Role of Physical Exercise in Promoting Cognitive and Mobility Outcomes in Older Adults

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Overview

Context → Studies → Conclusions
• Impaired cognitive function and mobility are “geriatric giants” that significantly increase morbidity and mortality

• Often co-exist and thus, likely share common pathophysiology
  – Cerebral small vessel disease
  – Amyloid
Cerebral Small Vessel Disease

Risk factors
- Age
- Hypertension
- Diabetes
- Dyslipidemia

These “silent” lesions are associated with increased risk of stroke, slow gait, falls, and dementia.
Cerebral Amyloid-Beta

- Cerebral Aβ (PiB-PET) in older adults without dementia is associated with:
  - Falls over 12 months
    » Stark *et al.*, Neurology, 2013
  - Slow gait
    » Nadkami *et al.*, JAMA Neurology, 2017
  - Age-related mobility decline
    - Decreased cadence and increased double support time
      » Wennberg *et al.*, J of Geron, 2018
Interplay: Cognition & Mobility

Cognitive Impairment → MCI → Dementia Syndromes
Cognitive Impairment ← Gait & Mobility Impairments ← Slow Gait ← Falls & Fractures

Montero-Odasso et al., JGMS, 2018

Spectrum of cognitive and mobility decline in aging and neurodegeneration
RCTs of Exercise

Cognition

Falls
GCBH experts agree that brain health is positively affected by physical activity. Purposeful exercise is proven to benefit brain structure and functioning, while an active lifestyle is proven to lower risk of cognitive decline.
Cohort
- No prescribed treatment/intervention
- Physical activity level
  - Questionnaires
  - Accelerometry data

Randomized Controlled Trials
- Treatments/interventions are randomly prescribed
- Purposeful exercise

Baseline Measurement

Randomization

Follow-Up Measurement

Aerobic Training
- Follow-Up Measurement

Resistance Training
- Follow-Up Measurement

Sham Exercise
- Follow-Up Measurement
Physical Activity & Dementia Risk

Larson et al., Annals of Internal Medicine, 2006
Results — Mixed effects models showed no association between physical activity and subsequent 15 year cognitive decline. Similarly, Cox regression showed no association between physical activity and risk of dementia over an average 27 year follow-up (hazard ratio in the “recommended” physical activity category 1.00, 95% confidence interval 0.80 to 1.24). For trajectories of hours/week of total, mild, and moderate to vigorous physical activity in people with dementia compared with those without dementia (all others), no differences were observed between 28 and 10 years before diagnosis of dementia. However, physical activity in people with dementia began to decline up to nine years before diagnosis (difference in moderate to vigorous physical activity −0.39 hours/week; P=0.05), and the difference became more pronounced (−1.03 hours/week; P=0.005) at diagnosis.
Moderate to vigorous physical activity (hours/week) vs. Years before dementia diagnosis.

- **Dementia free**
- **Dementia cases**

P = 0.001

*BMJ 2017;357:j2709 doi: 10.1136/bmj.j2709 (Published 22 June 2017)*
Previous findings showing a lower risk of dementia in physically active people may be attributable to reverse causation – that is, due to a decline in physical activity levels in the preclinical phase of dementia.
Exercise is Medicine

• Exercise
  – Subcategory of PA

• Types of Exercise
  – Aerobic Training
  – Resistance Training
  – Anaerobic Training
  – Balance/Agility Training
  – Multimodal
  – Others: Yoga, Tai Chi, dance
Domains of Cognition

• Hippocampal-Dependent Memory
  – Impairment common in dementia
  – Impairment associated with conversion from mild cognitive impairment (MCI) to AD

• Executive Functions
  – Planning, decision making, multi-tasking
  – Sensitive to aging effects
  – Impairment common in dementia
Response Inhibition: Stroop Test
Response Inhibition: Flanker Test

