Relationship between systemic metabolism and Alzheimer's Disease

Jill K. Morris, PhD

Assistant Professor, Neurology

University of Kansas Medical Center

Overview

- The scope of AD
- Metabolic risk factors
  - Energy metabolism
  - Lifestyle and genetics
- Exercise as a therapy
  - Rationale
  - Our past trials
  - Mechanistic studies/trials
- Mechanisms that underly these links

Dementia and Alzheimer's Disease

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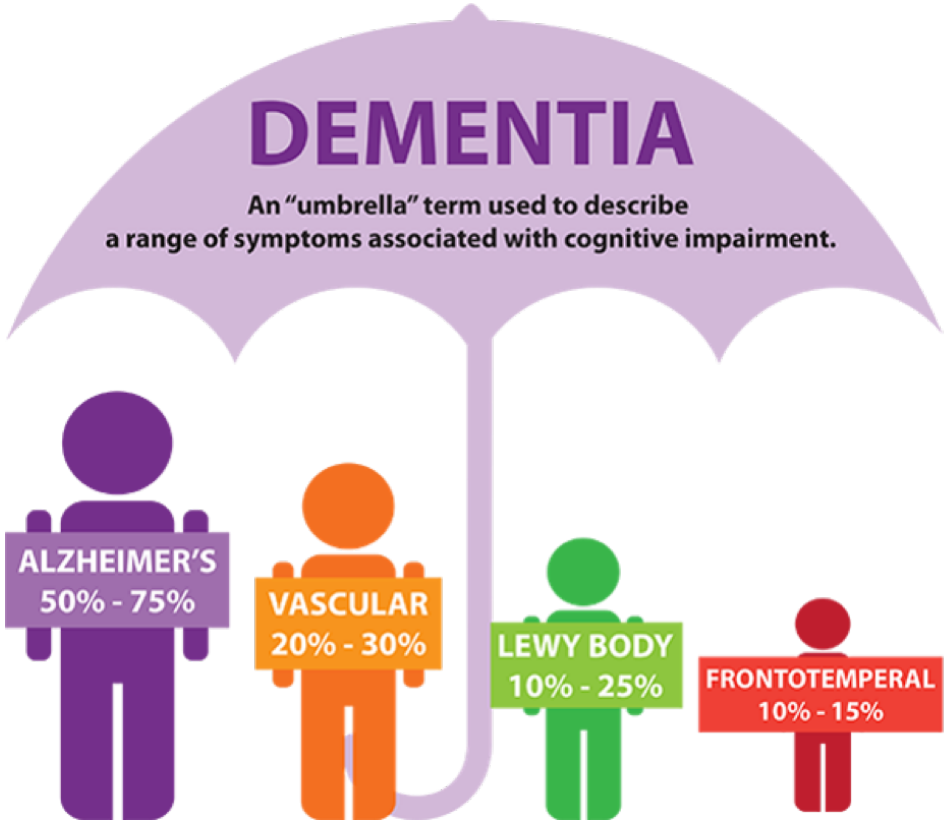
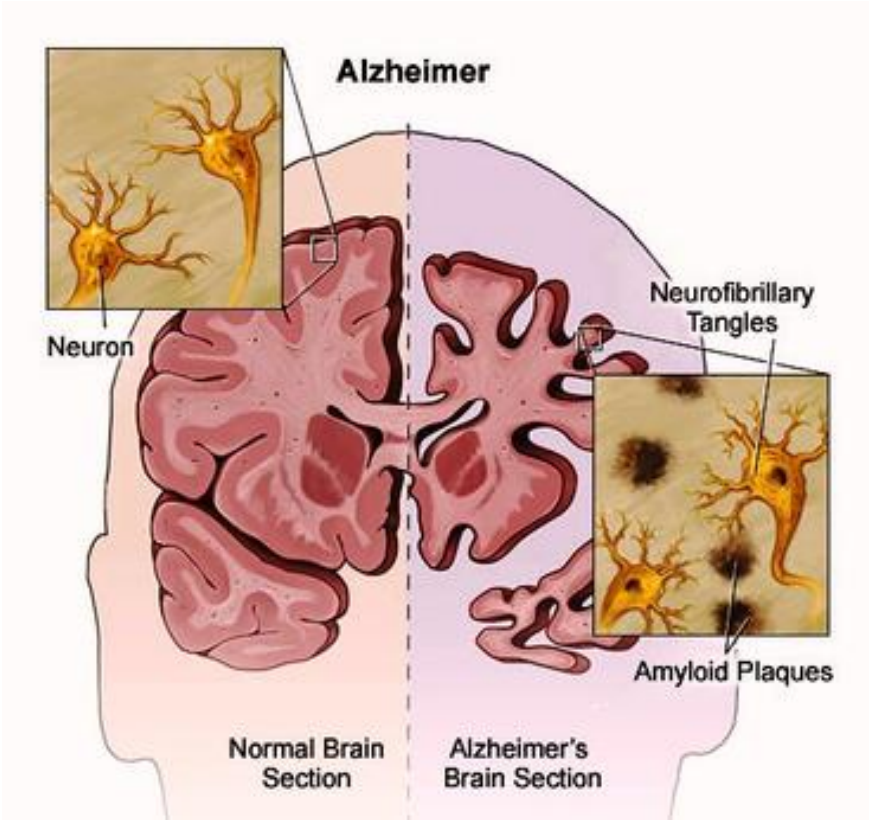
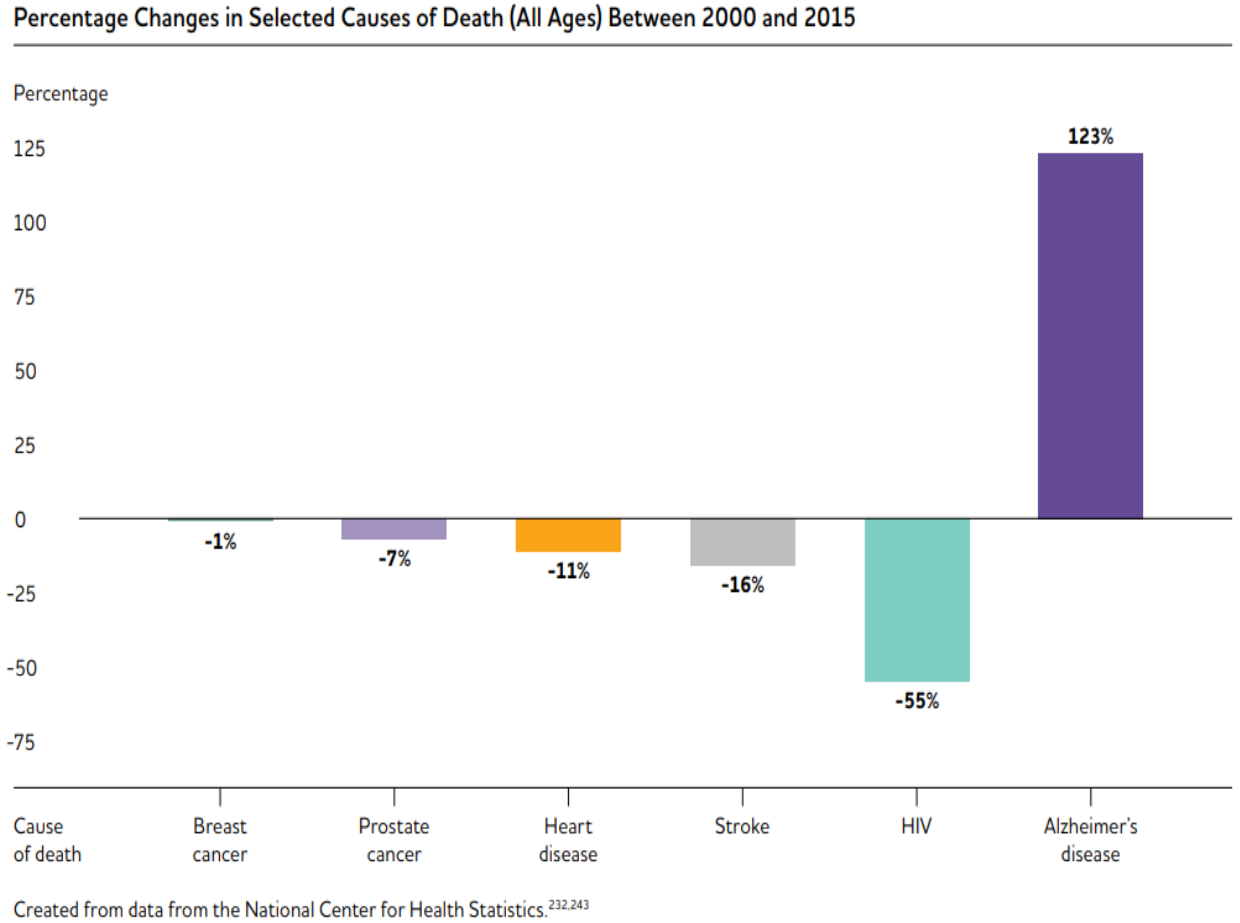




