Relations of midlife exercise blood pressure, heart rate and fitness to later life brain structure and function

Nicole L. Spartano, PhD
Postdoctoral Fellow
Section of Preventative Medicine and Epidemiology/
Whitaker Cardiovascular Institute
Boston University School of Medicine

Co-authors: Jayandra J. Himali, Alexa S. Beiser, Charles DeCarli, Ramachandran S. Vasan, Sudha Seshadri
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Fitness and Brain Aging

In older adults:
Previous studies have linked fitness to cognition/brain morphology

→ Gains in cognitive function\(^1\)
→ Decreased brain atrophy\(^2\)

• Vascular risk factors → brain aging\(^3,4,5\)

CV Response to Exercise as a Proxy for Fitness

Fitness

→ Lowers resting blood pressure and heart rate
→ Improves vascular compliance

→ Blunts the CV response to low-levels of exercise

Research question:

Does *midlife* fitness affect *late life* brain age?

Men’s Journal, Illustration by Arthur Chiverton
Methods

• Framingham Offspring with fitness assessed at exam 2 (1979-1982) and brain measures obtained 2 decades later at exam 7 (1999-2004)

  – N= 1271; 646 women
  – Mean age at exam 2 (40 years)

• Exclusions at exam 2 and 7: CVD (including stroke), beta-blockers, dementia and other neurological diseases
Fitness Assessed by:

Modified Bruce Protocol Treadmill Test

• Estimates exercise capacity \([\text{VO}_2 \text{ max}]\)
• 3 min stages 1-5 (increasing speed and grade)
  – stage 2 (2.5 MPH, 12% grade) “Exercise” BP and HR measured
• Terminated at 85% HR max (age-adjusted)
  – almost 90% completed the test, 10% terminated due to pain/exhaustion, etc.
Brain Aging Measures

Framingham Offspring exam 7 (1999-2001)

– Cognitive tests:
  • Trails A, Trails B-A, Logical Memory-delayed

– Brain MRI:
  • Total brain volume
  • Frontal lobe volume
  • White matter hyperintensity volume (WMHV)
Brain MRI Measures:

- Total brain volume
  - Mean % = 80.25% (±2.86)
  - Atrophy rate is 0.2% per year after age 60 (DeCarli C, et al. Neurobiology of aging 2005;26:491-510)

- Frontal lobe volume
  - Mean % = 36.94 % (± 3.15)

- White matter hyperintensity volume (WMHV)
  - Median % [Q1, Q3] = 0.04 % [0.02, 0.07]
# Descriptive and Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Exam 2</th>
<th>Exam 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>40 ±9</td>
<td>58 ±8</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>646 (54%)</td>
<td>646 (54%)</td>
</tr>
<tr>
<td>Hypertension (Stage 1), n (%)</td>
<td>109 (9%)</td>
<td>339 (28%)</td>
</tr>
<tr>
<td>Pre-hypertension or hypertension, n (%)</td>
<td>465 (39%)</td>
<td>715 (60%)</td>
</tr>
<tr>
<td>Antihypertensive medication, n (%)</td>
<td>24 (2%)</td>
<td>212 (18%)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>3 (0.3%)</td>
<td>75 (6%)</td>
</tr>
<tr>
<td>Current smoking, n (%)</td>
<td>371 (31%)</td>
<td>144 (12%)</td>
</tr>
<tr>
<td>Resting SBP, mm Hg</td>
<td>116 ±13</td>
<td>122 ±16</td>
</tr>
<tr>
<td>Resting DBP, mm Hg</td>
<td>75 ±9</td>
<td>74 ±9</td>
</tr>
<tr>
<td>Resting HR, bpm</td>
<td>64 ±10</td>
<td>66 ±10</td>
</tr>
</tbody>
</table>
Midlife resting BP and HR, later-life brain morphology

<table>
<thead>
<tr>
<th>Resting variables</th>
<th>Total Brain Volume</th>
<th>Frontal Lobe Volume</th>
<th>WMHV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Beta (SE)</td>
<td>p</td>
<td>Beta (SE)</td>
</tr>
<tr>
<td>SBP</td>
<td>-0.06 ±0.06</td>
<td>0.4</td>
<td>-0.18 ±0.07</td>
</tr>
<tr>
<td>DBP</td>
<td>-0.07±0.10</td>
<td>0.5</td>
<td>-0.27 ±0.11</td>
</tr>
<tr>
<td>HR</td>
<td>0.12±0.08</td>
<td>0.1</td>
<td>-0.06 ±0.09</td>
</tr>
</tbody>
</table>

