WHAT SHOULD WE DO UNTIL WE HAVE A PREVENTION FOR AD?

Physical Exercise & Non-Pharmacological Approaches to Protect Cognitive Function

Laura Baker

Associate Professor of Internal Medicine,
Neurology, & Public Health Sciences
Wake Forest School of Medicine

Disclosure

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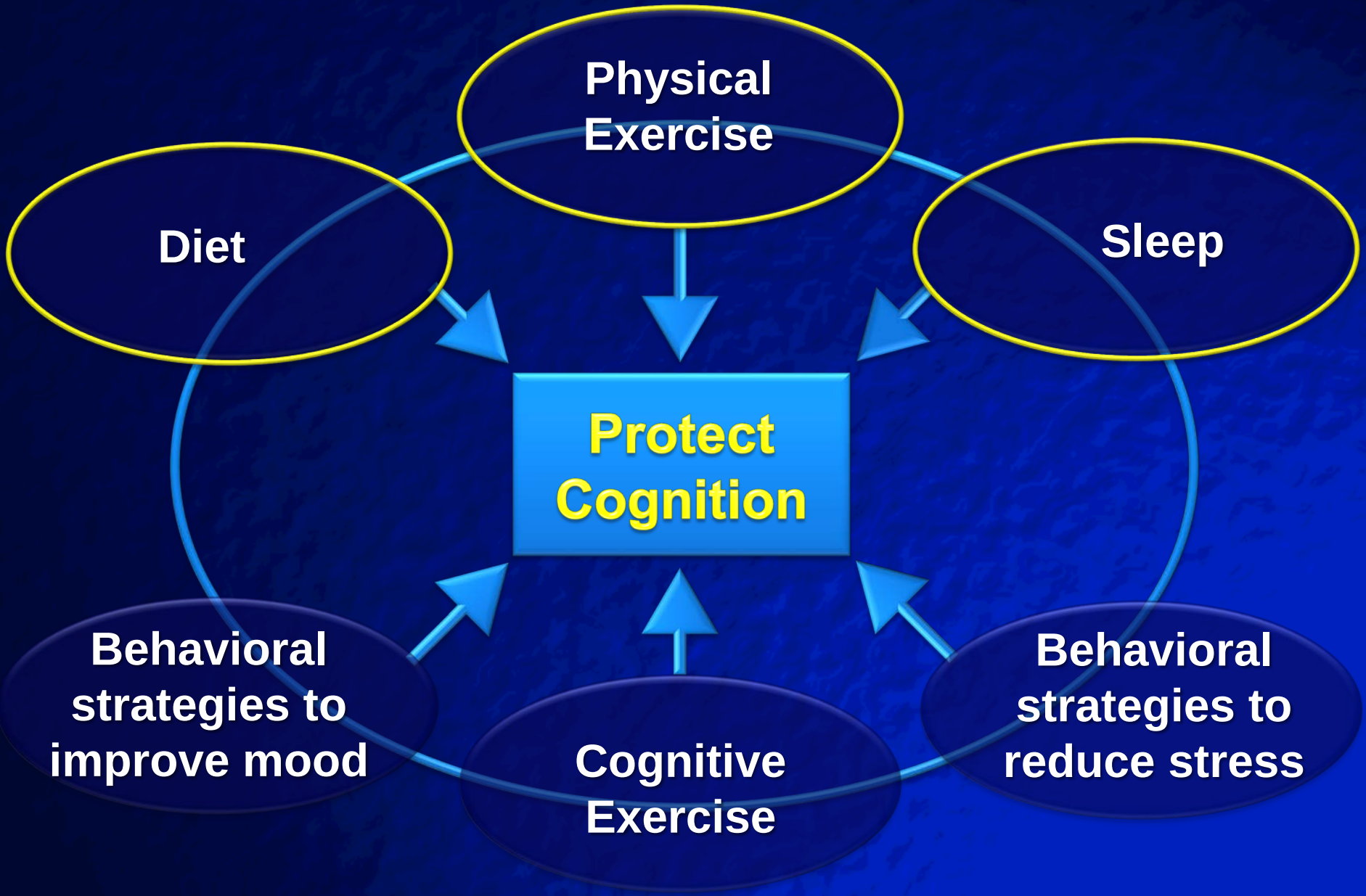
- NIH / NIA
- Wake Forest School of Medicine, Winston Salem NC
- Department of Veterans Affairs, Seattle WA
- University of WA, Seattle WA
- Alzheimer's Association
- American Diabetes Association

Non-Pharmacological Interventions



Exercise Benefits BRAIN

- Mouse experiments
- Exercise improves cognition & increases brain volume in healthy older adults
- Exercise associated with decreased risk of Alzheimer pathology and dementia (observational studies)
- Exercise as a therapeutic intervention to slow or prevent Alzheimer's disease?

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Exercise Effects on Brain Function in Animal Models

Numerous studies showing potent & quick effects of aerobic exercise on multiple targets in brain [Cotman et al. 2007]

- neuronal survivability & function
- growth factor activity (e.g., BDNF)
- inflammatory processes
- vascularization & integrity of cerebral blood vessels
- stress response
- brain amyloid burden

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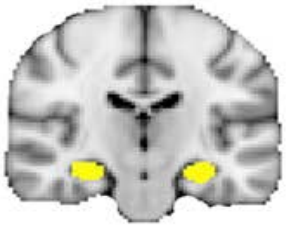
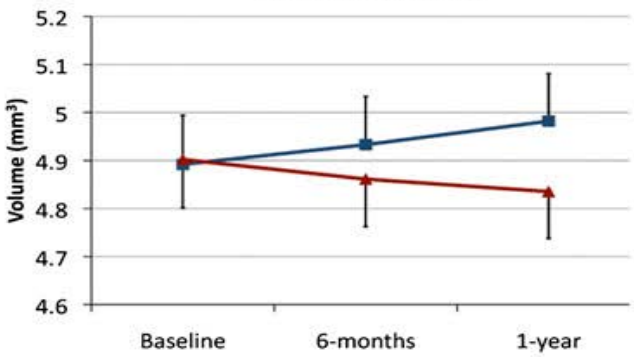
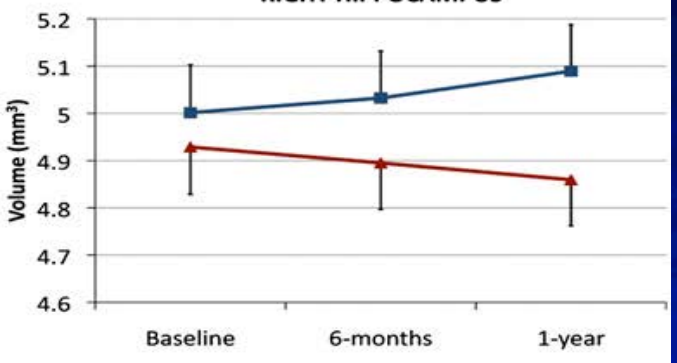
Aerobic Training Increases Size of Hippocampus & Improves Memory