Fixation

Pre Cue

Congruent

or

Incongruent
Set Shifting: Trail Making Test

Trails A

8  1  4  3  2  5  9

Trails B

A  1  2
D  B
E  3  5  4
Working Memory: Digit Span

• 4 – 8 – 2 → 2 – 8 – 4
• 9 – 3 – 1
• 6 – 3 – 4 – 7
• 2 – 3 – 7 – 4 – 5 – 1 – 9
Aerobic Training Improves Executive Functions and Associated Functional Plasticity

- A 6-month, 3x/week (moderate-intensity) walking program improved:
  - Selective attention and response inhibition (Ericksen Flanker Task)
    » Colcombe et al., PNAS, 2004
  - Functional plasticity associated with Flanker Task performance
  - Neural efficiency
Aerobic Training Improves Memory and Increases Hippocampal Volume

• A 12-month, 3x/week (moderate-intensity) walking program improved/increased:
  – Cognitive performance of spatial memory
  – Hippocampus volume by 2%
    • Reversing age-related loss in volume by 1-2 years
      » Erickson et al., PNAS, 2011
Aerobic Training and Mild VCI

• A 6-month, 3x/week (moderate-intensity) walking program improved/increased:
  – Memory performance (ADAS-Cog)
  – Neural efficiency (Flanker Task)
    » Liu-Ambrose et al., Neurology, 2016
    » Hsu et al., BJSM, 2017

* VCI = Vascular Cognitive Impairment
  • Neuroimaging evidence of cerebral small vessel disease
  • MoCA < 26/30
  • No impairment in iADLs
Aerobic Training may be Particularly Beneficial for Females

Barha et al., JAD, 2017
Aerobic Training Promotes Circulating BDNF Levels (in Females)

BDNF=brain derived neurotrophic factor

Barha et al., JAD, 2017

* P < 0.05
What about **resistance training**?
Lifting Weights is a Good Option!

Liu-Ambrose et al., 2010 & 2011
Nagamatsu et al., 2012 & 2013
Bolandzadeh et al., 2015
Resistance Training for Brain Health

- Women aged 65 to 75 years
- Otherwise healthy & community-dwelling

Liu-Ambrose et al., 2010 & 2011

Baseline Measurement

155 Randomized

1x/week Resistance Training
- 12-Month Measurement

2x/week Resistance Training
- 12-Month Measurement

2x/week Balance & Tone Exercises
- 12-Month Measurement
Resistance Training Improves Executive Functions and Functional Plasticity

- Lifting weights 1x/week or 2x/week significantly improved executive functions.
- Lifting weights 2x/week induced functional plasticity during the Flanker task.
Improved cognitive performance significantly associated with increased gait speed ($r=0.24; p<0.01$).
Lifting weights 2x/week significantly reduced progression of white matter lesions.

» Bolandzadeh et al., JAGS, 2015
Reduced WML progression was associated with maintenance of gait speed \((r=0.31, p=0.04)\) and to a lesser degree, with improved Stroop Test performance \((r=0.30, p=0.06)\).
RCTs of Exercise

Cognition

Falls
Aged 70 years and older

Presented to a health care provider (ED or GP) due to a fall

Liu-Ambrose et al., JAMA, 2019
Liu-Ambrose et al., JAGS, 2008

Baseline Measurement

344 Randomized

Otago Exercise Program (OEP)

Usual Care (CON)

6- & 12-Month Measurement

Primary Aim: To assess the efficacy of exercise as a secondary falls prevention strategy.
Otago Exercise Program (OEP)

- Home-based, delivered by PT
  - Strength and balance retraining (3x/week)
  - Walking (2x/week)

  » Campbell et al., BMJ, 1997 & 1999
Knowledge Gaps

1. Whether OEP reduces falls in older adults who have previously fallen is not established.
2. How does exercise reduce falls?
Participants

• All were patients of the Vancouver Falls Prevention Clinic (www.fallsclinic.ca)
• Referrals to the Vancouver Falls Prevention Clinic are from physicians for older adults who sought medical attention after a fall
• In addition, demonstrate risk for future falls based on clinic screening measures
Intervention Arms

