The ADEX Study:
Preserving Cognition, Quality of Life, Physical Health and Functional Ability in Alzheimer’s Disease: The Effect of Physical Exercise

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NO DISCLOSURES
Why study the effect of physical exercise?

- Mid-life physical activity is associated with lower risk of late-life dementia (Sofi et al., 2011)

- In animals exercise reduces Alzheimer pathology and neuronal damage (Brown et al., 2013)

- In older adults at risk moderate physical exercise improves cognitive function (Lautenschlager et al. 2008)

- Little evidence of the effect of physical exercise in people with Alzheimer dementia
Inconsistent findings from intervention studies

• Many studies performed in moderate to severe dementia stages (only two small-scale studies in mild to moderate AD)

• Physical activity of only moderate intensity and most often not supervised or monitored

• Many outcome measures that are difficult to compare

Exercise programs for people with dementia
Forbes D, Thiessen EJ, Blake CM, Forbes SC, Forbes S
Cochrane Database Syst Rev. 2013 Dec 4;12:CD006489
Physical exercise for preserving quality of life in AD. A nationwide Danish study (ADEX)
Multicenter study

DK: 5.5 mio
90,000 demented

A collaboration between
8 Memory clinics
7 Research units
in Denmark

Aalborg University Hospital
Aarhus University Hospital
Odense University Hospital
Center for Health Economy,
University of Southern Denmark
Svendborg University Hospital
Slagelse Sygehus
Institute for Sports Medicine
Bispebjerg Hospital
PET and Cyclotron Unit,
Rigshospitalet
Neurobiology Research
Unit, Rigshospitalet
Rigshospitalet
Glostrup University
Hospital
Roskilde University Hospital
Danish Dementia Research Centre,
Rigshospitalet
Danish Research Centre for Magnetic
Resonance, Hvidovre Hospital
Section for Clinical Information
and Data, The Capital Region
Institute for Sports Medicine
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Glostrup University
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Roskilde University Hospital
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Rigshospitalet
Danish Research Centre for Magnetic
Resonance, Hvidovre Hospital
Section for Clinical Information
and Data, The Capital Region
ADEX study overview

• Single-blinded randomized controlled trial
• Community-dwelling patients with mild to moderate AD
  • 50-90 years
  • MMSE > 19
  • No serious medical or psychiatric illnesses
  • If on medical treatment, stable for > 3 mo
• Randomized to 2 groups:
  • Intervention Group: Four months of exercise
  • Control Group: Treatment as usual, but 1 month of exercise after follow-up
The intervention

- Participants were randomized in blocks of 4-10 per participating center
- New groups initiated at each centre every 6 months over a period of 2.5 years (January 2012 – July 2014)
- Exercise performed in 7 local training centres close to the dementia clinics
- Transport to and from the centres was provided or reimbursed
The exercise program

One hour three times per week for 16 weeks

• Week 1-4: Adaptation exercise (strength + aerobic)
• Week 5-16: Aerobic exercise
• Supervised and surveilled by therapists in groups of 3-5 patients
• Patients used pulse watches, aimed for an intensity of 70-80% of maximum heart rate
• Each session was logged by the therapist to quantify frequency and intensity
Outcomes

Primary outcome:

- **Symbol digit modalities test** (mental speed and attention)

Secondary outcomes:

- **Cognitive:** ADAS-Cog Word List, Stroop Colour and Word Test, Verbal Fluency, MMSE
- **Depression:** Hamilton Depression Scale
- **Psychiatric symptoms:** Neuropsychiatric Inventory
- **Functional level:** Activities of daily living (ADCS-ADL)
- **Physical function:** Fitness, speed, strength, dual-task performance
- **Health-related quality of life:** EuroQol (patient & proxy-rated)
- **Cost-effectiveness**

All raters were blinded and attended regular centralized training sessions
## Baseline demographics

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Intervention</th>
<th>Total min-max</th>
<th>p-value&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>93</td>
<td>107</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (F/M)</td>
<td>36/57</td>
<td>51/56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years), median (IQR)</td>
<td>72 (67-76)</td>
<td>70 (65-76)</td>
<td>49-90</td>
<td>0,1634</td>
</tr>
<tr>
<td>Caregiver living with patient, n (%)</td>
<td>66 (71)</td>
<td>78 (73)</td>
<td></td>
<td>0,8747</td>
</tr>
<tr>
<td>Alzheimer medication, n (%)</td>
<td>88 (95)</td>
<td>105 (98)</td>
<td></td>
<td>0,2539</td>
</tr>
<tr>
<td>Physical activity scale for the elderly, (range: 0-500), median (IQR)</td>
<td>101 (55-131)</td>
<td>89 (65-124)</td>
<td>0-222</td>
<td>0,7895</td>
</tr>
</tbody>
</table>

