Cardiorespiratory Fitness: A Protective Factor Against Alzheimer’s Disease and Related Dementias

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Disclosures

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• EZ is a reviewer for the NIA ETTN-10 panel and does occasional other review work for the NIA and occasional consulting for various companies.
Outline

• The problem of ADRD
• Potential solutions
• One potential partial solution
  • Spoiler alert: Take home message: Cardiorespiratory fitness has a graded, incremental inverse relationship to onset of ADRD
• Work to be done
The Problem

Alzheimer’s Disease and Related Dementias

- Over 55 million people with ADRD worldwide
- Anticipated to reach 78 million by 2030, 139 million by 2050
- Annual global cost US$1.3 Trillion
- Expected to reach US$2.8 Trillion by 2030
- Life expectancy: 3-11+ years
Possible Solutions

Management of ADRD is complicated

• Clinical
  • Pathology may be too advanced
  • BUT buying time may be a meaningful outcome

• Symptomatic
  • Even as you treat symptoms, disease progresses

• Pharmacological strategies

• Pre-Clinical
  • Variety of pathologies
  • How to detect? Enter biomarkers

• Disease Modifying Therapy
  • May not improve symptoms, but slow progression

• Non-Pharmacological strategies
For the greatest impact on long-term outcomes in ADRD, prevention strategies are key.

Which is not a risk factor in the Lancet Commission list?

Less education,
Hearing impairment,
Diabetes,
Light walking,
Air pollution,
Updated 12 risk factor life-course model of dementia prevention

- less education,
- hypertension,
- hearing impairment,
- smoking,
- obesity,
- depression,
- physical inactivity,
- diabetes,
- low social contact,
- excessive alcohol consumption,
- traumatic brain injury, and
- air pollution

Livingston, Lancet 2020; 396: 413–46
AHRQ has identified XXXXXXXXXX as the only lifestyle intervention with plausible mechanistic evidence of dementia risk reduction: XXXXXXXXXX = Which item from the list below?

- less education,
- hypertension,
- hearing impairment,
- smoking,
- obesity,
- depression,
- physical inactivity,
- diabetes,
- low social contact,
- excessive alcohol consumption,
- traumatic brain injury, and
- air pollution
The AHRQ has identified physical activity as the only lifestyle intervention with strong evidence of mechanistic plausibility to prevent ADRD.

- Longitudinal neuroimaging studies: the volume of prefrontal and hippocampal brain areas are larger in individuals who engaged in more physical activity earlier in life. (Erickson, 2012 and 2019)

- In a population-based case-control study of 1324 subjects, moderate exercise performed in midlife or late life was associated with a reduced odds of having MCI. (Geda, 2010)

- Accelerometer-measured physical activity was associated with greater total gray matter volume in a population based cohort of 2550 participants. (Fox, 2022)

- In a study of 6104 veterans, followed for 10.3±5.5 years each 1-metabolic equivalent increase in exercise capacity conferred a nearly 8% reduction in the incidence of cognitive impairment. (Muller, 2016)
Which statement is True?

• Everyone can obtain the same benefit from the same amount of exercise.
• Mild, moderate, or intense exercise are equally beneficial.
• Genetics have no bearing on exercise capacity.
• Cardiorespiratory fitness (capacity of O2 utilization) influences exercise capacity.
• Benefits of exercise are greater late in life.
Pitfalls of measuring exercise

• Unless an objective measure is used, it is difficult to precisely quantitate exercise duration, intensity, regularity, and effectiveness.

• Even accelerometer-derived measures do not factor in genetic variation.

• Precisely quantifying modifiable risk factors is critical to designing individualized actionable preventive care plans.
Potential advantages of measuring CRF

• Cardio-Respiratory Fitness (CRF) refers to the capacity of the circulatory and respiratory systems to supply oxygen to skeletal muscle mitochondria for energy production needed during physical activity. (1)
• CRF is assessed objectively by an exercise treadmill test (ETT) and expressed in metabolic equivalents (METs; 1 MET=3.5 ml of oxygen/kg of body weight/minute).
• CRF is a robust objective measure of health that can be tracked over time and compared across age groups, populations, fitness levels. (1)
• Physical activity and CRF have an established role in reducing risk of cardiovascular disease, cancer, other morbidities, and mortality. (2)
Potential advantages of measuring CRF

