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

AD

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 a., 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

Does physical activity improve performance or symptoms in AD ?

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

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ADEX
The Effect of Physical Exercise in Alzheimer's Disease

Physical exercise for preserving quality of life in AD. A nationwide Danish study (ADEX)

Neuro
-epidemiology

Methods in Neuroepidemiology

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Preserving Cognition, Quality of Life, Physical Health and Functional Ability in Alzheimer's Disease: The Effect of Physical Exercise (ADEX Trial): Rationale and Design

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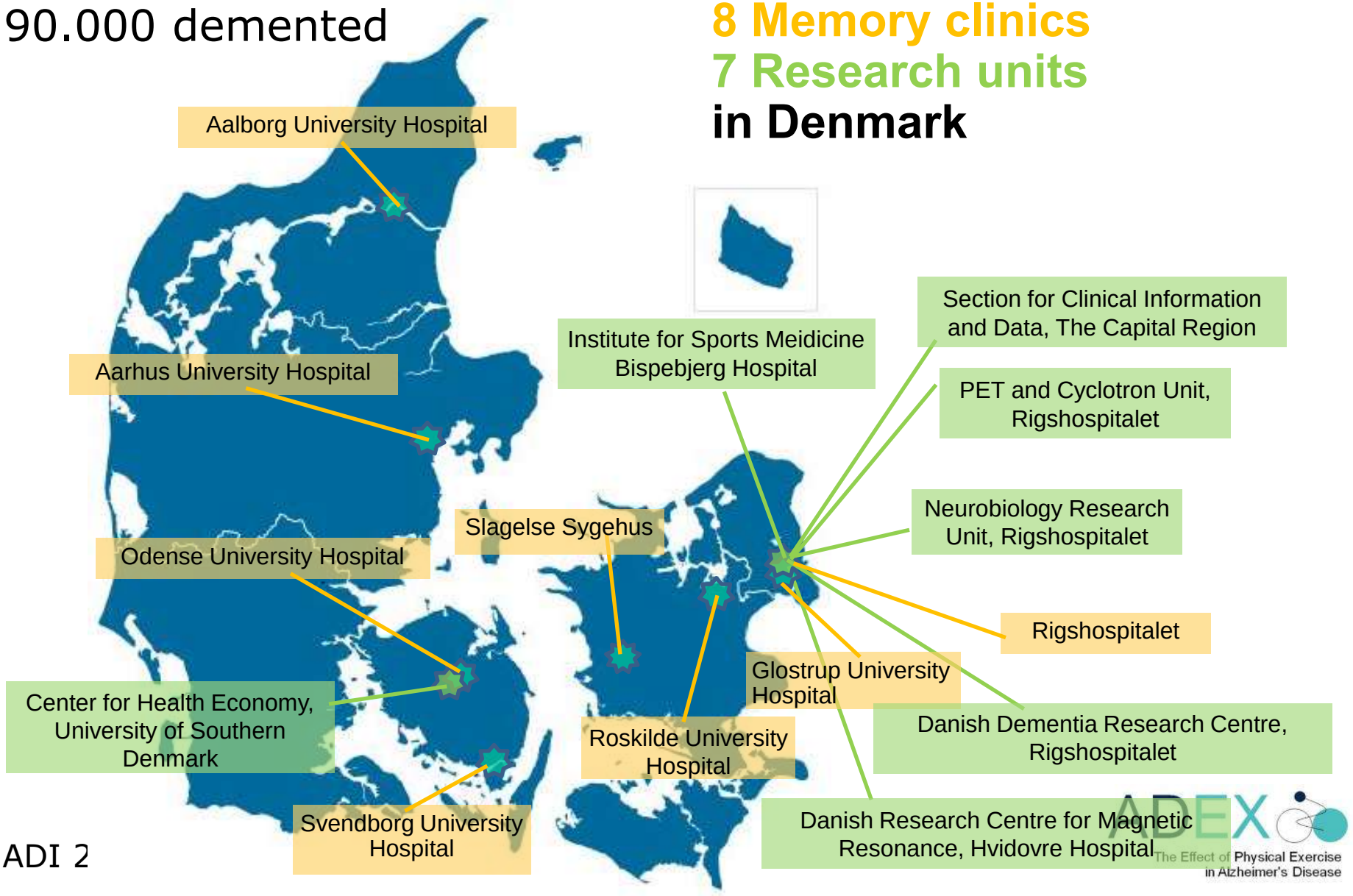
ADI 2015

