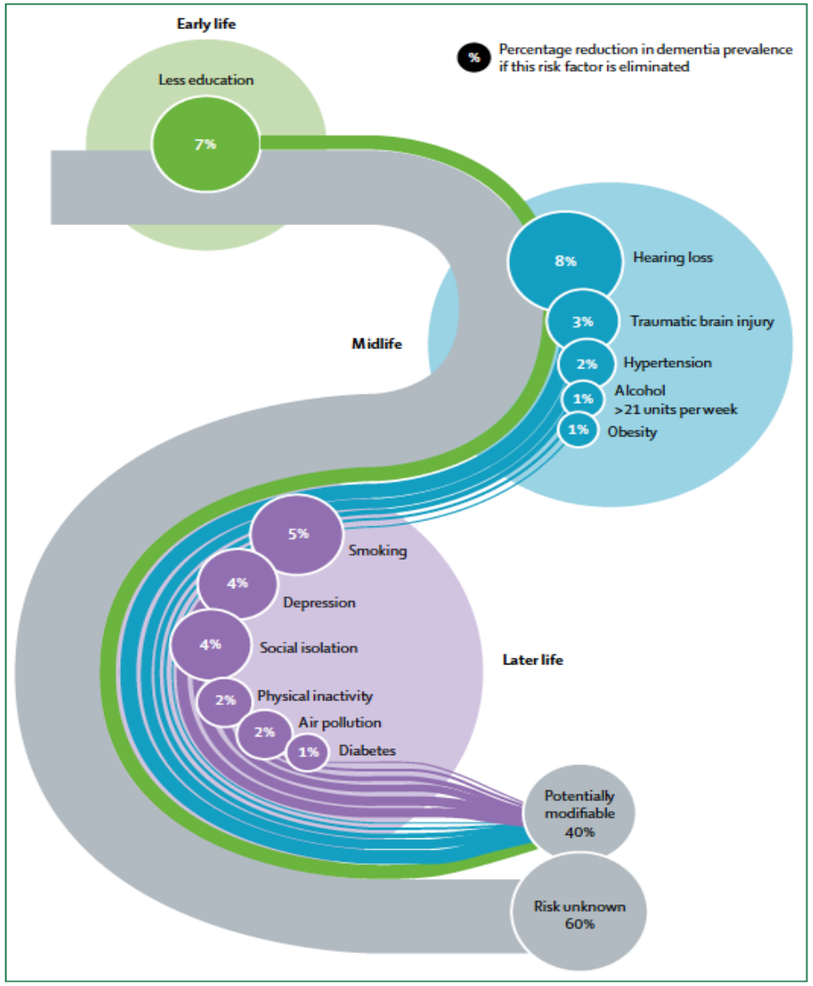
COGNITIVE RESILIENCE CLINICAL INTERVENTION TRIALS: BLOOD PRESSURE, STATINS AND FISH OILS WHAT'S GOOD FOR THE HEART *IS* GOOD FOR THE BRAIN

MARK A. SUPIANO, M.D.
PROFESSOR AND CHIEF, GERIATRICS DIVISION
EXECUTIVE DIRECTOR, UNIVERSITY OF UTAH CENTER ON AGING

EVIDENCE BASED TREATMENTS TO PREVENT DEMENTIA



- 40% of dementia risk is potentially modifiable
- CDC/ Alzheimer's Association Building Our Largest Dementia (BOLD) Infrastructure Public Health Center of Excellence on Dementia Risk Reduction

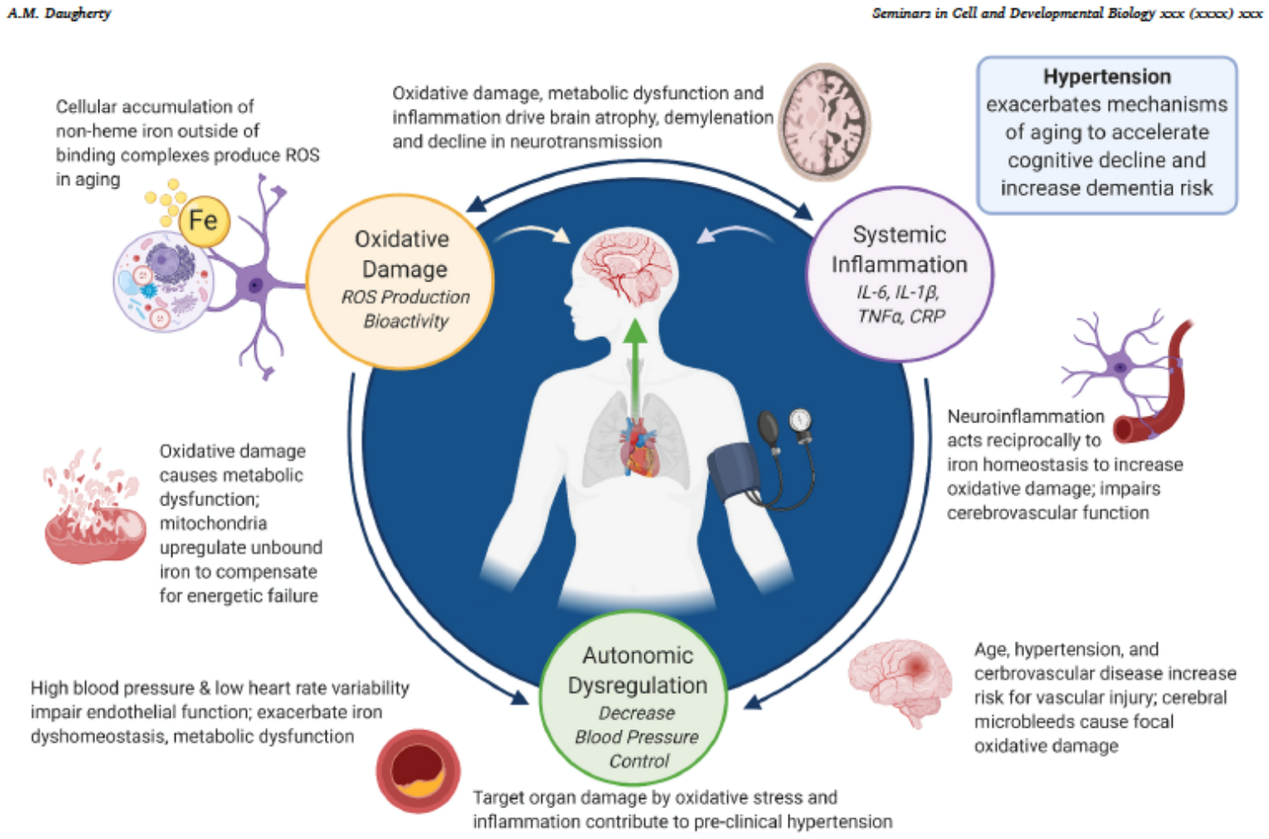
Livingston G, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission.

CLINICAL PRESENTATIONS

- Cardiovascular and Physical Activity
- Sensory and Sleep
- Neuropsychological

VASCULAR DEMENTIA RISKS = HYPERTENSION AND MORE

- Mechanisms
  - Arterial stiffness
  - Endothelial dysfunction
  - Oxidative Damage
  - Inflammation
- Confounding factors
  - Obesity
  - Diabetes
  - Smoking
  - Hyperlipidemia



Daugherty, Seminars in Cell and Developmental Biology, https://doi.org/10.1016/j.semcdb.2021.03.002

THE VASCULAR SIDE OF BRAIN AGING AND ALZHEIMER'S DISEASE

- "Chronic hypertension is the most prevalent and pernicious risk factor for cognitive impairment in aging."

  Daugherty, Seminars in Cell and Developmental Biology, https://doi.org/10.1016/j.semcdb.**2021**.03.002

- "Vascular risk may complement imaging biomarkers in assessing risk of prospective cognitive decline in preclinical Alzheimer disease."

  Liesz, 10.1126/science.aay2720

JAMA | Original Investigation

Effect of Intensive vs Standard Blood Pressure Control on Probable Dementia
A Randomized Clinical Trial

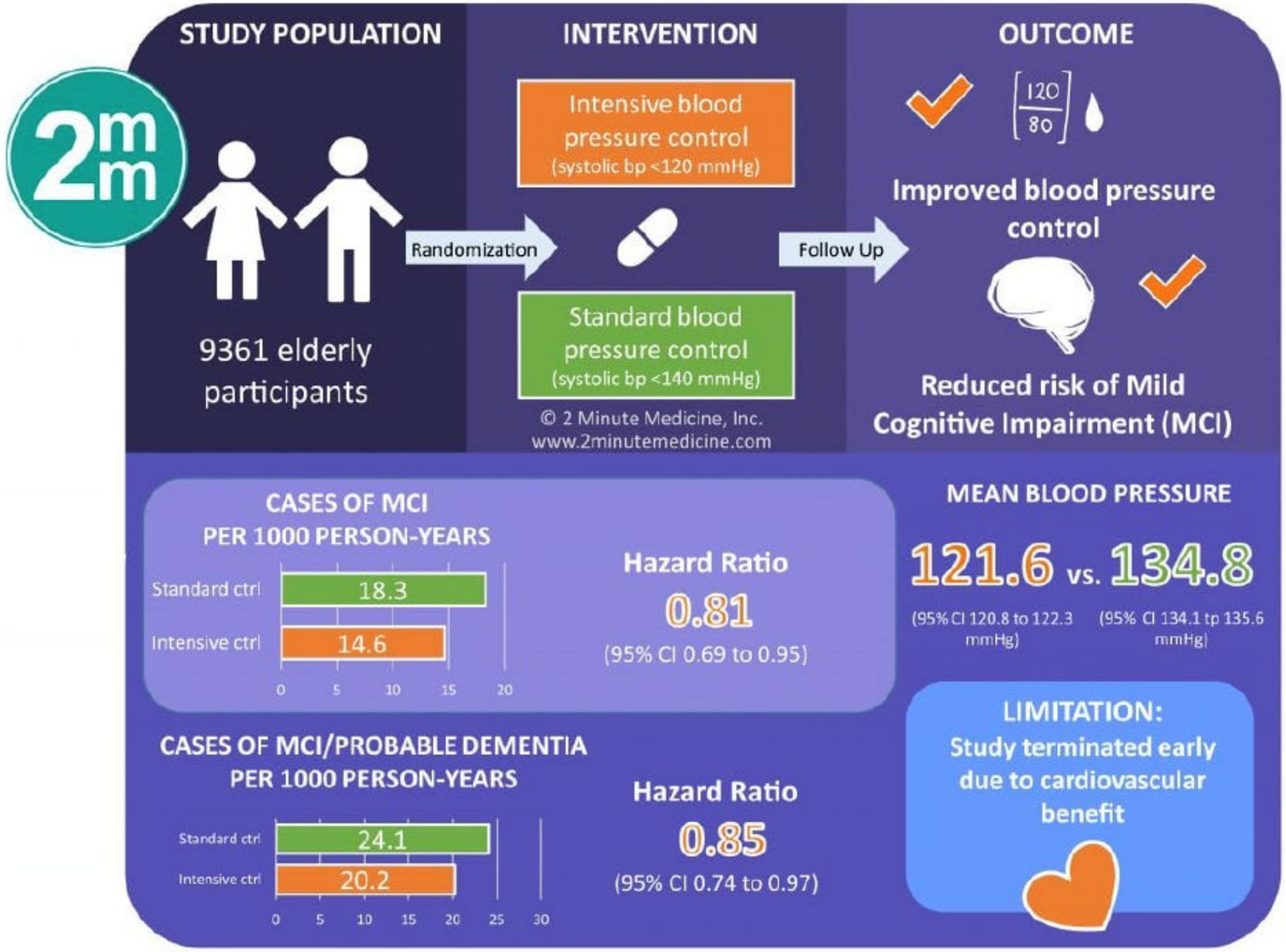
The SPRINT MIND Investigators for the SPRINT Research Group

JAMA | Original Investigation

Association of Intensive vs Standard Blood Pressure Control With Cerebral White Matter Lesions

The SPRINT MIND Investigators for the SPRINT Research Group

Effect of Intensive vs Standard Blood Pressure Control on Probable Dementia



SPRINT research group. *JAMA*. January 2019.

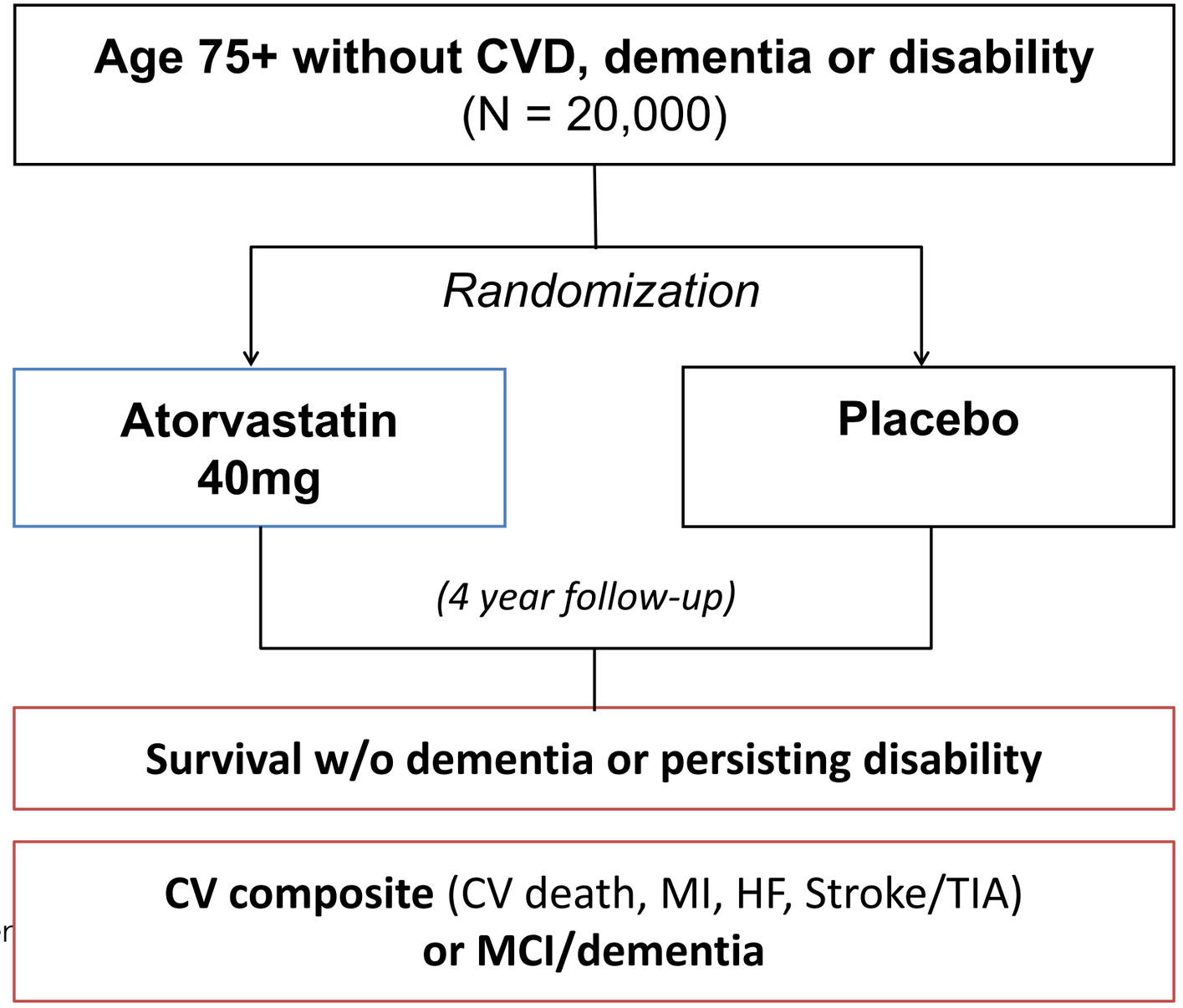
CENTER ON AGING
THE UNIVERSITY OF UTAH

PREVENTABLE

PRagmatic EValuation of evENTs And Benefits of Lipid-lowering in oldEr adults

Participants will:

- Be randomly assigned to atorvastatin 40 mg daily or matching placebo.
- Be followed through yearly phone calls for close to four years.
- Receive cognitive and physical function testing at screening, over the phone, and at home, if triggered.



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INFLAMMATION, COGNITIVE IMPAIRMENT AND DEPRESSIVE SYMPTOMS

Mark Rapaport, MD and team

- One-third of people with mild cognitive impairment (MCI) have comorbid depressive symptoms.
- Both MCI and depression are major ADRD predictors.
- Chronic inflammation may be a common mechanism underlying both
- Treatment with high-dose omega-3 fatty acids (n-3) has been shown to reduce systemic inflammation

HYPOTHESES

- Treatment with n-3 eicosapentaenoic acid (EPA) 4 gm/day vs. placebo will:
  - result in significantly better mean cognitive change scores
  - significantly reduce depressive symptom severity levels
  - significantly decrease inflammation

QUESTIONS…

About our logo…

The bristlecone pine tree (Pinus longaeva) - the earth's oldest inhabitant with a life span of 4,000 years - is found only in Utah and five other western states. Its extraordinary longevity and ability to adapt and survive in extremely harsh environmental conditions above 10,000 feet embodies the investigative spirit and mission of the Utah Center on Aging.

@Aging_MD

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Objectively Measured Sedentary Behavior and Physical Activity in PREVENTABLE Study

R01AG074592

Srinivasan Beddhu, MD
Professor of Internal Medicine
SLC VA Healthcare System and
University of Utah School of Medicine
Salt Lake City, UT

Sedentary Behavior

Classification of physical activity based on intensity levels

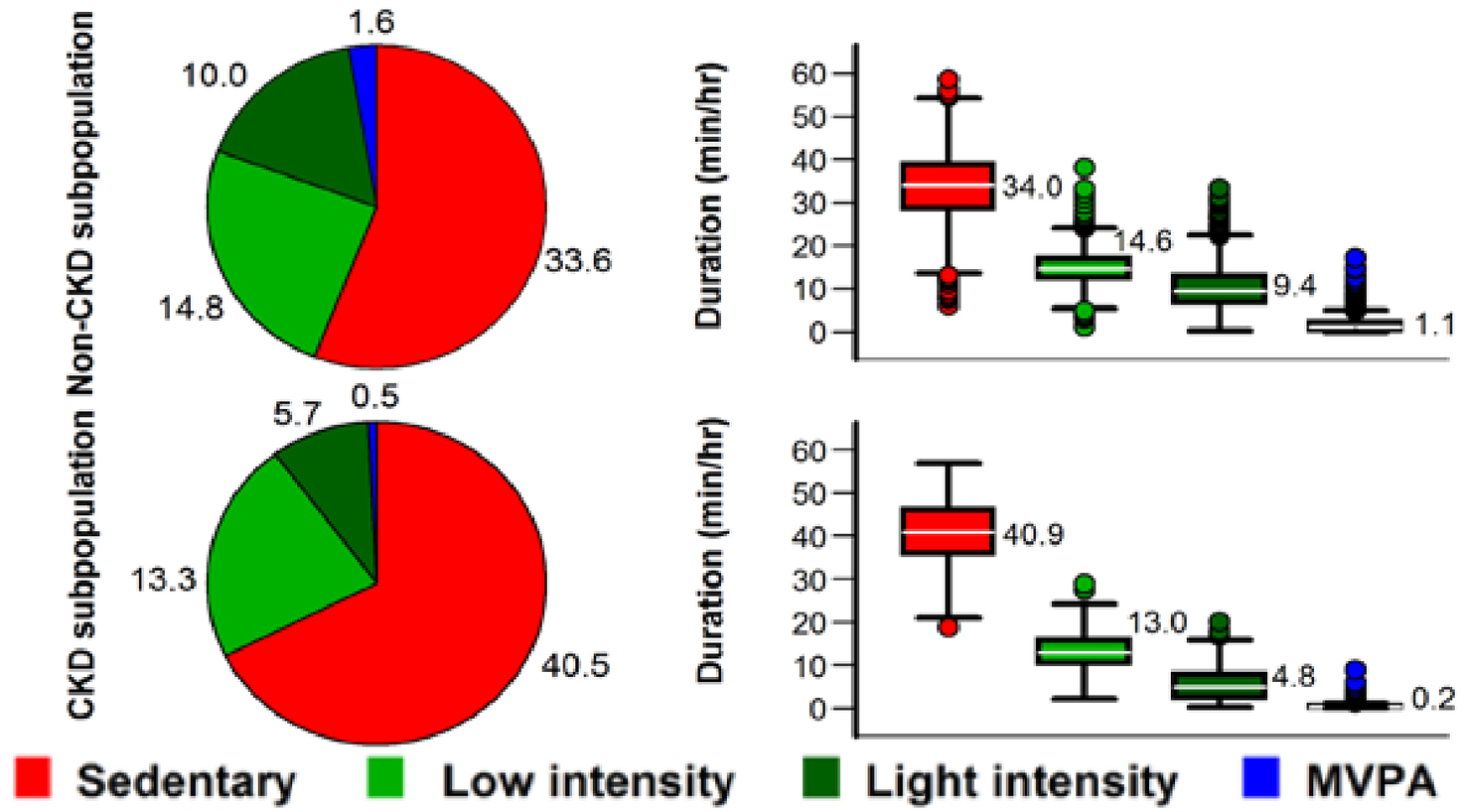
Type	Example	MET*
Sedentary	Sitting and watching TV	<1.5
Very light intensity	Standing, walking very slow (< 2.0 mph)	1.5-1.9
Light intensity	Casual walking (2 to 2.5 mph), light gardening	2.0-2.9
Moderate intensity	Brisk walking (~ 3.5 mph)	3.0-5.9
Vigorous intensity	Running, lifting heavy weights	≥6.0

***Based on 2011 Compendium of Physical Activities[1]**

Sedentary behavior

- Sedentary behavior is engaging in activities in the seated or lying position that barely raise the energy expenditure above this level (~ 1.0-1.4 METs)
- Distinct from “physical inactivity” i.e., not achieving weekly goal
- One can exercise for 150 min/ week and sit for the rest of the 98% of awake time (2.5 / (16x7))
- There is a large body of literature on physical inactivity and dementia risk but not on the associations of sedentary behavior with MCI/ dementia

Distribution of physical activity intensity durations per 60 minutes of awake time in non-CKD and CKD in NHANES



Beddhu et al. CJASN. 2015 Jul 7;10(7):1145-53

Hazard ratios of death per 2 min/hr trade-off of sedentary duration with equal duration of light activity or MVPA duration*

	↑ 2 min/hr of light activity duration HR (95% CI, p)**	↑ 2 min/hr of MVPA duration HR (95% CI, p)***
Entire cohort	0.67 (0.48, 0.93, p = 0.02)	0.80 (0.42, 1.51, p = 0.46)
CKD subgroup	0.59 (0.35, 0.98, p = 0.04)	0.46 (0.09, 2.45, p = 0.34)

*In Cox regression models taking survey design into account and adjusted for age, gender, race, education, smoke, alcohol use, lung disease, mobility limitations

**Mortality risk associated with each 2 min/hr decrement in a sedentary duration with a corresponding 2 min/hr increment in light activity duration while controlling for low intensity and MVPA durations

**Mortality risk associated with each 2 min/hr decrement in a sedentary duration with a corresponding 2 min/hr increment in MVPA duration while controlling for low intensity and light intensity activity durations

Beddhu et al. CJASN. 2015 Jul 7;10(7):1145-53

Ancillary study team

Principal Investigator
Srinivasan Beddhu, MD, University of Utah

PREVENTABLE Affiliated investigator
Mark Supiano, MD, University of Utah School of Medicine
Jeff Williamson, MD, Wake Forest University
Walter Ambrosius, PhD, Wake Forest University

Collaborators:
Tom Greene, PhD, University of Utah
Kate Lyden, PhD, Colorado State University
Aditi Gupta, MD, University of Kansas Medical Center

SPECIFIC AIM 1

- To examine the associations of sedentary duration with a composite of incident mild cognitive impairment (MCI) or dementia in older persons.
- To examine associations of ‘trade-off’ of 5 min/hr of sedentary duration to 5 min/hr of stepping duration with a composite of incident mild cognitive impairment (MCI) or dementia in older persons.