- The American Heart Association recommends adding CRF as a clinical vital sign. (Ross, 2016)
- CRF is a potentially stronger predictor of mortality than established risk factors such as smoking, hypertension, high cholesterol, and type 2 diabetes mellitus.
- Insufficient data on role of CRF and ADRD.
- We assessed the association of CRF with incident ADRD in a large clinical population.
Veterans who had a METs value extracted using NLP (N=975,214)

Veterans who had a METs during the period of 2000 and 2017 with the value falling in the range of 2 - <24 (N=655,441)

- Baseline age out of range of 30-95 (N=12,823)
- Exclude Veterans who had ADRD at baseline (N=22,633)
- Exclude Veterans who had severe mental illness or other dementia of known causes at baseline (N=55,402)

Veteran (N=764,583) free of ADRD at baseline

- Exclude patients who had following conditions:
  - No primary care in 2 years prior to baseline (N=8,422)
  - Had follow-up ≤1 year (N=33,264)
  - Aged 50 or above but with METs of 20 or above (N=131)
  - Weight > 450 pounds or BMI <18.5 (N=8,340)
  - CABG or PTCA within 3 months post fitness test (N=24,570)
  - MI or HF diagnosis in the period between 1 month prior to and 3 months post fitness test (N=28,291)
  - Patients with a pacemaker (N=11,746)
  - Death date inconsistent with other data (N=213)

Final Cohort (N=649,605)
We identified 649,605 Veterans (mean age 61 years old; 5.7% women; 16.6% African-Americans) free of ADRD who completed a standardized exercise tolerance test between 2000-2017, with no ischemia.

We formed five age-and-gender-specific fitness categories based on peak metabolic equivalents (METs) achieved:

- Least-fit (METs=3.8±0.6),
- Low-fit (METs=5.8±1.4),
- Moderately-fit (METs=7.5±1.5),
- Fit (METs=9.2±1.7), and
- High-fit (METs=11.7±2.1).

We used multivariate Cox regression models and propensity score-matching to estimate the association.
RESULTS

• During up to 20 (ave 8.8) y. follow-up 44,105 (6.8%) participants developed ADRD (average rate 7.7/1,000 person-years).

• ADRD Incidence rate for Least-fit to High-fit categories was: 9.5, 8.5, 7.4, 7.2 and 6.4 /1000 person-years, respectively (p<0.0001).

• Compared to the Least-fit category, multivariable-adjusted hazard ratios (95% CI) for incident ADRD were: 0.87 (0.85–0.90), 0.80 (0.78–0.83), 0.74 (0.72–0.76), and 0.67 (0.65–0.70) respectively.
<table>
<thead>
<tr>
<th>Fitness level</th>
<th>Rate per 1,000 person-years (events/person-years)</th>
<th>Hazard ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Least-fit (N=132,634)</td>
<td>9.5 (9160/966178)</td>
<td>Unadjusted: 1.00 (reference)</td>
</tr>
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<td></td>
<td></td>
<td>Age-sex-race-adjusted: 1.00 (reference)</td>
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<td></td>
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<td>Multivariable*-adjusted: 1.00 (reference)</td>
</tr>
<tr>
<td>Low fit (N=129,493)</td>
<td>8.5 (9332/1103713)</td>
<td>Unadjusted: 0.84 (0.81-0.86): p&lt;0.0001</td>
</tr>
<tr>
<td></td>
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<td>Age-sex-race-adjusted: 0.81 (0.78-0.83): p&lt;0.0001</td>
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<tr>
<td></td>
<td></td>
<td>Multivariable*-adjusted: 0.87 (0.85-0.90): p&lt;0.0001</td>
</tr>
<tr>
<td>Moderate fit (N=120,988)</td>
<td>7.4 (8132/1105981)</td>
<td>Unadjusted: 0.71 (0.69-0.73): p&lt;0.0001</td>
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<td>Age-sex-race-adjusted: 0.72 (0.70-0.74): p&lt;0.0001</td>
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<tr>
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<td>Multivariable*-adjusted: 0.80 (0.78-0.83): p&lt;0.0001</td>
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<tr>
<td>Fit (N=137,122)</td>
<td>7.2 (9430/1304546)</td>
<td>Unadjusted: 0.69 (0.67-0.71): p&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age-sex-race-adjusted: 0.65 (0.63-0.67): p&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multivariable*-adjusted: 0.74 (0.72-0.76): p&lt;0.0001</td>
</tr>
<tr>
<td>High-Fit (N=129,368)</td>
<td>6.4 (8051/1253071)</td>
<td>Unadjusted: 0.61 (0.59-0.63): p&lt;0.0001</td>
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<tr>
<td></td>
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<td>Age-sex-race-adjusted: 0.58 (0.56-0.59): p&lt;0.0001</td>
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<tr>
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<td>Multivariable*-adjusted: 0.67 (0.65-0.70): p&lt;0.0001</td>
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<tr>
<td>p Trend</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
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<td>&lt;0.0001</td>
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</tbody>
</table>

