The ATN framework: The importance of lifestyle factors in predicting progression

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Disclosures

• I have no disclosures

Modifiable risk factors

- A third of Alzheimer's disease dementia cases might be attributable to 7 modifiable risk factors
 - Diabetes
 - Hypertension
 - Obesity
 - Smoking
 - Depression
 - Low education
 - Physical inactivity



Barnes & Yaffe, 2011; Livingstone et al., 2016; Norton et al., 2014; Sperling et al., 2011





Harvard Aging Brain Study (HABS)

- Longitudinal study of 300+ adults
- At study entry:
 - -60-90 years of age
 - Clinically normal (MMSE > 26, CDR = 0, LM-delayed recall = WNL)
 - No significant depressive symptoms (GDS < 11)

• Exclusion criteria:

- Major vascular event or extensive white matter changes
- Unstable hypertension or diabetes
- Current major medical or psychiatric illness
- History of substance abuse
- Head trauma



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Methods

- Vascular risk was quantified at <u>baseline</u> with the Framingham Heart Study cardiovascular disease risk score (FHS-CVD) (D'Agostino et al., 2008)
 - Age, sex, use of antihypertensive medication, body mass index, systolic blood pressure, history of diabetes, smoking status
- **Amyloid** was measured at <u>baseline</u> with ^{C11}Pittsburgh Compound B
- Cognition was measured <u>longitudinally</u> with the Preclinical Alzheimer Cognitive Composite (PACC); mean follow-up = 3.7±1.2 years

Baseline demographic information

| | Overall (n = 223) | Αβ– (n=166) | Αβ+ (n=57) | P value |
|-------------------------------|----------------------|----------------|---------------|---------|
| Age in years, mean (SD) | 73.7 (6.1) | 73.3 (6.0) | 74.7 (5.9) | 0.13 |
| Education in years, mean (SD) | 16.0 (2.9) | 15.8 (3.1) | 16.2 (3.0) | 0.39 |
| Female, n (%) | 137 (59%) | 99 (57%) | 38 (64%) | 0.37 |
| PiB DVR FLR , mean (SD) | 1.15 (0.20) | 1.06 (0.05) | 1.44 (0.18) | < 0.001 |
| Αβ+ (%) | 27% | | | |
| APOE e4 status | 65 (29%) | 29 (18%) | 36 (63%) | < 0.001 |
| Follow-up visits, mean (SD) | 3.7 (1.2) | 3.6 (1.2) | 3.9 (1.2) | 0.18 |
| FHS-CVD, mean (SD) | 33.0 (18.6) | 33.1 (18.8) | 32.4 (16.1) | 0.77 |

Rabin et al., 2018, JAMA Neurology

Higher vascular risk accelerates cognitive decline in individuals with elevated Aβ burden



FHS-CVD components predict cognitive decline







Is higher vascular risk associated with greater regional tau pathology in individuals with elevated Aβ burden?



Entorhinal cortex (EC)



Inferior temporal cortex (ITC)

Higher vascular risk is associated with greater ITC tau in individuals with elevated Aβ burden



PIB FLR 75^{th} percentile (DVR = 1.4)

PIB FLR 25^{th} percentile (DVR = 1.1)

Covariates: age, sex, APOE ε4 status

Most FHS-CVD components predict greater ITC tau



Higher vascular risk is associated with greater Aβ-related tau deposition in regions beyond the ITC



Regions shown are at p < 0.05, corrected for multiple comparisons (family-wise error).



Objective

To test the hypothesis that physical activity (PA) protects against longitudinal cognitive decline and neurodegeneration in clinically normal older adults with elevated Aβ burden

• Of particular interest is whether these effects are independent of vascular risk

Rabin, Klein, et al., 2019, JAMA Neurology

Methods: Baseline Measures

- 182 clinically normal individuals from HABS (63 90 yrs old)
- **Physical activity** was measured at <u>baseline</u> with a pedometer (mean steps per day)
- **Cognitive decline** was measured <u>longitudinally</u> with the PACC; median follow-up = 6.0±1.1 years
- **Neurodegeneration** was measured <u>longitudinally</u> using total gray matter volume; median follow-up = 4.5±1.3 years

Rabin, Klein, et al., 2019, JAMA Neurology

Associations of PA with FHS-CVD and $A\beta$



Rabin, Klein, et al., 2019, *JAMA Neurology*

Greater PA is associated with slower cognitive decline in individuals with elevated Aβ burden

Lower Physical Activity (PA)

(2900 mean steps/day)

Higher Physical Activity (PA)

(8300 mean steps/day)



Greater PA is associated with less brain atrophy in individuals with elevated Aβ burden



Summary

- In clinically normal adults with elevated Aβ burden:
 - Higher vascular risk may accelerate tau deposition, cognitive decline, and neurodegeneration
 - Physical activity may protect against cognitive decline and neurodegeneration
- Interventional approaches that target both physical activity and management of vascular risk factors may have additive beneficial effects on delaying the progression of AD
- Our results are based on observational data and it is important to formally test these lifestyle interventions in clinical trials

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Thank you for listening!