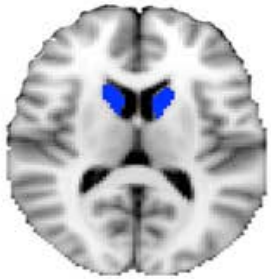
A Hippocampus

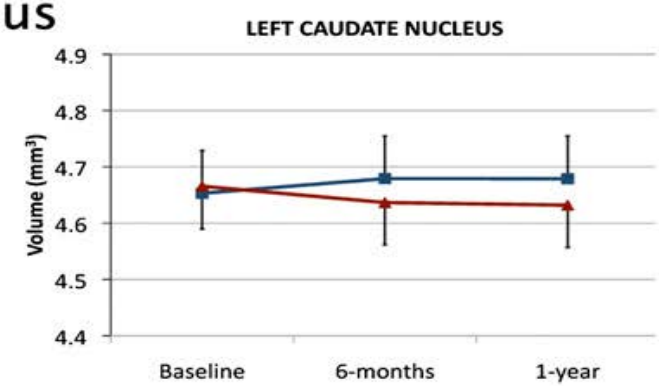


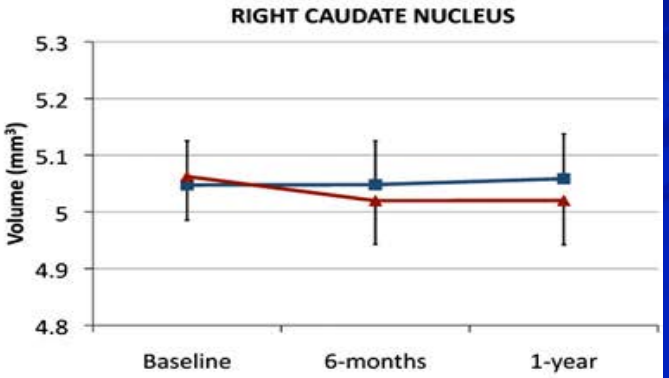




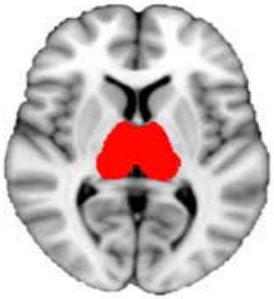
B Caudate Nucleus

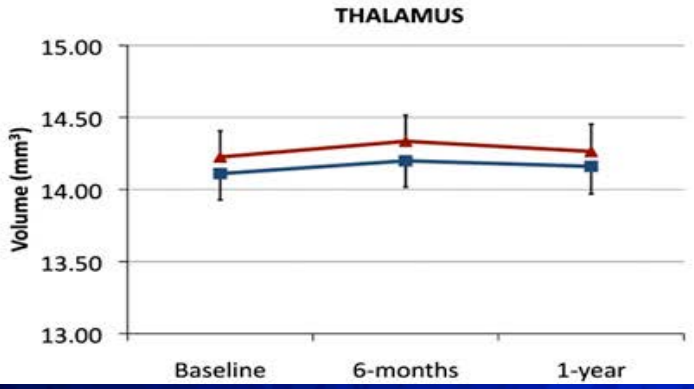






C Thalamus





Exercise
Stretching

Erickson et al. 2011

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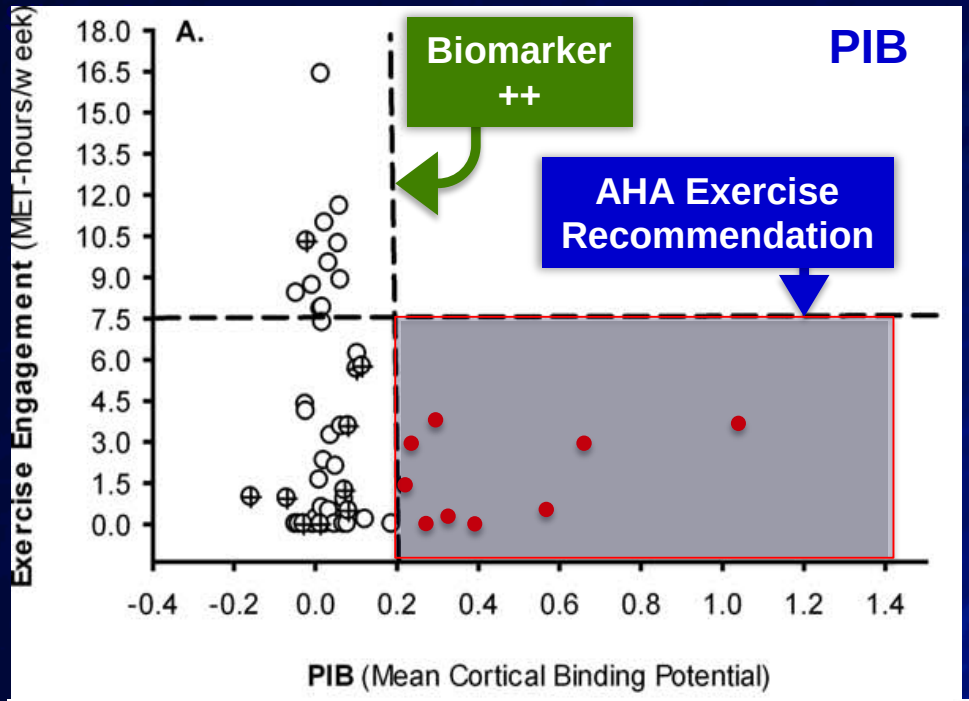
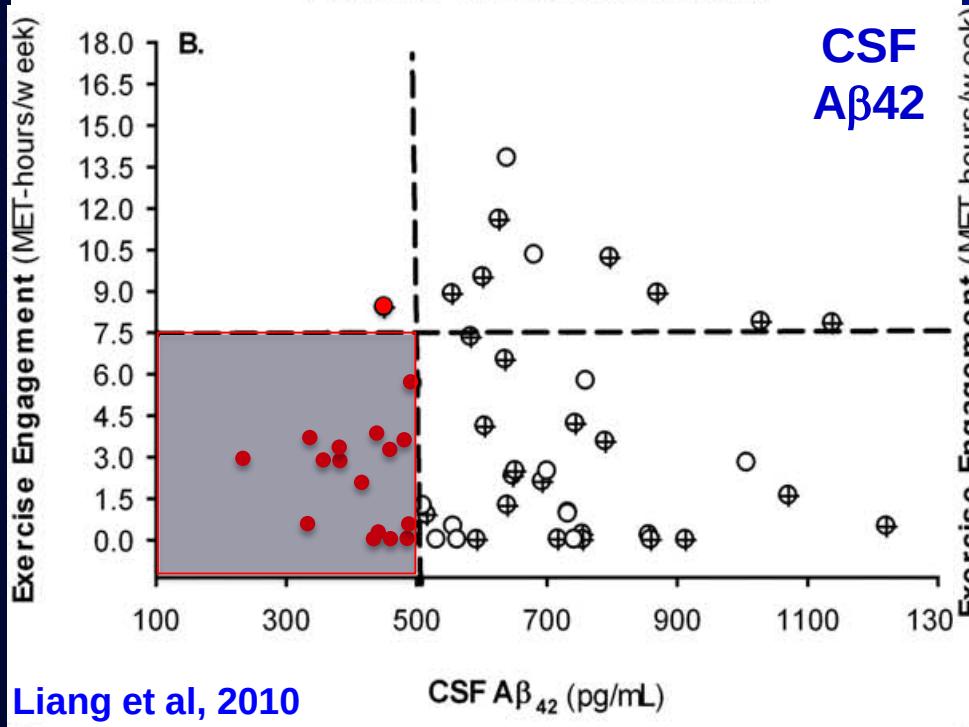
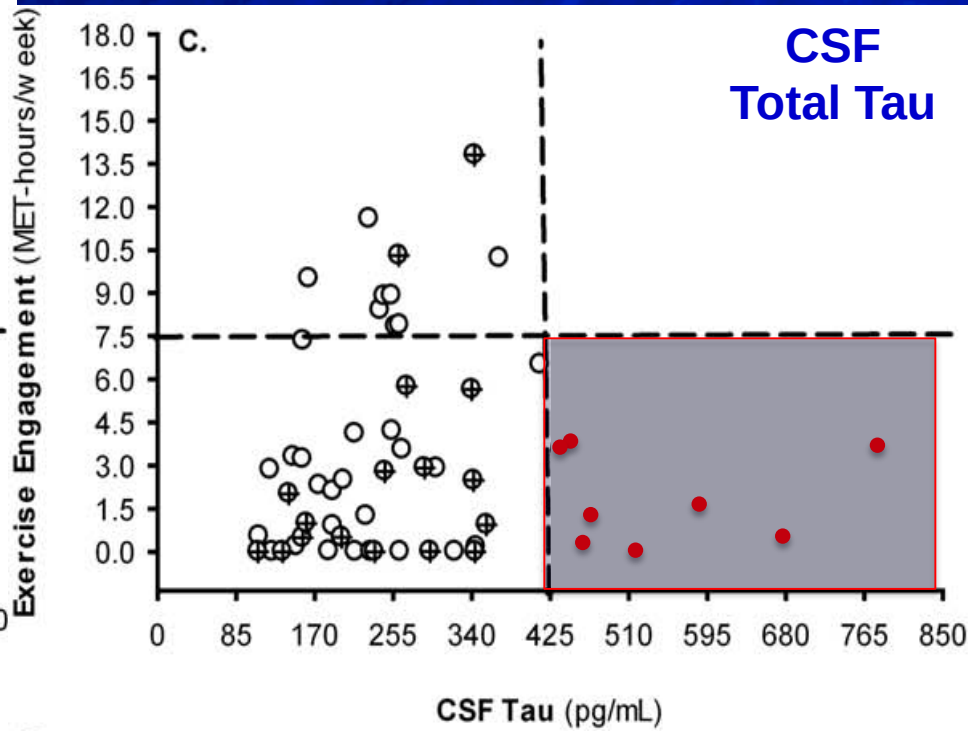