Hypothesis: Longer sedentary duration promotes faster decline of cognitive function decline; whereas, trade-off of sedentary duration for stepping duration is associated with slower cognitive function decline in older persons.

SPECIFIC AIM 2

- To examine whether PREVENTABLE intervention (atorvastatin compared to placebo) impacts on

A. the number of steps/day and

B. Sedentary and stepping durations/ day.

Hypothesis: Randomization to atorvastatin will result in lower incidence of physical disability which will associate with lower sedentary duration and higher physical activity levels relative to older persons randomized to placebo.

Ancillary study procedures

Visit (Month)/	Within 3 months of Randomization	Month 12	Month 36
Activity monitor training/education	X		
Wearing of activity monitor for 7 days	X	X	X
Completing wear time diary for 7 days	X	X	X
Sedentary Behavior Questionnaire	X	X	X

OPENING OUR MINDS: BROADENING THE DEFINITION OF 'SYMPTOMATIC' ATRIAL FIBRILLATION

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CLINICAL CARDIAC ELECTROPHYSIOLOGY

UNIVERSITY OF UTAH HEALTH SCIENCES CENTER

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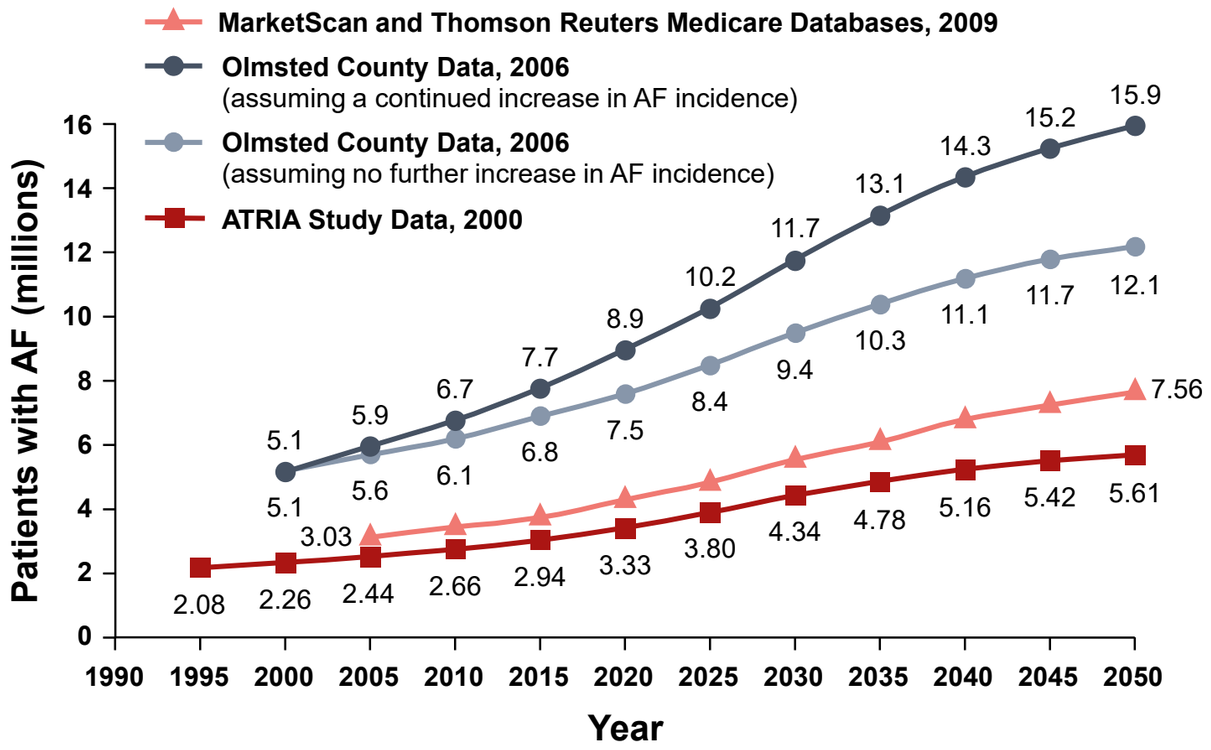
DISCLOSURES

- Research Support
  - NIH / NHLBI (K23HL143156)
  - AHA/PCORI
  - Boston Scientific
  - Abbott
  - AltaThera
- Consulting / Speaking
  - AltaThera
  - Sanofi
  - InCarda

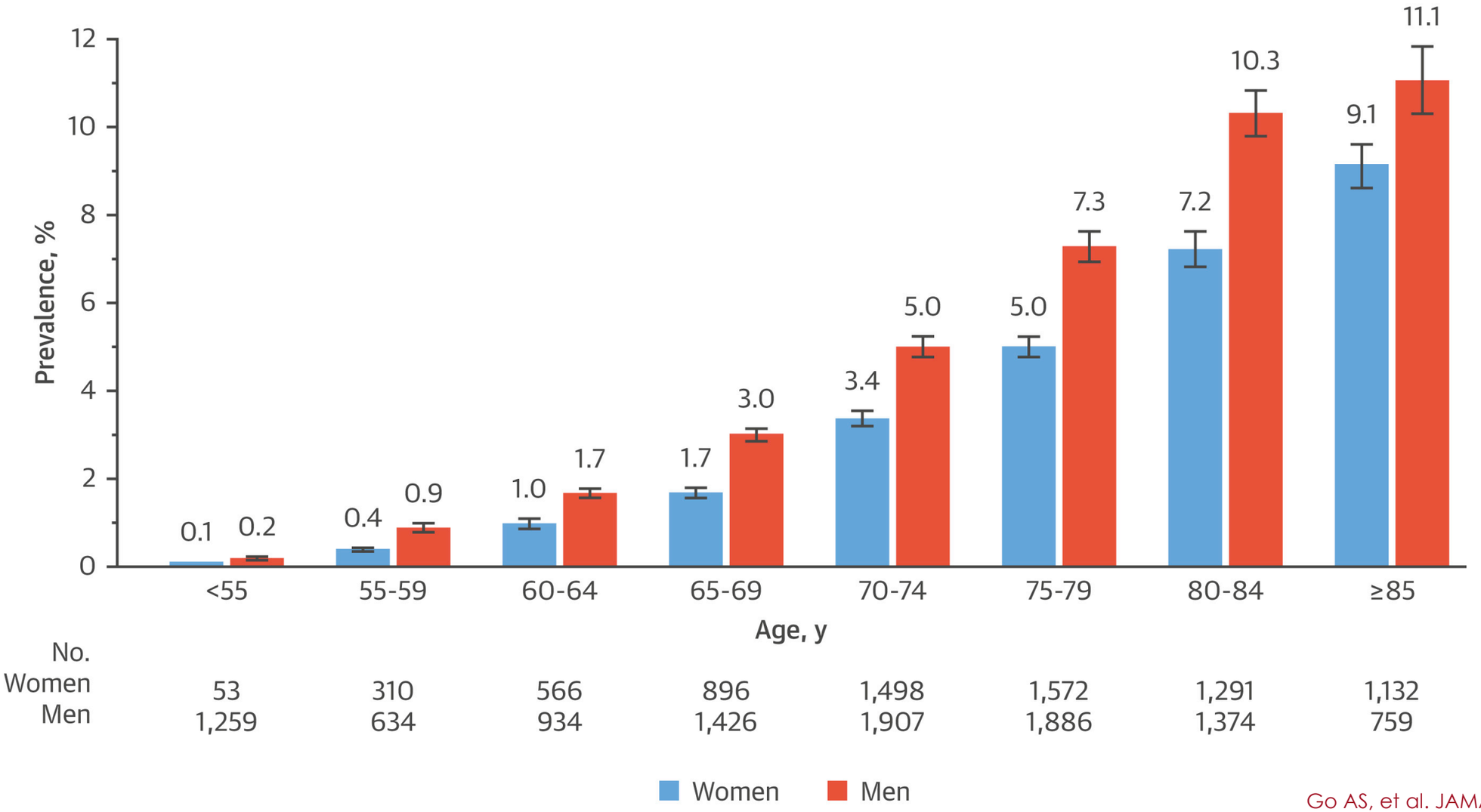
ATRIAL FIBRILLATION (AF) IN THE US: 10 MILLION BY 2025



ATRIA = Anticoagulation and Risk Factors in Atrial Fibrillation.

Go AS, et al. *JAMA*. 2001;285(18):2370-2375.
Miyasaka Y, et al. *Circulation*. 2006;114:119-125. Naccarelli GV, et al. *Am J Cardiol*. 2009; 104(11):1534-1539.

AF PREVALENCE



Go AS, et al. JAMA. 2001;285(18):2370-2375.
Curtis AB, et al. J Am Coll Cardiol. 2018; 71(18):2041-57.

SYMPTOMS ≠ ARRHYTHMIA

- Same-day ECG
- No paced/ indeterminate ECGs
- Pt ID of Rhythm
  - Sensitivity: 63%
  - Specificity: 91%
  - PPV: 63%
  - NPV: 91%

	ECG +AT/AF (n=114)	ECG –AT/AF (n=391)
Patient "Yes" (n=107)	72 11.68	35 11.70
Patient "No" (n=389)	42 6.76	356 7.59

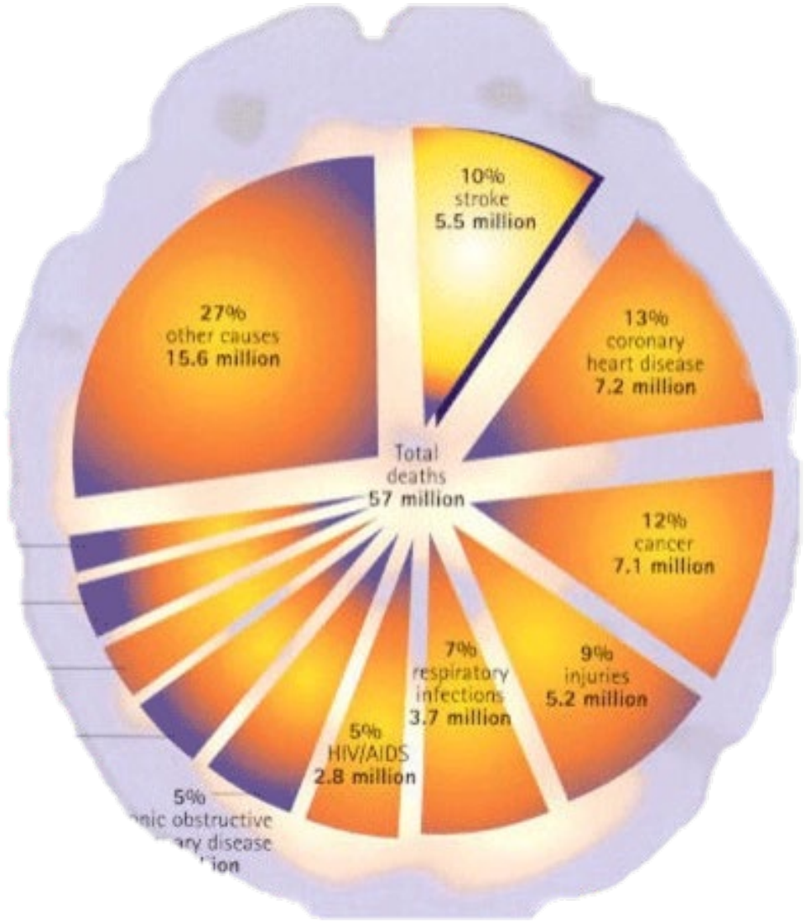
AF Symptom Score (mean), p<0.001

Turner JT…Steinberg BA. JAMA Network Open. 2020;3(5):e205431.

15-20% OF ALL STROKES DUE TO AF

- Stroke is a leading cause of death and disability

- AF-related strokes are worse than strokes of other causes



World Health Organization atlas of burden of disease and disability

AF & COGNITION

	N	Follow-Up (yrs)	Cognitive Decline	Dementia
Bunch et al.	37,025	5		1.06–1.73
Marzona et al.	31,506	5	1.14 (1.03–1.26)	1.30 (1.14–1.54)
De Bruijn et al.	6,514	21		1.33 (1.02–1.73)
Singh-Manoux et al.	10,308	15	1.87 (1.37–2.55)	
Liao et al.	332,664	15		1.42 (1.40–1.45)

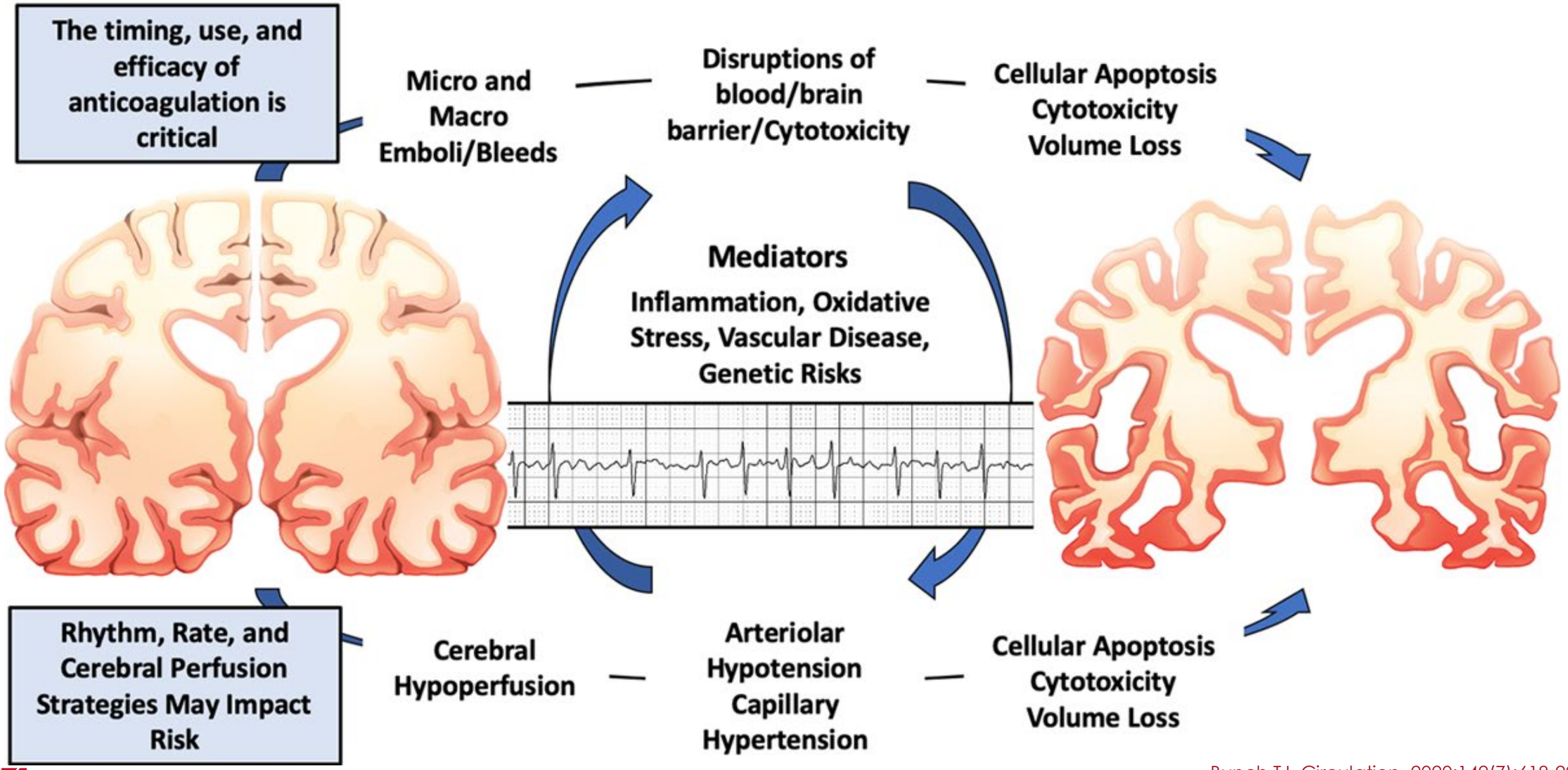
Diener H-C, et al. J Am Coll Cardiol. 2019 Feb 12;73(5):612-619.
T.J. Bunch, J.P. Weiss, B.G. Crandall, et al. Heart Rhythm, 7 (2010), pp. 433-437.
I. Marzona, M. O'Donnell, K. Teo, et al. CMAJ, 184 (2012), pp. E329-E336.
R.F. de Bruijn, J. Heeringa, F.J. Wolters, et al. JAMA Neurol, 72 (2015), pp. 1288-1294.
A. Singh-Manoux, A. Fayosse, et al.Eur Heart J, 38 (2017), pp. 2612-2618.
J.N. Liao, T.F. Chao, C.J. Liu, et al. Int J Cardiol, 199 (2015), pp. 25-30.

AF & COGNITION: META-ANALYSIS

	Studies (n)	RR	95% CI
AF & cognitive impairment with or without stroke	14	1.40	1.19–1.64
AF & dementia	8	1.38	1.22–1.56
AF & cognitive impairment	9	1.50	1.18–1.91
AF & cognitive impairment independent of stroke	10	1.34	1.13–1.58
AF and cognitive impairment after stroke	7	2.70	1.82–4.00

Kalantarian, T.A. Stern, M. Mansour, J.N. Ruskin. Ann Intern Med, 158 (5 Pt 1) (2013), pp. 338-346
Diener H-C, et al. J Am Coll Cardiol. 2019 Feb 12;73(5):612-619.

POTENTIAL MECHANISMS: AF & COGNITION

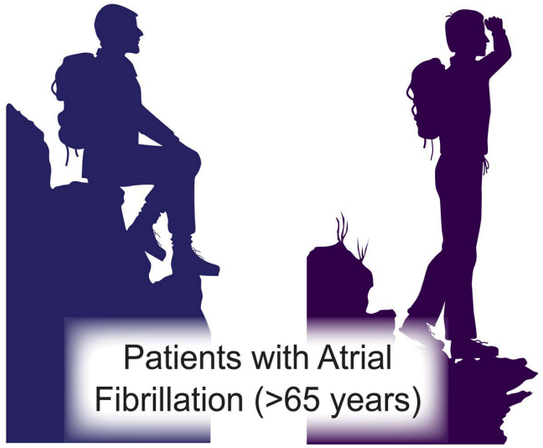


Bunch TJ. Circulation. 2020;142(7):618-20.

AF & STROKE (& COGNITION)

Incidence of Stroke is Directly Dependent on Diagnostic Methods Used and Traditional Stroke Symptoms Correlate Inconsistently with Infarcts on MRI

Different Viewpoints/Perspectives



Clinical Stroke/TIA Symptoms at 2 years

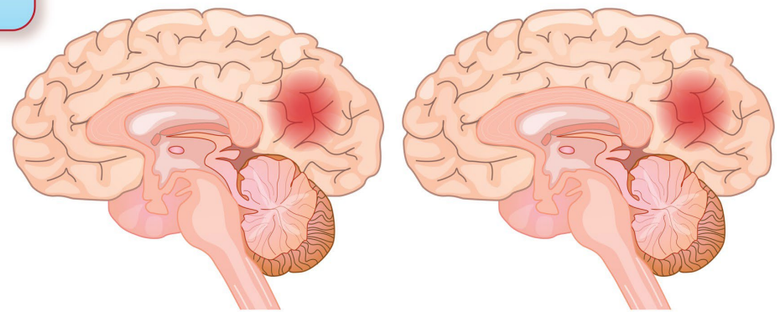
2.3% Incidence

Brain MRI at 2 Years

5.5% Incidence

2.4x Increase

Are "Silent" Strokes Really Silent?