Courtesy: Dementia Friendly America

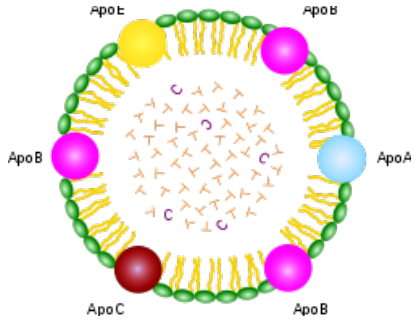
The scope of Alzheimer's Disease

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



Courtesy: Alzheimer's Association

Risk factors



Genes

Advancing Age

Energy Metabolism Insulin Resistance

Lifestyle

Energy metabolism may represent a relatively unexplored therapeutic target in AD

Hyperinsulinemic-euglycemic clamp shows insulin resistance in AD

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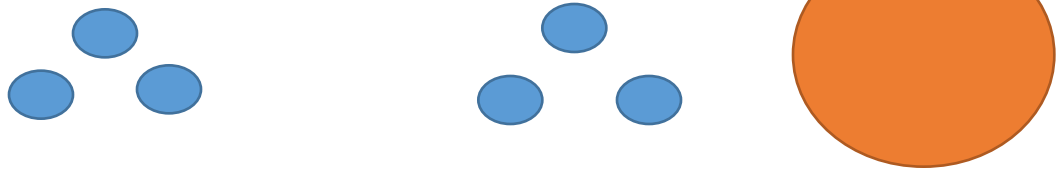
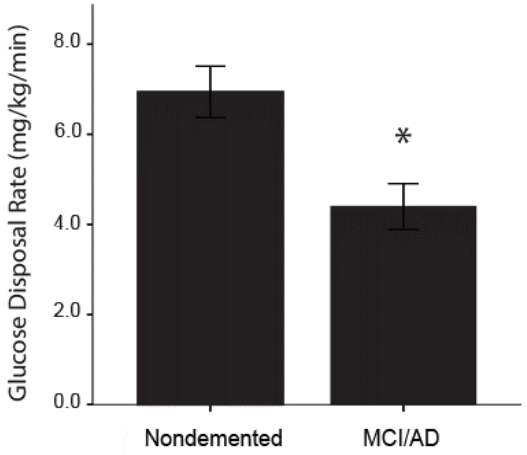
Glucose infusion | Blood glucose | Cell

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





Morris et al 2016, NBA

Impaired meal-stimulated metabolic response in AD

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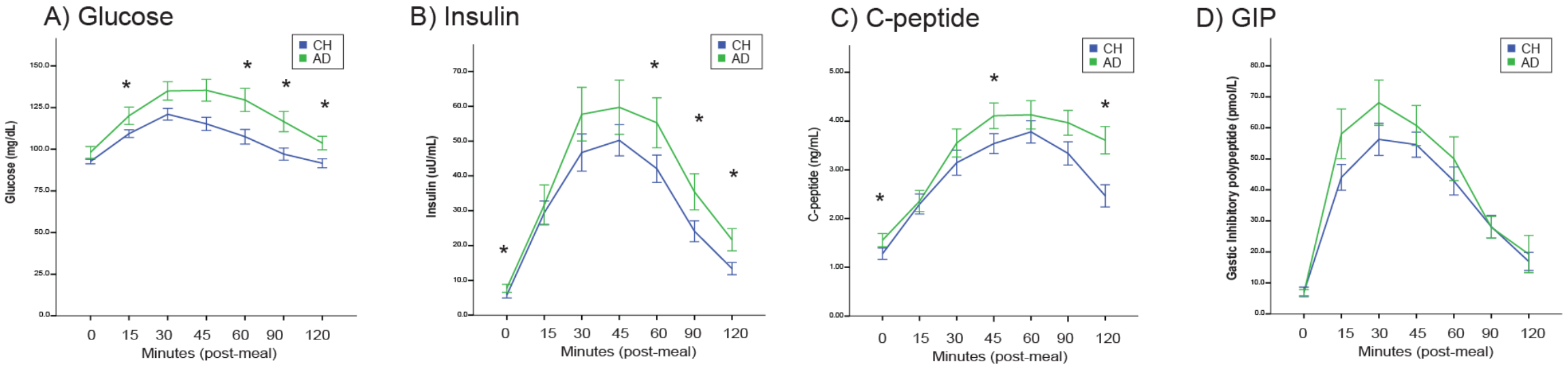
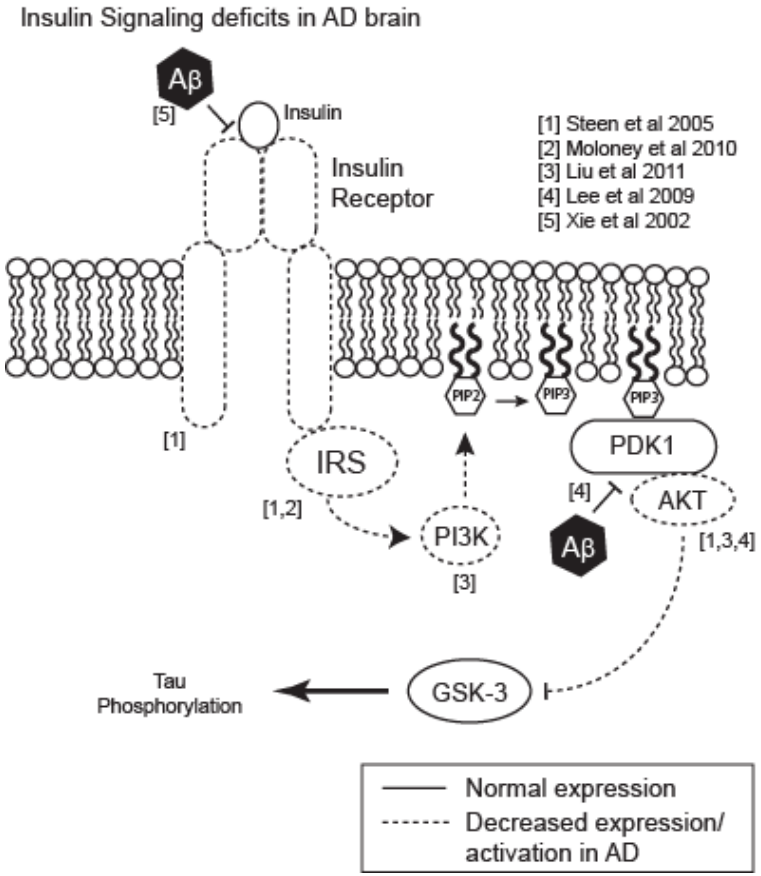
Measure	Cognitively Healthy(n =28)	AD (N=17)	p-value
Age (y)	74.0 (5.4)	77.5 (6.5)	0.73
Sex (#/%male)	13(4 6.4%)	10(5 8.8%)	0.42
APOE (#/%carri er)	11(3 9.2%)	11(6 4.7%)	0.10
MMSE	29.2 (0.88)	22.4 (5.2)	<0.01*
CDR-SB	0 (0)	4.26 (2.4)	<0.01*
BMI	28.0 (4.2)	28.7 (5.6)	0.49
Weight (kg)	77.9 (14.4)	79.8 (23.0)	0.43
Systolic BP (mmHg)	134.1(16.4)	131.0 (10.6)	0.23
Diastolic BP (mmHg)	75.2 (8.1)	74.5 (5.6)	0.27