- N=56 CN older adults; + biomarker status associated with SEDENTARY
- Those completing more exercise (30 min, 5x/wk) had lower PIB binding (p=0.006) & higher CSF Aβ42 (p=0.001)





Liang et al, 2010

Neurologist. 2015 Feb;19(3):89-91. doi: 10.1097/NRL.0000000000000013.

Physical activity level and future risk of mild cognitive impairment or dementia: a critically appraised topic.

Schlosser Covell GE[1], Hoffman-Snyder CR, Wellik KE, Woodruff BK, Geda YE, Caselli RJ, Demaerschalk BM, Wingerchuk DM.

⊕ Author information

Abstract

BACKGROUND: The relationships between physical activity, cognition, and development of neurodegenerative diseases represent an area of intense research interest. Meta-analyses and prospective cohort studies show that greater levels of physical activity are associated with lower dementia risk. Most studies, however, depend on self-report data that are subject to recall and other biases. Obtaining objective and

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ME sce com librarian, and behavioral neurology and neuropsychiatry content experts.

RESULTS: We selected a prospective, single-center cohort study of 716 cognitively normal elderly participants followed for 3.5 years. Greater levels of physical activity, as measured using wrist actigraphy, were associated with a lower risk of incident MCI or AD (hazard ratio, 0.477; 95% confidence interval, 0.273-0.832).

CONCLUSIONS: Objective measurement confirms that greater levels of physical activity are associated with decreased risk of a future diagnosis of MCI or AD. Further studies are needed to confirm the temporal association of exercise and future cognitive health and understand the relevant underlying biological mechanisms.

Higher levels of actigraphy-measured PA associated with a 50% reduction in MCI/AD risk

(N= 716 CN adults followed for 3.5 years)

Schlosser et al. 2015

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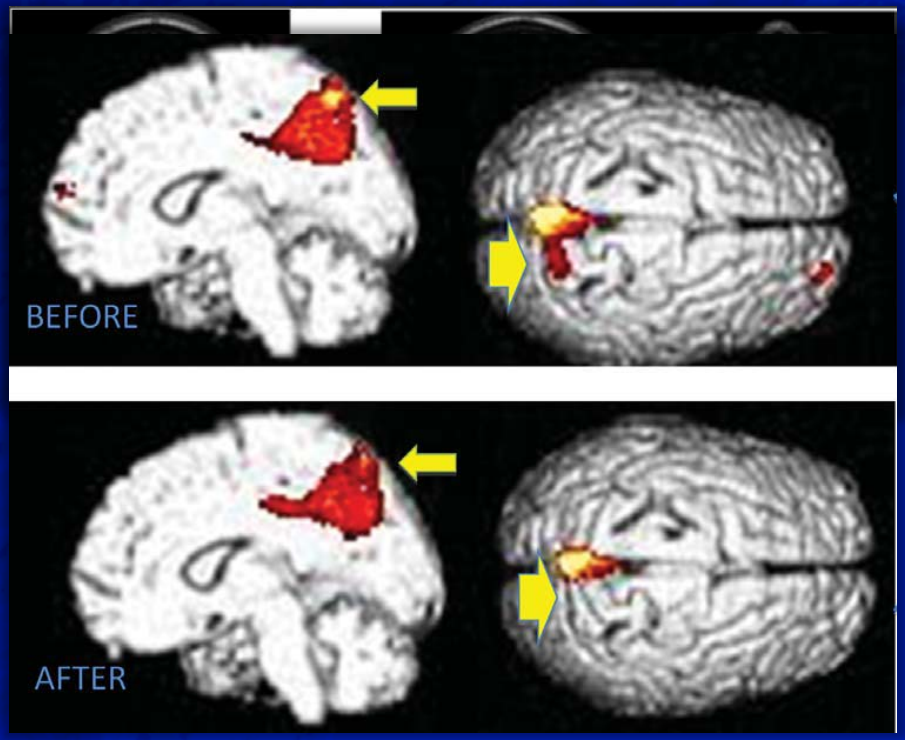
Aerobic Training Has Favorable Effects on Regional Brain Glucose Metabolism

[Porto et al. JAD 2015]

- N=40 aMCI (mean MMSE=27)
- Supervised aerobic training, twice per week x 6 months
- No control group
- Improvements on ADAS-Cog, delayed visual memory, FDG regional brain GM
  - reduced in dorsal anterior cingulate, & increased in precuneus region
  - when compared to cognitive normal older adults, aerobic exercise attenuated disease-related hypometabolism



Does Aerobic Exercise Benefit Cognition in MCI ?

Randomized controlled trial for older adults with subjective memory complaints in Perth AU
[Lautenschlager JAMA 2008]

- **6 months of home-based walking program (+150 min/week)**
- **Active group outperformed the control group (usual care) on the ADAS-Cog & CDR-SB at the 18 month follow-up period**

Does Aerobic Exercise Benefit Cognition in MCI ?