Traditional Clinical Symptoms

No Traditional Clinical Symptoms

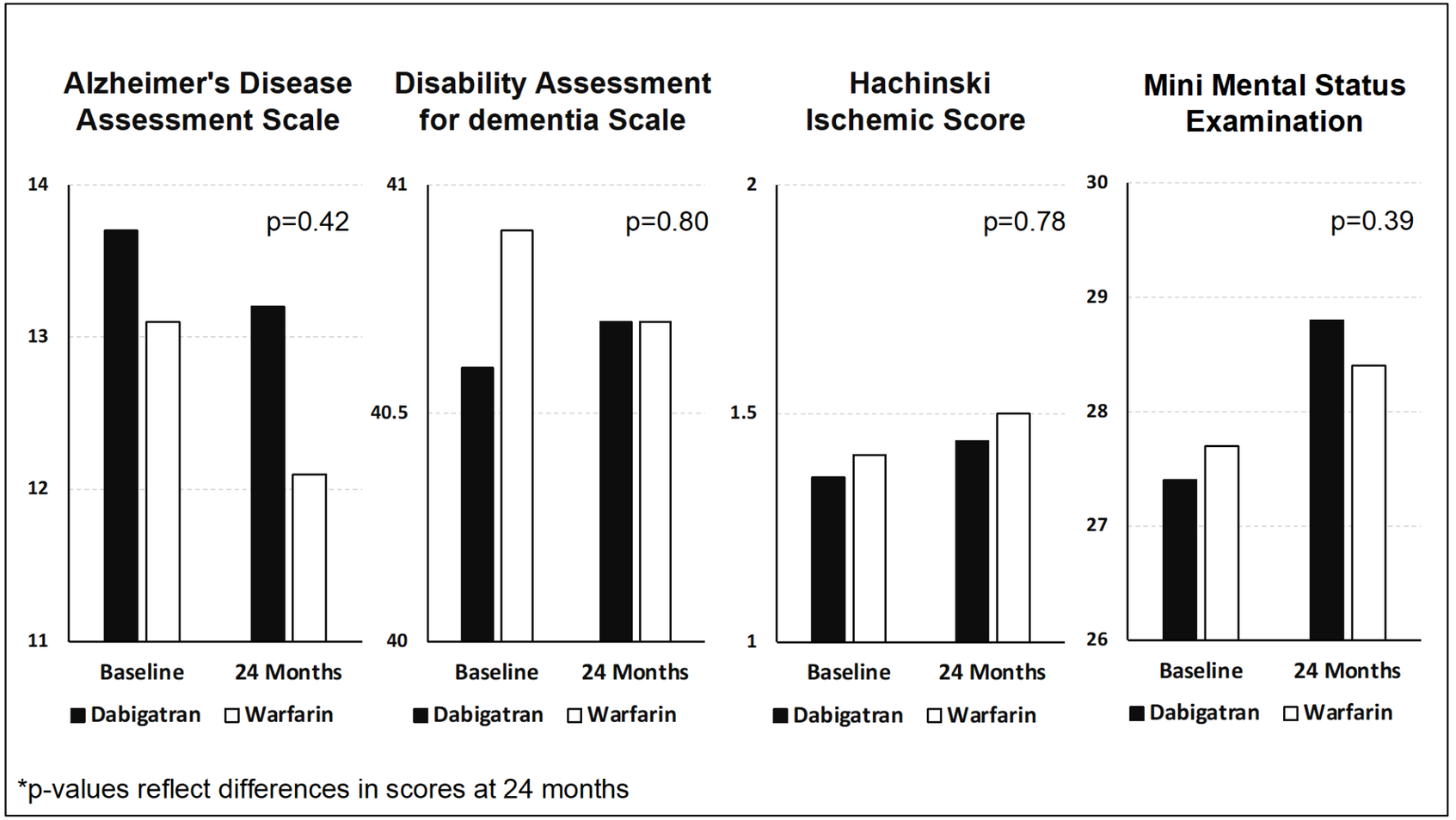
Deficiencies of cognitive operations, semantic memory, language production and mental flexibility are present with testing at 2 years

Brain Injury in Patients with Atrial Fibrillation

1. "Clinical" Stroke/TIA diagnosis significantly underestimated incidence
2. "Silent" Strokes is a misnomer and these infarcts impact function when targeted testing is used

Bunch TJ, Steinberg BA. Eur Heart J. 2022 Feb 18;ehab900.

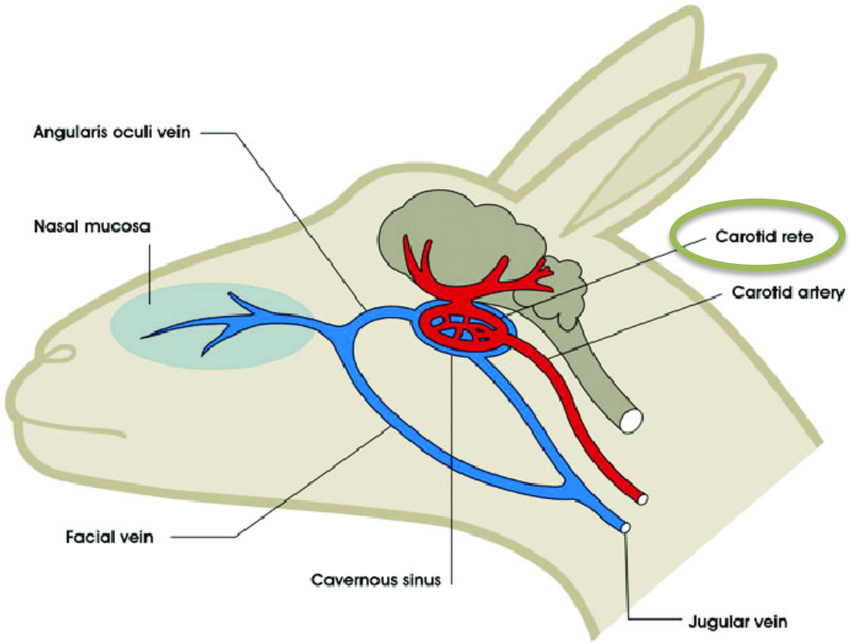
COGNITIVE DECLINE AND DEMENTIA IN PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION (CAF) TRIAL



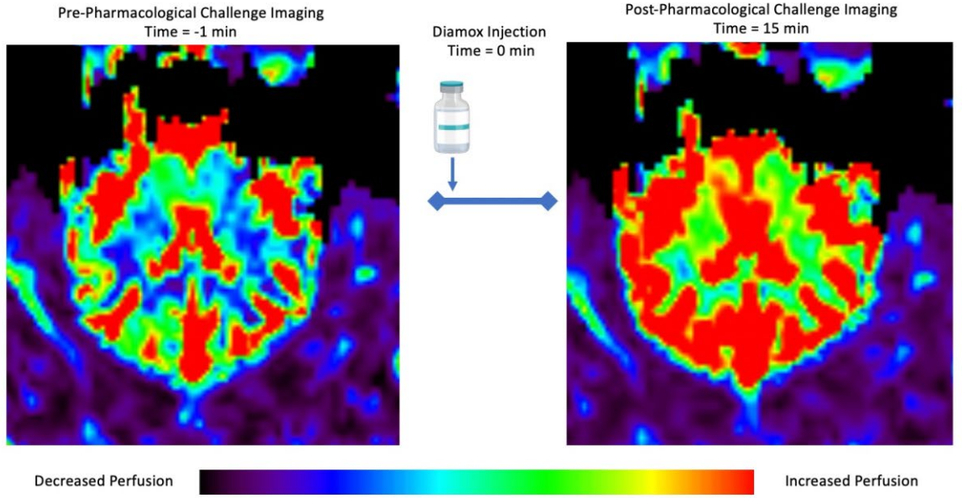
*p-values reflect differences in scores at 24 months

Bunch TJ, et al. Submitted.

CEREBROVASCULAR RESERVE IN AF (CANINE)



A



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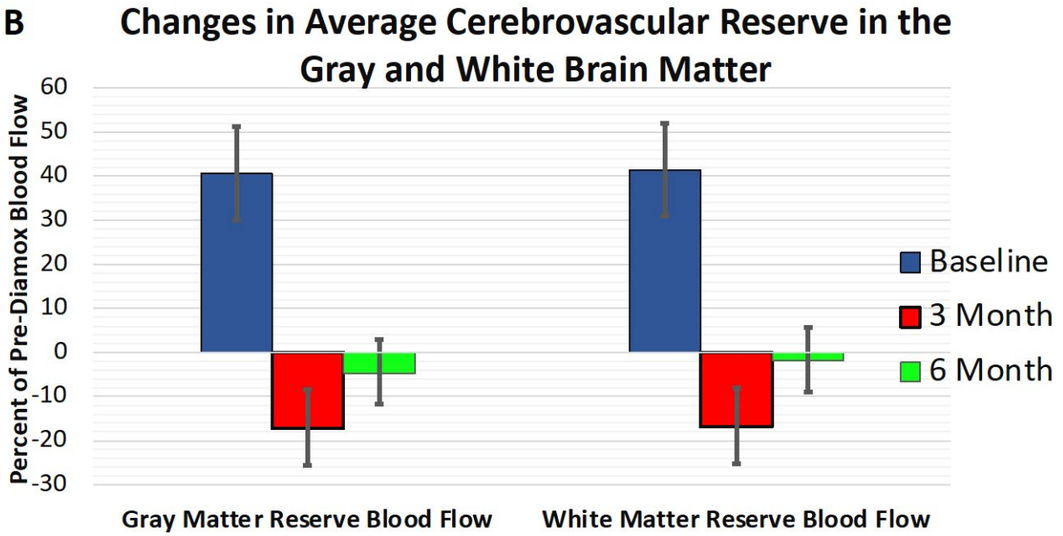

Strauss W et at. Conservation Physiology. 2017;5(1), cow078.
Zenger B…Bunch TJ. JACC EP. In Revision.

SUMMARY: AF & COGNITION

- Causal relationship beyond stroke
  - Mechnism unclear (?cerebrovascular reserve)

- Future directions
  - Additional animal work (mechanism)
  - Patient Reported Outcomes vis-à-vis memory, cognition
    - Not-so-'silent' infarcts
  - Potential interventions (e.g., 'novel-er' blood thinners, ablation)


THANK YOU
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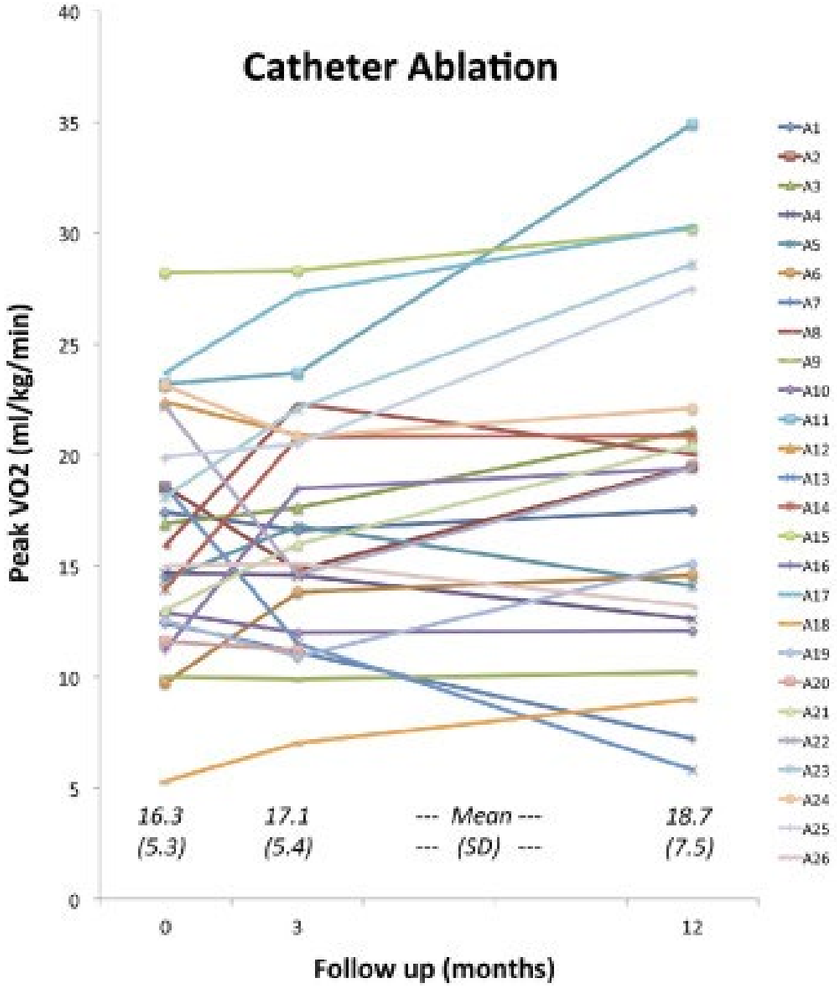
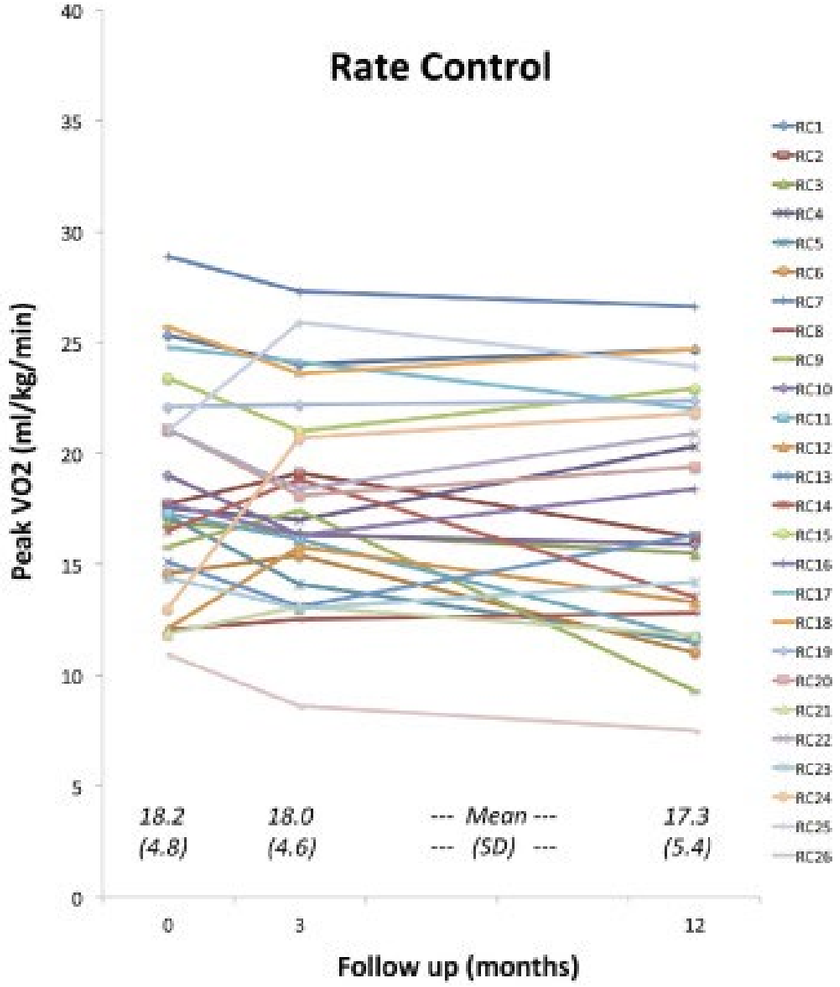
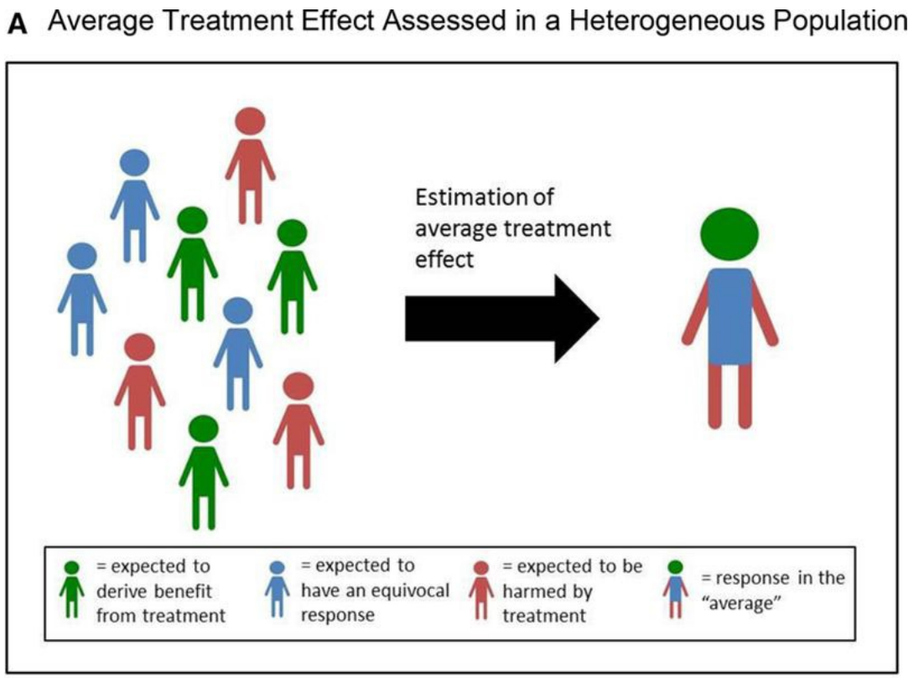
AF ABLATION IN HF: NOT EVERYONE WINS

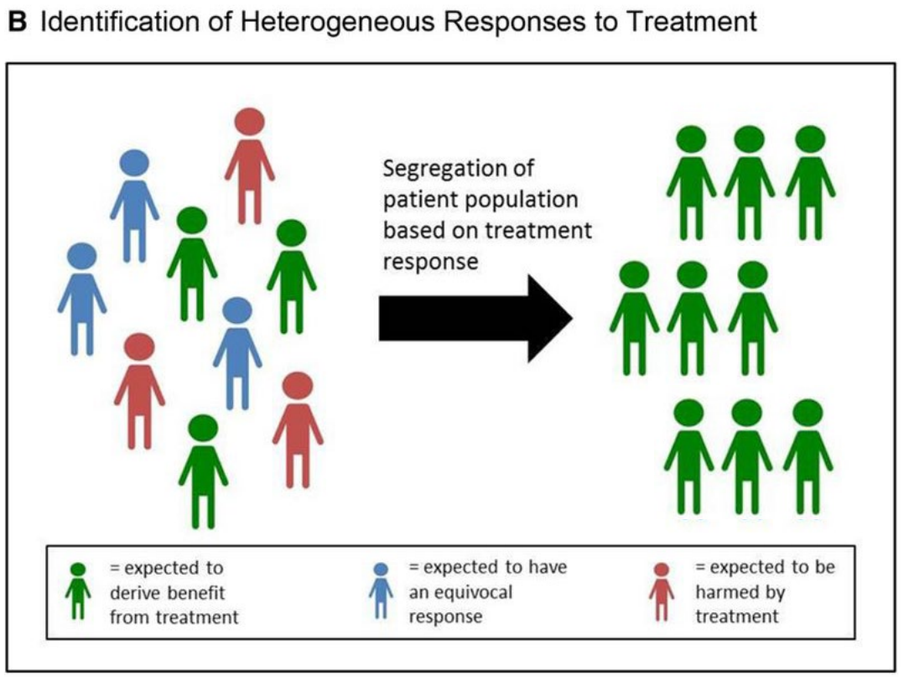




Jones DG, et al. J Am Coll Cardiol, 2013; 61(18): 1894-1903.

HETEROGENEITY OF TREATMENT EFFECTS





Yeh RW and Kramer DB. Circulation. 2017;135:1097-1100.
Adapted from the ideas of John A. Spertus, MD, MPH.

