Exercise and Brain Health

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The scope of Alzheimer’s Disease

- 5.4 million Americans
- Age associated
  - 65 years: 1 in 9
  - 85 years: 1 in 3
- Health care burden

Courtesy: Alzheimer's Association
Effect of Medications on AD Course

Investigational Medicines

• Approved drugs alleviate symptoms but do not stop the underlying disease.

• Current investigational disease-modifying medications are primarily focused on amyloid:
  • Tricking the body into digesting amyloid by tagging it with an antibody (like when you have an infection)
  • Blocking the formation of amyloid
Results of Amyloid Therapeutics

- **2005: AN-1792**: active Abeta vaccination (Phase 2)
  - 300 AD participants – halted due to meningoencephalitis
  - Fewer Abeta plaques in brain despite dementia progression
- **2008: Flurizan (tarenflurbil)**: reduces amyloid levels
  - 1649 mild AD participants: no evidence of efficacy
- **2009: Alzhemed (tramiprosate)**: inhibits Abeta formation and deposition
  - 1052 AD participants: no evidence of efficacy
- **2010: Semagacestat**: gamma secretase inhibitor
  - 2600 AD participants: halted early due to greater rates of progression
- **2012: Bapinezumab**: antibody for amyloid
  - No effect in those 2400 patients with or without the ApoE4 genetic risk
- **2016: Solanezumab**: antibody for amyloid
  - Minimal clinical benefit in 2100 patients with known elevated amyloid burden
- **2017: Verubecestat**: BACE inhibitor blocks the first step in amyloid formation
  - Halted early due to no effect
- **2018: Azeliragon**: RAGE inhibitor thought to block a key element of plaque formation
  - No evidence of efficacy
- **2018: Crenezumab**: antibody for amyloid
  - Halted early due to no effect

Natural Selection – beneficial traits that are heritable increase in frequency over time.
1) Physical activity/fitness/strength obligatory for survival?
2) Thrifty Genes – highly efficient – store and conserve energy
### Physical Activity: Then vs. Now

<table>
<thead>
<tr>
<th>Group</th>
<th>Steps/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paleolithic Stone Agers¹</td>
<td>24,000</td>
</tr>
<tr>
<td>Amish²</td>
<td>18,000 (men)</td>
</tr>
<tr>
<td></td>
<td>14,000 (women)</td>
</tr>
<tr>
<td>Colorado²</td>
<td>6,733 (men)</td>
</tr>
<tr>
<td></td>
<td>6,384 (women)</td>
</tr>
<tr>
<td>26 studies with 2767 subjects⁵</td>
<td>7,473</td>
</tr>
<tr>
<td></td>
<td>(range, 2,140–12,371)</td>
</tr>
<tr>
<td>Drew (Pennington)⁴</td>
<td>Mean = 5,000</td>
</tr>
<tr>
<td></td>
<td>16% of 463 &lt; 3,000</td>
</tr>
<tr>
<td>1136 subjects⁵</td>
<td>5,117</td>
</tr>
</tbody>
</table>


>90% of US citizens do not get enough exercise
What kind of exercise?

- Aerobic
- Resistance
- Stretching
- Balance Training

Guidelines

- ≥150 minutes/week moderate aerobic activity or ≥75 minutes vigorous aerobic activity (HHS¹, ACSM², WHO³)
- Resistance exercise at least 2 days/week (HHS, ACSM, WHO)
- Flexibility (e.g., yoga) 2-3 days/week (ACSM)
- “Neuromotor” (functional, balance) 2-3 days/week (ACSM, WHO)

¹Dept. Health & Human Services (2018)
²American College of Sports Medicine (2011)
³World Health Organization (2012)
Evidence?

Exercise

- Benefits patients with dementia

Groot et al., 2016
Exercise

- Decreases risk of cognitive decline

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Risk ratio</th>
<th>Weight</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bok et al. [10]</td>
<td>2.7%</td>
<td>0.13</td>
<td>0.21 - 1.52</td>
</tr>
<tr>
<td>Bok et al. [9]</td>
<td>5.3%</td>
<td>0.11</td>
<td>0.22 - 2.07</td>
</tr>
<tr>
<td>Larsson et al. [8]</td>
<td>4.8%</td>
<td>0.66</td>
<td>0.35 - 1.23</td>
</tr>
<tr>
<td>Larsson et al. [10]</td>
<td>3.8%</td>
<td>0.47</td>
<td>0.21 - 0.99</td>
</tr>
<tr>
<td>Bluhm et al. [11]</td>
<td>1.9%</td>
<td>0.11</td>
<td>0.58 - 1.43</td>
</tr>
</tbody>
</table>

Sofi et al., 2010

- May prevent Alzheimer’s disease!