Multicenter study

DK: 5.5 mio
90.000 demented

A collaboration between
8 Memory clinics
7 Research units
in Denmark



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ADEX The Effect of Physical Exercise in Alzheimer's Disease

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 ilnesses
  - 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

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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

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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

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

[1]Fisher's exact test was used for categorical variables and Wilcoxon signed-rank test was used for continuous variables

Baseline scores

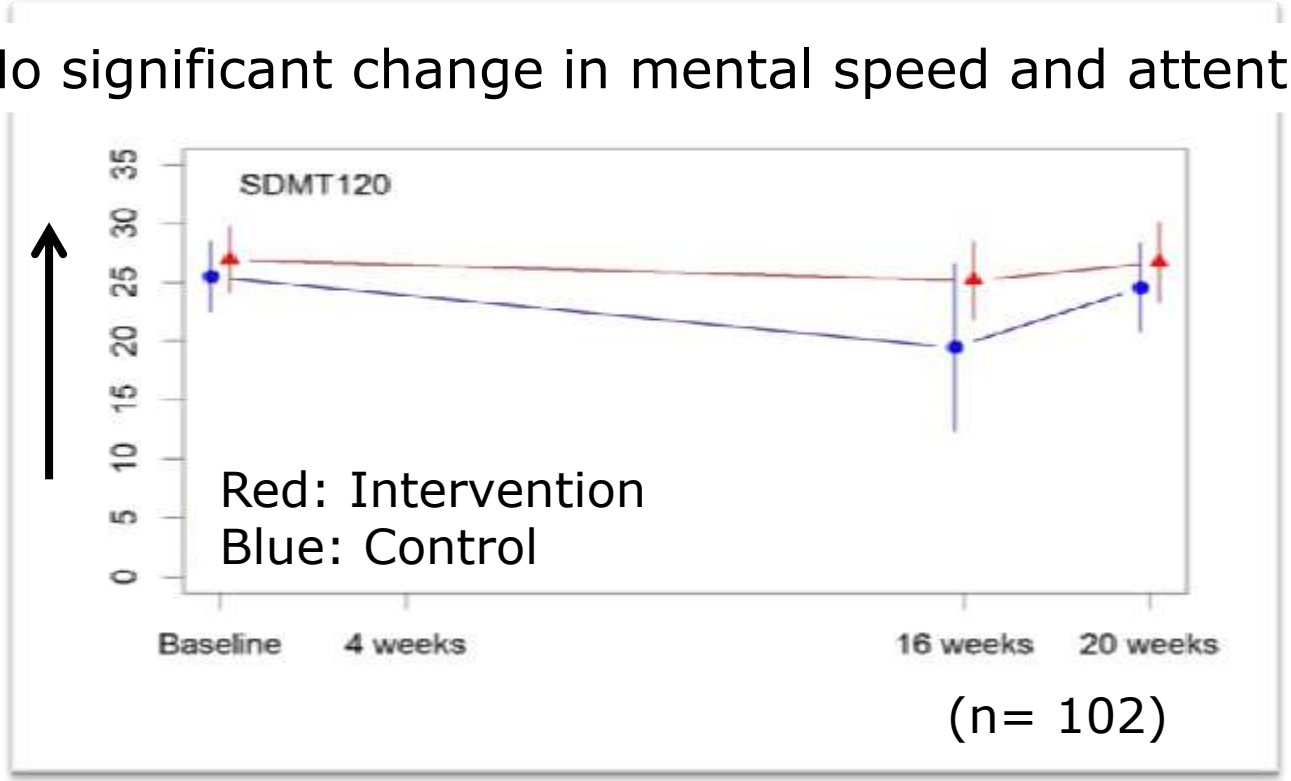
Mean (SD)	Control	Intervention	Total min-max	p-value[1]
Mini-Mental State Examination	24.1 (3.8)	23.8 (3.4)	14-30	0.53
Symbol Digit Modalities Test	25.4 (14.3)	27.1 (14.7)	0-63	0.41
Hamilton Depression Rating Scale 17 items	2.0 (2.5)	1.9 (2.6)	0-11	0.82
Neuropsychiatric Inventory	9.4 (9.7)	10.0(10.8)	0-42	0.70