Figure 1. Metabolic response to a mixed meal



Morris et al, in preparation

CNS insulin resistance in AD

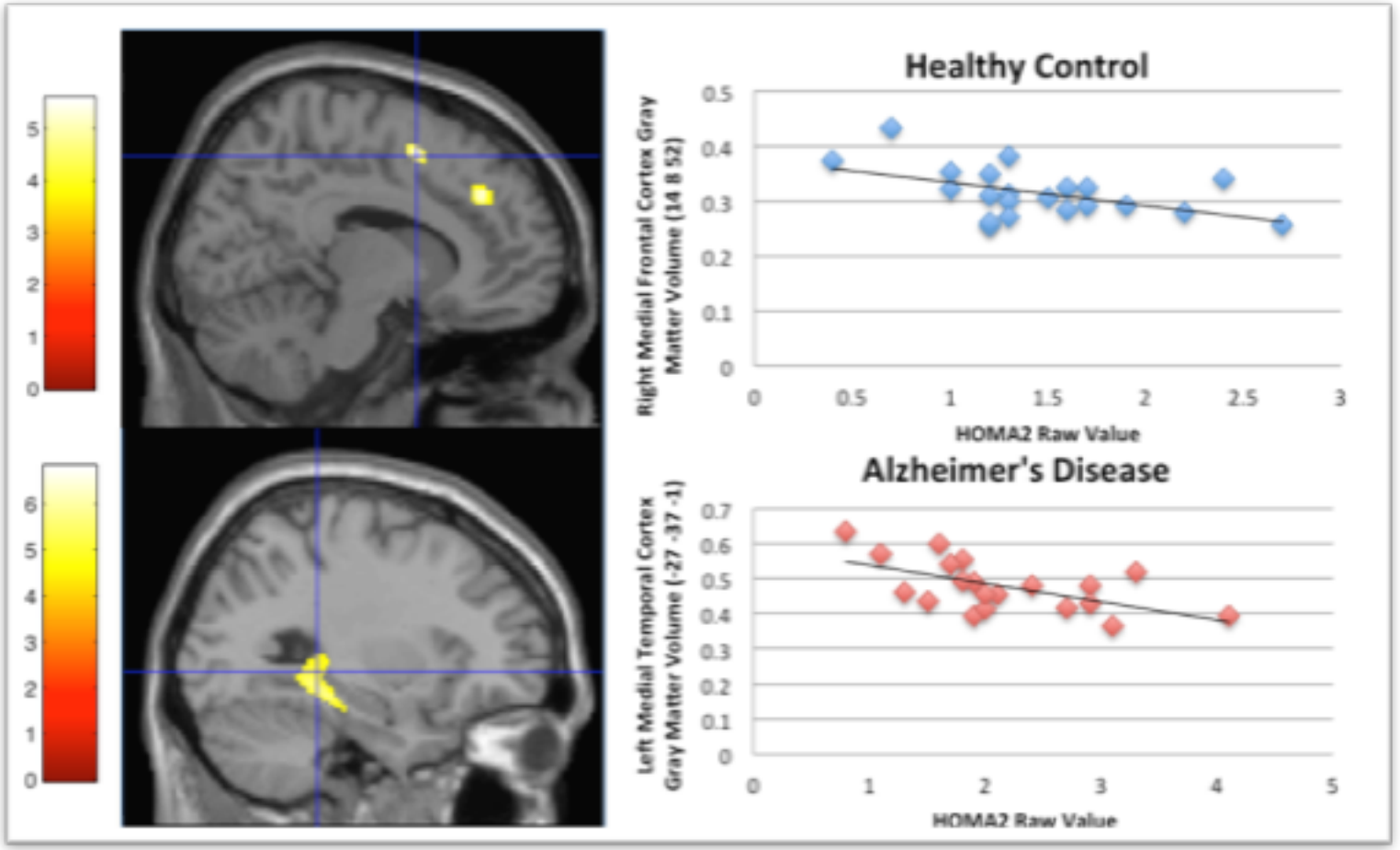


Morris et al 2012

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

Neurotransmission
Cell survival
Amyloid clearance
Tau phosphorylation
Energy production