Pilot randomized trial of aerobic exercise vs. stretching/balance (control) in 33 sedentary older adults with aMCI [Baker et al. 2010]

- **Intervention: 45-60 min/day x 4 days/wk x 6 mos at local YMCAs**
  - **AEROBIC group: training HR = 70-80% of maximum using predominantly treadmill**
  - **CONTROL group: stretching & balance exercises maintaining HR < ~90 bpm**

- **Results: Executive function (Trails, Fluency, Stroop, working memory task) improved for aerobic group only; no effect on STM**

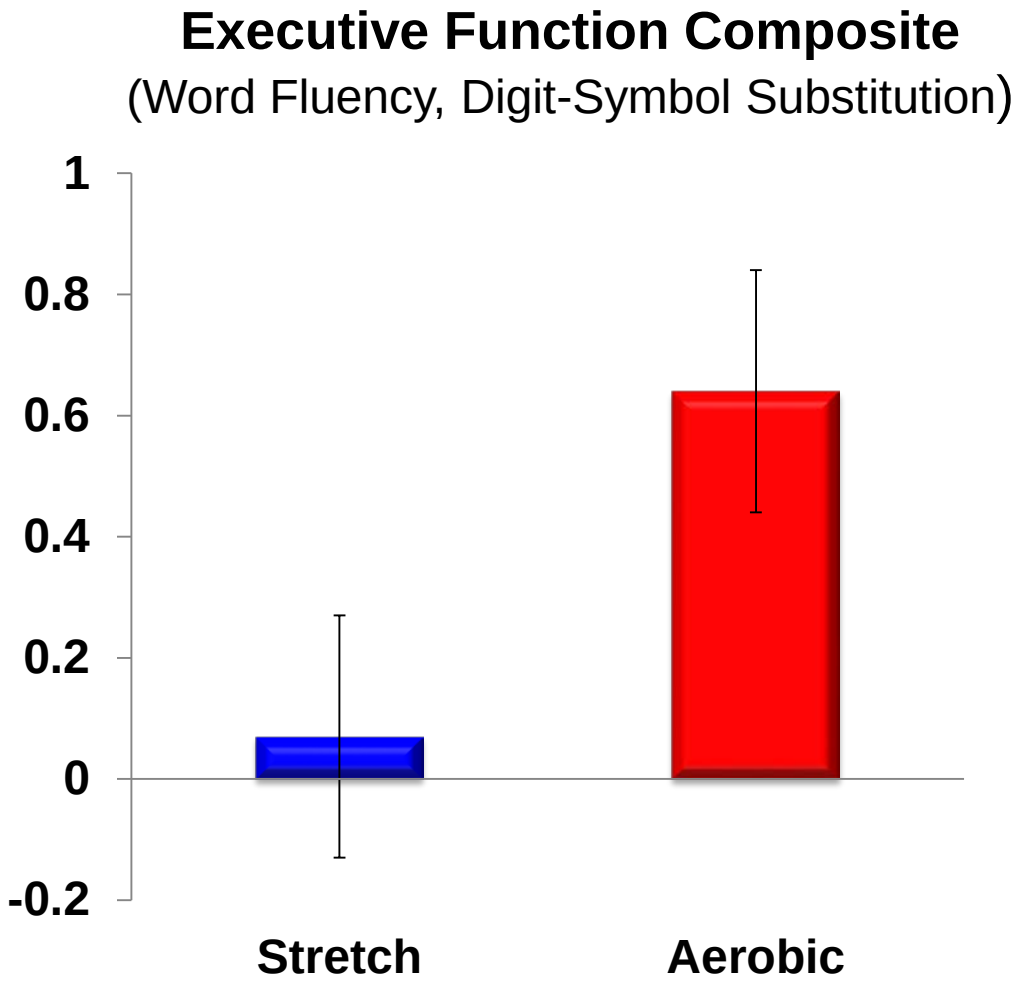
Does Aerobic Exercise Benefit Cognition in MCI ?

Now completing larger 6-month RCT of aerobic exercise vs. stretching control in aMCI who also have pre-diabetes, a double risk for AD (?)

- **Subjects: N=65 (N=40 with Imaging), 65% F, MMSE=28.5**
- **Intervention: same as in our earlier RCT (high intensity aerobic training vs. stretching/balance control)**
- **Outcomes: cognition (includes computer tests targeting executive function), s/fMRI, AD biomarkers in CSF & blood**

Aerobic Exercise Effects on Cognition

Change from Baseline
(N=42)

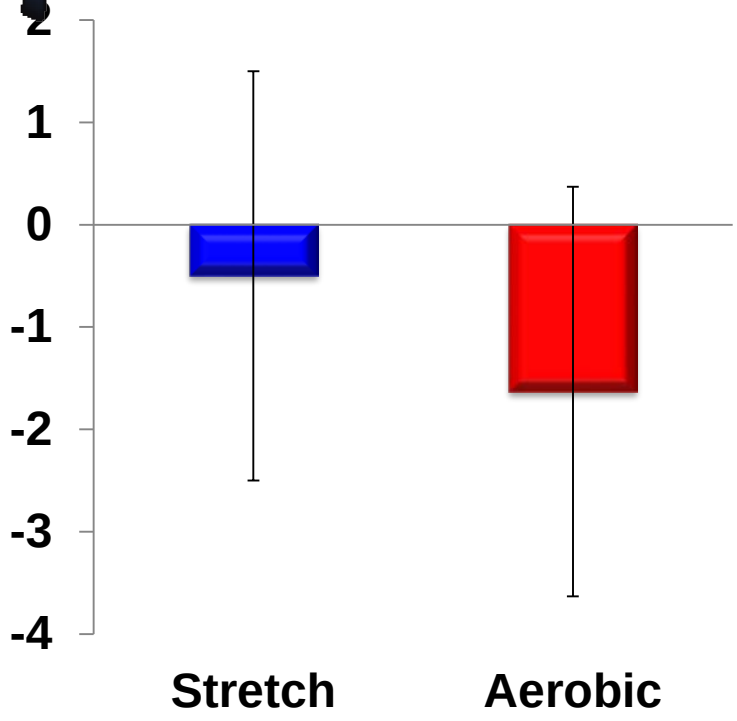


** p=0.03*

Aerobic Exercise Effects on AD Biomarkers in CSF

Phosphorylated Tau Protein (pg/ml)

Change from Baseline (N=22)