Exercise

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Risk ratio</th>
<th>Weight</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scarmeas et al. [15]</td>
<td>20.73%</td>
<td>-0.46</td>
<td>[-0.83, -0.11]</td>
</tr>
<tr>
<td>Buchman et al. [9]</td>
<td>7.74%</td>
<td>-0.63</td>
<td>[-1.22, -0.05]</td>
</tr>
<tr>
<td>Scarmeas et al. [13]</td>
<td>9.20%</td>
<td>-0.73</td>
<td>[-1.27, -0.20]</td>
</tr>
<tr>
<td>Larson et al. [14]</td>
<td>14.96%</td>
<td>-0.37</td>
<td>[-0.79, 0.05]</td>
</tr>
<tr>
<td>Lindsay et al. [12]</td>
<td>24.18%</td>
<td>-0.37</td>
<td>[-0.70, -0.04]</td>
</tr>
<tr>
<td>Podewils et al. [7]</td>
<td>11.94%</td>
<td>-0.36</td>
<td>[-0.83, 0.11]</td>
</tr>
<tr>
<td>Abbott et al. [16]</td>
<td>4.69%</td>
<td>-0.90</td>
<td>[-1.54, 0.00]</td>
</tr>
<tr>
<td>Yoshitake et al. [17]</td>
<td>1.77%</td>
<td>-1.71</td>
<td>[-2.94, -0.49]</td>
</tr>
<tr>
<td>Ravaglia et al. [18]</td>
<td>4.62%</td>
<td>-0.35</td>
<td>[-1.11, 0.40]</td>
</tr>
</tbody>
</table>

FE Model

Sofi et al., 2010

Beckett et al., 2015
Exercise, Hippocampal Volume, and Memory Performance in Older Adults


Improving Fitness -> Bigger Brain

Hyperinsulinemic-euglycemic clamp shows insulin resistance in AD

More insulin sensitive (FASTER infusion to maintain glucose level, efficient glucose uptake)

More insulin resistant (SLOWER infusion to maintain glucose level, efficient glucose uptake)

Impaired meal-stimulated metabolic response in AD

Figure 1. Metabolic response to a mixed meal
A) Glucose  B) Insulin  C) C-peptide  D) GIP

Morris et al, in preparation
CNS insulin resistance in AD

- Receptors widely distributed
- Increasing plasma insulin increases insulin binding in hippocampus

Morris et al. 2012

Insulin resistance is negatively correlated with brain volume in aging and AD

Morris et al. 2014, Neuroscience
Cerebral glucose hypometabolism: a marker of AD


Impaired fasting glucose and progression of cognitive impairment

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline</th>
<th>2yr A</th>
<th>p-value</th>
<th>Δ MCI to AD converters*</th>
<th>Δ CDR SB*</th>
<th>Δ Global Cognition*</th>
<th>Δ Whole Brain Volume*</th>
<th>Δ Hippocampal Volume*</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCI to AD converters*</td>
<td>Normal</td>
<td>0.015</td>
<td>0.02</td>
<td>0.006</td>
<td>0.046</td>
<td>0.001</td>
<td>0.002</td>
<td>0.045</td>
</tr>
<tr>
<td>CDR-SD*</td>
<td>Baseline</td>
<td>1.56</td>
<td>1.61</td>
<td>0.044</td>
<td>0.044</td>
<td>0.001</td>
<td>0.001</td>
<td>0.044</td>
</tr>
<tr>
<td>Global Cognition*</td>
<td>Baseline</td>
<td>0.615</td>
<td>0.764</td>
<td>0.019</td>
<td>0.019</td>
<td>0.001</td>
<td>0.001</td>
<td>0.019</td>
</tr>
<tr>
<td>Whole Brain Volume*</td>
<td>Baseline</td>
<td>0.677</td>
<td>0.672</td>
<td>0.002</td>
<td>0.002</td>
<td>0.001</td>
<td>0.001</td>
<td>0.002</td>
</tr>
<tr>
<td>Hippocampal Volume*</td>
<td>Baseline</td>
<td>0.655</td>
<td>0.642</td>
<td>0.039</td>
<td>0.049</td>
<td>0.001</td>
<td>0.001</td>
<td>0.039</td>
</tr>
</tbody>
</table>

Morris et. al. 2014, NBA
Glycemic intake is related to regional cerebral amyloid

Taylor et al, Am J Clin Nutrition, 2017

Impaired fasting glucose is related to regional cerebral amyloid

Morris et al 2016, NBA
Potential therapies (metabolism)

- Intranasal insulin
- Insulin sensitizers
- Mediterranean diet
- Ketogenic diet
- Exercise

AD and ND subjects differ in fitness

- AD subjects have lower VO2 peak (Vidoni et al. 2012)
- Greater decline in VO2 over time
- Confounding effects of sex, genotype?
Exercise in Aging and AD

- **BAP** (Brain Aging Project: 2006-2008)
  - Longitudinal observational study, ND and AD
- **TEAM** (Trial of Exercise on Aging and Memory: 2008-2013)
  - Exercise trial, cognitively healthy elderly
- **ADEPT** (Alzheimer’s Disease Exercise Program Trial: 2010-2015)
  - Exercise trial, probable AD
- **APEX** (Alzheimer’s Prevention through Exercise: 2014-ongoing)
  - Exercise trial, cognitively healthy elderly “at risk” for AD