Balance, Mobility, and Concussion in Older Adults

University of Utah Center on Aging

15th Annual Research Retreat

May 26, 2022

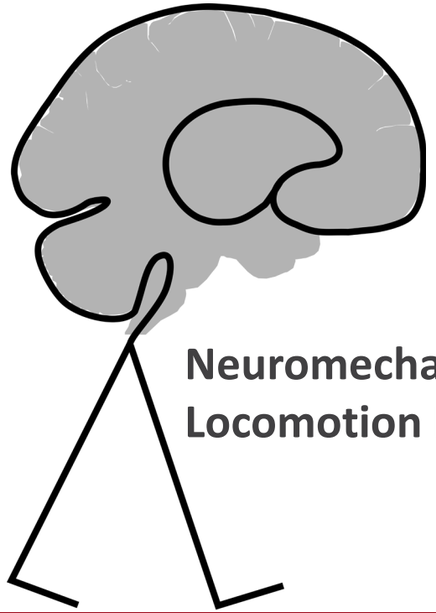
Peter Fino, PhD

Assistant Professor

Health and Kinesiology

College of Health

University of Utah

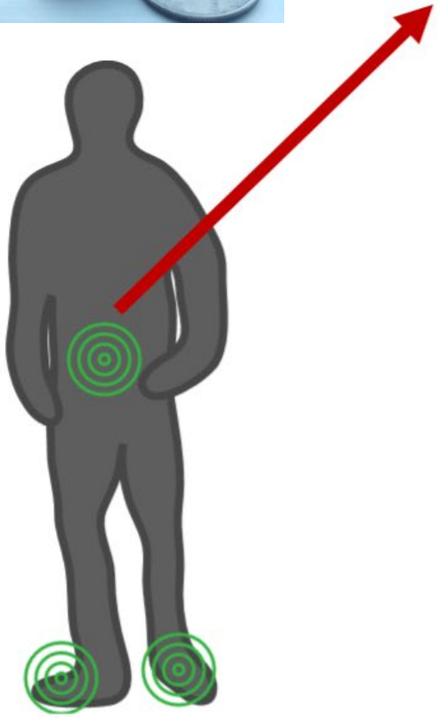


Neuromechanics & Applied Locomotion Laboratory

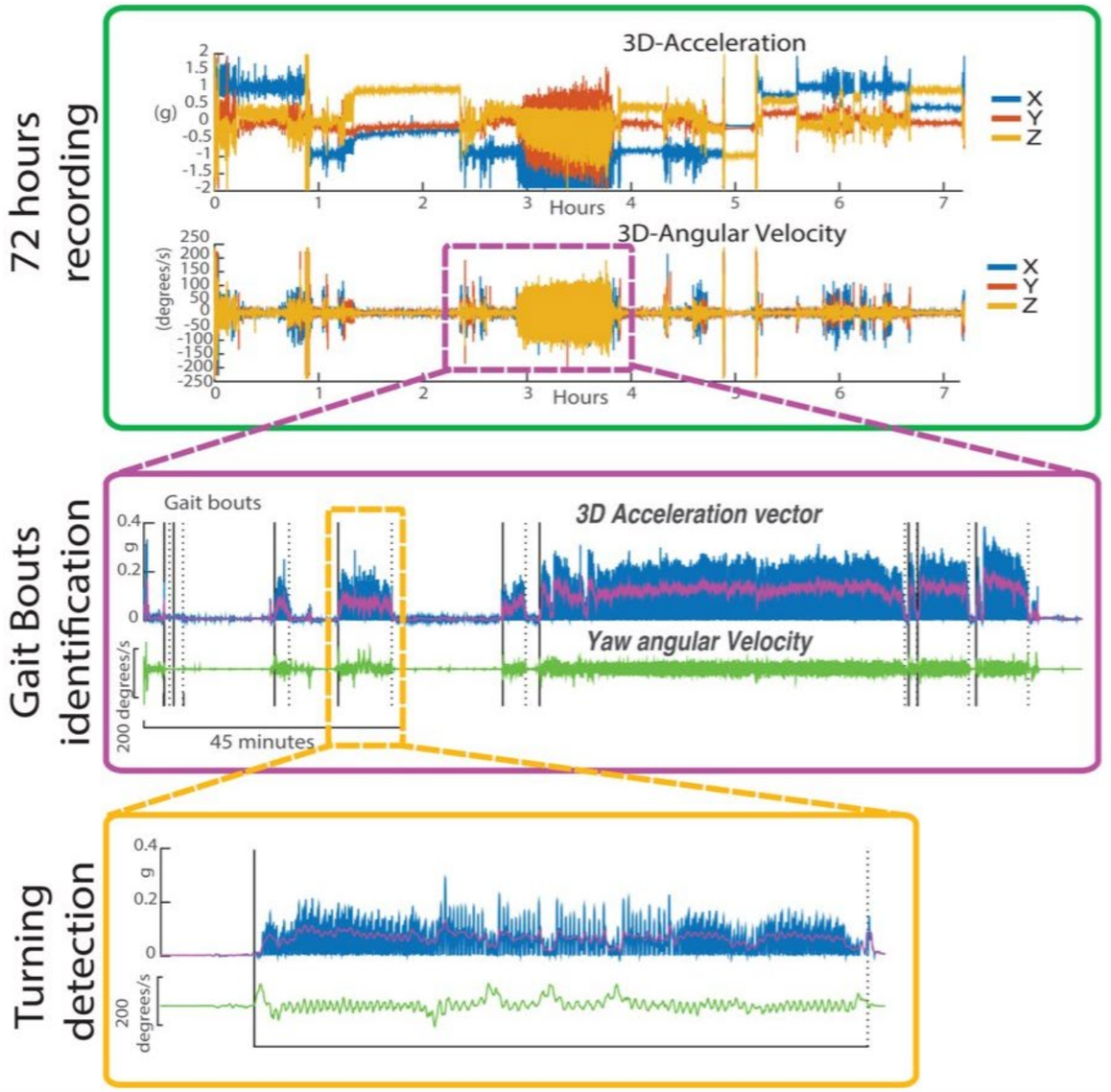
My research focuses on quantifying balance and mobility during functionally relevant tasks to inform rehabilitative care and clinical decisions

Ecologically relevant and real-world tasks

Wearables / clinically deployable tools

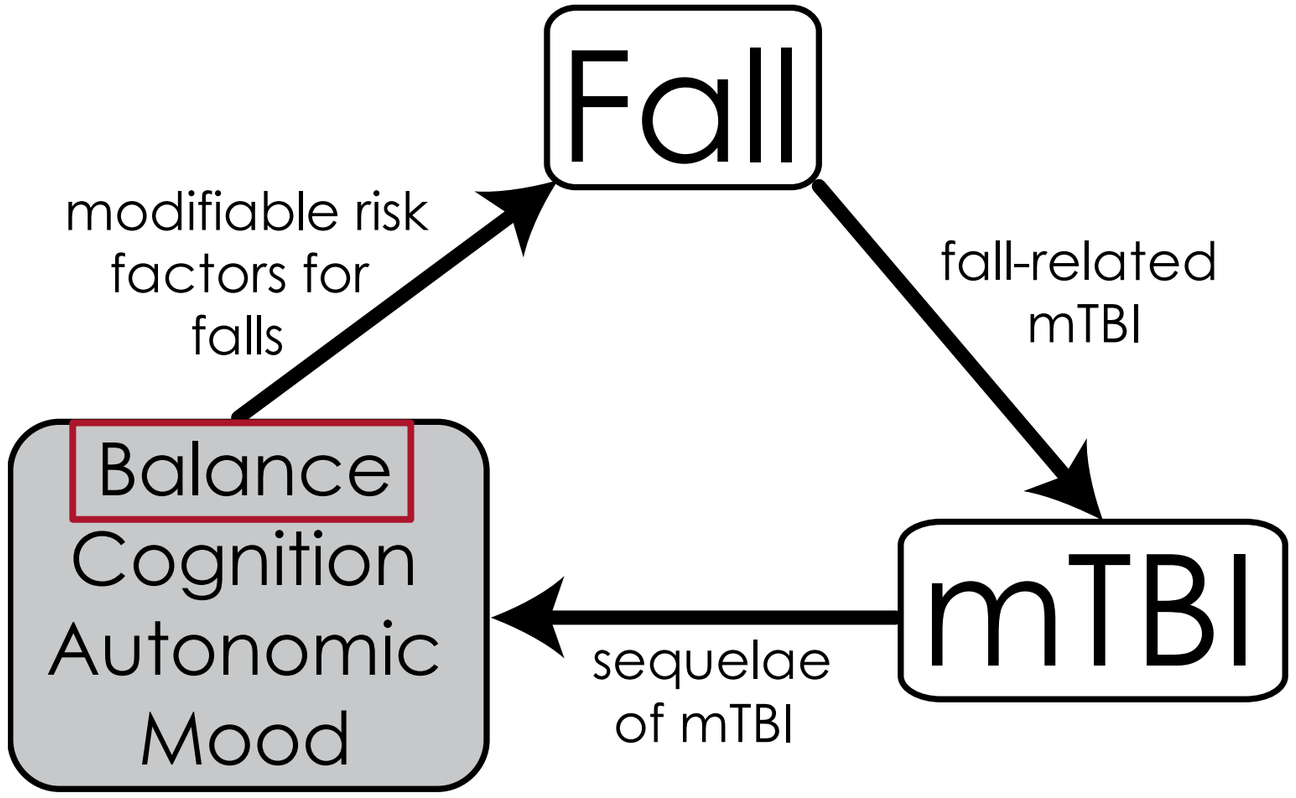


Return-to-life after concussion



Older adults suffer more concussions (i.e., mTBIs) than any other age group and the majority are caused by falls[1]

Greater mortality from nervous system (e.g., PD) and dementia-related disorders[3]



1. Taylor et al. MMWR Surveill Summ 2017; 2. Komisar et al. BMC Geriatrics 2022
3. Harrison-Felix et al. J Head Trauma Rehabil 2012

We have very little knowledge of the effects of concussions in older adults

Young adults

≠

Older adults

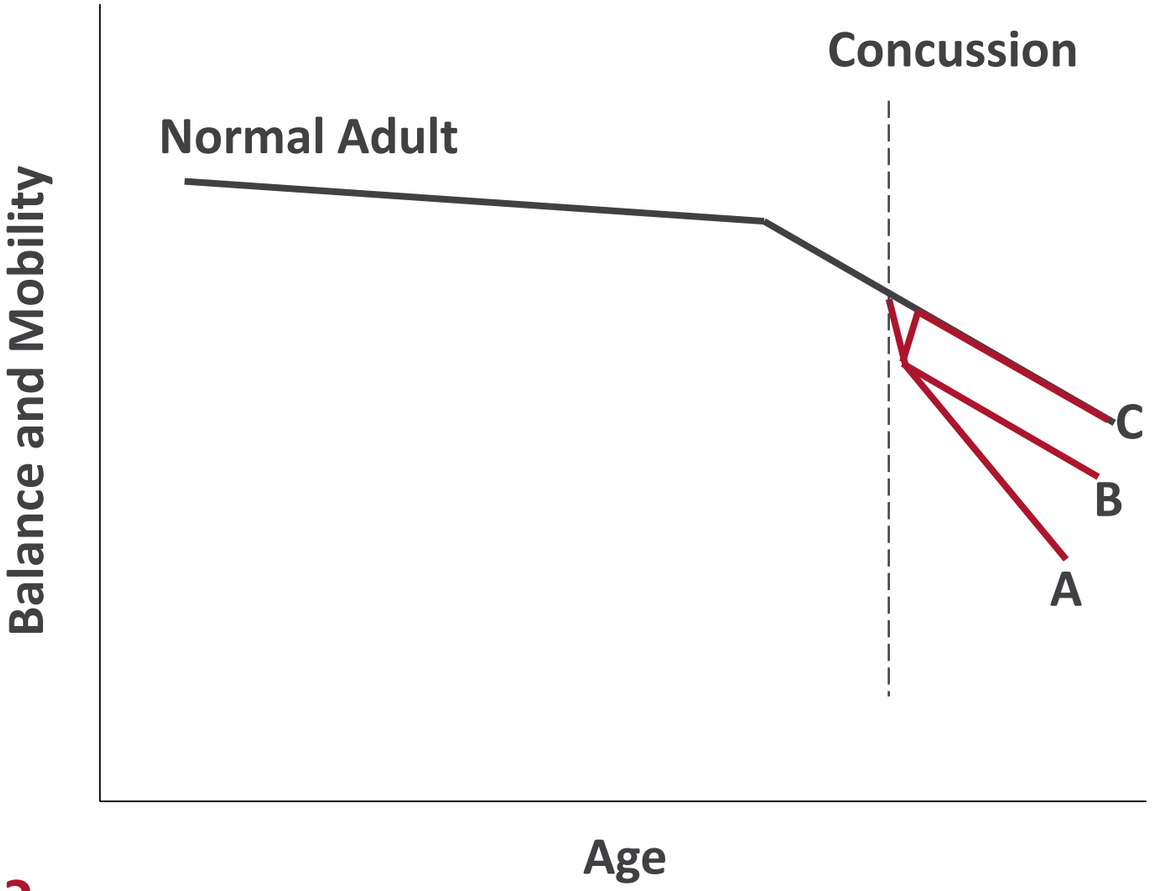
Review = Systematic review or Meta-analysis
Retro = Association with retrospective falls
Pro = Association with prospective falls

Between = Comparison to healthy subjects
Within = Comparison to baseline or pre-injury

Step 1: Establish the ‘natural history of concussion’ in older adults
Step 1B: Establish guidelines for care for older adults after concussion

What factors influence recovery?

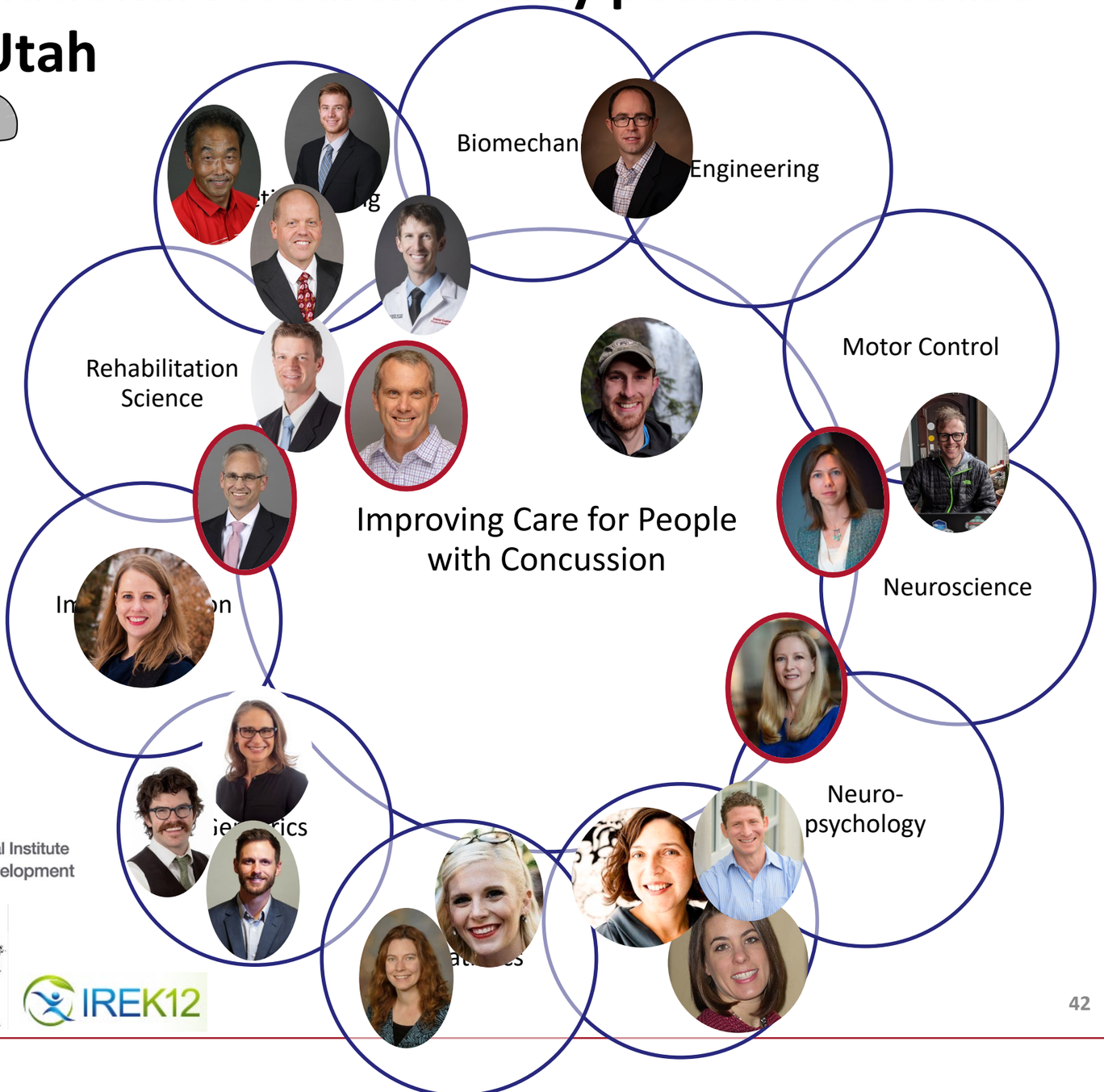
- Neuromuscular
- Cognitive
- Physiological
- Psychosocial
- Healthcare resources
- Social determinants
- Genetic



Can we change someone’s trajectory?

Concussions are complex - our translational research is only possible because of interdisciplinary perspectives at Utah

Neuromechanics & Applied Locomotion Lab



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NIH Eunice Kennedy Shriver National Institute of Child Health and Human Development
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College of Health University of Utah
Center on Aging The University of Utah
IREK12

HEALTH
UNIVERSITY OF UTAH

Optimizing Antihypertensive Treatment in 2022 to Prevent Cardiovascular Disease and Dementia: Lessons Using Pharmacoepidemiology

Adam Bress, Pharm.D., M.S.
Associate Professor

Department of Population Health Sciences
Division of Health System Innovation and Research
University of Utah School of Medicine
VA Salt Lake Health Care System

@adambress

May 25, 2022, Center on Aging Cognitive Resilience Retreat, University of Utah

Background: blood pressure & cognitive outcomes

- Hypertension, particularly in mid-life, is a modifiable risk factor for cognitive decline and dementia
  - Hypertension affects ~50% of the US adult population

- Meta-analyses of BP-lowering RCTs show that lowering BP with antihypertensive medication reduces risk of cognitive outcomes, yet precise causal mechanisms remain unclear

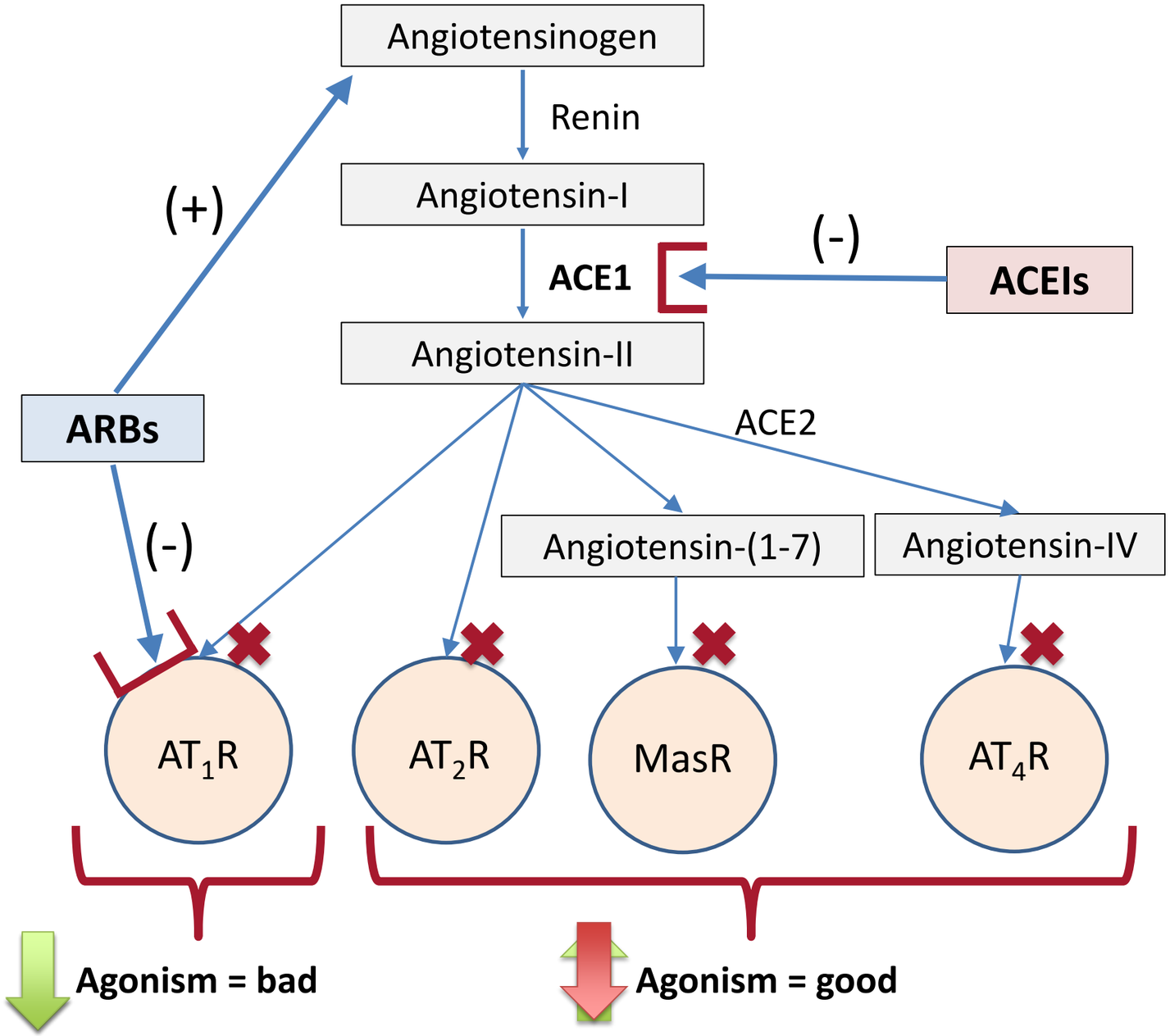
- Whether cognitive benefits are achieved via BP reduction alone or via direct effects of antihypertensive medications on the brain, independent of BP-lowering effects is unclear

Should we be using ARBs routinely over ACEIs?

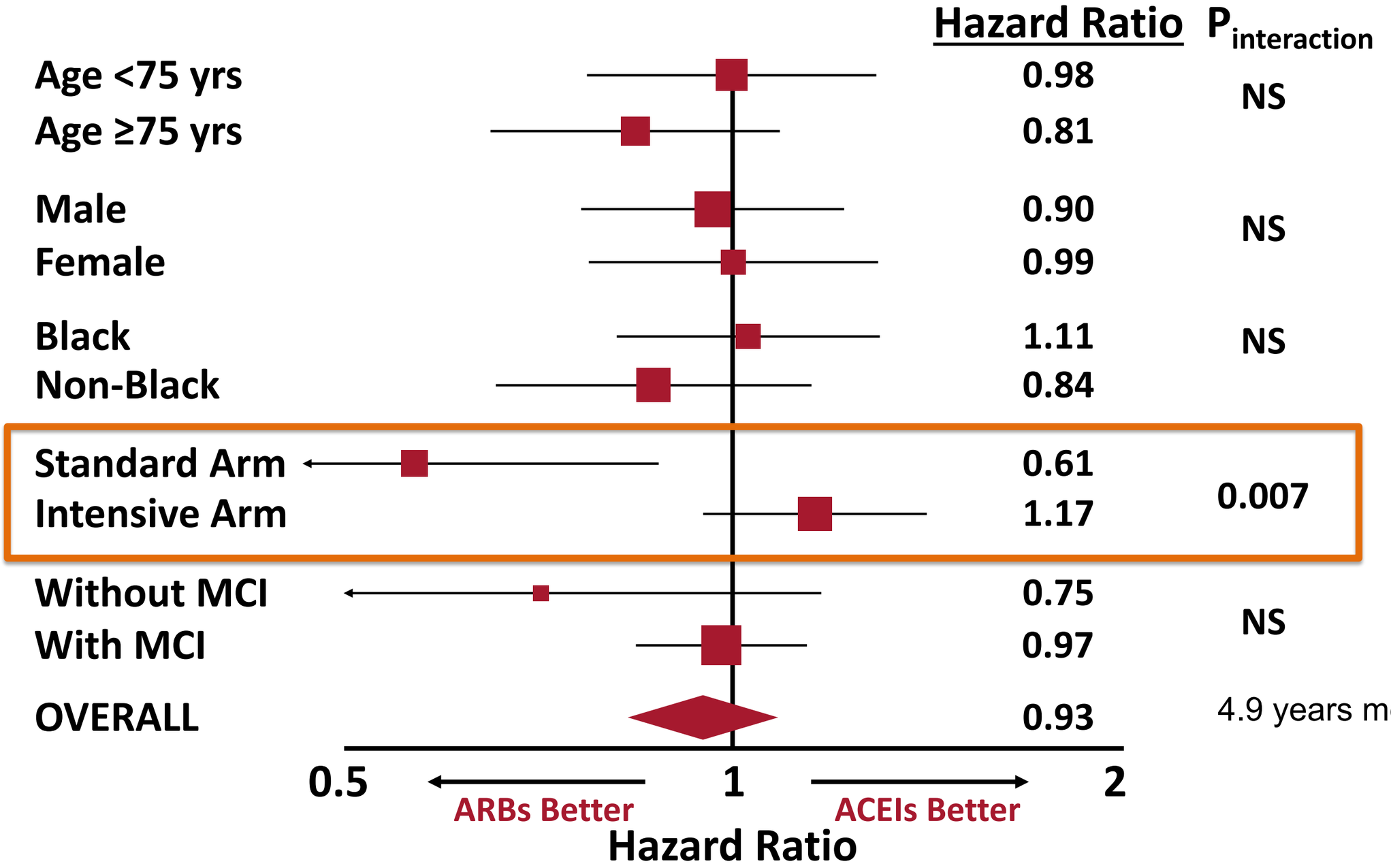
- Angiotensin II receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs) are used by approximately 33 million US adults
  - ~20 million taking an ACEI
  - ~13 million taking an ARB
- Current guidelines recommend ARBs and ACEIs interchangeably for hypertension treatment
- Notably, ARBs and ACEIs work distinctly on the renin-angiotensin system (RAS)

Proposed mechanism of differential effects of ARBs vs. ACEIs?