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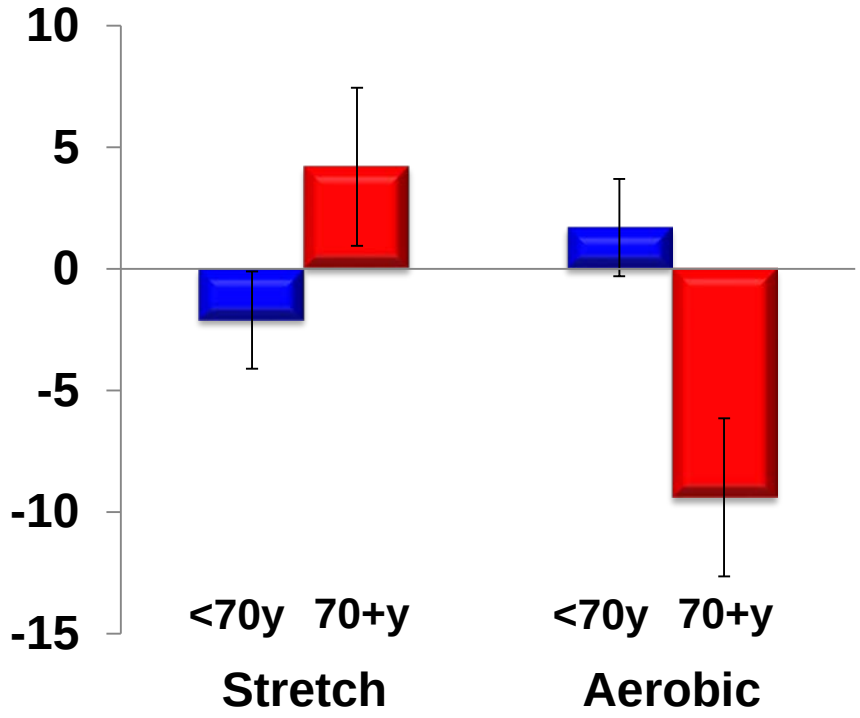
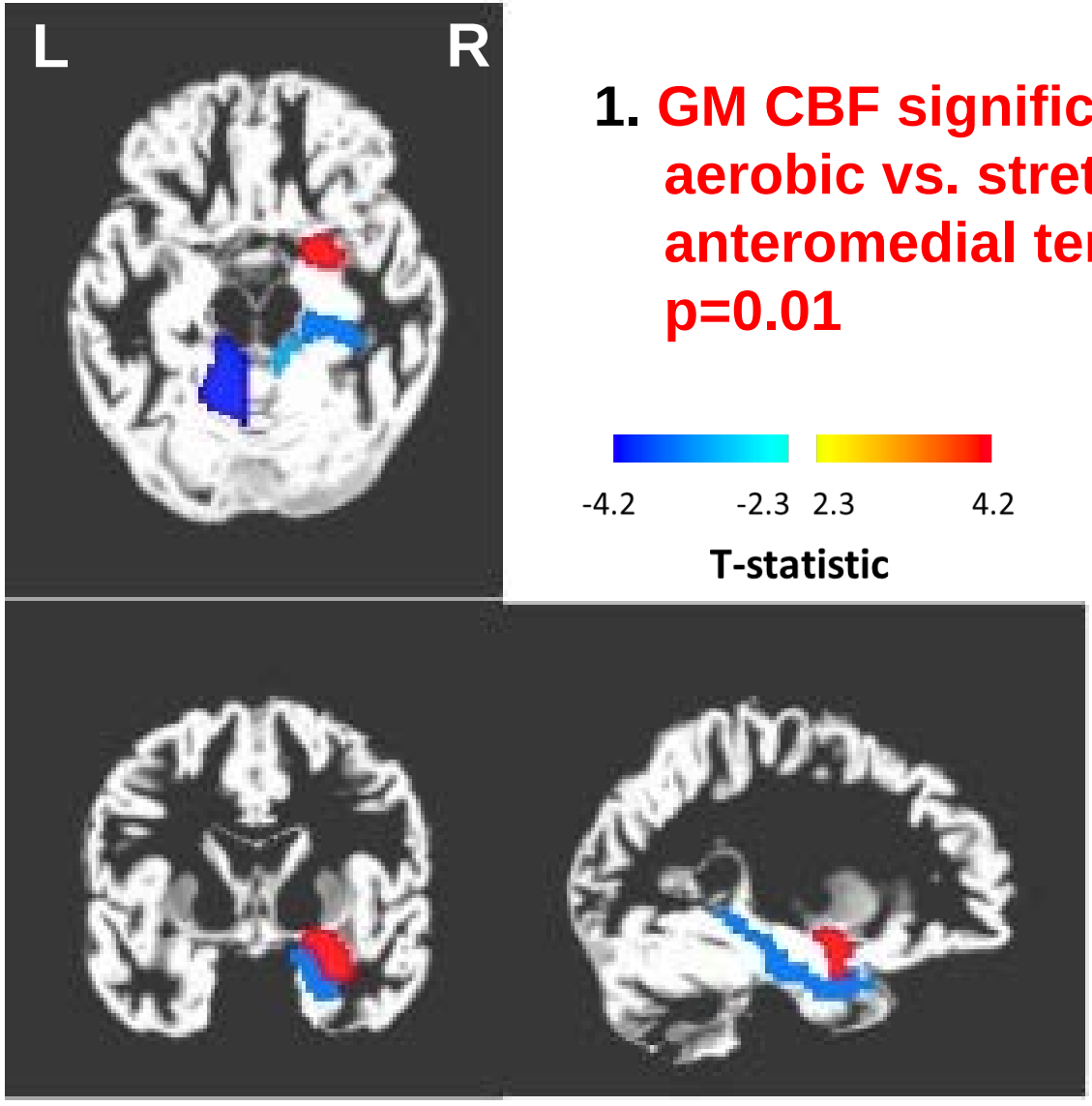


**** Exercise x Age: p=0.0037***

Aerobic Exercise Effects on Brain Perfusion

(pcASL, Change from Baseline, N=15)

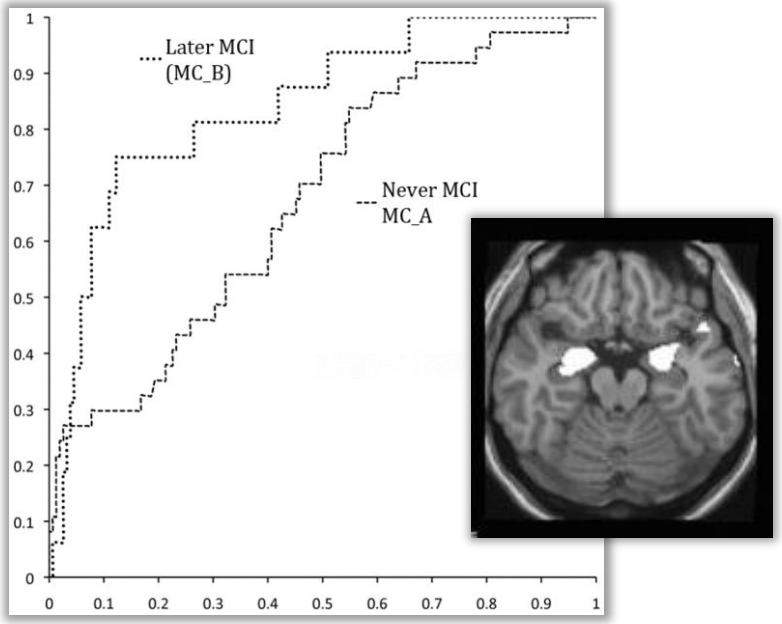


1. **GM CBF significantly <u>INCREASED</u> for aerobic vs. stretching group in R anteromedial temporal region/amygdala, p=0.01**

2. **GM CBF significantly <u>DECREASED</u> for aerobic vs. stretching group in**
   - **R middle temporal cortex (p=0.05) & R parahippocampal region (p=0.02)**
   - **Multiple cerebellar regions**

Importance of Anteromedial Temporal Region for AD

- **Volume in the anteromedial temporal region (includes amygdala) predicts later classification of MCI in baseline CN adults in ADNI with 84% accuracy** [Smith et al, 2012]



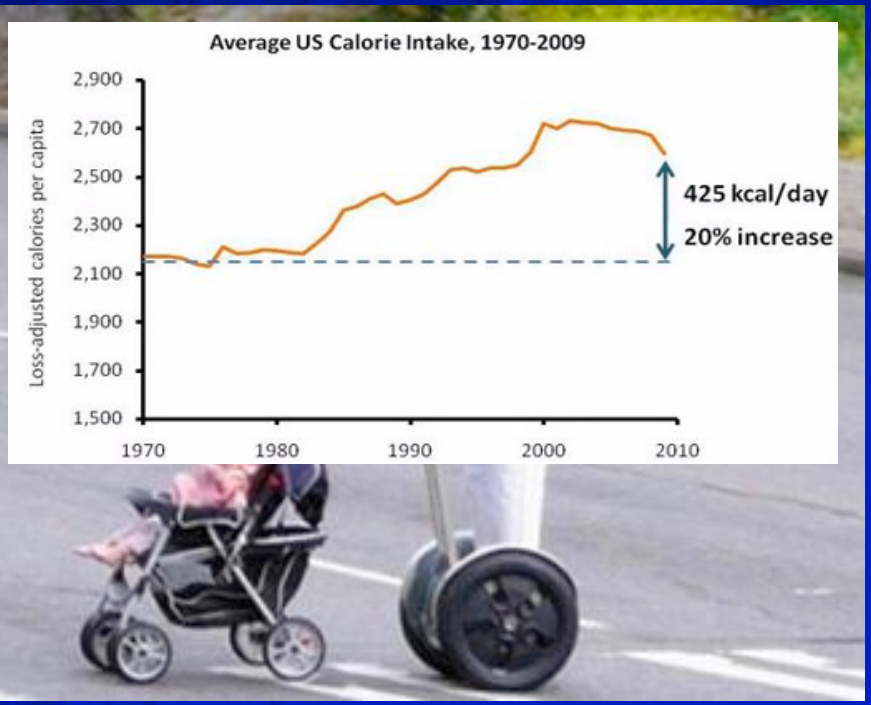
- **Decreased functional connectivity in MCI & AD relative to controls between amygdala & regions included in the default mode** [Yao et al, 2013]

- **AMTR may be a critical target for therapeutic interventions**

REDUCING RISK
Synergistic Effects of Diet and Exercise?

