effects.”

### **Aerobic Exercise Improves Cognition in Vascular Cognitive Impairment in a 6-Month Trial**

Cerebrovascular disease is the second most common cause of dementia in older adults, behind Alzheimer’s. Research suggests that reducing heart health risk factors, such as high blood pressure and high cholesterol, may reduce dementia risk, and possibly even slow down the progression of cognitive decline due to mini-strokes – known as vascular cognitive impairment (VCI).

“This made us believe that aerobic exercise, such as running and brisk walking, may be a very promising strategy against vascular cognitive impairment,” said Teresa Liu-Ambrose, Canada Research Chair, PhD, PT, University of British Columbia and researcher at the Djavad Mowafaghian Centre for Brain Health, which is part of the Vancouver Coastal Health Research Institute, Vancouver, BC, Canada. “Research shows that aerobic exercise not only decreases heart health risk factors but may also improve brain structure and function.”

At AAIC 2015, Liu-Ambrose and colleagues reported results from a six-month study of 71 adults 56–96 years old with confirmed cases of mild VCI. Participants were assigned to two groups: one did supervised aerobic exercise three times per week for 60 minutes with certified fitness instructors, the other group received usual care plus an education seminar on nutrition once per month. All received the ADAS-Cog, a standard test of memory and thinking, at the beginning and end of the study.

Sixty-two of the 71 participants completed the full six-month study. The researchers found that study participants who took the aerobics classes significantly ( $p < 0.05$ ) improved their cognitive function, including memory and selective attention, compared to the people receiving usual care. In addition, functional brain scans acquired before and after the six-month study showed that the brains of study participants became more efficient with aerobic exercise training.

“While these promising results need to be replicated in larger and more diverse populations, the fact that aerobic exercise can improve cognitive function in VCI means that people with the condition have hope there may soon be a proven tool they can use to prolong their independence and improve their quality of life,” said Liu-Ambrose. “Exercise is a strategy that can be inexpensively delivered at the population level.”

**About AAIC**

The Alzheimer's Association International Conference (AAIC) is the world's largest gathering of leading 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 2015 home page: [www.alz.org/aaic/](http://www.alz.org/aaic/)

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**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](http://alz.org) or call 800.272.3900.

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- Steen Hasselbalch, MD, et al. Moderate to High Intensity Physical Exercise in Patients with Alzheimer's Disease. (Funder: Innovation Fund Denmark)
- Laura Baker, PhD, et al. Aerobic Exercise Reduces Phosphorylated Tau Protein in Cerebrospinal Fluid in Older Adults with Mild Cognitive Impairment. (Funder: American Diabetes Association, Wake Forest School of Medicine)
- Teresa Liu-Ambrose, PhD, PT, et al. Vascular Cognitive Impairment and Aerobic Exercise: A 6-Month Randomized Controlled Trial. (Funders: Canadian Stroke Network, Heart and Stroke Foundation of Canada)

Proposal ID: O5-04-06

Oral session, Thursday, July 23, 11:30 am-1 pm, #146

Theme Selection: Therapeutics

Topic Selection: Clinical: Clinical Trials Non-Pharmacologic

### **Moderate to High Intensity Physical Exercise in Patients with Alzheimer's Disease**

**Steen Hasselbalch, MD**

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Background: Although exercise has the potential to postpone decline in cognition and reduce neuropsychiatric symptoms in patients with Alzheimer's disease (AD), only a few programs in home-dwelling patients with AD have been conducted with small sample sizes and other methodological problems, and results have been inconsistent.

Methods: We conducted a multi-center randomized, controlled trial to determine whether a supervised aerobic exercise program could slow down rate of cognitive decline, improve ability to perform activities of daily living, quality of life, neuropsychiatric and depressive symptoms. Patients were randomized in two groups: An exercise group (60-minute exercise sessions three times a week for 16 weeks) or to a control group (usual care). Primary outcome was change from baseline to 16 week follow-up in cognitive performance estimated by Symbol-Digit Modalities test (SDMT) in the intention-to-treat group. Secondary outcomes were: Neuropsychiatric and depressive symptoms, activities of daily living, quality of life and cognitive measures.

Results: We randomized 200 patients with mild AD, median age of 70.9 years and median MMSE score of 24.0. In the intention-to-treat analysis, no significant difference between intervention and control group was found on the primary outcome, but a significant difference in neuropsychiatric symptoms in favor of the intervention group was found (Mean: 3.52 (95% confidence interval [CI], (1.29 to 5.75),  $p=0.002$ ). Further, in a per protocol analysis (defined as attendance  $>80\%$  and exercise intensity  $>70\%$  of maximal heart rate) we found a significant effect on the primary outcome in favor of the intervention group (SDMT: Mean: 4.18; (95% CI, -7.91 to -0.45);  $p=0.03$ ). For patients who exercised with the intended predefined intensity above 70 % of maximal heart rate, a positive correlation was found between attendance and improvement in SDMT (spearman  $r=0.28$ ;  $p=0.01$ ), suggesting a dose-response relationship between moderate to high intensity exercise and cognition.

