

## **NeuroExercise**

### **The effect of a 12-month exercise intervention on cognition in mild cognitive impairment – A multicenter randomized controlled trial**

#### **Background**

The development of effective interventions to attenuate cognitive decline in individuals at high risk for Alzheimer's disease is a global priority. Exercise intervention studies in Mild Cognitive Impairment, a prodromal stage of Alzheimer's disease, have demonstrated inconsistent yet promising results on cognition.

Addressing the limitations of previous studies, the multicenter NeuroExercise study investigated the effects of a 12-month structured exercise program (either aerobic exercise or stretching and toning exercises) on the progression of cognitive decline in MCI compared to a control group.

#### **Methods and findings**

A randomized controlled trial was conducted in three European countries (Dublin, Ireland; Nijmegen, Netherlands; Cologne, Germany). A total number of 183 individuals with amnesic MCI were included. Participants were randomized to either a yearlong supervised and home-based aerobic exercise program (n = 60), an equivalent stretching and toning program (n = 65) or to a non-exercise control group (n = 58). The primary outcome, cognitive performance, was determined by a neuropsychological test battery averaging six cognitive domains (verbal episodic memory, visual episodic memory, working memory, psychomotor function, executive function, attention) into a composite score. Secondary outcomes included the individual cognitive domain scores, cardiovascular fitness ( $\dot{V}O_2$ peak), and quality of life measures (DEMQOL). All outcomes were measured before and after the 12-month intervention period.

For the primary complete case (CC) analyses, between-group differences were analyzed with analysis of covariance under two conditions: 1) the exercise group (combined aerobic exercise, and stretching and toning groups) compared to the control group and 2) aerobic exercise compared to stretching and toning group as independent input.

For further exploration of the data and to determine the effect of center, and per protocol participation, which was defined at >66% class attendance, on primary outcome measures, a secondary analysis of covariance was performed.

Primary analysis of the full cohort (n = 166) revealed no between-group differences in composite cognitive score (mean difference [95% CI], 0.12 [-0.03, 0.27], p = 0.13) or in any individual cognitive domain or quality of life.  $\dot{V}O_2$ peak was significantly higher in the combined intervention arms compared to the control group at T2 (-1.76 [-3.39, -0.10], p = 0.04). Comparing the two intervention groups revealed a higher  $\dot{V}O_2$ peak level in the aerobic exercise group compared to the stretching and toning group, but no differences for the other outcomes. Secondary analysis was also insignificant for composite cognitive score, but revealed an intervention effect on  $\dot{V}O_2$ peak and quality of life in Germany.

#### **Conclusions**

A 12-month exercise intervention did not change cognitive performance in individuals with amnesic MCI in comparison to a non-exercise control group. An intervention effect on physical fitness was found, which may be an important moderator for long term disease progression and warrants long-term follow-up investigations. The large heterogeneity present in the amnesic MCI group may favor personalized intervention, based on individual responder analyses.

#### **Trial registration**

ClinicalTrials.gov NCT02913053