Prevalence of medical risk factors for MCI & AD, including insulin resistance, CVD & obesity → dramatically increased likely due to:

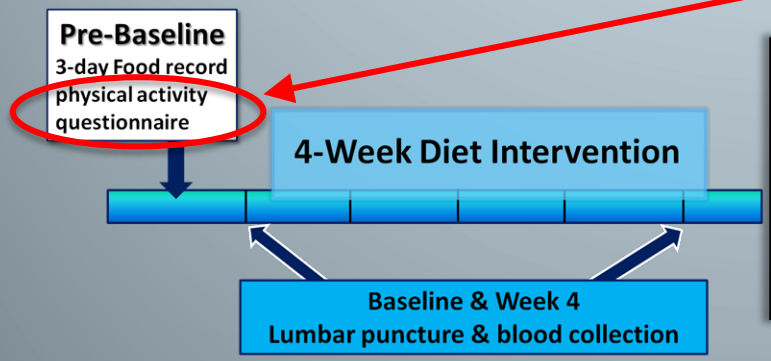
- **Evolution of the *Western Diet***
-



4-Week Diet Intervention in MCI & Cognitively Normal Older Adults

[Carter et al. JAMA Neurol 2012]

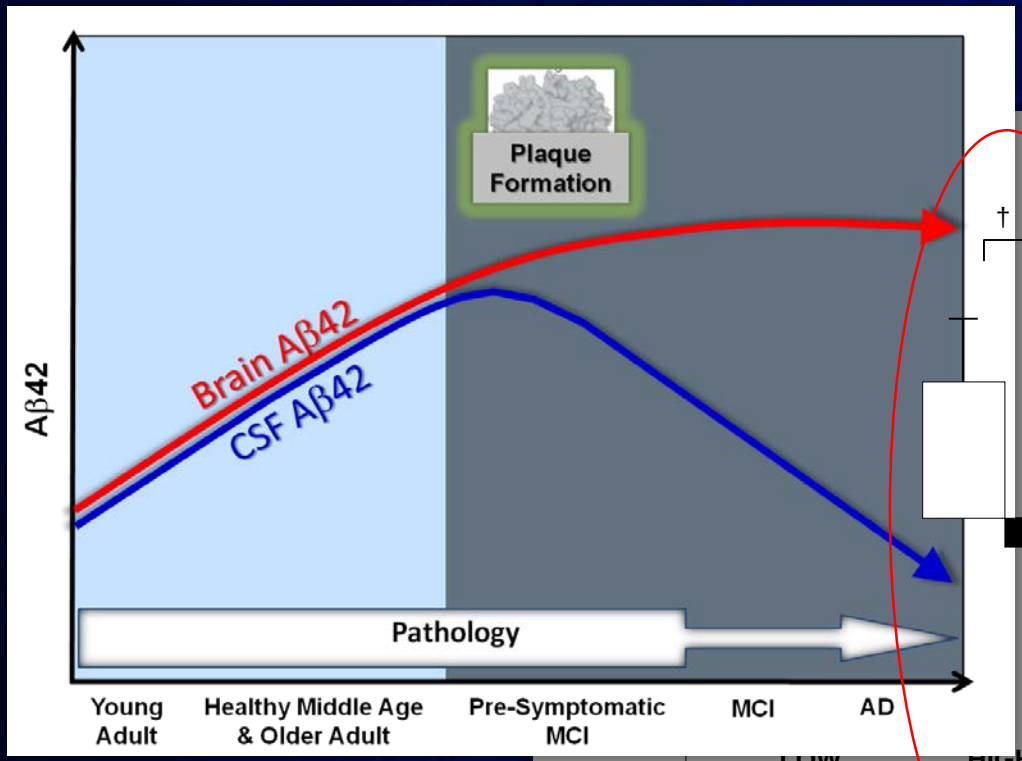
- List physical activities for past week (or typical week)
- Duration (min)/activity recorded
- Intensity/activity rated (0-5); 4-5 = increased HR & breathing rate
- Reports confirmed during interview
- All groups = at baseline



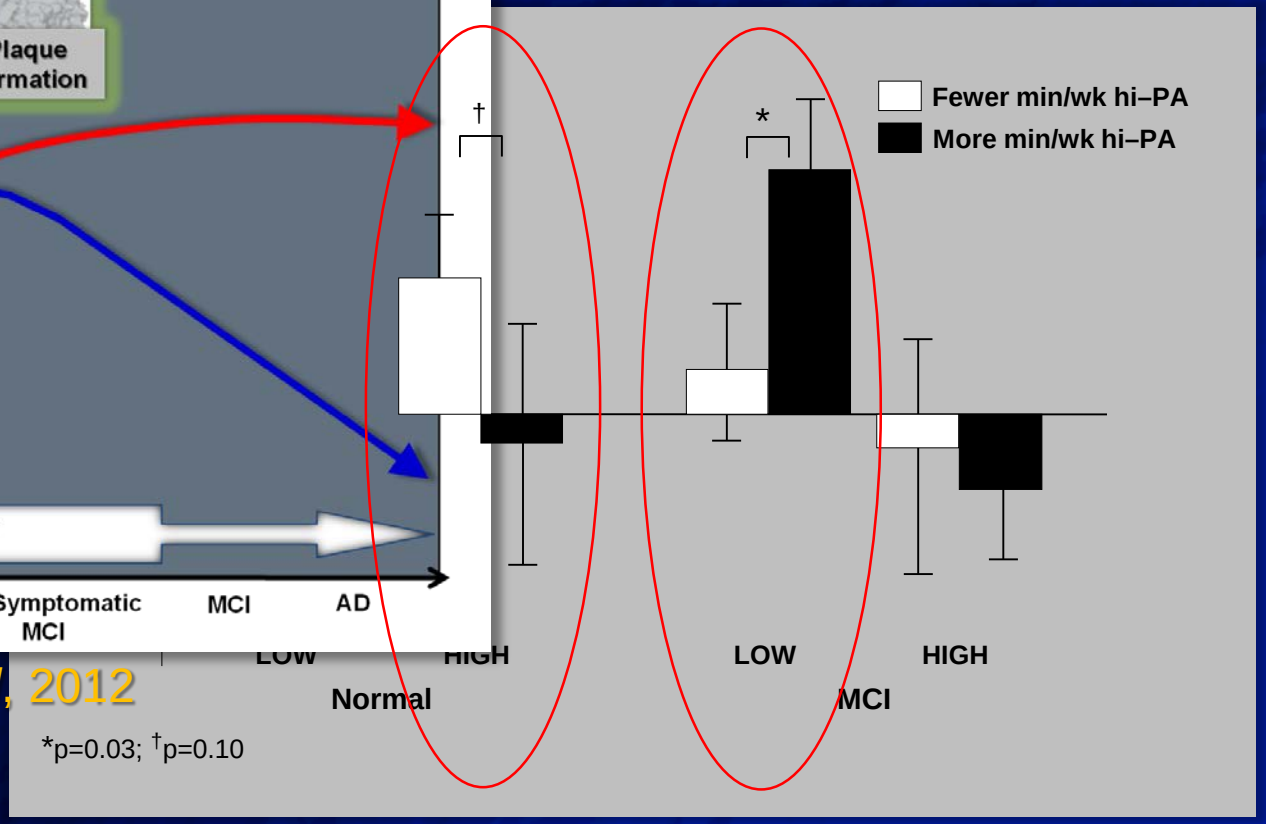
mean (SD)	Normal		MCI	
	LOW	HIGH	LOW	HIGH
N	11	9	14	15
Age, yrs	69.7 (8.0)	68.8 (7.0)	67.1 (6.8)	68.1 (6.9)
Educ, yrs	13.5 (1.8)	15.7 (2.2)	15.6 (2.3)	14.9 (2.2)
BMI kg/m^2	26.4 (2.6)	27.5 (4.5)	27.4 (3.8)	27.5 (3.4)
3MSE	96.6 (2.6)	97.8 (2.8)	95.0 (5.0)	93.1 (4.4)