Conclusions: Although the study was negative on the primary outcome, exercise appears to reduce neuropsychiatric symptoms in patients with mild Alzheimer's disease, with additional benefits of preserved cognition in a subgroup of patients with high attendance and intensity. (Funded by The Danish Council for Strategic Research (j. no.: 10-092814); ClinicalTrials.gov number, NCT01681602)

Proposal ID: O5-04-05

Oral session, Thursday, July 23, 11:30 am-1 pm, #146

Theme Selection: Therapeutics

Topic Selection: Clinical: Clinical Trials Non-Pharmacologic

**Aerobic Exercise Reduces Phosphorylated Tau Protein in Cerebrospinal Fluid in Older Adults with Mild Cognitive Impairment**

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Background: We have shown that in older adults with mild cognitive impairment, aerobic exercise has favorable effects on executive function and plasma beta amyloid, a biomarker linked to Alzheimer's disease pathology. These and similar findings by other investigators suggest that aerobic exercise may be a disease-modifying intervention for adults in the earliest stages of the disease. High tau protein levels in the brain predict rate of progression to Alzheimer's dementia; thus, identifying interventions that can successfully reduce tau levels is a priority in clinical treatment trials.

Methods: We enrolled 65 sedentary older adults (age: 55-89yrs) with amnesic MCI and prediabetes, as per American Diabetes Association hemoglobin A1c criteria given the added dementia risk conferred by early glucometabolic disease. Participants were randomized to an aerobic training or a stretching control group, and completed structured exercise under the supervision of a trainer for 45-60min, 4 times/week for 6 months using community facilities. The aerobic group exercised at 70-80% of heart rate reserve (HRR), while the stretching group exercised at an intensity below 35% HRR. At baseline and month 6, participants completed cognitive testing (verbal recall, tests of executive function), a 400m timed walk test, glucose tolerance test, body fat assessment, and blood and cerebrospinal fluid (CSF) collection. Forty participants also received structural and functional brain MRI. ANCOVA models were used with adjustments for age and education.

Results: Adherence to the intervention protocols was 92%, and aerobic exercise improved walk times and glucose tolerance relative to the control group ( $p<0.05$ ). Six months of structured moderate-to-high intensity aerobic exercise reduced CSF levels of phosphorylated and total tau protein, particularly for adults over the age of 70 years ( $p<0.05$ ). We also report exercise-induced increases in blood flow in the right anteromedial temporal lobe region ( $p<0.05$ ), and favorable effects on a composite measure of executive function ( $p<0.05$ ).

Conclusions: Six months of aerobic exercise is sufficient to favorably move tau protein levels in older adults at high risk of progression to dementia. These findings provide important evidence to support a disease-modifying effect and thus high therapeutic relevance of a readily accessible nonpharmacological intervention for adults with MCI.

Proposal ID: O5-04-04

Oral session, Thursday, July 23, 11:30 am-1 pm, #146

Theme Selection: Therapeutics

Topic Selection: Clinical: Clinical Trials Non-Pharmacologic

**Vascular Cognitive Impairment and Aerobic Exercise: A 6-Month Randomized Controlled Trial**

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Background: Worldwide, vascular cognitive impairment (VCI) is the second most common etiology contributing to cognitive impairment among older adults. Yet, VCI may be the most treatable form of cognitive impairment as many of its risk factors can be reduced with exercise. Nevertheless, few randomized controlled trials to date have specifically assessed the efficacy of exercise training on cognitive function in this high-risk group. Thus, we conducted a 6-month proof-of-concept randomized controlled trial of thrice-weekly aerobic exercise training (AE) among adults with mild sub-cortical ischemic VCI (SIVCI).

Methods: Seventy-one adults (56-96 years) with SIVCI were recruited and randomized (1:1) to one of two experimental groups: 1) 3x/week AE or 2) usual care (UC). SIVCI was confirmed by: 1) evidence of subcortical white matter lesions from neuroimaging (i.e., CT or MRI); 2) a score of less than 26 on the Montreal Cognitive Assessment (MoCA); and 3) clinical assessment by neurologist. The primary outcome for this study was the Alzheimer's Disease Assessment Scale (ADAS-Cog). The AE classes were 60 minutes in duration and led by certified fitness instructors. Target heart rates were determined by the Karvonen formula. Participants of the UC group received an education seminar on nutrition once per month. Between-group differences in ADAS-Cog at trial completion was determined by analysis of covariance, with baseline ADAS-Cog and baseline MoCA score included as covariates.

Results: At trial completion, 62 of the 71 participants completed the trial. There were 2 drop outs from AE group and 7 from the UC group. Two additional individuals from the AE group were excluded from analyses due to medical reasons: 1 due to terminal and aggressive brain tumor and 1 due to rapid decline in overall function (likely due to mixed dementia). Compared with the UC group, participants in the AE group significantly improved their cognitive function, as measured by the ADAS-Cog ( $p < 0.05$ ). We also observed significant between-group differences in the Six-Minute Walk Test, providing evidence of treatment fidelity.

Conclusions: AE may be an efficacious approach to improve cognitive function among individuals with mild SIVCI, and thereby, may prolong their functional independence and quality of life.

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