Betas standardized to 10 units
Multivariable-adjusted

MIDLIFE (age=40) poor fitness, LATER-LIFE (age=58) smaller brain volumes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Brain Volume</th>
<th>Frontal Lobe Volume</th>
<th>WMHV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Beta±SE</td>
<td>p</td>
<td>Beta±SE</td>
</tr>
<tr>
<td>Estimated exercise capacity</td>
<td>0.03 ±0.01</td>
<td>0.027</td>
<td>0.02 ±0.01</td>
</tr>
<tr>
<td>Exercise HR</td>
<td>-0.12 ±0.05</td>
<td>0.021</td>
<td>-0.02 ±0.02</td>
</tr>
</tbody>
</table>

Multivariable-adjusted*

Every 1 SD lower fitness equivalent to approximately 1 yr brain aging

<table>
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<tr>
<th>Variable</th>
<th>Exam 2</th>
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<tr>
<td>Resting SBP, mm Hg</td>
<td>116 ±13</td>
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<tr>
<td>Resting DBP, mm Hg</td>
<td>75 ±9</td>
</tr>
<tr>
<td>Resting HR, bpm</td>
<td>64 ±10</td>
</tr>
<tr>
<td>Stage 2 exercise SBP, mm Hg</td>
<td>155 ±23</td>
</tr>
<tr>
<td>Stage 2 exercise DBP, mm Hg</td>
<td>82 ±13</td>
</tr>
<tr>
<td>Stage 2 exercise HR, bpm</td>
<td>132 ±19</td>
</tr>
<tr>
<td>Estimated exercise capacity (ml/kg/min)</td>
<td>39 ±8</td>
</tr>
</tbody>
</table>

*adjusted for age, sex and time from exam to MRI, smoking status, diabetes, ApoE 4 genotype, and anti-hypertension medication + additional...
MIDLIFE elevated BP-response to exercise, LATER-LIFE smaller brain volumes

<table>
<thead>
<tr>
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<th>Total Brain Volume</th>
<th>Frontal Lobe Volume</th>
<th>WMHV</th>
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<tr>
<td></td>
<td>Beta (SE)</td>
<td>p</td>
<td>Beta (SE)</td>
</tr>
<tr>
<td>Exercise SBP</td>
<td>-0.06 ±0.05</td>
<td>0.2</td>
<td>-0.08 ±0.05</td>
</tr>
<tr>
<td>Exercise DBP</td>
<td><strong>-0.14±0.07</strong></td>
<td><strong>0.049</strong></td>
<td>-0.14 ±0.08</td>
</tr>
</tbody>
</table>

No similar relations were revealed with cognitive tests (Trails A, Trails B-A or Logical Memory-delayed)

**Every 1 SD higher exercise DBP is equivalent to approximately 1 year brain aging**
Effect size modification, by sex and hypertension (HTN) status

<table>
<thead>
<tr>
<th></th>
<th>Total Brain Volume</th>
<th>x HTN STATUS (midlife)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>x SEX</td>
<td>preHTN and HTN</td>
</tr>
<tr>
<td><strong>Exercise</strong></td>
<td><strong>Male</strong></td>
<td><strong>Female</strong></td>
</tr>
<tr>
<td>SBP</td>
<td>p 0.095 -0.10 ±0.05 0.046</td>
<td>p -0.07±0.05 0.2</td>
</tr>
<tr>
<td></td>
<td>Betas standardized to 10 units</td>
<td>Multivariable-adjusted</td>
</tr>
<tr>
<td>Exercise DBP</td>
<td>0.3</td>
<td>--</td>
</tr>
</tbody>
</table>

• In men and pre-HTN/HTN (SBP >120, or DBP >80)
  • Every 1 SD higher exercise SBP equivalent to 0.5 - 1 yr brain aging
Discussion

Fitness in midlife is related to brain aging, two decades later

- Potential mechanisms include increased oxygen delivery to the brain and neuro-signaling
  - Brain-derived neurotrophic factor (BDNF)

- Vascular mechanism?

- Future Studies:
  - Do fitness and exercise BP predict dementia in this population?
Limitations

• Generalizable largely to individuals of European-descent

• Results of this investigation may only be applicable to individuals with otherwise healthy aging

• Confirming these observations in other studies will be important
Conclusion

- Midlife fitness may be important for healthy brain aging at the population level.

- Fitness may be especially important for men and individuals with pre-HTN/HTN in midlife.
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Contact: spartano@bu.edu