- ARBs bind AT1 receptors, downstream from where ACEIs act
- Shifting circulating Ang II to bind/stimulate AT2, AT4 Mas receptors leading to:
  - ⬇ oxidative stress, neuroinflammation, and endothelial dysfunction
  - ⬆ cerebral hypoperfusion and potentially memory-enhancing effects
- In contrast, by inhibiting conversion of Ang I to Ang II, ACEIs ⬇ circulating Ang II
- Thereby, ⬇ stimulation of AT1 and AT2/AT4 receptors and ⬇ potential for beneficial effects of agonism at AT2/4 receptors



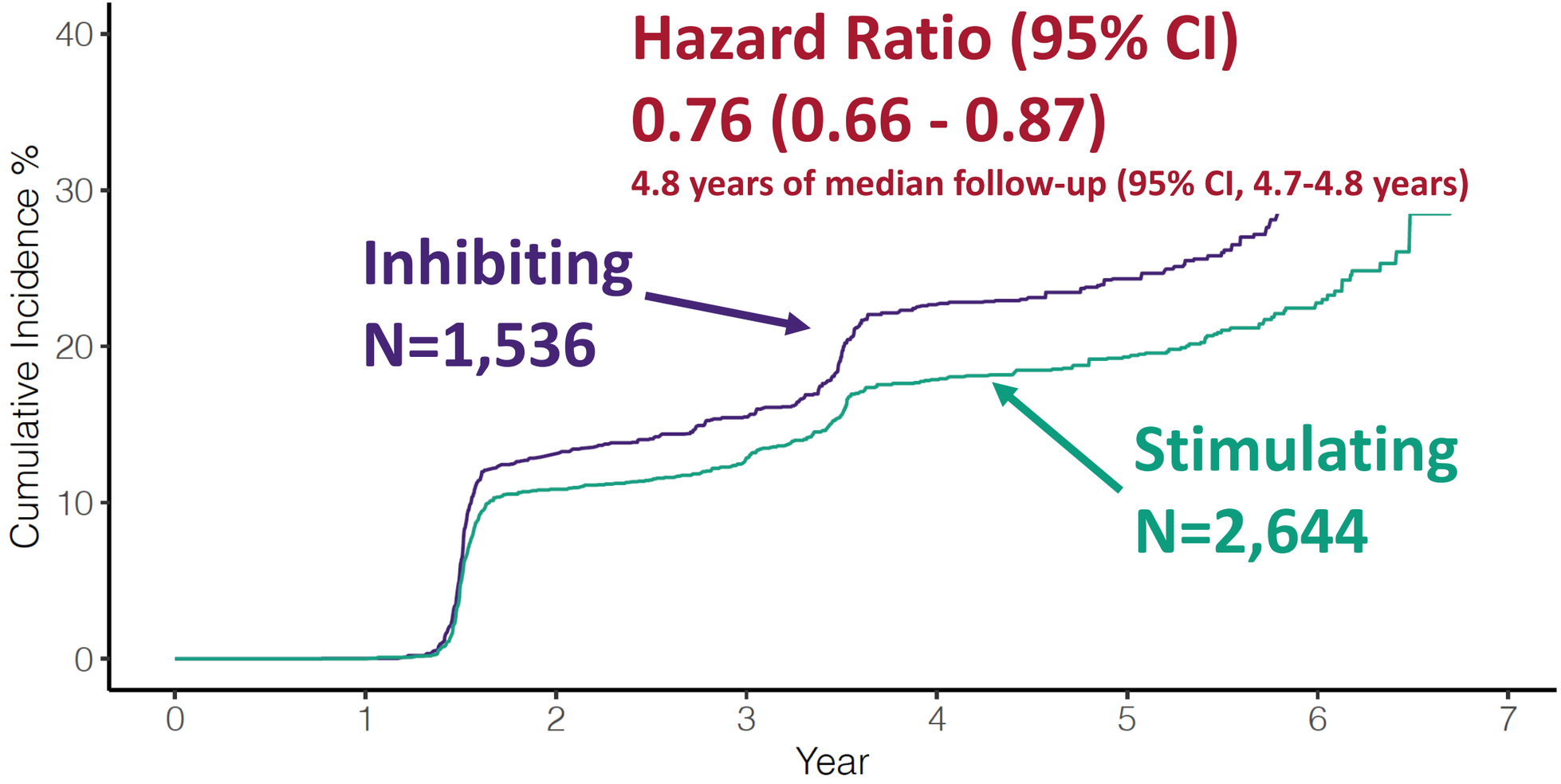
In an active-comparator, new-user design, we emulated a target trial to evaluate the effect of initiating an ARB (N=727) vs. ACEI (N=1,313) on MCI of dementia using SPRINT MIND



4.9 years median follow-up

Comparing the incidence of dementia or MCI among users of regimens that contained exclusively stimulating vs inhibiting antihypertensives

Secondary analysis of SPRINT MIND, cohort study comparing prevalent users of regimens containing exclusively stimulating vs inhibiting antihypertensives at the 6-month study visit.



Implications

- We ***did not*** find evidence of an appreciable effect of initiation of an ARB- vs. ACEI-based medication regimen on MCI or probable dementia in SPRINT MIND.

- ***We did find evidence*** of lower risk of MCI or probable dementia among new users of an ARB vs. ACEI in ***the standard treatment arm***, suggesting benefits of intensive BP control may have diminished any potential beneficial effects of ARBs over ACEIs.

- Prevalent users of regimens that contain exclusively **antihypertensives that stimulate** vs inhibit type 2 and 4 angiotensin II receptors **had lower rates of incident cognitive impairment.**

Implications

- The US prevalence of hypertension is large (~45%)
- CVD and ADRD prevalence will rise substantially with the aging US population
  - The potential for public health benefit of optimizing anti-HTN medication use to prevent CVD and ADRD is enormous.
- ~33 million US adults are currently taking RAS blockade
- ~20 million are on an ACEI
- Even a 10% relative benefit of ARBs could provide an enormous population health impact of switching first-line RAS-blockade from ACEIs to ARBs

NATIONAL ACADEMY OF MEDICINE

DISCUSSION PAPER

Can Preferentially Prescribing Angiotensin II Receptor Blockers (ARBs) over Angiotensin-Converting Enzyme Inhibitors (ACEIs) Decrease Dementia Risk and Improve Brain Health Equity?

Zachary A. Marcum, PharmD, PhD, University of Washington; **Jordana B. Cohen, MD, MSCE,** University of Pennsylvania; **Eric B. Larson, MD, MPH,** Kaiser Permanente Washington Health Research Institute; **Jeff Williamson, MD, MHS,** Wake Forest School of Medicine; and **Adam P. Bress, PharmD, MS,** University of Utah

May 9, 2022

Central Points Made in the NAM Discussion Paper

Introduction

Part I: ARBs vs. ACEIs

Background

Methods

Results

Conclusions

Part II: Therapeutic Inertia

Background

Methods

Results

Conclusions

Summary

1. ARBs and ACEIs have similar efficacy in terms of blood pressure-lowering and CVD event reduction
2. ARBs have a more favorable safety profile than ACEIs
3. Short-term RCT data suggest a comparative benefit of ARBs over ACEIs in preventing cognitive decline
4. There is biological plausibility of a cognitive benefit of ARBs over ACEIs
5. There is growing data from secondary data analyses suggesting a comparative benefit of ARBs over ACEIs
6. There is currently no effective disease-modifying treatment for dementia

THANK YOU!

Collaborators, Mentees, & Supporters

- Tom Greene
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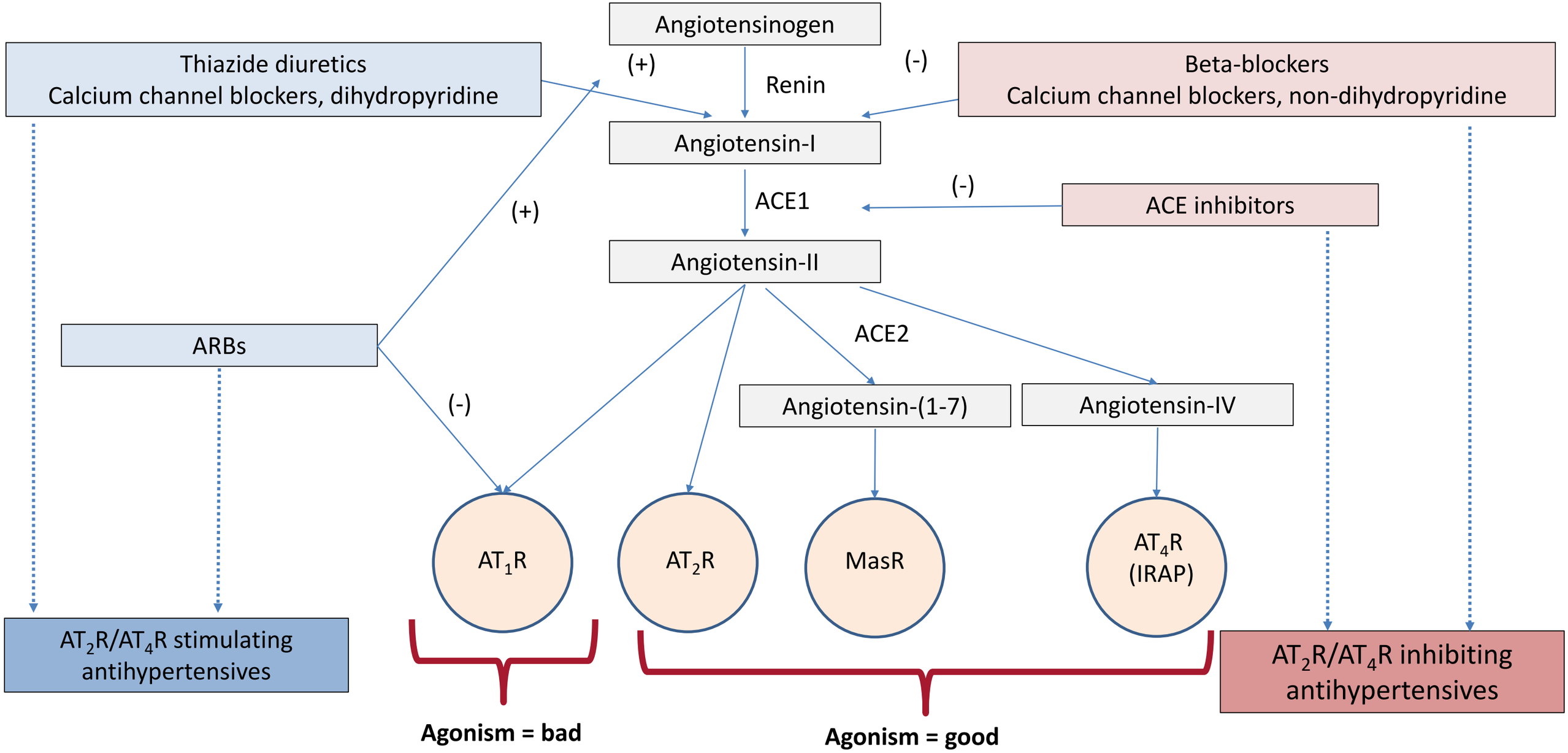
JHS Partipcants
REGARDS Participants
SPRINT Participants
SPRINT Coordinating Center
SPRINT Research Group
- Investigators
- Staff

NHLBI, NIA, and NINDS Support

There is one more thing…



Funding & Acknowledgements

- **Principial Investigator**
  - R01 AG065805 (Bress)
  - R01 AG074989 (Multi-PI: Bress and Cohen)
  - R01 HL139837 (Multi-PI: Moran/Bress/Weintraub)
  - National Academy of Medicine Fellowship in Pharmacy
- **Co-Investigator**
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  - R01 NR01889 (Baron, PI)
  - R01 HL157439 (King, PI)

Central

Thank you to my team!

Primary outcome results

ACEI

ARB

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Part II: Therapeutic Inertia

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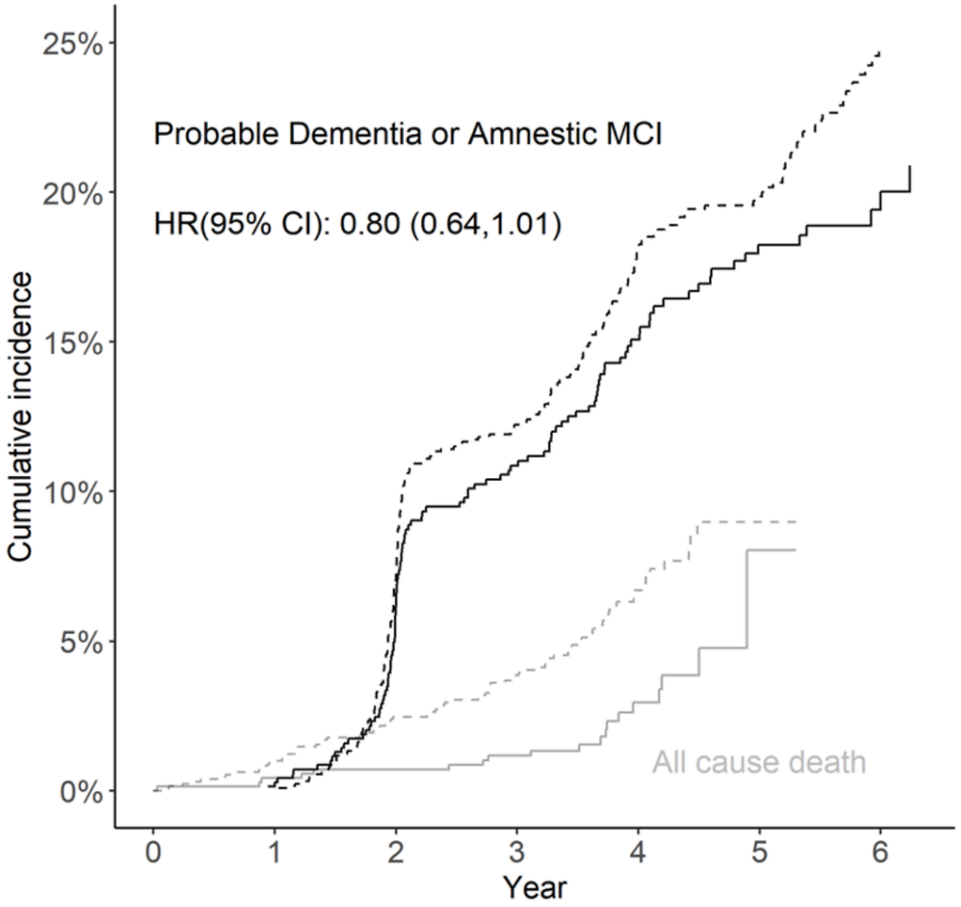
Before IP Weighting



4.9 years median follow-up

SENSITIVITY ANALYSES

Introduction

Part I: ARBs vs. ACEIs

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Part II: Therapeutic Inertia

- Background
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Summary

- SPRINT was designed to achieve an SBP goal of 135 to 139 mm Hg in the standard arm.
- However, intensification only indicated in the standard group if:
  - SBP >140 mm Hg at 2 consecutive study visits or
  - SBP >160 mm Hg at a single visit
- To address, we performed 2 sensitivity analyses:
  1. Redefining therapeutic inertia to require 2 consecutive study visits where SBP was above goal with no change or a reduction in the participant's antihypertensive medication regimen intensity for both randomized treatment groups.
  2. Restrict to the standard group and required either 1 study visit with SBP ≥160 mm Hg or 2 consecutive study visits with SBP ≥140 mm Hg.

WAS OUR DEFINITION OF TI STRICT ENOUGH? SENSITIVITY ANALYSIS REQUIRING TWO CONSECUTIVE VISITS

Standard arm			
	Non-Hispanic White	**Non-Hispanic Black**	**Hispanic**
Unique participants, n	2451	1306	383
Participant-visits, n	13704	7364	1739
Overall Prevalence, % (95% CI)	12.7 (12.0,13.5)	10.6 (9.0,12.4)	9.3 (7.1,11.9)
12 Month Prevalence, % (95% CI)	10.8 (8.3,13.9)	10.5 (7.3,15.0)	1.8 (0.1,9.4)
36 Month Prevalence, % (95% CI)	10.1 (6.8,14.8)	5.3 (2.5,11.1)	20.5 (10.8,35.5)
Adjusted OR (95% CI) ***N=4091***	1 (Reference)	0.83 (0.73,0.94)	0.73 (0.57,0.92)
Intensive arm			
	Non-Hispanic White	**Non-Hispanic Black**	**Hispanic**
Unique participants, n	2638	1328	445
Participant-visits, n	22290	10688	2404
Overall Prevalence, % (95% CI)	21.2 (20.4,22.1)	19.5 (17.3,21.7)	16.3 (13.3,20.1)
12 Month Prevalence, % (95% CI)	20.3 (17.4,23.6)	17.8 (13.8,22.6)	10.5 (5.4,19.4)
36 Month Prevalence, % (95% CI)	23.9 (19.8,28.6)	24.3 (18.2,31.7)	12.5 (5.0,28.1)
§Adjusted OR (95% CI) ***N=4373***	1 (Reference)	0.93 (0.84,1.04)	0.78 (0.65,0.95)

NO DIFFERENCE IN FOLLOW-UP SYSTOLIC BLOOD PRESSURE AMONG NEW USERS OF ARBS AND ACEIS

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Summary

Receptor	Actions	Location
AT_1	Vasoconstriction, increase sodium retention, suppress renin secretion, increase endothelin secretion, increase vasopressin release, activate sympathetic activity, promote myocyte hypertrophy, stimulate vascular and cardiac fibrosis, increase myocardial contractility, induce arrhythmias, stimulate plasminogen activator inhibitor 1, and stimulate superanoxide formation	Vessels, brain, heart, kidney, adrenal gland, and nerves
AT_2	Antiproliferation/inhibition of cell growth, cell differentiation, tissue repair, apoptosis, vasodilation (NO mediated?), kidney and urinary tract development, control of pressure/natriuresis, stimulate renal prostaglandins, and stimulate renal bradykinin and NO	Adrenal gland, heart, brain, myometrium, fetus, and injured tissues
AT_3	Unknown	Neuroblastoma cells in amphibians
AT_4	Renal vasodilator; stimulate plasminogen activator inhibitor 1	Brain, heart, vessels, lungs, prostate, adrenal gland, and kidney

DID PROGRESSIVE COVARIATE ADJUSTMENT IMPACT THE ASSOCIATIONS IN THE STANDARD ARM?

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Summary

	Standard arm		
	Non-Hispanic White	**Non-Hispanic Black**	**Hispanic**
Odds ratio (95% CI)			
Model 1 ***N=4,141†***	1 (Reference)	0.89 (0.84, 0.95)	1.00 (0.91,1.11)
Model 2 ***N=4,069†***	1 (Reference)	0.92 (0.86, 0.99)	1.01 (0.90,1.12)
Model 3 ***N=4,092†***	1 (Reference)	0.85 (0.79, 0.92)	1.00 (0.90,1.13)
Model 4 ***N=4092†***	1 (Reference)	0.88 (0.82,0.96)	1.08 (0.97,1.22)
Model 5 * ***N=4,092†***	1 (Reference)	0.89 (0.82,0.97)	0.98 (0.86,1.13)

Model 1 included race/ethnicity and time as the only fixed effects.
Model 2 was adjusted for race and time, in addition to age, sex, education, employment, living with others, insurance status, source of care, smoking status, BMI, depression, statin use, aspirin use, as well as baseline SBP, eGFR, serum potassium, serum sodium, number of antihypertensive medications, prior mTIS, ACEI/ARB, CCB, thiazide diuretic, loop diuretic, beta-blocker, alpha-blocker, and number of non-antihypertensive medications.
Model 3 added clinical measurements and serious adverse events reported within one month prior of the study visit.
Model 4 added mm Hg the SBP is above the treatment goal and the number of prior study visits with therapeutic inertia.
Model 5 added an interaction between race/ethnicity and time.

DID PROGRESSIVE COVARIATE ADJUSTMENT IMPACT THE ASSOCIATIONS IN THE INTENSIVE ARM?