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



Morris et al 2014, Neuroscience

Cerebral glucose hypometabolism: a marker of AD

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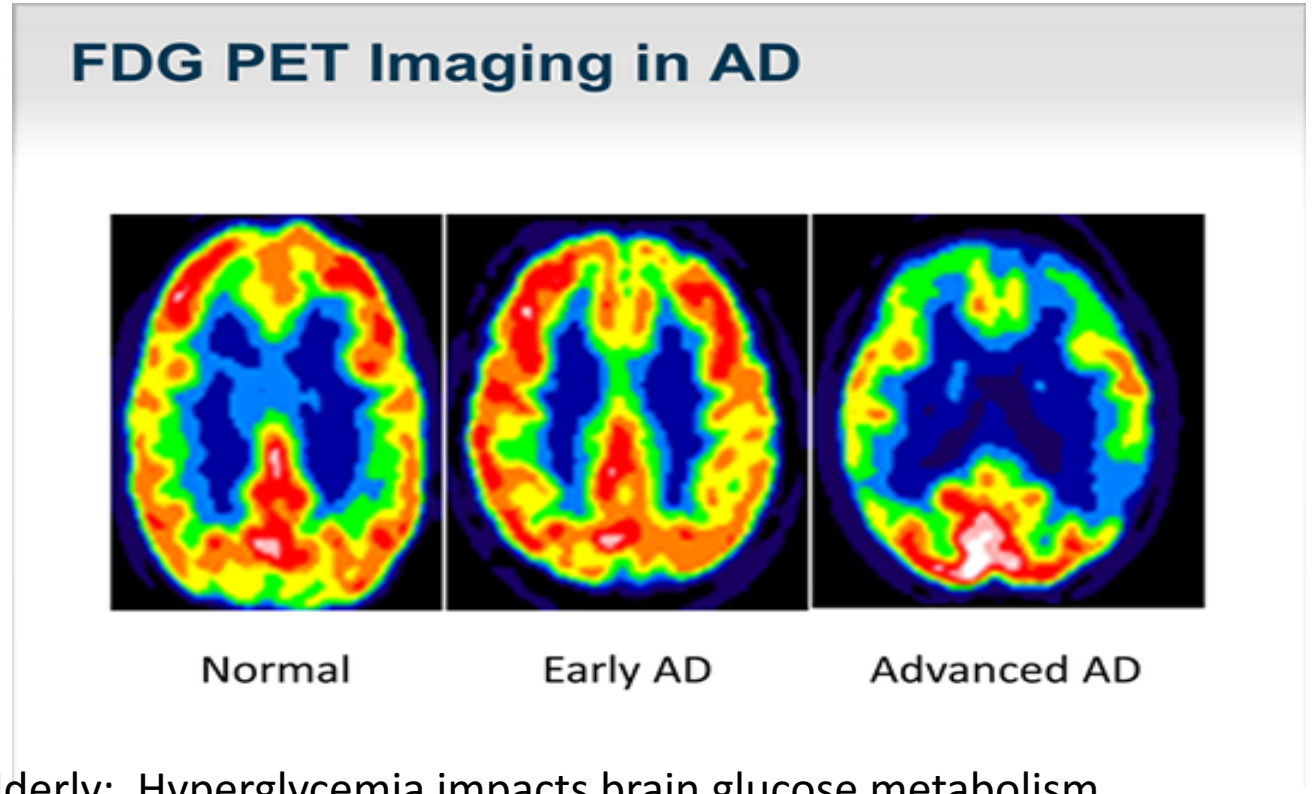

Cognitively healthy elderly: Hyperglycemia impacts brain glucose metabolism
(*Kawasaki et al 2008, Ann Nucl Med, Ishibashi et al 2015 J Nucl Med, Ishibashi et al 2015, JCBM*)

Impaired fasting glucose and progression of cognitive impairment

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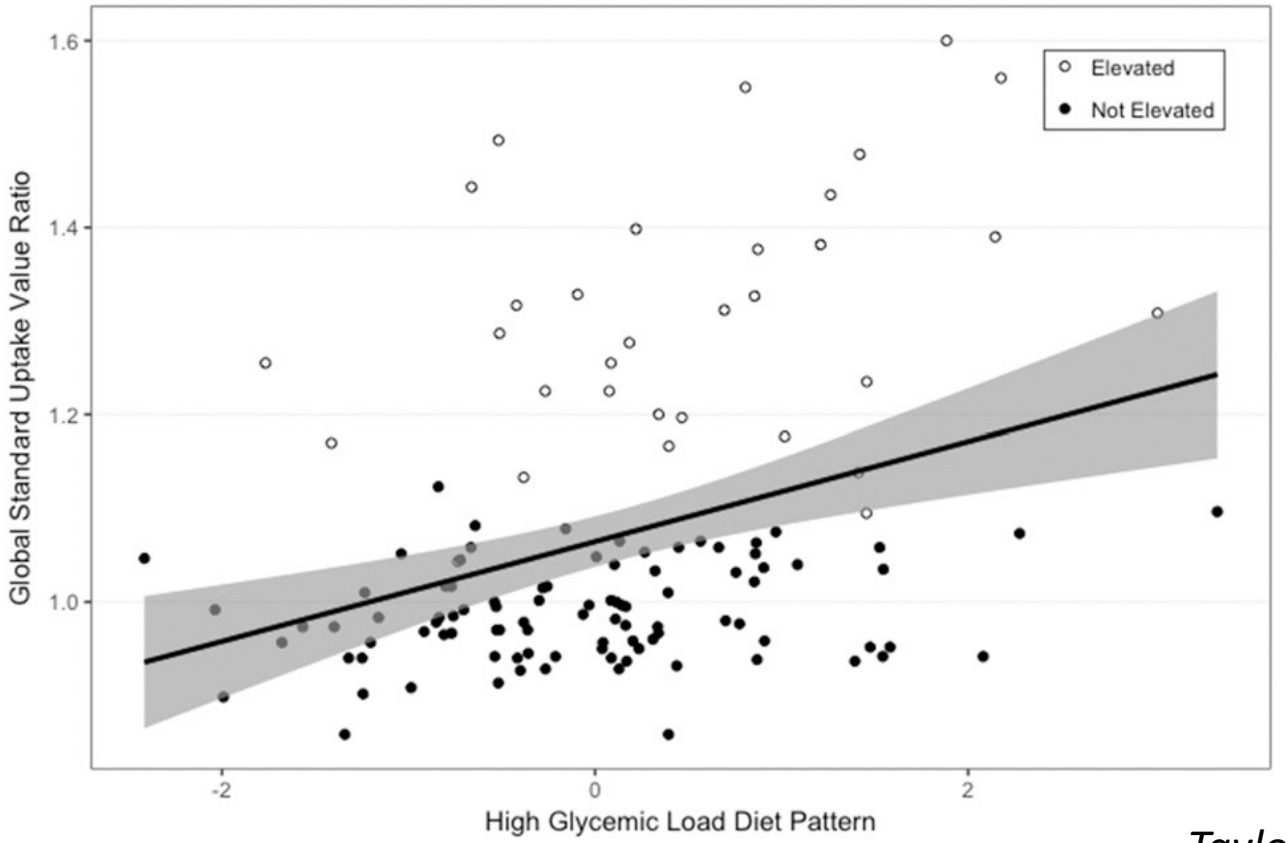
Measure	Timepoint	Normoglycemia	Impaired Glycemia	p-value (2yr D)
MCI to AD converters*	Baseline	N/A	N/A	0.015
	2yr Δ	32.7% (16.4%/yr)	47.9% (24.0%/yr)	
CDR-SB*	Baseline	1.56 (0.86)	1.61 (0.84)	0.044
	2yr Δ	1.35 (1.9)	1.88 (1.9)	
Global Cognition*	Baseline	-0.615 (0.55)	-0.761 (0.61)	0.019
	2yr Δ	-0.193 (0.55)	-0.366 (0.58)	
Whole Brain Volume*	Baseline	0.677 (0.027)	0.672 (0.02)	0.024
	2yr Δ	-0.012 (0.007)	-0.0152 (0.009)	
Hippocampal Volume	Baseline	0.655 (0.90)	0.642 (0.08)	0.439
	2yr Δ	-0.0152 (-.016)	-0.0194 (0.019)	

Morris et. al. 2014, NBA

Glycemic intake is related to regional cerebral amyloid



Relation of glycemic dietary intake measures with global and regional cerebral amyloid burden[1]

	HGLDiet[2] pattern	Sugar intake	Glycemic load	Carbohydrate intake
Global	0.36***	0.21*	0.22*	0.24*
Anterior cingulate gyrus	0.38***	0.20*	0.23*	0.25**
Inferior medial frontal gyrus	0.33***	0.17	0.16	0.18
Lateral temporal lobe	0.34***	0.22*	0.22*	0.24*
Posterior cingulate gyrus	0.31***	0.17	0.18*	0.21*
Precuneus	0.32***	0.22*	0.21*	0.24*
Superior parietal lobule	0.30***	0.19*	0.20*	0.21*

[1] Values are standardized β values for the respective dietary glycemic measure determined by multivariate linear regression controlling for age, sex, and education; $n = 128$. $^{*}P \leq 0.05$, $^{**}P \leq 0.01$, $^{***}P \leq 0.001$.
[2] HGLDiet, high-glycemic-load diet.