*Adjusting for age (continuous variable), gender, race, ethnicity, marital status, region, living area median income category, BMI category and comorbid conditions, and medications

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Cohort (N=649,605)

Unadjusted KM Curve

Multivariate-adjusted KM Curve

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<table>
<thead>
<tr>
<th>Fitness Level</th>
<th>HR (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Least-fit</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Low-fit</td>
<td>0.94 (0.91-0.98): p=0.0012</td>
</tr>
<tr>
<td>Moderate-fit</td>
<td>0.85 (0.82-0.89): p&lt;0.0001</td>
</tr>
<tr>
<td>Fit</td>
<td>0.82 (0.79-0.85): p&lt;0.0001</td>
</tr>
<tr>
<td>High-fit</td>
<td>0.75 (0.72-0.78): p&lt;0.0001</td>
</tr>
</tbody>
</table>

Propensity Score Matched Cohort
(N=393,625)
<table>
<thead>
<tr>
<th>Fitness</th>
<th>Age 50-59</th>
<th>Age 60-69</th>
<th>Age 70-79</th>
<th>Age 80+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low vs Least</td>
<td>0.93 (0.86-0.99);</td>
<td>0.85 (0.81-0.90);</td>
<td>0.81 (0.77-0.86);</td>
<td>0.84 (0.78-0.91);</td>
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<tr>
<td></td>
<td>p=0.0365</td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Moderate vs Least</td>
<td>0.80 (0.74-0.87);</td>
<td>0.76 (0.74-0.81);</td>
<td>0.78 (0.74-0.82);</td>
<td>0.78 (0.71-0.86);</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Fit vs Least</td>
<td>0.74 (0.68-0.80);</td>
<td>0.71 (0.67-0.74);</td>
<td>0.71 (0.68-0.75);</td>
<td>0.77 (0.71-0.84);</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>High vs Least</td>
<td>0.67 (0.62-0.73);</td>
<td>0.61 (0.57-0.64);</td>
<td>0.67 (0.64-0.71);</td>
<td>0.72 (0.66-0.78);</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.0001</td>
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<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>

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Figure e) Kaplan Meier plots of CRF in patients aged 60-69 (N=244469)

Figure f) Kaplan Meier plots of CRF in patients aged 70-79 (N=95082)
CONCLUSIONS:
This is the largest study that examines the association between objectively determined CRF and incident ADRD in up to two decades of follow-up.

Our finding of an independent, inverse, and graded association supports considering improving physical activities and CRF as an ADRD prevention strategy.
LIMITATIONS:

• Veterans may not be representative of the general population
• Differences between standard care and specialty dementia clinic care/ research work-up.
  • Lack of biomarkers. Biomarkers are not yet part of standard care.
  • ADRD typically underdiagnosed, but results in the diagnosed cases can still be informative.
  • AD and ADRD. Future studies can sort out biomarker-supported diagnosis and be more specific for AD vs other neurodegenerative conditions.
NEXT STEPS

- Reproduce our findings in a cohort that represents general population
- Correlate CRF with ADRD biomarkers including biofluid biomarkers, cognitive test results, imaging biomarkers, and autopsy.
- Correlate CRF with ADRD biomarkers over time in a longitudinal study.
- Identify optimal values of CRF by age that are linked to the lowest risk of AD/ADRD
- Develop and validate a deep learning-based risk prediction model to determine the optimal CRF level for individuals to achieve the lowest risk of AD/ADRD
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