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Part II: Therapeutic Inertia

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Summary

	Intensive arm		
	Non-Hispanic White	**Non-Hispanic Black**	**Hispanic**
Odds ratio (95% CI)	-	-	-
Model 1 ***N=4,415†***	1 (Reference)	0.94 (0.90, 1.00)	0.86 (0.76, 0.95)
Model 2 ***N=4,364†***	1 (Reference)	0.96 (0.90, 1.02)	0.87 (0.78, 0.97)
Model 3 ***N=4,377†***	1 (Reference)	0.94 (0.88, 1.01)	0.89 (0.79, 1.00)
Model 4 ***N=4377†***	1 (Reference)	0.99 (0.92,1.05)	0.99 (0.87,1.10)
Model 5 * ***N=4,377†***	1 (Reference)	0.99 (0.92,1.05)	0.95 (0.84,1.06)

Model 1 included race/ethnicity and time as the only fixed effects.
Model 2 was adjusted for race and time, in addition to age, sex, education, employment, living with others, insurance status, source of care, smoking status, BMI, depression, statin use, aspirin use, as well as baseline SBP, eGFR, serum potassium, serum sodium, number of antihypertensive medications, prior mTIS, ACEI/ARB, CCB, thiazide diuretic, loop diuretic, beta-blocker, alpha-blocker, and number of non-antihypertensive medications.
Model 3 added clinical measurements and serious adverse events reported within one month prior of the study visit.
Model 4 added mm Hg the SBP is above the treatment goal and the number of prior study visits with therapeutic inertia.
Model 5 added an interaction between race/ethnicity and time.

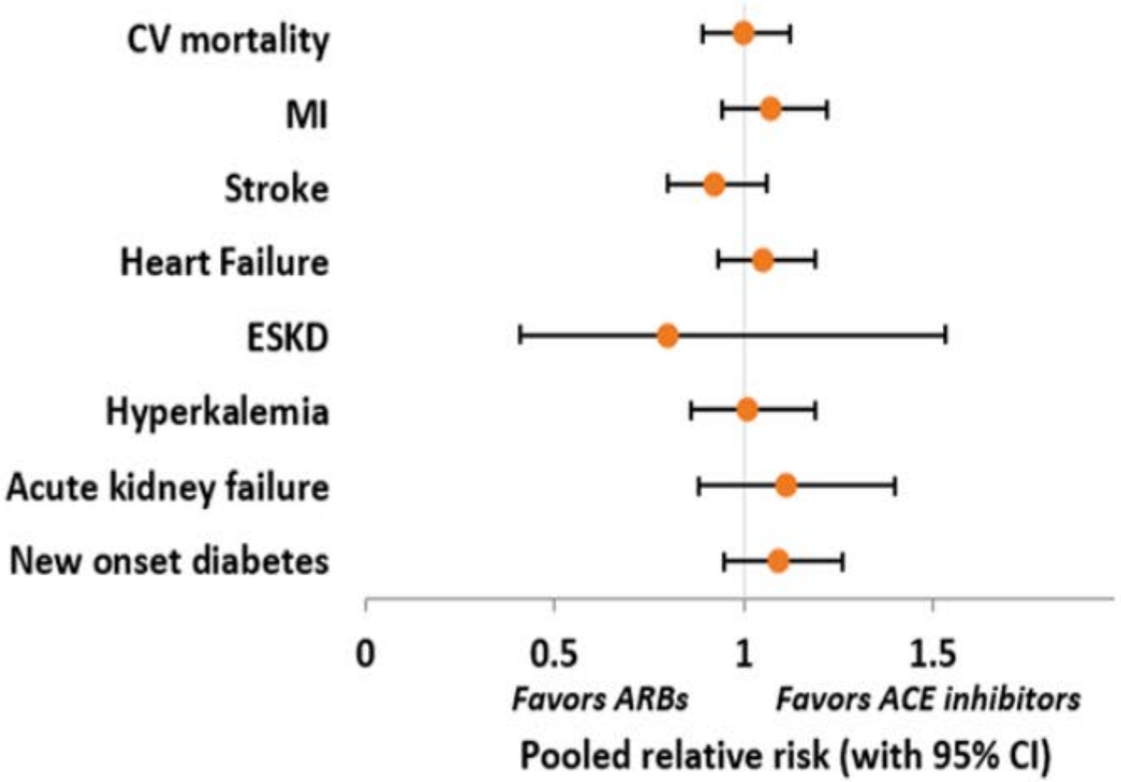
ANGIOTENSIN II RECEPTORS, THEIR FUNCTIONS AND LOCATION

Drug (Active Metabolite)	AT_1 Receptor Affinity, nmol/L	Bioavailability, %	Food Effect	Active Metabolite	Half-Life, h	Protein Binding, %	Dosage, mg/d
Losartan (EXP 3174)	IC_{50}, 20	33	No	Yes	2 (6–9)	98.7 (99.8)	50–100
Valsartan	IC_{50}, 2.7	25	Yes, −40%	No	9	95	80–320
Irbesartan	IC_{50}, 1.3	70	No	No	11–15	90*	150–300
Candesartan cilexetil							
(TCV 116)	. . .	. . .	No	Yes	3.5–4	. . .	4–16 (32)
(CV11974)	K_i, 0.6	42			3–11	99.5	
Telmisartan	K_i, 3.7	43	No	No	24	>99	40–80
Eprosartan	IC_{50}, 1.4–3.9	15	No†	No	5–7	98	400–800

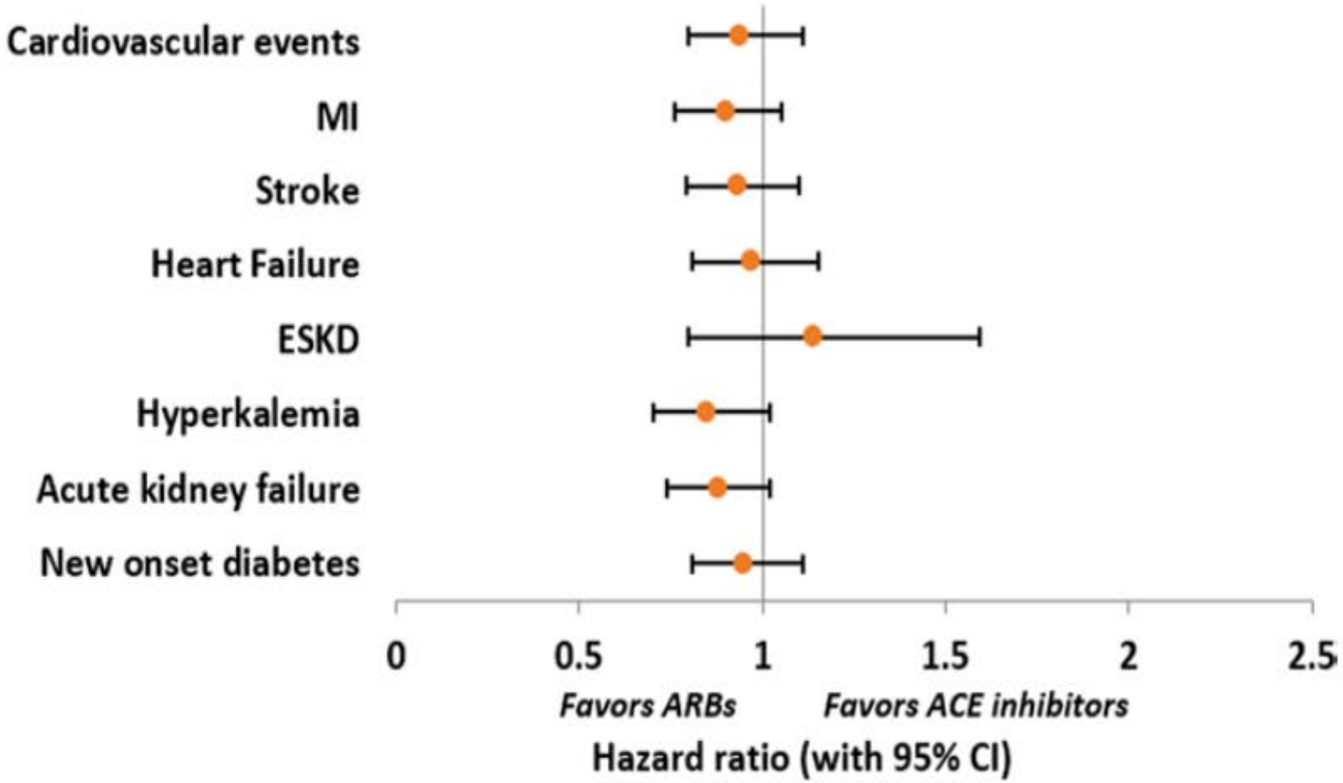
Values are mean or range. K_i indicates inhibition constant.
*Some studies suggest that irbesartan has a greater protein binding (>95%).
†Depending on the formulation, there may be a food effect.

PK DIFFERENCES BETWEEN INDIVIDUAL ARBS

Meta-analysis by Bangalore et al. on head-to-head trials (7 trials)



Multinational cohort study by Chen et al. (>3 million patients)



META-ANALYSIS OF RCTS- COMPARATIVE EFFECTS OF ARBS VS ACEIS ON CVD OUTCOMES

Treatment \ Comparison group	Placebo	CCBs	ACE inhibitors	β-blockers	Diuretics
ARBs	0.60 ± 0.18 ($P = 0.02$)	0.57 ± 0.24 ($P = 0.06$)	0.47 ± 0.17 ($P = 0.04$)	0.67 ± 0.18 ($P = 0.01$)	0.54 ± 0.19 ($P = 0.04$)
CCBs	0.02 ± 0.19 ($P = 0.91$)	–	–0.11 ± 0.22 ($P = 0.65$)	0.10 ± 0.17 ($P = 0.58$)	–0.03 ± 0.24 ($P = 0.89$)
ACE inhibitors	0.13 ± 0.17 ($P = 0.49$)		–	0.21 ± 0.15 ($P = 0.23$)	0.07 ± 0.17 ($P = 0.70$)
β-blockers	–0.08 ± 0.13 ($P = 0.59$)			–	–0.13 ± 0.19 ($P = 0.50$)
Diuretics	0.06 ± 0.17 ($P = 0.76$)				–

Messerli FH, Circulation. 2022.

NETWORK META-ANALYSIS OF RCTS- COMPARATIVE EFFECTS OF ARBS VS ACEIS ON COGNITION

17 RCTs (n =13,734) to compare effects of the different drug classes on overall cognition.

Mean difference of change in overall cognition (expressed as effect size) of treatment – comparison group standard deviation (P-value).

Treatment \ Comparison group	Placebo	CCBs	ACE inhibitors	β-blockers	Diuretics
ARBs	0.60 ± 0.18 (*P* = 0.02)	0.57 ± 0.24 (*P* = 0.06)	0.47 ± 0.17 (*P* = 0.04)	0.67 ± 0.18 (*P* = 0.01)	0.54 ± 0.19 (*P* = 0.04)
CCBs	0.02 ± 0.19 (*P* = 0.91)	–	–0.11 ± 0.22 (*P* = 0.65)	0.10 ± 0.17 (*P* = 0.58)	–0.03 ± 0.24 (*P* = 0.89)
ACE inhibitors	0.13 ± 0.17 (*P* = 0.49)		–	0.21 ± 0.15 (*P* = 0.23)	0.07 ± 0.17 (*P* = 0.70)
β-blockers	–0.08 ± 0.13 (*P* = 0.59)			–	–0.13 ± 0.19 (*P* = 0.50)
Diuretics	0.06 ± 0.17 (*P* = 0.76)				–

Marpillat ML, Journal of Human Hypertension. 2013.

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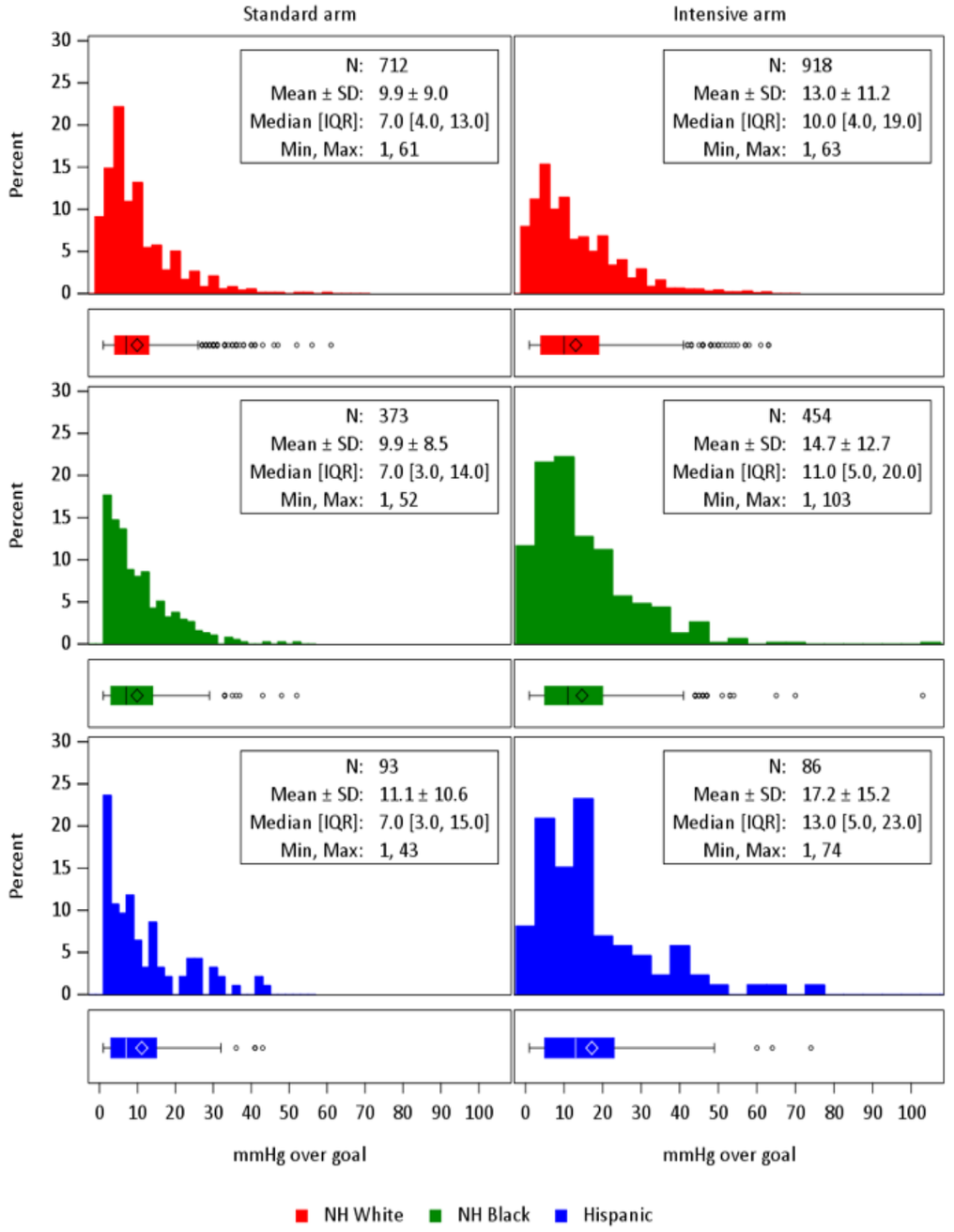
AMONG THOSE WITH THERAPEUTIC INERTIA, HOW MUCH WAS THEIR BLOOD PRESSURE ABOVE GOAL ON AVERAGE?



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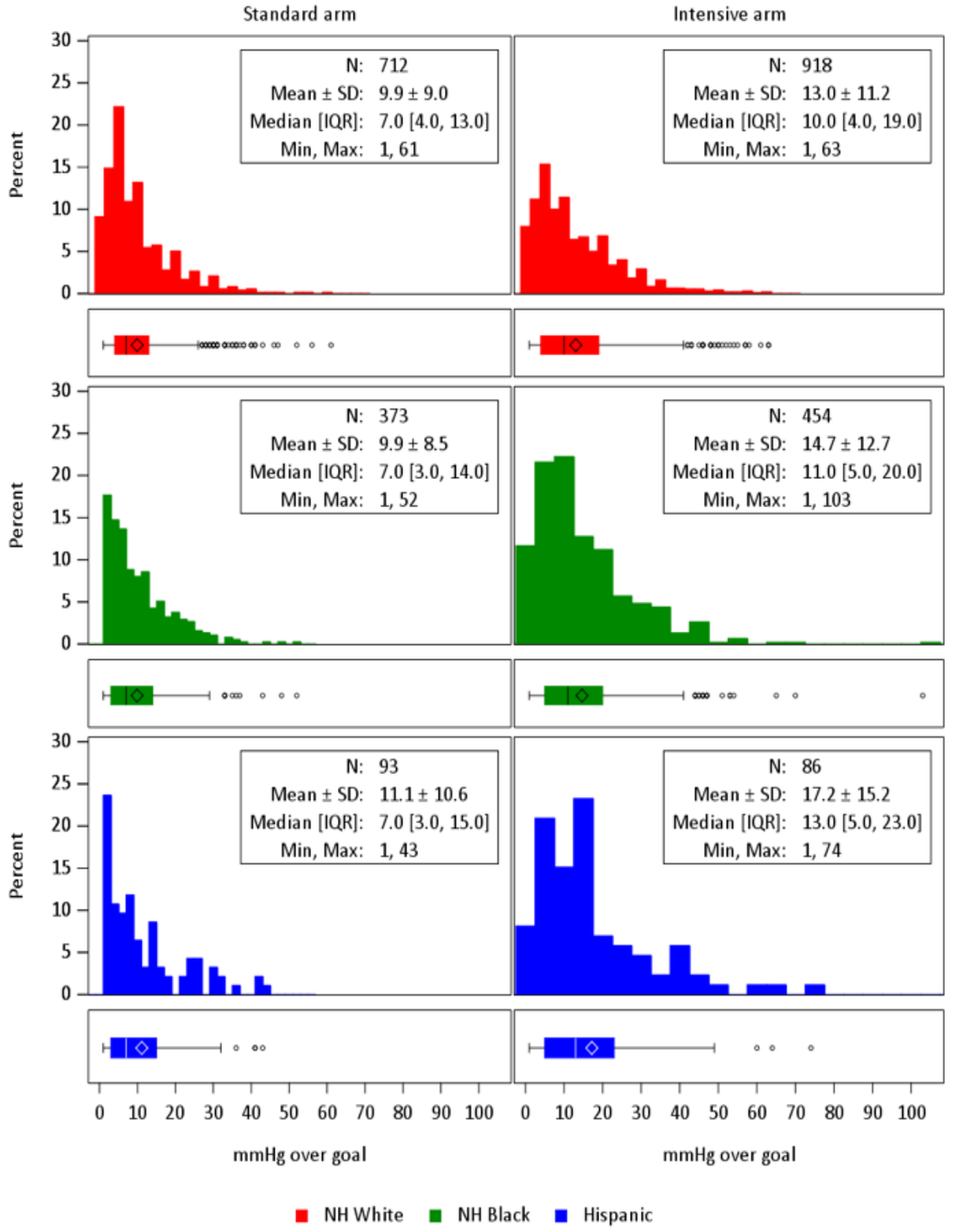

COGNITIVE OUTCOME ASCERTAINMENT IN SPRINT

Introduction

Part I: Pharmacoepi

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Results

Conclusions

Part II: PATH and HTEs

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Results

Conclusions

Summary

MIND Questionnaires/Tests	Screening or RZ	2 yr	4 yr	Close Out A*	Close Out B**
Dementia Screening					
MoCA	X	X	X		X
Digits Symbol Coding Test	X	X	X		X
Logical Memory Test Story A	X	X	X		X
Cognitive Battery (subset)					
Hopkins Verbal Learning Test	X	X	X		X
Trail Making Tests A and B	X	X	X		X
Digit Span	X	X	X		X
Boston Naming Test	X	X	X		X
Modified Rey-Osterrieth Figure	X	X	X		X
Verbal Fluency Animals	X	X	X		X

Neurocognitive Battery

COGNITIVE DOMAIN	TEST
Global Functioning	• **Montreal Cognitive Assessment (MoCA)**
Executive Function, *Speed of Processing*	• **Digit Symbol Coding Test** • Trail Making Test
Learning and Memory	• **Logical Memory I** • Hopkins Verbal Learning Test–R
Visual-Spatial Memory	• Modified Rey-Osterreith Figure
Working Memory, Attention, Verbal Fluency	• Digit Span Forward and Backward • Category Fluency-Animals
Language and Naming	• Boston Naming Test (15 item)

Bold = Tests in Cognitive Screening Battery

Participants scoring below education and race/ethnicity-specific thresholds on the MoCA were then administered remaining tests, and the Functional Assessment Questionnaire was administered to a proxy

Participants that could not complete in-person testing were administered a validated telephone battery See Rapp *et al.* ***J Am Geriatr Soc*** (2012)

Adjudication Components for Determining Cognitive Status

SPRINT MIND Screening Cognitive Battery

+

SPRINT MIND Extended Cognitive Battery

+

Proxy Report (FAQ or Modified Dementia Questionnaire)

+

Depression (PHQ-9) and Medications

=

Expert Adjudication (w/classification: PD, MCI, No Impairment)

Adjudicators were blinded to treatment group and BPs

3 STEP PROCESS FOR COGNITIVE OUTCOME ASCERTAINMENT IN SPRINT

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Part I: Pharmacoepi

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Part II: PATH and HTEs

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Summary

1. To identify possible cases of dementia a brief Cognition Screening Battery will be administered to all participants.
2. Participants who score below the pre-designated screening cut-point for possible cognitive impairment were administered a more comprehensive and detailed neurocognitive test battery (the Extended Cognitive Assessment Battery) plus the Functional Assessment Questionnaire (FAQ) which assesses impairments in daily living skills as a result of cognitive impairments.
3. All the above available tests and questionnaire data were submitted to a centralized, web-based system for adjudication by a panel of dementia experts who will assign final study classifications of probable dementia, MCI or no impairment (NI).