• Usual Care (CON)
  – Falls risk factor assessment and a comprehensive assessment by a geriatrician
  – The care pathway is based on the American Geriatrics Society/British Geriatrics Society/American Academy of Orthopaedic Surgeons Falls Prevention Guidelines
Intervention Arms

• Otago Exercise (OEP)
  – Usual Care + OEP
  – Home-based, delivered by PT
    • 5 home visits over 6 months
  – Strength and balance retraining (3x/week)
    • Manual provided with monthly check ins by RA
  – Walking (2x/week)
  – Monthly calendars tracked compliance
    » Campbell et al., BMJ, 1997 & 1999
Primary Outcome

• Self-reported number of falls over 12 months
• Documented prospectively on monthly calendars
• Monthly phone calls to verify calendar information and circumstances of falls
Secondary Outcomes

- Executive Functions
- Physiological Profile Assessment (PPA)
- Timed Up and Go Test (TUG)
- Short Physical Performance Test (SPPB)
## Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>CON</th>
<th>OEP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CON n = 172</strong></td>
<td><strong>OEP n = 172</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td>81.9 (6.0)</td>
<td>81.2 (6.1)</td>
</tr>
<tr>
<td><strong>Sex, male</strong></td>
<td>53 (31%)</td>
<td>62 (36%)</td>
</tr>
<tr>
<td><strong>Number of Falls 12M Prior, n (%)</strong></td>
<td>3.0 (4.3)</td>
<td>2.8 (2.3)</td>
</tr>
<tr>
<td><strong>Number of Fall-Related Fractures 12M Prior, n (%)</strong></td>
<td>32 (19)</td>
<td>33 (18)</td>
</tr>
<tr>
<td><strong>Use of Walker, Brace, or Cane, n (%)</strong></td>
<td>37 (22%)</td>
<td>46 (27%)</td>
</tr>
<tr>
<td><strong>Geriatric Depression Scale</strong></td>
<td>3.0 (2.6)</td>
<td>2.8 (2.4)</td>
</tr>
<tr>
<td><strong>Functional Comorbidity Index</strong></td>
<td>4.0 (2.0)</td>
<td>4.1 (2.2)</td>
</tr>
<tr>
<td><strong>Instrumental Activities of Daily Living</strong></td>
<td>7.4 (1.1)</td>
<td>7.2 (1.2)</td>
</tr>
<tr>
<td><strong>Mini-Mental State Examination (30 pts max)</strong></td>
<td>27.9 (1.6)</td>
<td>27.7 (1.7)</td>
</tr>
<tr>
<td><strong>Montreal Cognitive Assessment (30 pts max)</strong></td>
<td>23.4 (3.3)</td>
<td>22.9 (3.4)</td>
</tr>
<tr>
<td><strong>Timed-Up and Go Test, sec</strong></td>
<td>16.9 (6.4)</td>
<td>16.3 (7.0)</td>
</tr>
<tr>
<td><strong>Short Physical Performance Battery (12 pts max)</strong></td>
<td>7.8 (2.3)</td>
<td>7.9 (2.2)</td>
</tr>
<tr>
<td><strong>Gait Speed, m/s</strong></td>
<td>0.8 (0.2)</td>
<td>0.9 (0.2)</td>
</tr>
<tr>
<td><strong>OEP Compliance</strong></td>
<td>NA</td>
<td>63%</td>
</tr>
</tbody>
</table>
Results

• Compared with the CON group, the OEP group:
  – Experienced 36% fewer falls (Incident Rate Ratio = 0.64, 95% CI: 0.46, 0.90, $p = .009$)
  – Improved executive functions, specifically processing speed ($p = .047$)
  – No significant differences in PPA, TUG, or SPPB
• OEP-induced reductions in falls were partially mediated by changes in processing speed
OEP Reduced the Rate of Falls

Liu-Ambrose et al., JAMA, 2019
OEP Improved Processing Speed (DSST)
### Improved Processing Speed: Possible Mechanism of Falls Reduction