Taylor et al, Am J Clin Nutrition, 2017

T2D subjects cannot be identified in AD populations using –omics approaches

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Am J Physiol Endocrinol Metab 314: E584–E596, 2018.
First published December 26, 2017; doi:10.1152/ajpendo.00377.2017.

RESEARCH ARTICLE | *Translational Physiology*

The serum metabolomics signature of type 2 diabetes is obscured in Alzheimer's disease

Jill K. Morris,[1,2]* Brian D. Piccolo,[3,4]* Kartik Shankar,[3,4] John P. Thyfault,[1,2,5,6] and Sean H. Adams[3,4]

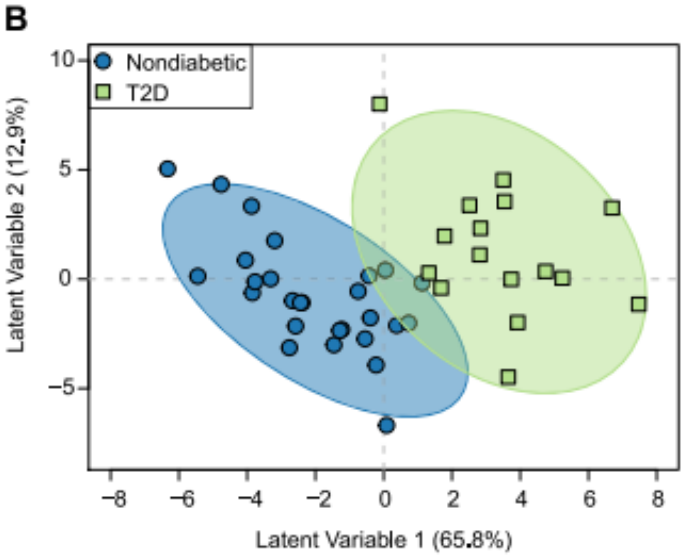
[1]University of Kansas Department of Neurology, University of Kansas Alzheimer's Disease Center, Kansas City, Kansas; [2]University of Kansas Alzheimer's Disease Center, Fairway, Kansas; [3]Arkansas Children's Nutrition Center, Little Rock, Arkansas; [4]Department of Pediatrics, University of Arkansas for Medical Sciences, Little Rock, Arkansas; [5]University of Kansas Department of Molecular and Integrative Physiology, Kansas City, Kansas; and [6]Kansas City Veterans Affairs Medical Center, Kansas City, Missouri

Submitted 13 October 2017; accepted in final form 20 December 2017

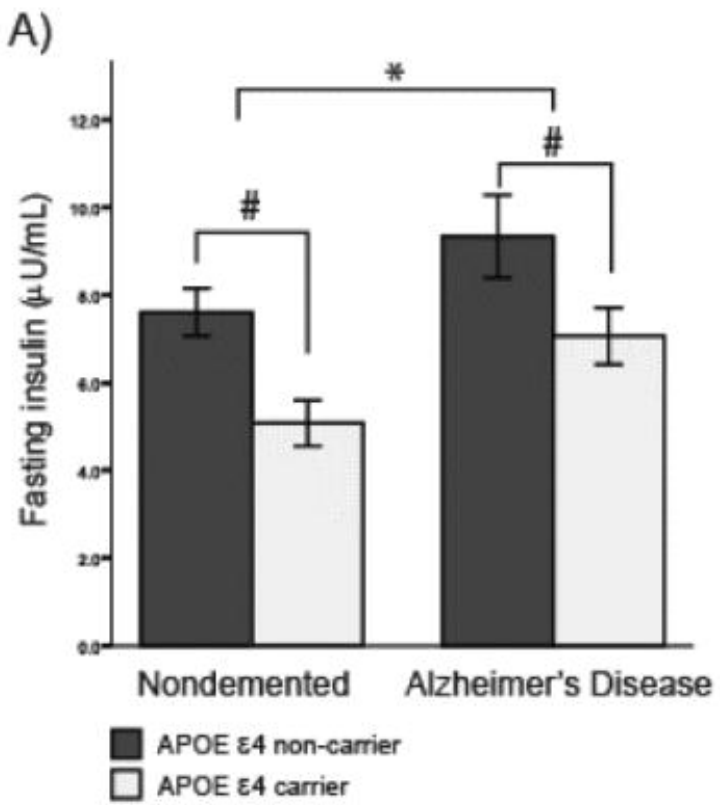
Morris JK, Piccolo BD, Shankar K, Thyfault JP, Adams SH. The serum metabolomics signature of type 2 diabetes is obscured in Alzheimer's disease. *Am J Physiol Endocrinol Metab* 314: E584–E596, 2018. First published December 26, 2017; doi:10.1152/ajpendo.00377.2017.—There is evidence for systemic metabolic impairment in Alzheimer's disease (AD), and type 2 diabetes (T2D) increases AD risk. Although studies analyzing blood metabolomics signatures have shown differences between cognitively healthy (CH) and AD subjects, these signatures have not been compared with individuals with T2D. We utilized untargeted analysis platforms (primary metabolism and complex lipids) to characterize the serum metabolome of 126 overnight-fasted elderly subjects classified into four groups based upon AD status (CH or AD) and T2D status [nondiabetic (ND) or T2D]. Cognitive diagnosis groups were a priori