TEAM (Cognitively healthy elderly)

Vidoni et al. 2015, Plos ONE
**ADEPT (Alzheimer’s Disease)**

- **Aerobic Exercise**
- **S/T control**

**Over 6 months**
- AEx group maintained (+1.5)
- ST group declined (-4.5)

Normal course of AD equates to loss of 1 point per month

*Morris, Vidoni et al 2017, Plos ONE*

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**Fitness change tracks with memory change in exercising AD subjects**

*Morris, Vidoni et al 2017, PLOS One*
Summary of past KU ADC trials

- Modest fitness gain overall in AD compared to ND elderly
  - Good compliance and benefit in functional fitness (6 min walk)

- Subjects with early AD may have a limited or more variable physiologic response to exercise
  - Disease severity

- Do inherent physiological differences limit cardiorespiratory fitness response?
  - Can these differences be overcome (and underlie benefit)?

ADMIT – Aging and Disease Mitochondria

Cross sectional study, 2 visits
- Visit 1: Cardiorespiratory fitness assessment (treadmill)
- Visit 2: Fasting blood draw & muscle biopsy

- Goals:
  - 1) Compare mitochondrial energy metabolism in cognitively normal elderly and mild cognitive impairment
  - 2) Determine the relationship between muscle mitochondrial metabolism and whole-body cardiorespiratory fitness
MCI subjects exhibit impaired mitochondrial function in muscle

Mechanisms

- Increased blood flow/vascularization
- Neurotrophins (e.g., BDNF; IGF-1)
- Neurogenesis
- Reduce aggregation of pathogenic proteins
Rodent Exercise Protocols

Endurance/Aerobic

Resistance

Exercise in a Tau Pathology Mouse Model

Belarbi et al., 2011
Exercise in a PS2 Mouse Model

Um et al., 2011
Um et al., 2011

Strength training in rats?
Isometric Forelimb Press-While-Licking Task


Aged Sprague-Dawley Rats
Isometric forelimb force training increases bone mineral density

Rat Groups: LCR and HCR

- Low Capacity Runners (LCR):
  - Greater body weight
  - Lower metabolism
  - Lower voluntary wheel running
  - Cognitive deficits and ↑pTau @ 22 months
LCR vs HCR Data

Task Engagement
Resistance Exercise Performance

Heat-Treatment, Exosomes & β-Amyloid Accumulation

PC Geiger lab
HSP72 in Exosomes from Trained LCR Rats = HCR Rats

Value of Delaying AD Onset

<table>
<thead>
<tr>
<th></th>
<th>Individuals without AD</th>
<th>Individuals with AD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2010</td>
<td>2030</td>
</tr>
<tr>
<td>Medicare</td>
<td>10,904</td>
<td>16,143</td>
</tr>
<tr>
<td>Medicaid</td>
<td>1,700</td>
<td>1,949</td>
</tr>
<tr>
<td>Total care costs</td>
<td>12,604</td>
<td>18,092</td>
</tr>
</tbody>
</table>

Per capita annual cost of care of person 70+ years old (2010 dollars)
Value of Delaying AD Onset

Per Capita Health Effects, Formal And Informal Costs Of 70–74 Year Olds For Status Quo and Year(s) Delay In Onset Scenarios.

<table>
<thead>
<tr>
<th>Status Quo</th>
<th>1-year delay</th>
<th>3-years delay</th>
<th>5-years delay</th>
</tr>
</thead>
<tbody>
<tr>
<td>70–74 year olds with AD at death (%)</td>
<td>100%</td>
<td>89%</td>
<td>79%</td>
</tr>
<tr>
<td>Life years Remaining</td>
<td>15.6</td>
<td>16.6</td>
<td>17.5</td>
</tr>
<tr>
<td>Without AD</td>
<td>9.8</td>
<td>11.5</td>
<td>13.2</td>
</tr>
<tr>
<td>In a nursing home</td>
<td>1.94</td>
<td>1.81</td>
<td>1.7</td>
</tr>
</tbody>
</table>

Per Capita Spending Over Remaining Life Years (2010 dollars)

<table>
<thead>
<tr>
<th></th>
<th>2010</th>
<th>2030</th>
<th>2050</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formal ($)</td>
<td>493,837</td>
<td>500,256</td>
<td>507,125</td>
</tr>
<tr>
<td>Informal ($)</td>
<td>126,215</td>
<td>127,256</td>
<td>137,201</td>
</tr>
<tr>
<td>Total ($)</td>
<td>624,052</td>
<td>627,512</td>
<td>644,326</td>
</tr>
</tbody>
</table>

Value of Treatment Total ($) = 183,227, 355,222, 511,208

Conclusions

- Exercise should be prescribed for all adults
- Exercise may preserve brain health by improving central metabolic function
- Preclinical studies are essential to determine mechanistic effects of exercise
- Resistance training systemically upregulates HSPs; further research is needed to determine central effects
- Compliance with prescribed exercise protocols would lead to significant increases in quality of life and financial savings
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- Alex Rorie
- T.J. Murray
- Emma Renwick
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