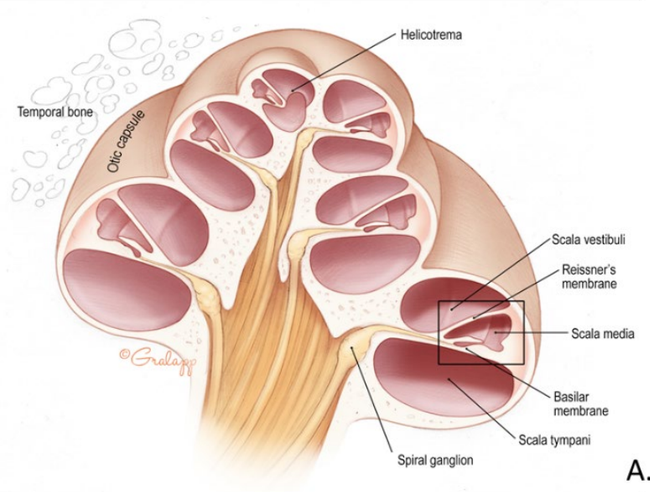
The Hear and Know: Hearing Loss, Cognition, and Cochlear Implants in Older Adults

HEALTH
UNIVERSITY OF UTAH

Thoughts by
Richard K. Gurgel, MD, MSCI
Associate Professor – Otolaryngology

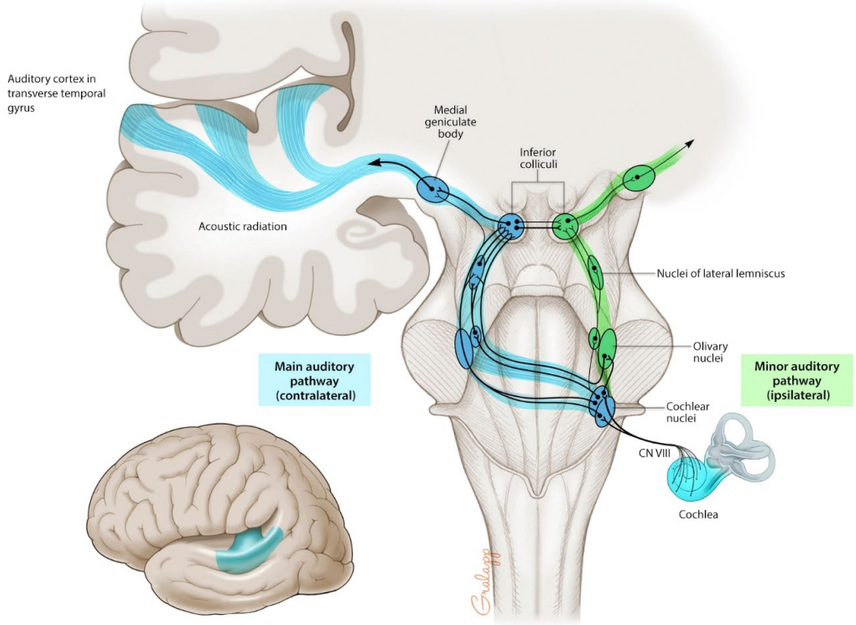
DISCLOSURES

- Research funding:
  - NIH/NIA - 1 R21 AG067403-01A1
  - Center on Aging Pilot Grant
- Surgical Advisory Board: Med-El
- Industry: Institutional Research Funding from Cochlear Corp and Advanced Bionics



OVERVIEW

- Hearing loss and dementia
- Treating hearing loss:
  - Cochlear implants and cognition



HEARING LOSS AND DEMENTIA

ORIGINAL ARTICLE

Central Auditory Dysfunction as a Harbinger of Alzheimer Dementia

George A. Gates, MD; Melissa L. Anderson, MS; Susan M. McCurry, PhD; M. Patrick Feeney, PhD; Eric B. Larson, MD, MPH

Neuropsychology
2011, Vol. 25, No. 6, 763–770
In the public domain
DOI: 10.1037/a0024238

Hearing Loss and Cognition in the Baltimore Longitudinal Study of Aging

Frank R. Lin
Hopkins University

Luigi Ferrucci, E. Jeffrey Metter, Yang An,
Alan B. Zonderman, and Susan M. Resnick
National Institute on Aging, Baltimore, Maryland

ORIGINAL INVESTIGATION

ONLINE FIRST

Hearing Loss and Cognitive Decline in Older Adults

Frank R. Lin, MD, PhD; Kristine Yaffe, MD; Jin Xia, MS; Qian-Li Xue, PhD; Tamara B. Harris, MD, MS; Elizabeth Purchase-Helzner, PhD; Suzanne Satterfield, MD, DrPH; Hilsa N. Ayonayon, PhD; Luigi Ferrucci, MD, PhD; Eleanor M. Simonsick, PhD; for the Health ABC Study Group

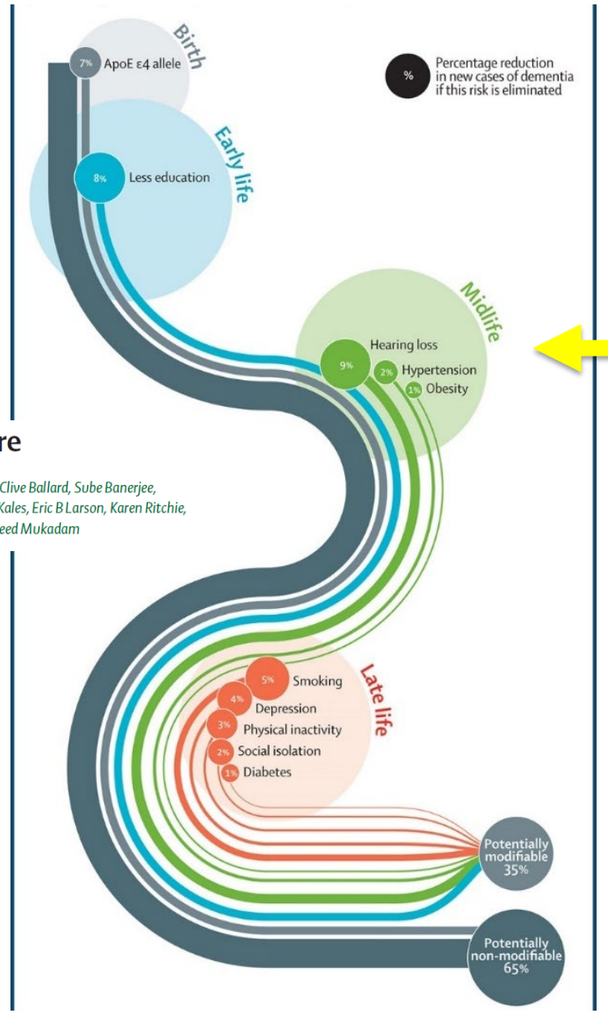
Relationship of Hearing Loss and Dementia: A Prospective, Population-Based Study

*Richard Klaus Gurgel, *Preston Daniel Ward, †Sarah Schwartz, †‡§Maria C. Norton, ||Norman L. Foster, and †§JoAnn T. Tschanz

Laryngoscope Investigative Otolaryngology

Hearing Loss as a Risk Factor for Dementia: A Systematic Review

Rhett S. Thomson, BA; Priscilla Auduong, MD; Alexander T. Miller, BS; Richard K. Gurgel, MD



Dementia prevention, intervention, and care

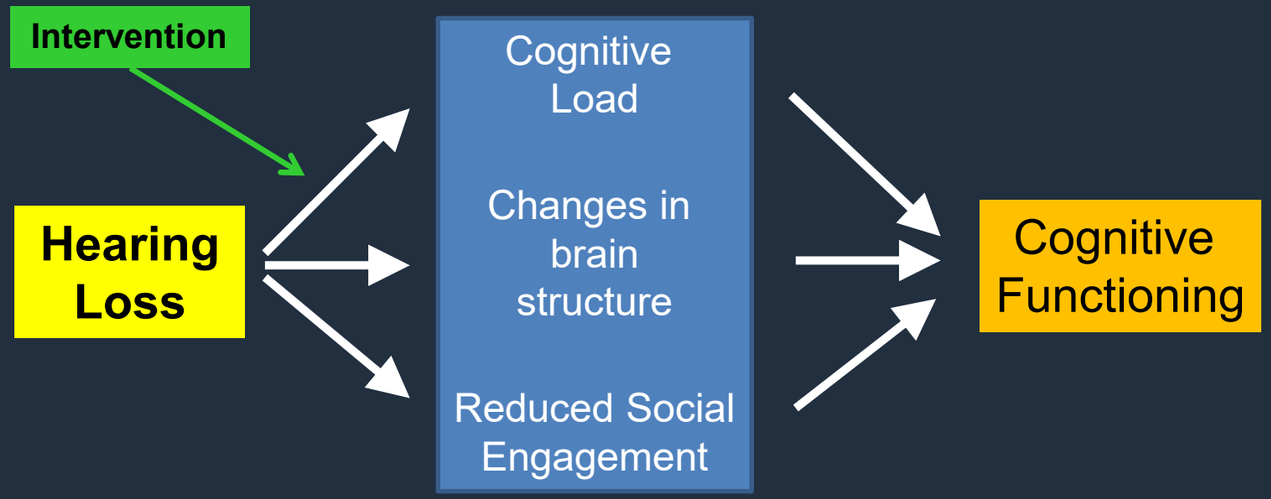
Gill Livingston, Andrew Sommerlad, Vasiliki Orgeta, Sergi G Costafreda, Jonathan Huntley, David Ames, Clive Ballard, Sube Banerjee, Alistair Burns, Jiska Cohen-Mansfield, Claudia Cooper, Nick Fox, Laura N Gitlin, Robert Howard, Helen C Kales, Eric B Larson, Karen Ritchie, Kenneth Rockwood, Elizabeth L Sampson, Quincy Samus, Lon S Schneider, Geir Selbæk, Linda Teri, Naaheed Mukadam

9% of modifiable risk of Alzheimers disease attributed to hearing loss

G. LIVINGSTON ET AL., LANCET, 19 JULY 2017

Hearing Loss & Cognition

Hearing Loss as a Modifiable Risk Factor

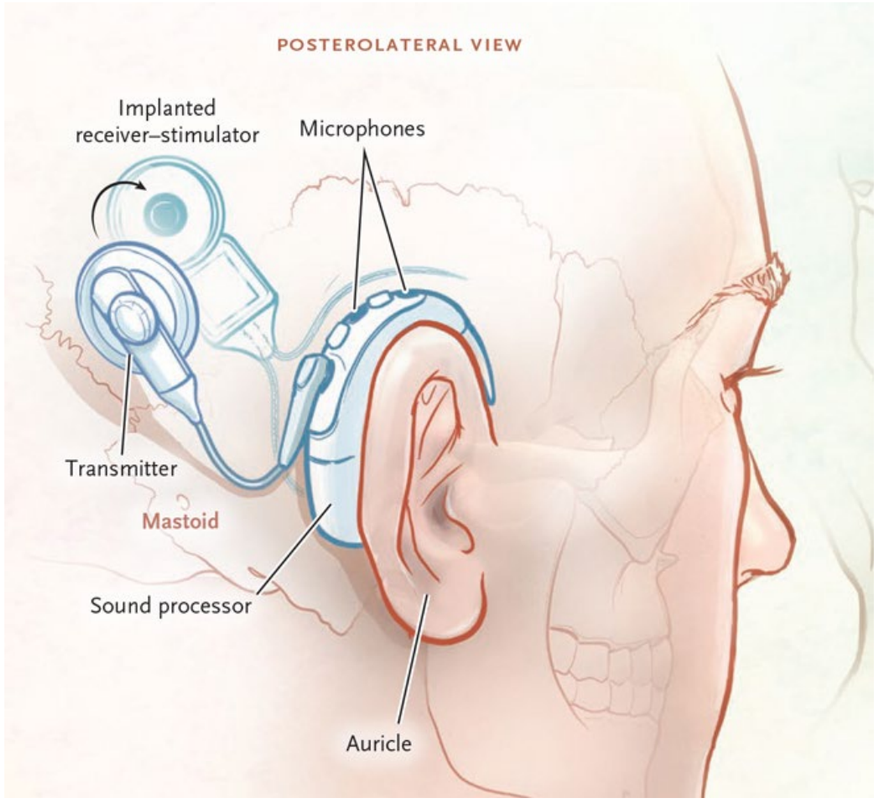


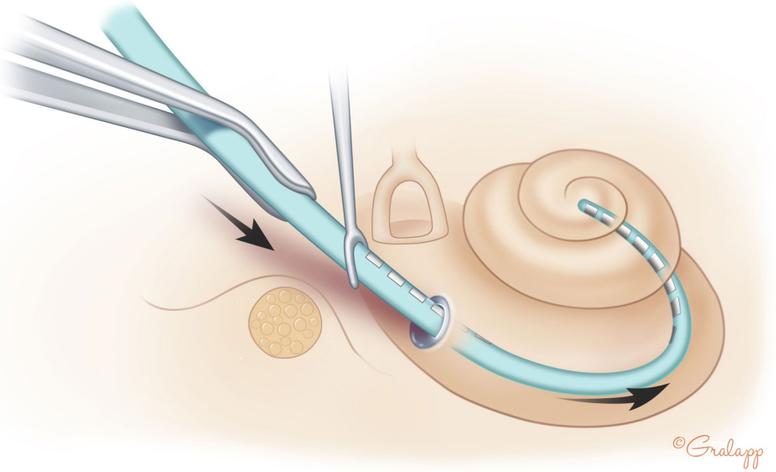
Hearing loss intervention could:

- Reduce the cognitive load of processing degraded sound
- Provide increased brain stimulation
- Improve social engagement

Role of HL as a potentially modifiable, mid & late-life risk factor for cognitive decline & dementia

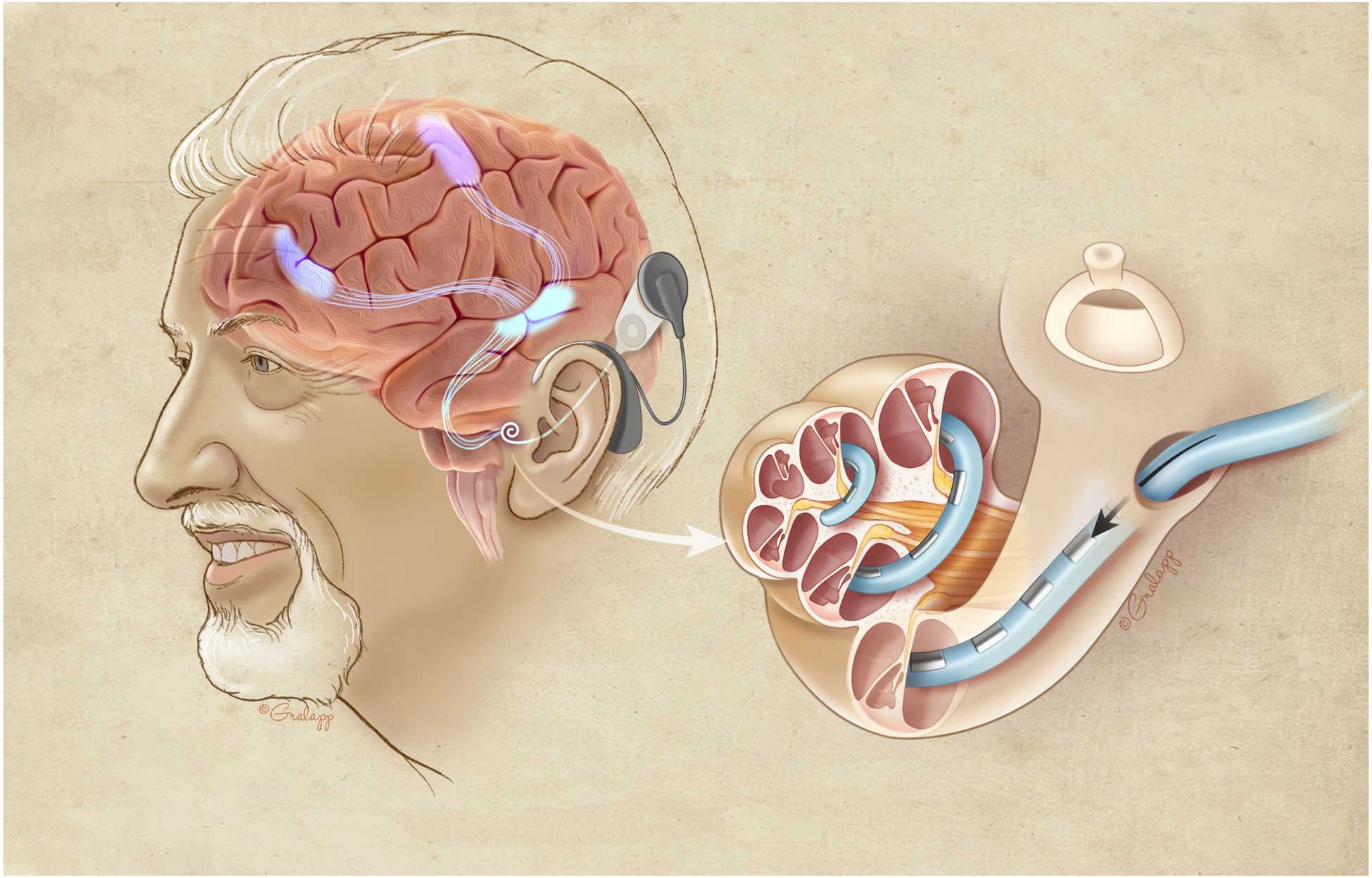
COCHLEAR IMPLANTS





COCHLEAR IMPLANTS IN OLDER ADULTS

- Only 5-10% of adult cochlear implant candidates in the US have received cochlear implants
- Average delay from time of profound ARHL to CI is 10 years
- Fastest growing segment of CI users = older adults



COCHLEAR IMPLANT COGNITION

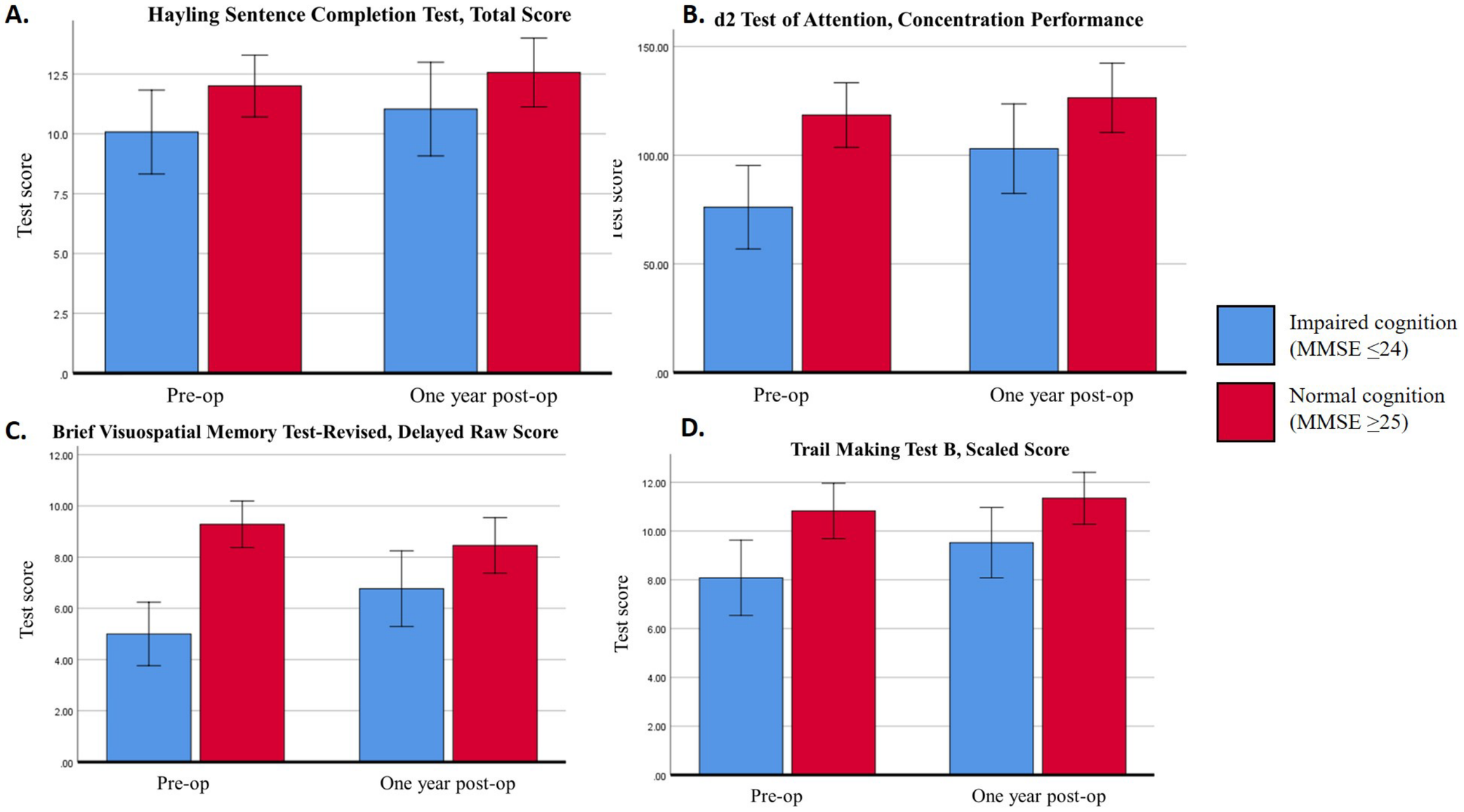
The Laryngoscope

Evaluating the Impact of Cochlear Implantation on Cognitive Function in Older Adults

Richard K. Gurgel, MD, MSCI; Kevin Duff, PhD; Norman L. Foster, MD; Kaitlynn A. Urano, AuD; Alvin deTorres, MD

- 37 patients, ≥65 yo
- Cognitive testing before and 1 year after cochlear implant

Cognitive domain	Verbal stimuli/responses	Visual stimuli/responses
Simple attention	Digit Span	Spatial Span
Sustained attention	Stroop Color Word Test	d2 Test of Attention
Learning and memory	HVLT-R	BVMT-R
Executive functioning	Hayling Sentence Completion Test	Trail Making Test Part B



COCHLEAR IMPLANTS COGNITION

- Cochlear implants improve cognition in older adults
- Individuals with cognitive impairment - Even more improvement
- Do cochlear implants protect against dementia?