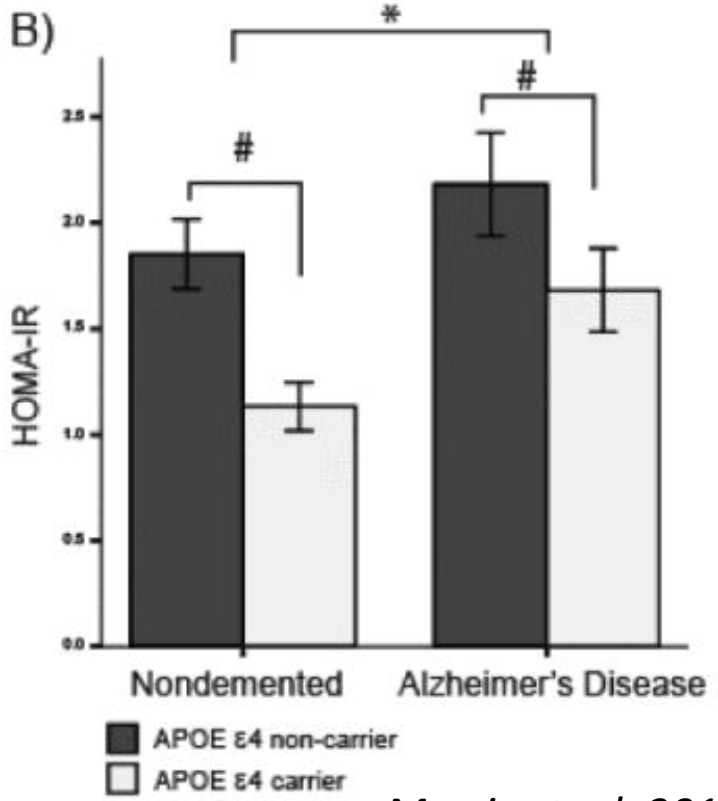
prevented (2). We and others have shown that insulin resistance and prediabetes are linked to accelerated clinical progression, cognitive decline, and brain atrophy early in the AD process (42, 64). However, it is unclear whether glucose, alterations in related metabolic hormones such as insulin or incretins, or other related pathways and metabolites such as lipids contribute to the observed associations between diabetes status and AD.

Recent plasma metabolomics studies have found differences between AD patients and cognitively normal subjects (49, 50), but the mechanistic underpinnings of the relationships between metabolites and AD remain unclear. Amyloid deposition in the brain is a primary pathological feature of AD development (5)



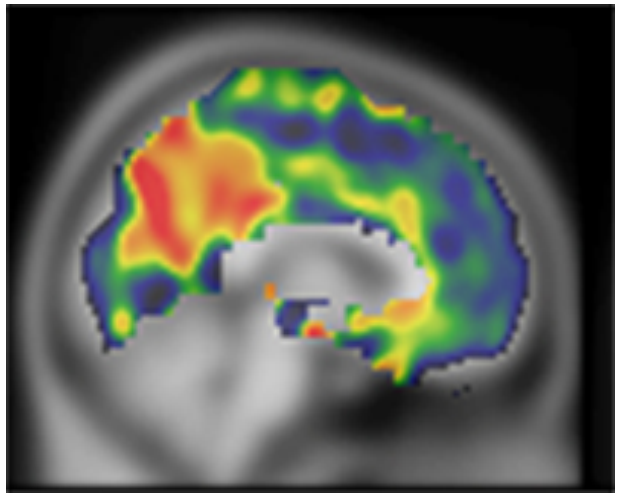
LOAD genetic risk and metabolic outcomes





Morris et. al. 2016, JAD

Impaired fasting glucose is related to regional cerebral amyloid



NG vs. IFG
cerebral amyloid

Region	E4	IG	IG+E4
Precuneus	↑ vs. CNT	↑ vs. CNT	↑ vs. CNT
Posterior cingulate (PCC)	↑ vs. CNT	↑ vs. CNT	
Superior parietal cortex (SPC)	↑ vs. CNT	↑ vs. CNT	
Anterior cingulate (ACC)	↑ vs. CNT		
Medial and superior frontal	↑ vs. CNT		
Global cortical	↑ vs. CNT		

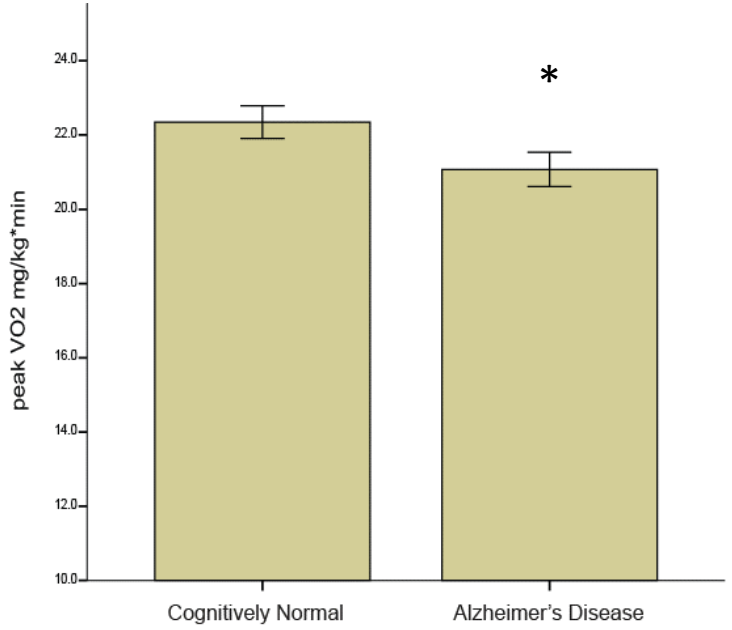
Morris et al 2016, NBA

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

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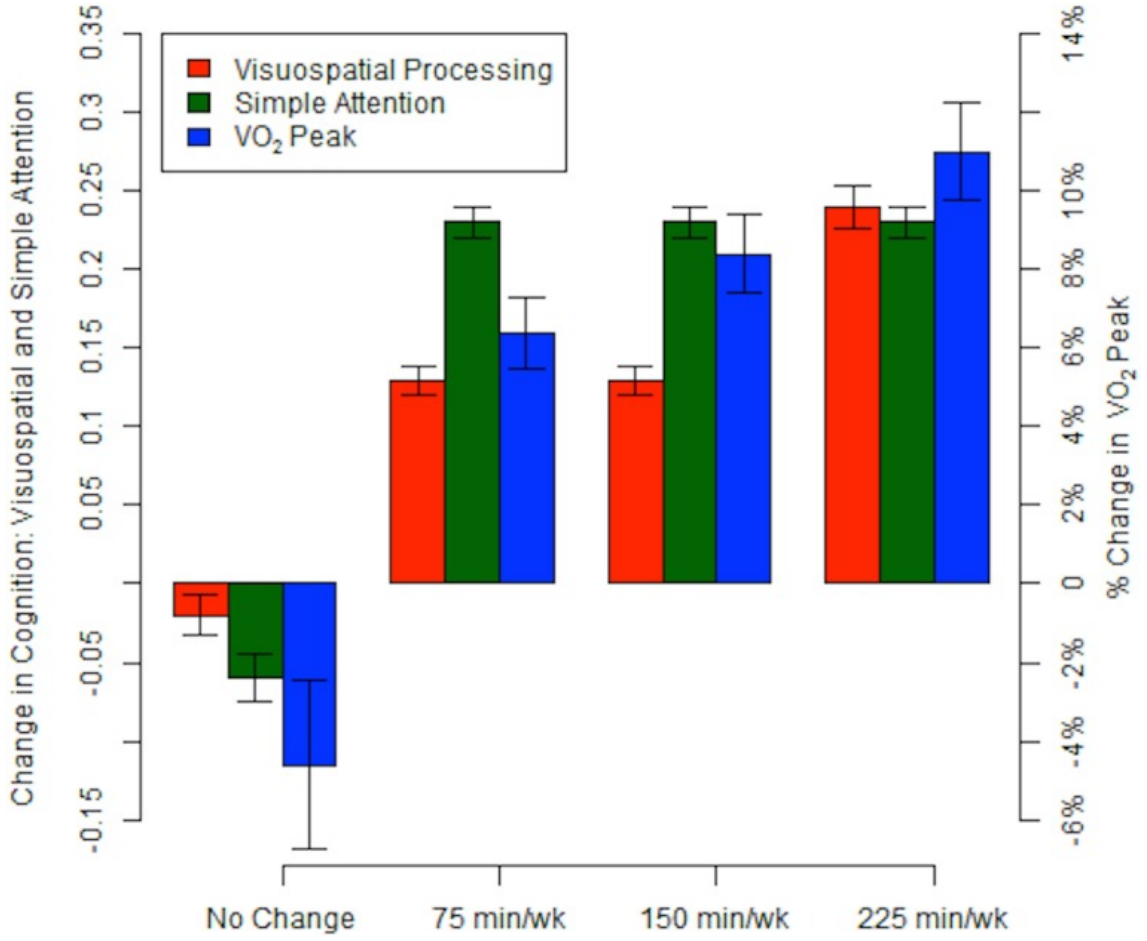
- BAP *(Brain Aging Project: 2006-2008)*
  - Longitudinal observational study, ND and AD
- TEAM *(Trial of Exercise on Aging and Memory: 2008-2013)*
  - Exercise trial, cognitively healthy elderly
- ADEPT *(Alzheimer's Disease Exercise Program Trial: 2010-2015)*
  - Exercise trial, probable AD
- APEX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