<sup>1</sup>Fisher’s exact test was used for categorical variables and Wilcoxon signed-rank test was used for continuous variables
# Baseline scores

<table>
<thead>
<tr>
<th>Mean (SD)</th>
<th>Control</th>
<th>Intervention</th>
<th>Total min-max</th>
<th>p-value¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mini-Mental State Examination</td>
<td>24.1 (3.8)</td>
<td>23.8 (3.4)</td>
<td>14-30</td>
<td>0.53</td>
</tr>
<tr>
<td>Symbol Digit Modalities Test</td>
<td>25.4 (14.3)</td>
<td>27.1 (14.7)</td>
<td>0-63</td>
<td>0.41</td>
</tr>
<tr>
<td>Hamilton Depression Rating Scale 17 items</td>
<td>2.0 (2.5)</td>
<td>1.9 (2.6)</td>
<td>0-11</td>
<td>0.82</td>
</tr>
<tr>
<td>Neuropsychiatric Inventory</td>
<td>9.4 (9.7)</td>
<td>10.0 (10.8)</td>
<td>0-42</td>
<td>0.70</td>
</tr>
</tbody>
</table>

¹Fisher’s exact test was used for categorical variables and Wilcoxon signed-rank test was used for continuous variables
Results: change from baseline to 16 weeks

Primary outcome – SDMT in all subjects (ITT analysis*)

No significant change in mental speed and attention

Secondary cognitive outcomes also negative in ITT analysis

*Between group differences in the change from baseline using linear regression models accounting for clustering, missing data and differences in baseline values
Results: change from baseline to 16 weeks

Neuropsychiatric symptoms in all subjects (ITT analysis*)

Significant difference of 3.5 point on NPI

Red: Intervention
Blue: Control

(n= 102)

Other secondary outcomes negative in ITT analysis

*Between group differences in the change from baseline using linear regression models accounting for clustering, missing data and differences in baseline values
Results: Subjects adhering to the protocol “high exercise” group (n=66)

Does the intensity and frequency of exercise matter? High exercise: >80% attendance and >70% HRM

<table>
<thead>
<tr>
<th></th>
<th>Exercise versus control (ITT) (n=102)</th>
<th>p-value</th>
<th>High exercise versus control (n=66)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symbol Digit Modalities Test</td>
<td>-2.5 (-6.1 ; 1.1)</td>
<td>0.18</td>
<td>-4.2 (-7.9 ; -0.45)</td>
<td>0.03</td>
</tr>
<tr>
<td>Neuropsychiatric Inventory</td>
<td>3.5 (1.3 ; 5.8)</td>
<td>0.002</td>
<td>3.4 (0.9 ; 6.0)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Per Protocol analysis

*Between group differences in the change from baseline using linear regression models accounting for clustering, missing data and differences in baseline values.
Results: Adverse events and drop-out

- Very low drop-out: 5 in each group (5%)
- Adverse events: Only one SAE possibly related to study

<table>
<thead>
<tr>
<th>AE</th>
<th>CONTROL</th>
<th>INTERVENTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculoskeletal problems</td>
<td>4</td>
<td>12 (6 related)</td>
</tr>
<tr>
<td>Dizziness or faintness</td>
<td>1</td>
<td>10 (6 related)</td>
</tr>
<tr>
<td>Symptoms related to AD</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Somatic disease (i.e. cold, anemia, erysipelas)</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>20</td>
<td>38</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SAE</th>
<th>CONTROL</th>
<th>INTERVENTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>UVI</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Nephrolithiasis</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td></td>
<td>2(1)</td>
</tr>
<tr>
<td>Fracture</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Cancer mammae</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>
Discussion

- First rigorously conducted study of moderate to high intensity aerobic exercise in mild to moderate AD
- It is feasible: Attendance was high (mean: 84%) and low adverse events rate
- Dose response effect?
  - provided that high attendance and intensity is maintained, physical exercise may have an effect also on cognition
Discussion

• Clinical relevant findings: Neuropsychiatric symptoms associated with increased caregiver distress, increased admissions to nursing homes, and reduced quality of life

• Effect of social interaction between patients during group exercise or effect of exercise itself?

• The results may not necessarily apply to the general AD population due to selection bias (motivated and physically fit subjects)
Conclusion

- Even a modest relatively short term physical exercise intervention can be effective on the overall well-being of patients with mild to moderate AD
- This study and other ongoing studies will hopefully encourage national policy makers to support non-pharmacological treatment strategies
- While we wait for a cure, we have to implement multimodal treatments now
Acknowledgments

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