- HIGH diet: 45% fat w/ 25% sat fat, GI>70
- LOW diet: 25% fat w/ 7% sat fat, GI<55
- All food prepared by metabolic kitchen & delivered to pts 2x/wk
- Eucaloric diet w/normal calorie intake; no weight change
- Total Aβ42 measured with INNO-BIA Alz, ApoE with ELISA
- LD-Aβ42 ApoE measured with sequential density flotation ultracentrifugation & ELISA [Takamura, 2011]

High Intensity Physical Activity Modulates Diet Effects on Cerebrospinal Aβ Levels in Normal Aging & MCI



Carter et al, *Arch Neurol*, 2012



Baker et al, 2012

Sleep Protects Cognition

- Sleep-disordered breathing (SDB) associated with low global cognitive function [Spira et al. 2008]
- SDB predicts MCI / dementia in prospective 2-year study (N=298, mean age=82 y) [Yaffe et al. 2011]
- Sleep fragmentation in older adults is associated with incident AD & the rate of cognitive declien [Lim et al. 2013]
  - Sleep disturbances may impair sleep-dependent memory consolidation processes **[Peutz et al. 2013]**
  - Sleep disturbance may disturb processes associated with removal of neurotoxic waste from the CNS **[Xie et al. 2013]**

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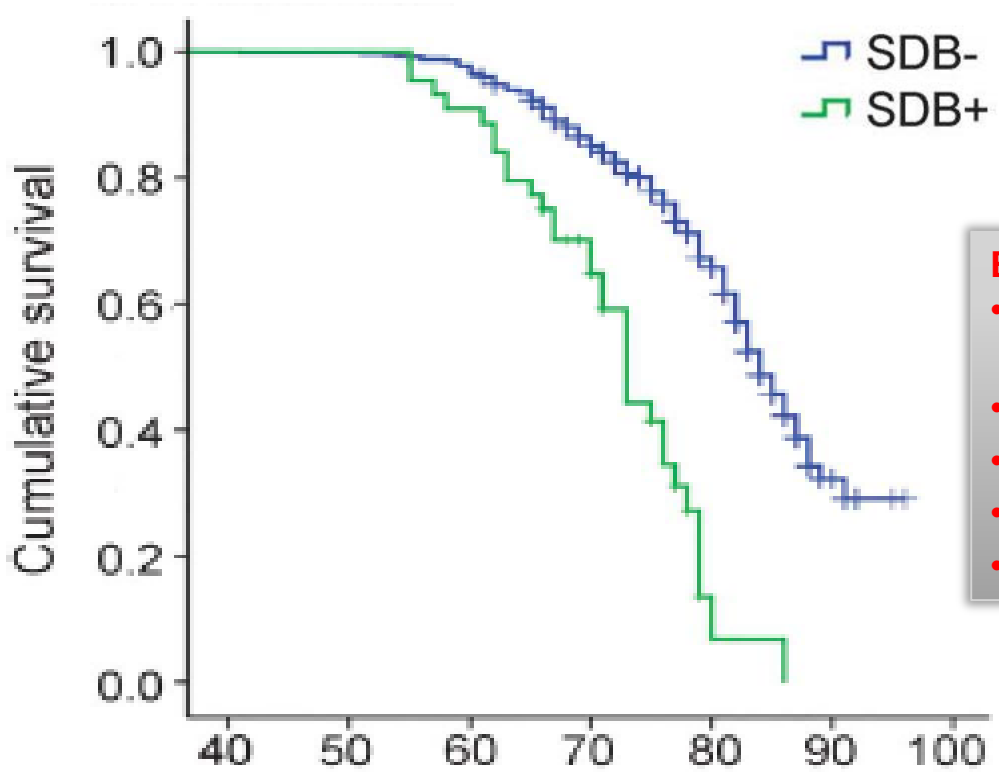
Sleep-disordered breathing advances cognitive decline in the elderly

Neurology®

Ricardo S. Osorio, MD
Tyler Gumb, BA
Elizabeth Pirraglia, MA
Andrew W. Varga, PhD, MD
Shou-en Lu, PhD
Jason Lim, BA
Margaret E. Wohlleber, BA
Emma L. Ducca, BA
Viachaslau Koushyk, MD
Lidia Glodzik, MD
Lisa Mosconi, PhD
Indu Ayappa, PhD
David M. Rapoport, MD
Mony J. de Leon, EdD
For the Alzheimer's Disease Neuroimaging Initiative



Excluded:

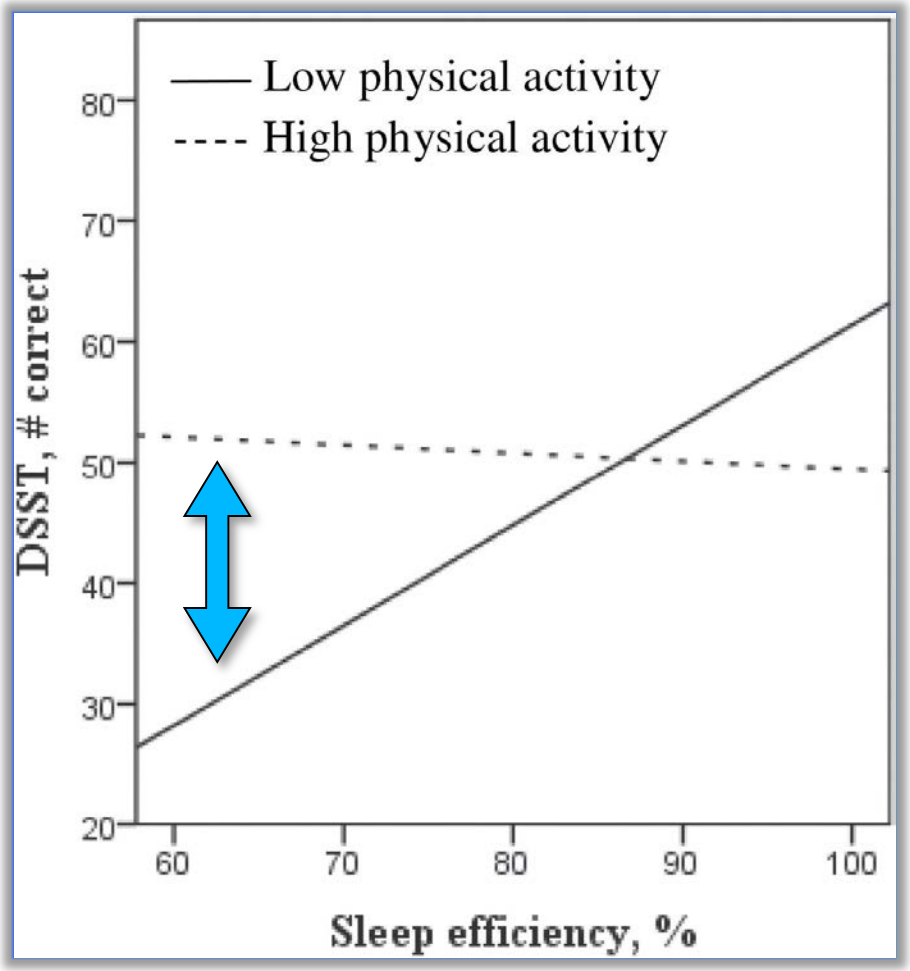
- co-morbid sleep disorders
- OSA surgeries
- no f/u data
- reversible dx
- +BMI > 5