TEAM: 26 weeks, 4 dose groups
ADEPT: 26 weeks, 2 dose groups

TEAM (Cognitively healthy elderly)



Vidoni et. al. 2015, Plos ONE

ADEPT (Alzheimer's Disease)

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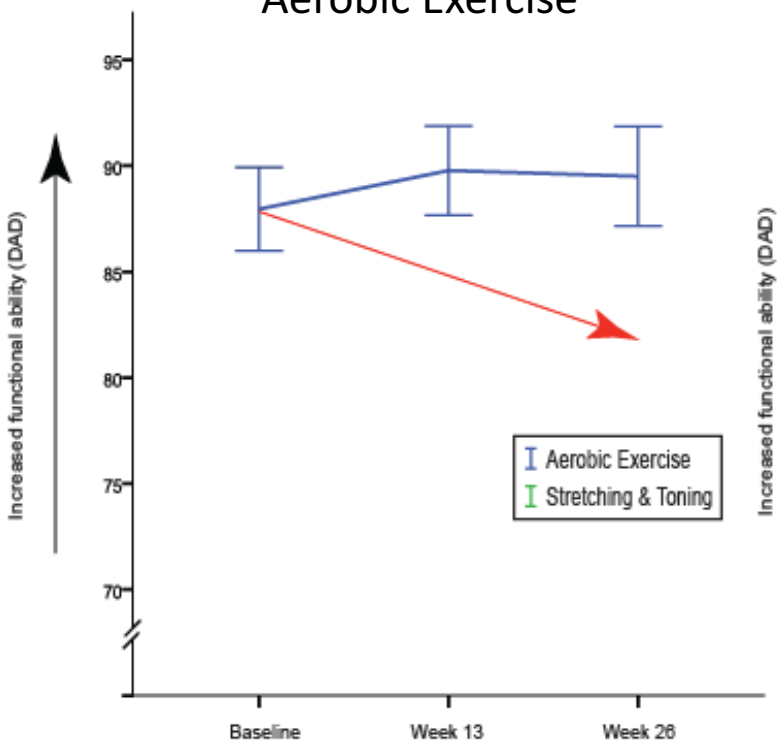
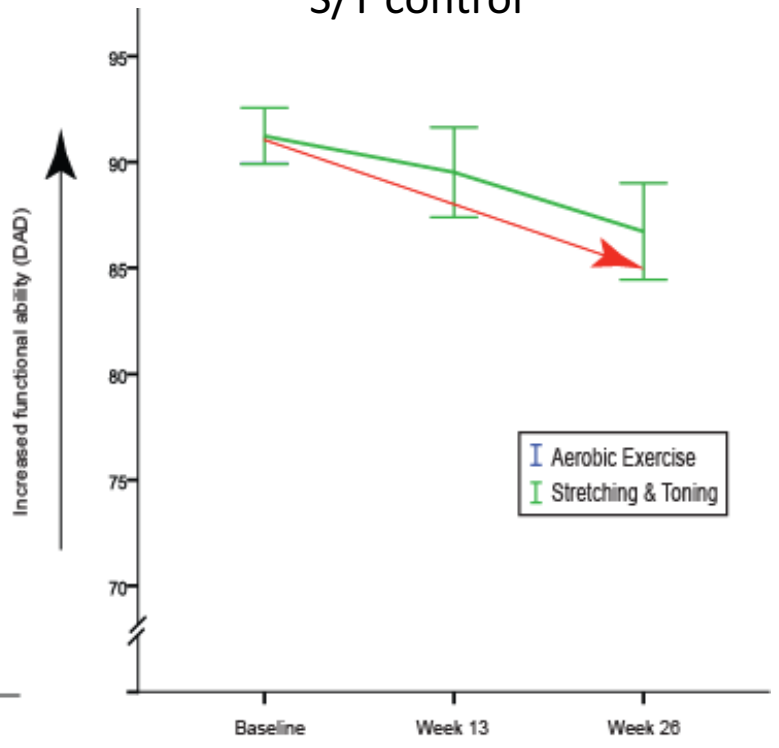
Aerobic Exercise



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

Fitness change tracks with memory change in exercising AD subjects

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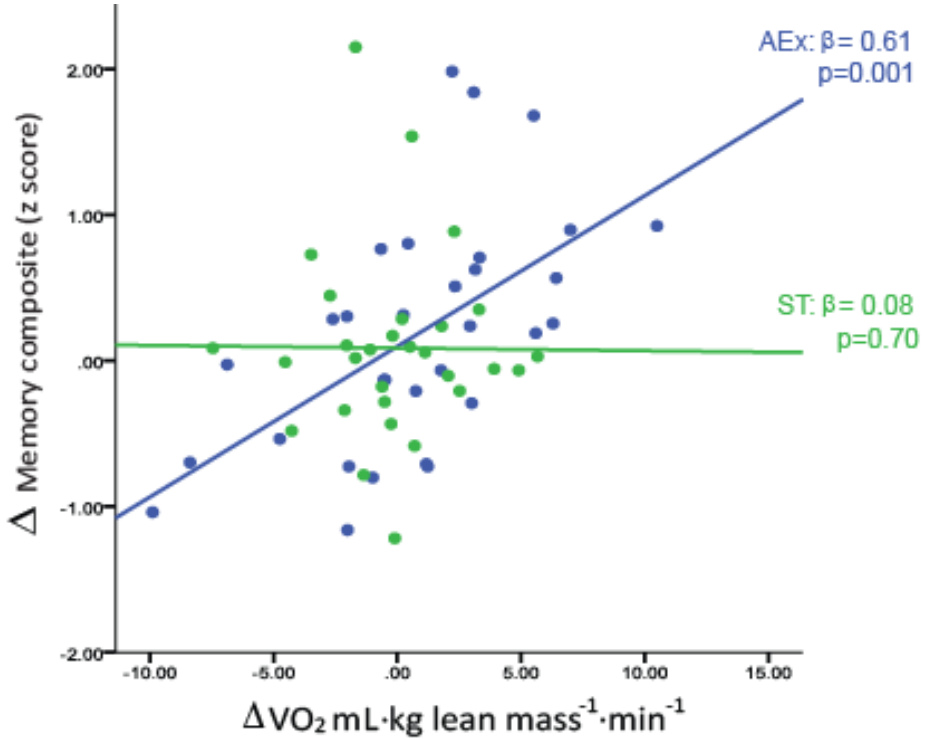