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Predictor</th>
<th>IRR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male</td>
<td>1.72</td>
<td>1.24 to 2.38</td>
<td>.001</td>
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<tr>
<td>Group</td>
<td>0.64</td>
<td>0.46 to 0.89</td>
<td>.008</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 2</th>
<th>Predictor</th>
<th>IRR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male</td>
<td>1.66</td>
<td>1.20 to 2.31</td>
<td>.002</td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>0.69</td>
<td>0.49 to 0.95</td>
<td>.026</td>
<td></td>
</tr>
<tr>
<td>Change in DSST</td>
<td>0.80</td>
<td>0.68 to 0.95</td>
<td>.008</td>
<td></td>
</tr>
</tbody>
</table>

DSST change accounted for 9% of the effect of OEP on falls reduction.
Discussion

• OEP is an efficacious secondary falls prevention strategy

• Improved processing speed may be an underlying mechanism by which OEP reduces falls
Discussion

• Processing speed, as measured by DSST, is a predictor of future falls among older fallers
  – Predicts a greater number of total, indoor, outdoor, and non-injurious falls
  – Also, greater likelihood of one mild or severe injurious fall
    » Davis et al., JAGS, 2017
Discussion

• The elephant in the room
  – No significant changes in falls risk and mobility outcomes

• Prior pilot work in the same high-risk population demonstrated similar findings
  » Liu-Ambrose et al., JAGS, 2008
Discussion

• Despite demonstrating an overall effect of reducing the number of falls by 35%, the OEP did not significantly improve balance and only small gains for lower extremity strength were observed
  » Robertson et al., JAGS, 2002

• Improved cognition may be unrecognized pathway by which exercise improves mobility and reduces falls
  » Liu-Ambrose et al., BJSM, 2012
Interplay: Cognition & Mobility

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Gait & Mobility Impairments

Slow Gait → Falls & Fractures

Montero-Odasso et al., JGMS, 2018

Spectrum of cognitive and mobility decline in aging and neurodegeneration
Overview

Context → Studies → Conclusions
Conclusions: Cognition

- Sufficient evidence for exercise to be included in practice guideline on mild cognitive impairment
Conclusions

• Multimodal training likely provides the most benefit
Conclusions

• Physical activity is a legitimate medical therapy for promoting cognitive health
  – Degree of benefit equal or exceeds that of pharmaceutical agents
  – Minimal adverse effects

• Reducing physical inactivity by 25% could prevent one million cases of dementia worldwide
  » Barnes and Yaffe, Lancet Neurol, 2011
Conclusions: Falls

• Exercise reduces falls by promoting physical and cognitive function

• Growing interest in:
  – Pairing cognitive training with exercise training
    • Sequential or concurrent
  – Adding or increasing cognitive load to exercise
    • Tai Chi

• The inclusion of measures of cognitive function in falls risk screening, especially in high-risk groups
“Refusing to go to the gym is not the same thing as resistance training.”
Conclusions

- As a profession, we are well situated to promote physical activity as a strategy for healthy aging
  - Not to just for rehabilitation purposes, but for prevention and overall health
    - Recurring theme of CPA 2019
- Common barriers to physical activity/exercise uptake and adherence are magnified among those with impaired cognition (even without dementia) and mobility
Conclusions

• Clear communication to minimize anxiety and confusion, repeat often
  – Telehealth

• Facilitate compliance
  – Personalize as appropriate
  – Encourage problem-solving and discussion
  – Establish achievable goals, monitor progress, and provide feedback often
  – Make it bite size/manageable = exercise “snacks”
    • Bouts of activity can be very beneficial
Conclusions

• Facilitate compliance (cont.)
  – Involve caregivers and friends (as appropriate)
  – Encourage socialization

• Change perspective

Limiting our daily sitting/lying to just 23.5 hours: too ambitious?

Karim Khan

Thank you to BJSM guest editor Steven Blair and all our January and February authors (http://bjsm.bmj.com/content/).