Onset of MCI, N=622

Osorio et al. 2015

Higher Levels of Physical Activity Mitigate Negative Effects of Poor Sleep Efficiency on Cognition

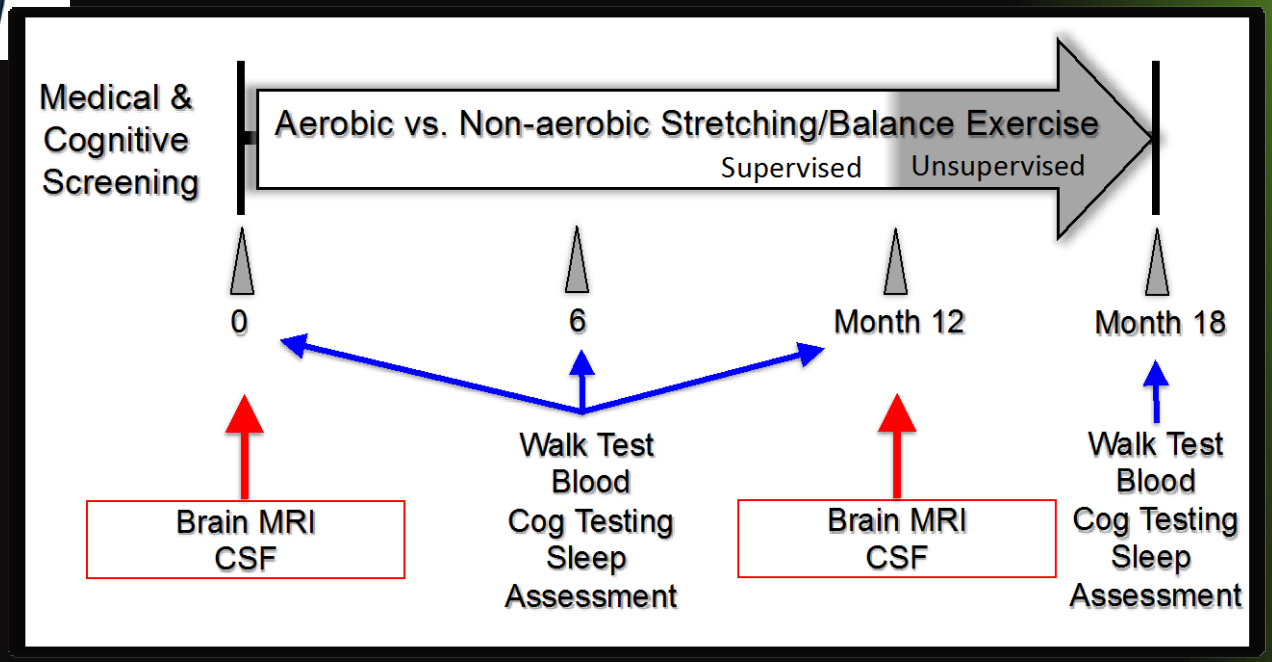
- N =121 from the Healthy Women Study
- Mean (SD) age =73.3 (1.7) yrs
- 7-day measurement of sleep efficiency & physical activity using actigraphy
- Executive function measured with DSST & Trails B



Maya J. Lambiase et al. J Gerontol A Biol Sci Med Sci 2014;69:1170-1176

the Journals of gerontology Series a

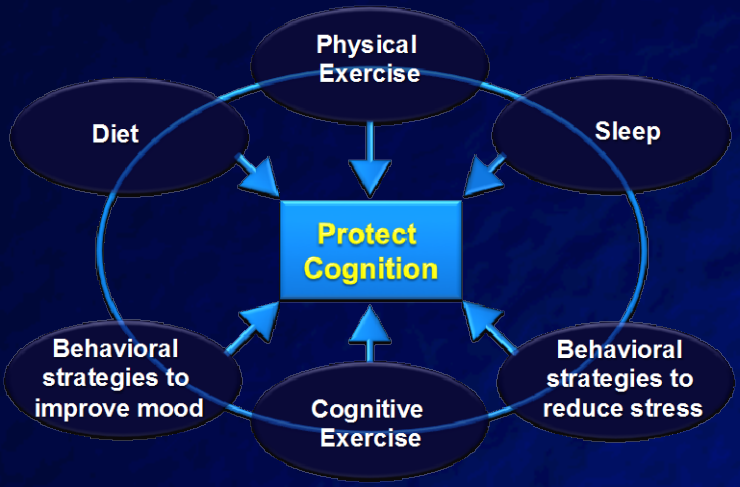
ADCS RCT of Aerobic Exercise to Slow Disease Progression in MCI



PDs: Cotman, Baker

ADCS Aerobic Exercise to Slow Disease Progression in MCI

- **Subjects:** N=300 sedentary adults with aMCI (single/multi-domain), 20% minority, 65-85 yrs old with PCP approval, enrolled over 1.5 years at 15 sites
- **Intervention:** 45 min per session, 4x per week; supervised twice per week for first 12 months, unsupervised for last 6 months
  - "High Intensity" exercise at 75% heart rate reserve (HRR) for 30 of 45 min per session (~ 130 bpm for a 70 year old)
  - "Low Intensity" exercise < 35% HRR (~ < 95 bpm for a 70 y.o.)
- **Outcomes:** Cognition (ADAS-Cog13 + suppl EF tasks, NIH Toolbox, CogState), CDR-SB, IADL-MCI, AD chemical biomarkers, s/fMRI, sleep efficiency
- **Translation:** Partnership with the national YMCA (Y-USA)
- **Timeline:** Enrollment, Fall 2015



Summary

- Physical activity, given its restorative effects on multiple biological systems, holds promise as a disease-modifying intervention – needs to be tested in Phase III trial
- Physical activity & health-restoring effects likely interact with other exposures (diet, sleep disturbance, depression, stress) to increase potency of risk modification
- If only we had a pill….

Collaborators

Wake Forest School of Medicine, Winston-Salem NC

Suzanne Craft, PhD
Kaycee Sink, MD
Tim Hughes, PhD
Jeff Katula, PhD
Sally Shumaker, PhD

Jeff Williamson, MD
Valerie Wilson, MD
Barb Nicklas, PhD
Mark Espeland, PhD
Steve Rapp, PhD

UC Irvine, CA

Carl Cotman, PhD

UC San Diego, CA

Paul Aisen, MD & the ADCS

U of Washington, Seattle WA

Tom Montine, MD PhD
Brenna Cholerton, PhD
Angela Hanson, MD

Stephen Plymate, MD
Charles Wilkinson, PhD
Maureen Callaghan, MD

Blue Ridge Mountains, NC