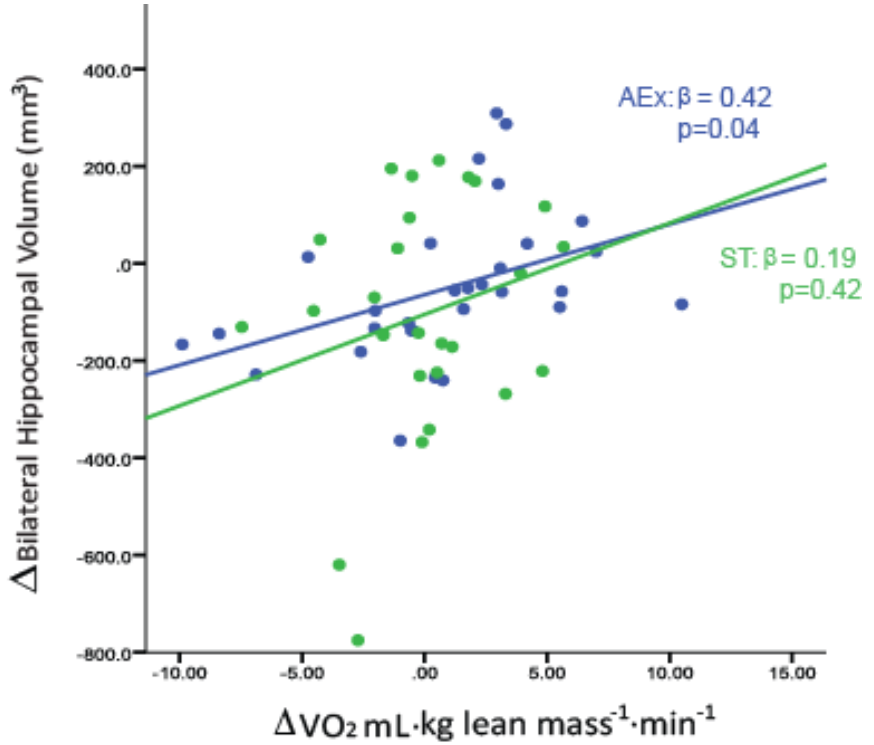

Morris, Vidoni et al 2017, PLOS One

Summary of past KU ADC trials

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- 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 underly benefit)?

ADMIT – Aging and Disease Mitochondria

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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

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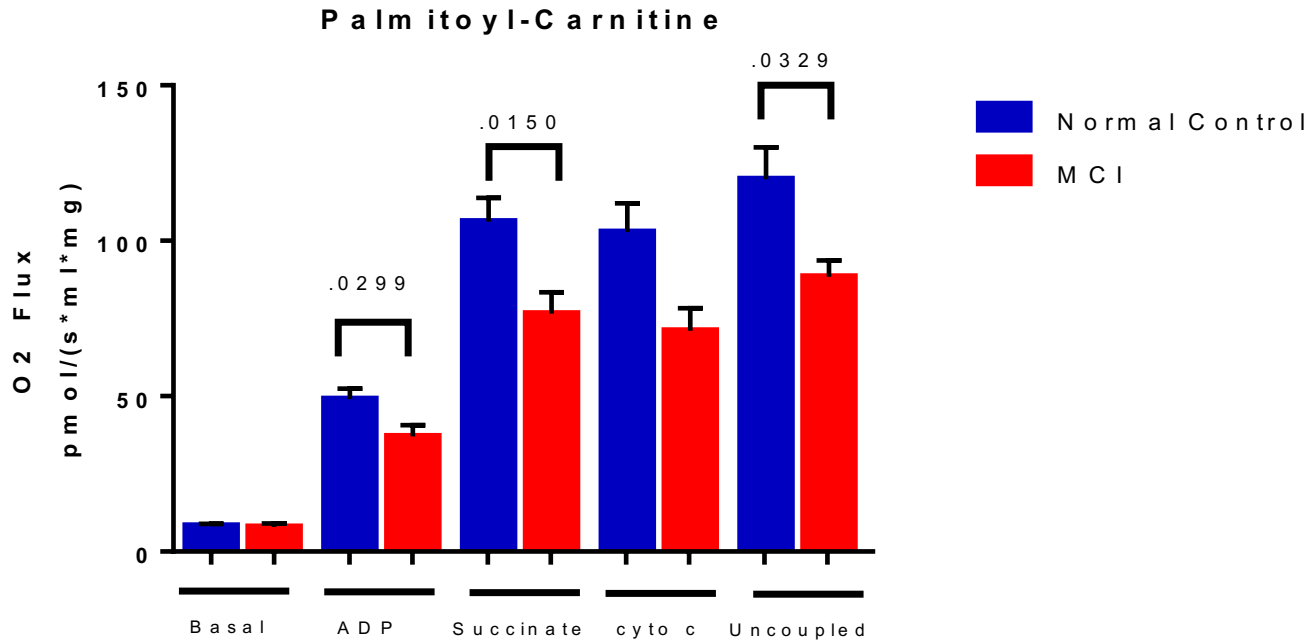

Future directions/Summary

- Short term studies
  - Acute effects of exercise on biomarker response
  - Does this modulate brain effects (i.e. cerebral glucose metabolism)

- Clinical trials
  - Can we improve energy metabolism (mito function, IR, -omics profiles, etc)?
  - Does this drive brain benefit?

- Individualized medicine
  - Different groups exhibit different responses
  - Peripheral energetics as a measure of target engagement in the brain?

Deficits in energy metabolism exist in AD and are likely an important therapeutic target for interventions

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Morris Laboratory
Casey John, MS
Ashwini Kamat

KU ADC
Anne Arthur, ARNP
Ashley Thompson
Kayla Meyer
Angela Van Sciver
Ian Weidling
Arianna Christian, MS
Briana Bright
Mark McClellan

Students
Zachary Green
Nicole Burns
Alexis Aiman

KUMC Collaborators
Jeffrey Burns, MD
Eric Vidoni, PhD
John Thyfault, PhD
Russell Swerdlow, MD
Colin McCoin, PhD
Heather Wilkins, PhD
Xiaowan Wang, PhD
Jonathan Mahnken, PhD
Matthew Taylor, PhD

External collaborators
Sid O'Bryant, PhD (UNT Health)
Sean Adams, PhD (UAMS)
Brian Piccolo, PhD (UAMS)
Ozioma Okonkwo, PhD (Wisconsin)

CTSU nursing support
Elizabeth Pauley
Andra Lahner
Kimberly Cygan
Jill Torneden
Kristy Anderson

FUNDING
NIA R00 AG050490
NIA R21 AG056062
NIA P30 AG035982
CTSA intra-institutional pilot

Our Research Volunteers

KU

ALZHEIMER'S DISEASE CENTER

The University of Kansas Medical Center

4350 Shawnee Mission Parkway
Fairway, KS 66205
913-588-0555
kualzheimer.org