[1]Fisher'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



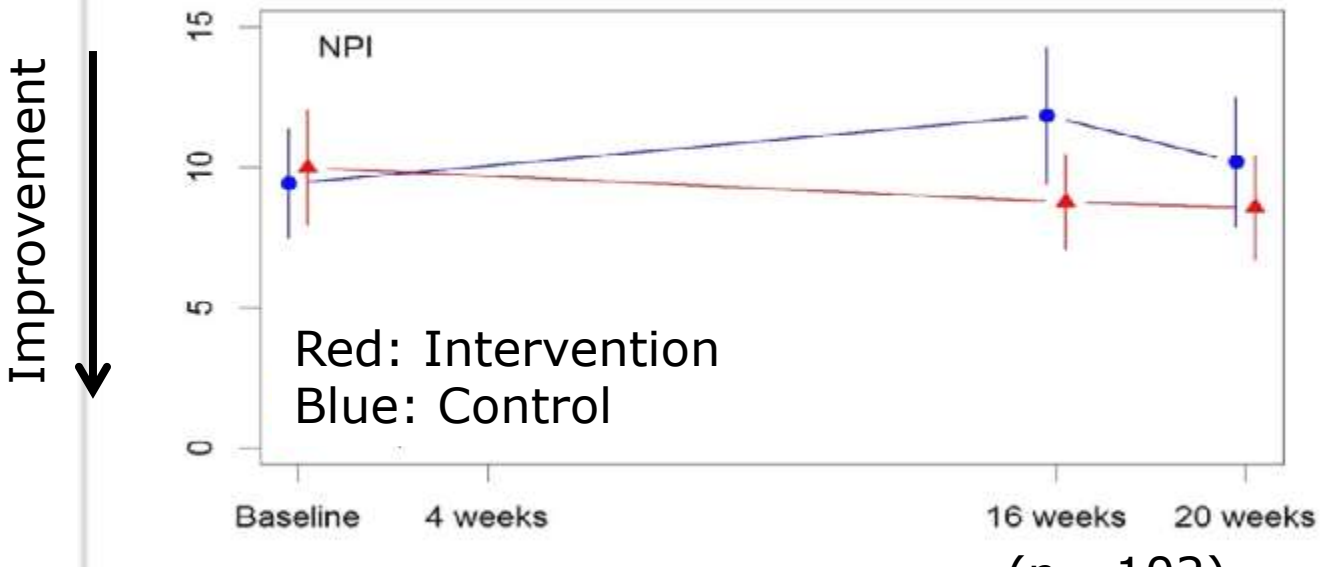
Secondary cognitive outcomes also negative in ITT analysis

*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



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

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

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

		CONTROL	INTERVENTION
	AE	NUMBER (relation to study)	
AE n=58	Musculoskeletal problems	4	12 (6 related)
	Dizziness or faintness	1	10 (6 related)
	Symptoms related to AD	4	3
	Somatic disease (i.e. cold, anemia, erysipelas)	11	10
Total		20	38
	SAE	NUMBER(relation to study)	
SAE n=13	Pneumonia	1	1
	UVI	1	
	Pulmonary edema	1	
	Nephrolithiasis	1	
	Atrial fibrillation		2(1)
	Fracture	2	3
	Cancer mammae		1
Total		6	7

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

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