Could physical activity delay cognitive decline in older adults with vascular risk factors?

The AIBL active study

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Physical activity and vascular risk factors

Underlying mechanisms? Barber et al., 2012

Figure 1. Underlying mechanisms through which physical activity may exert neuro-protective effects. ↑, increased; ↓, decreased; IGF, insulin-like growth factor; BDNF, brain-derived neurotrophic growth factor; VEGF, vascular endothelial growth factor.
Physical activity and vascular risk factors

What do recent systematic reviews find?

Angevaren et al., 2008 (Cochrane): for healthy: “aerobic physical activity which improves cardiorespiratory fitness is beneficial for cognitive function in cognitive healthy older adults“

Hamer & Chida, 2009: 14 observational studies, 27255 participants (92731 incident AD cases): RR for dementia: 0.72 (95% CI: 0.60-0.86) for AD: 0.55 (95% CI: 0.36-0.84)

Sofi et al., 2010: 12 cohort studies, 33816 participants, (3210 cognitive decline): HR for high level PA: 0.62 (95% CI: 0.54-0.70); HR for low-to-moderate level PA: 0.65 (95% CI: 0.57-0.75)

Smith et al., 2010: 1966 – 2009: age: 18y and older (normal, MCI or medical illness); n=29 RCTs (> 1 month; aerobic exercise): modest improvements in attention and processing speed, executive functions and memory.

Wang et al., 2012: 1991-2011: focus on observational studies with follow-up time of at least 2 years: n=23 on outcome cognitive function and n=22 on outcome dementia: huge variation in regards to methodology, but protective effect in 70% for cognitive decline and in 73% for dementia risk.
Figure 1. Effect of aerobic exercise on attention and processing speed ($n = 24$). Individuals randomized to aerobic exercise treatment exhibited improved attention and processing speed relative to controls ($g = 0.158$; 95% confidence interval [CI], 0.055–0.260; $p = .003$). Each study is denoted with a circle, with larger sample sizes corresponding to larger marks.
Figure 2. Effect of aerobic exercise on executive function ($n = 19$). Individuals randomized to aerobic exercise treatment exhibited improved executive function ($g = 0.123$; 95% confidence interval [CI], 0.021–0.225; $p = .018$). Each study is denoted with a circle, with larger sample sizes corresponding to larger marks.
Figure 3. Effect of aerobic exercise on working memory \((n = 12)\). Individuals randomized to aerobic exercise treatment did not exhibit significant improvements in working memory relative to controls \((g = 0.032; 95\% \text{ confidence interval } [CI], -0.103 \text{ to } 0.166; p = .642)\). Each study is denoted with a circle, with larger sample sizes corresponding to larger marks.
### Study Name and Statistics

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Hedges' g</th>
<th>Standard Error</th>
<th>p-Value</th>
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<tbody>
<tr>
<td>Blumenthal, 1989</td>
<td>-0.066</td>
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<td>Fabre, 2002</td>
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<td>Hassmen, 1992</td>
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<td>Hoffman, 2008</td>
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<td>Khatri, 2001</td>
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<td>Kramer, 2002</td>
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<td>Lautenschlager, 2008</td>
<td>0.322</td>
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<td>Moul, 1995</td>
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<td>Oken, 2004</td>
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<td>Oken, 2006</td>
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<td>Perri, 1985</td>
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<td>Pierce, 1993</td>
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<td>Scherder, 2005</td>
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<td>Stroth, 2009</td>
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<td>van Uffelen, 2008</td>
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<td>Williamson, 2009</td>
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<td>0.128</td>
<td>0.058</td>
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**Figure 4.** Effect of aerobic exercise on memory ($n = 16$). Individuals randomized to aerobic exercise treatment exhibited improved memory relative to controls ($g = 0.128$; 95% confidence interval [CI], 0.015–0.241; $p = .026$). Each study is denoted with a circle, with larger sample sizes corresponding to larger marks.
Physical activity and vascular risk factors

What do recent systematic reviews find?

Forbes et al., 2008 (Cochrane): dementia: “There is insufficient evidence to determine the effectiveness of physical activity programs in managing or improving cognition, function, behaviour, depression, and mortality in people with dementia.”

Orgeta et al., 2010 (Cochrane): protocol for PA in MCI

Blankevoort et al., 2010: dementia: 16 clinical trials: physical functioning can be improved at almost all stages of dementia and combinations of different types of PA work better; 4 studies included ADLs as outcome with inconsistent results

Littbrand et al., 2011: dementia: 10 RCTs included: only 4 RCTs of moderate quality: benefits on ADLs and mobility, no effects on cognition. Whether PA can improve cognitive function in dementia is unclear

Potter et al., 2011: dementia: 13 RCTs included: some physical improvement (walking speed, getting out of chairs, lower limb strength, flexibility – higher intensity more effective). Very limited evidence for depression and QoL

Tseng et al., 2011: from 2006-2009: 12 trials (normal or cognitive impairment): 8 of 12 showed cognitive benefit: needed to be at least 6 weeks and 3 times per week for 60min. If normal cognition multi-component better, if cognitively impaired single-component better.

Hahn & Andel, 2011: from 2000-2010: only MCI: n=5 trials: positive effects on executive functions, but not much on memory and recommendations to target high intensity physical activity.
Investigated systematic reviews on the risk factors: cognitive inactivity, smoking, physical inactivity, depression, midlife hypertension, diabetes and midlife obesity

AD attributable to:

- 2% diabetes mellitus
- 2% midlife obesity
- 5% midlife hypertension
- 10% depression
- 13% physical inactivity
- 14% smoking
- 19% cognitive inactivity
Physical activity and vascular risk factors

- Up to 50% of AD cases might be attributable to these factors
- If prevalence would be 10% lower: 1.1 million fewer AD cases worldwide
- If prevalence would be 25% lower: 3.0 million fewer AD cases worldwide
- Based on the assumption that there is a causal relationship and that risk factor removal will lower AD incidence
- Targeting multiple risk factors might be necessary

Barnes & Yaffe, 2011
Physical activity and vascular risk factors

The vascular risk factor and AD connection

Vascular disease risk factors
- Stroke, hypertension, diabetes, dyslipidemia, obesity, atherosclerosis,
  - Vessel wall changes
  - Hypoperfusion (Oligemia/Ischemia)
    - (microinfarction)
    - White matter lesions
    - Axonal pathology (disconnection)
  - AD
    - Neurofibrillary pathology
    - ↑APP/Aβ
    - VaD/PSD/VCI

Host factors
- Age
- Genes
- Lifestyle

Progression

Kalaria, 2010
Areas of increased signal on T2-weighted MRI scans

Common in old age (11-21% at age 64y to 94% at age 82y)

Etiology not entirely clear (ischemia, neurodegeneration, inflammation, hypoperfusion, disruption of blood-brain barrier, etc.)

Pathology: heterogenous → arteriosclerosis, gliosis, demyelination (disruption of neural circuitry)

Associated with stroke, executive dysfunction, dementias (including AD), MI, problems with motor function and gait, neuropsychiatric symptoms and increased mortality (depends on affected region)

Gouw et al., 2008; Silbert et al., 2008; Debette & Markus, 2010; Warsch & Wright, 2010; Murray et al., 2011
Physical activity and vascular risk factors

White matter changes and cognition and gait over time
104 cognitive healthy older adults, follow-up of 13 years: subcortical (cognition) and periventricular (gait)

Figure 1
Relationship between baseline periventricular white matter hyperintensity (WMH) volume and rate of change of gait performance over time

Figure 2
Relationship between rate of subcortical white matter hyperintensity (WMH) volume change and rate of cognitive change over time

Silbert et al., 2008
Physical activity and vascular risk factors

Observational: treatment of vascular risk factors in AD: does it make a difference?

Observational study, memory clinic
301 patients with AD without CVD
Mean follow-up: 2.3 years

Figure 2: Multivariate mixed random effects regression model of MMSE progression over time in patients with AD without CVD

Model is adjusted for age, sex, education level, first Mini-Mental State Examination (MMSE) score, cholinesterase inhibitor use, number of vascular risk factors (VRF), year of first visit, duration of symptoms before first visit, and propensity score. AD = Alzheimer disease; CVD = cerebrovascular disease.

Deschaintre et al., 2009
Physical activity and vascular risk factors

RCT: does vascular care make a difference in AD?

RCT with 123 patients with AD: vascular care vs standard over 2 years
Vascular care: treating vascular risk factors as good as possible with lifestyle advice and medication, 3 monthly follow-ups

Result: significant less progression of WMH in vascular care group (p=0.009). No clinical sig. difference, so is AD dementia stage too late?

Figure. White matter lesion change score in the SC group and the VC group.

Richard et al., 2010
Physical activity and vascular risk factors

**aibl Active: physical activity RCT for aibl participants**

- 24 months home-based physical activity intervention with Melbourne aibl (FABS extra long)
- Participants: subjective memory complaints or MCI ≥ 60 years
- Need to have at least one CVD risk factor: ↑body mass index and waist circumference, hypertension, dyslipidemia, diabetes mellitus or insulin resistance, tobacco smoking, atherosclerotic disease
- Primary outcome: change on WMH on follow-up MRI at 24 months
- Secondary outcomes: cognition, fitness, QoL, depression scores, functional levels, plasma biomarkers, other pathologies on MRI, interaction between WMH and PET amyloid load
- Results expected: end of 2014
# Physical activity and vascular risk factors

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<th>Investigators</th>
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<td>Dr Christopher Fowler</td>
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<td>Prof David Ames</td>
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<td>Prof Ralph Martins</td>
<td>Mr Brett Trounson</td>
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<th>Melbourne Health</th>
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<td>Dr Elizabeth Cyarto</td>
<td>Prof Danny Liew</td>
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<td>Dr Michelle Lai</td>
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<td>Ms Caroline Marczak</td>
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<td>Ms Freda Vrantsidis</td>
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Physical activity and vascular risk factors

Work to do….

- Aim for Standardisation across studies
- Exposure age, type of PA, intensity, duration, biomarkers
- Clinical significance
- Better observational studies where RCTs are not possible? Or pooling of data?
- Multidomain RCTs? In different age groups?
- Public health campaigns instead of RCTs? Health economics
- Wait with RCTs until biological rational is discovered?

In the meantime in the clinical setting….

- Encourage screening and best possible management of vascular risk factors, esp. in primary care
- Inform about the potential of protective factors
- Point out limits of current knowledge, but multiple benefits expected
- If symptomatic follow up regularly
- Encourage research participation

Ganguli & Kukull, 2010; Middleton & Yaffe, 2010; Plassman et al., 2010; Ellison, 2008; Petersen et al., 2011; Lautenschlager et al., 2010 & 2012
Fitness of the Ageing Brain Study II

FABS II - multicentre RCT (Melbourne, Perth, Brisbane)
Patients with mild to moderate Alzheimer’s Disease will be randomised to physical activity or usual care
Intervention for 24 weeks, follow-up for 12 months, carer participates as “coach”
Inclusion criteria: AD, MMSE > 9, carer available, lives in the community, can exercise, fluent in English
Outcomes: Cognition on ADAS-cog, BPSD, functional level, quality of life, carer’s burden

If you are interested in FABS II please contact NARI
Project coordinator: Dr. Liz Cyarto
Phone: 8387 2305
Email: e.cyarto@nari.unimelb.edu.au