CONCLUSIONS

- There is an association between hearing loss and dementia
- Cochlear implants are safe and effective in older adults, and can improve cognition
- Cochlear implants may reduce risk of dementia

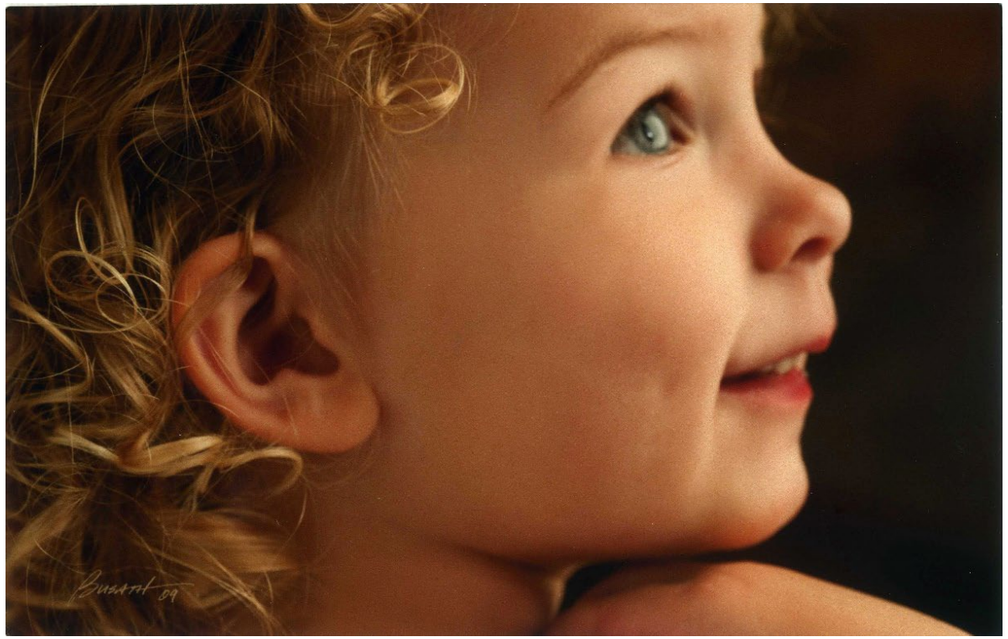
INTRODUCTION OF TEAM





- Ankita Date (UPDB), Mike Newman (EDW), Tom Belnap (IHC), Alison Fraser (UPDB)

THANK YOU



Questions

HEALTH
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Sensory Integration for Navigation:
Effects of Age and Sensory Impairment

Sarah Creem-Regehr
Department of Psychology
University of Utah

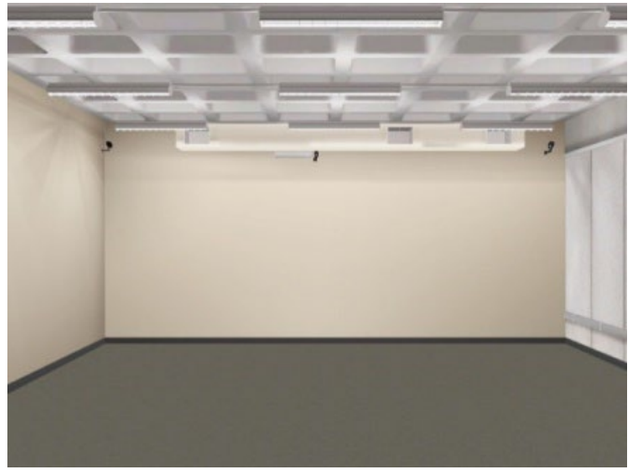
Visual Perception and Spatial Cognition
THE UNIVERSITY OF UTAH
http://www.cs.utah.edu/research/groups/percept/

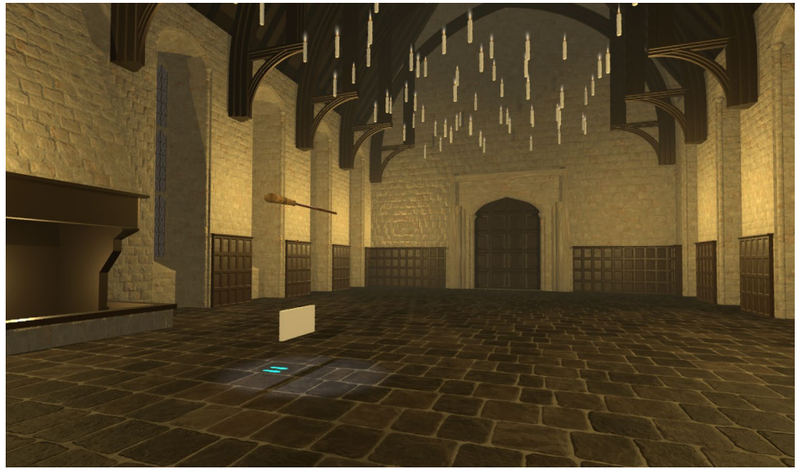
Visual Perception and Spatial Cognition Lab

We study how people perceive, learn, and navigate spaces in natural, virtual, and visually impoverished environments.

Basic research motivated by real world problems

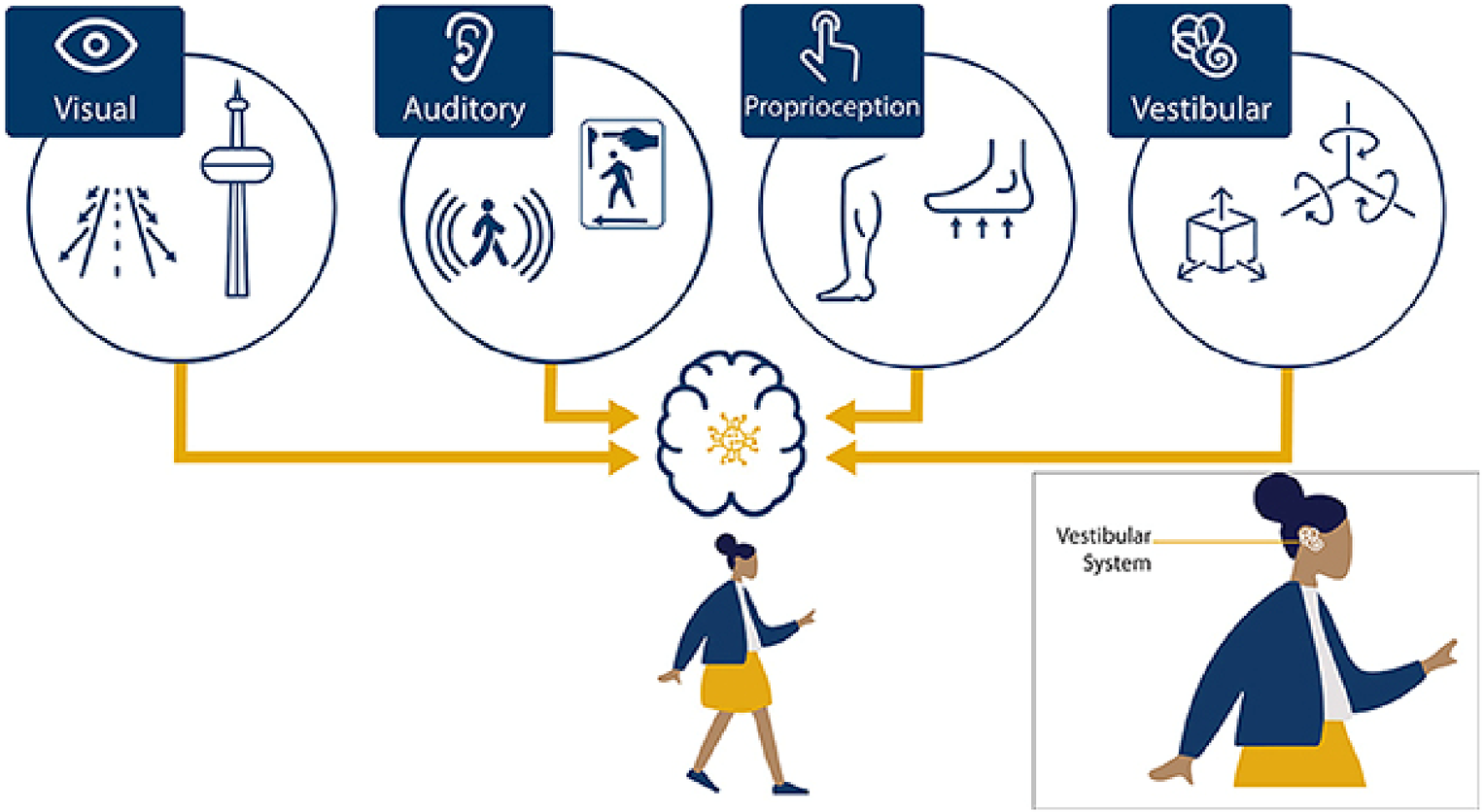
- Perceptual fidelity of virtual environments
- Navigation challenges with healthy aging and sensory pathology





Navigation and Aging

Navigation ability is critical for independent living and influenced by age-related changes in sensory processing

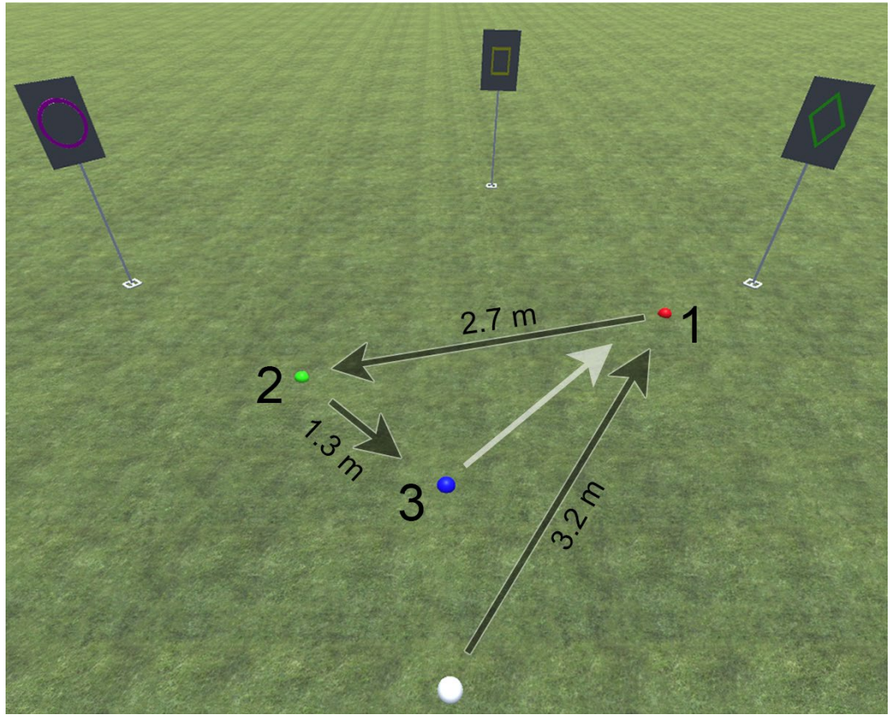


Campos et al, 2020
Frontiers for Young Minds

Navigation and Aging

How are visual and self-motion cues integrated for balance and navigation? (CoA pilot grant with P. Fino and J. Stefanucci)

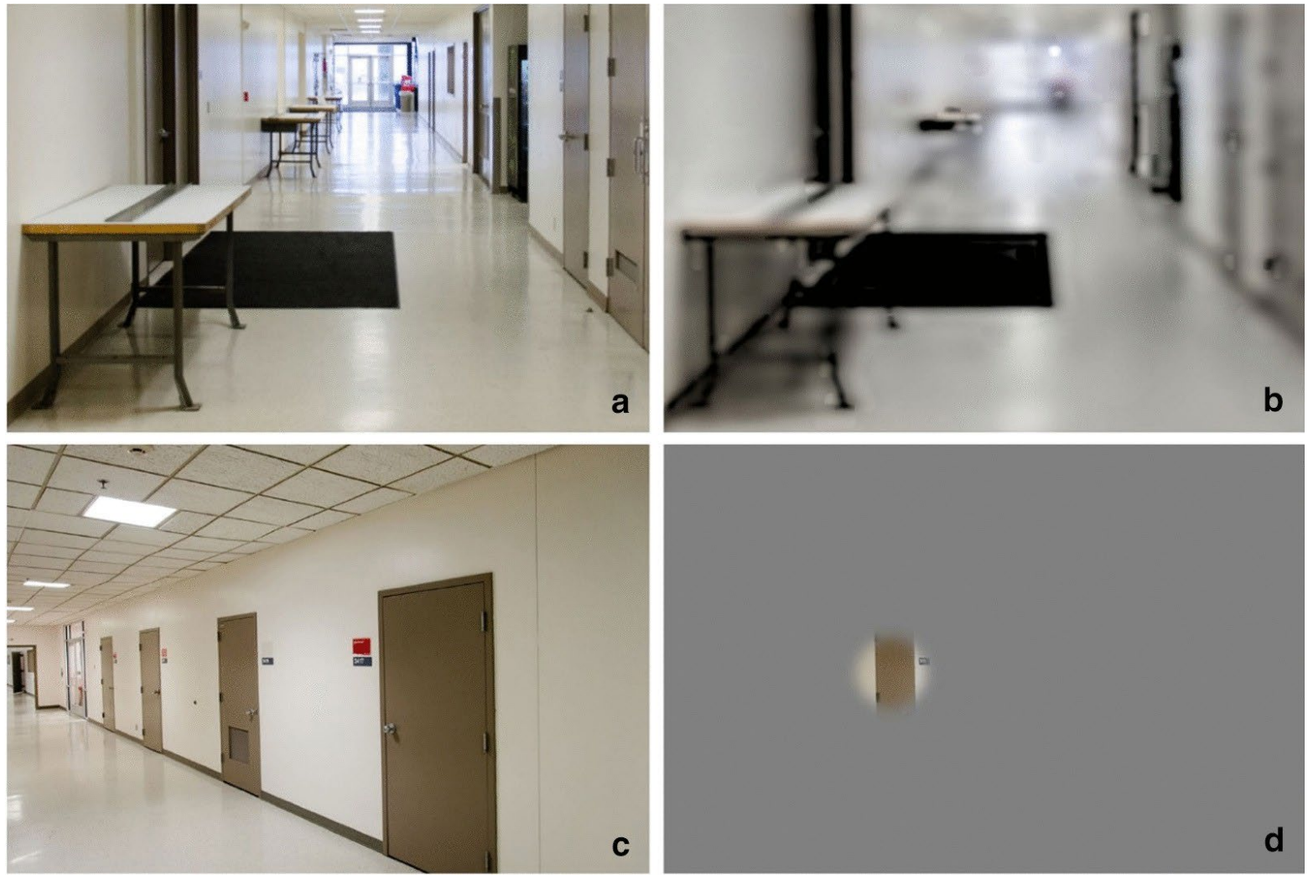
- Do younger and well-aging older adults use the same sensory weighting strategies?
- How does sensory weighting for balance relate to navigation?
- Is sensory weighting similar in real and virtual environments?



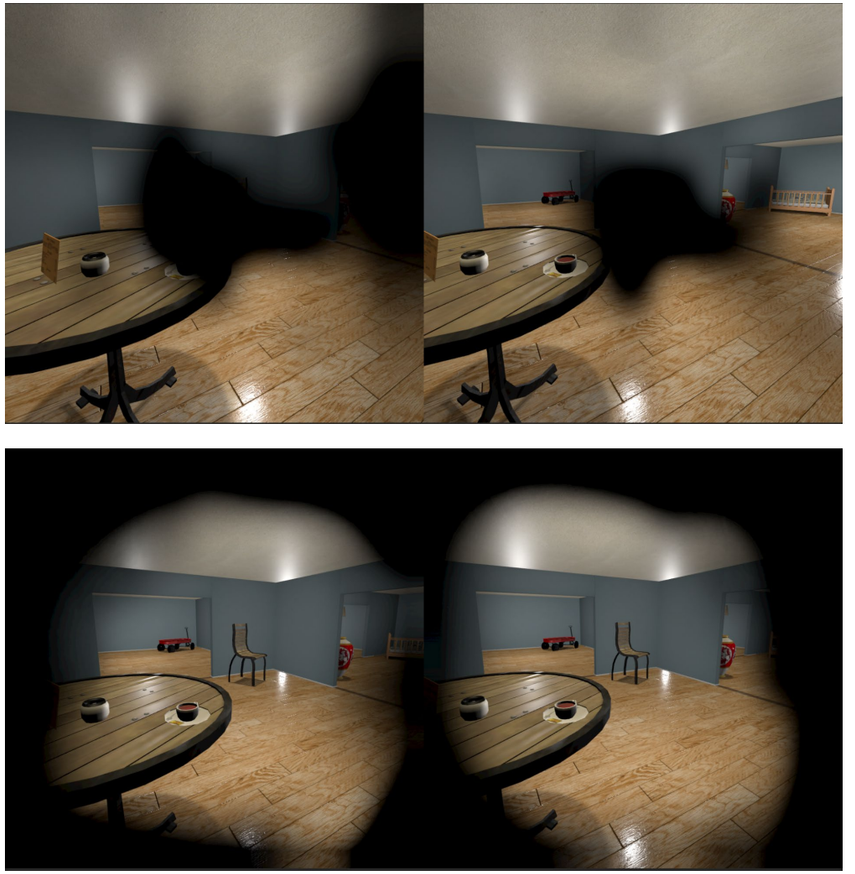
Homing Task in Virtual Reality

Navigation and Sensory Impairment

How does severe vision loss (low vision) influence sensory integration for navigation?



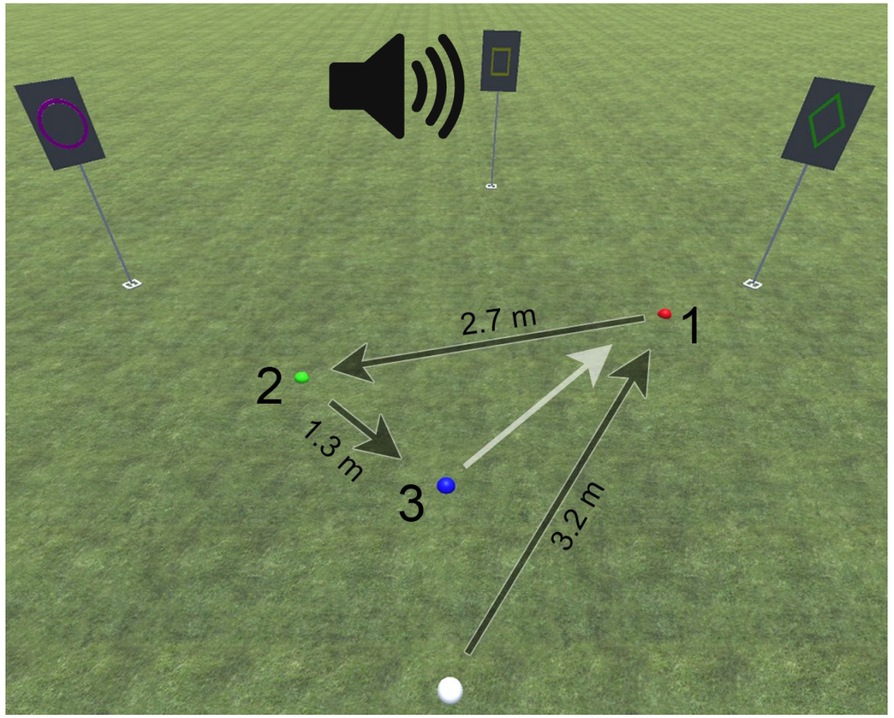
VR Low Vision Simulation



Navigation and Sensory Impairment

How are <u>auditory</u> cues integrated with vision and self-motion to influence balance and navigation? (American Otological Society grant to Corey Shayman, MD-PhD student)

- In well-aging individuals
- In simulated vision or vestibular loss



Homing Task in Virtual Reality

Cognitive Resilience and Collaborations

Development of virtual reality methods for use in research and clinical applications

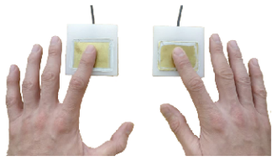
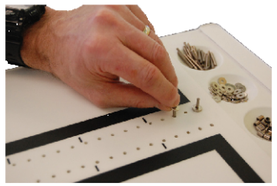
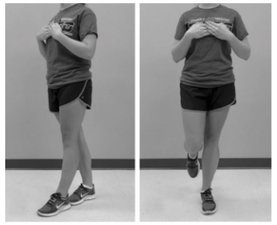
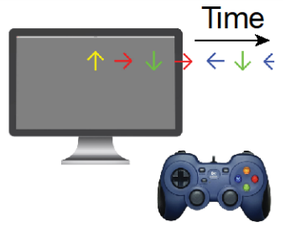
- Controlled simulations
- Accessible and interesting to participants

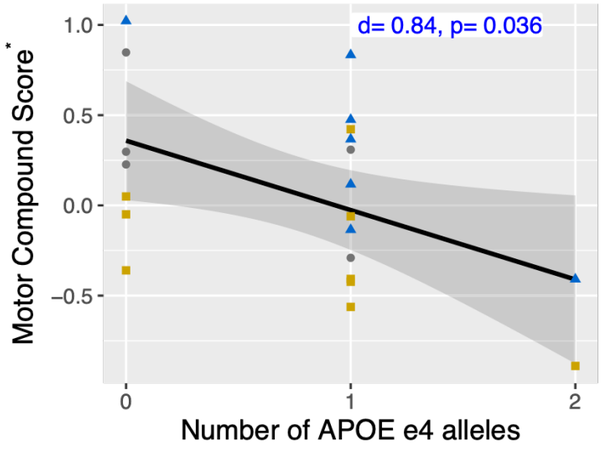
Understanding sensory weighting to improve rehabilitation, training, and assistive devices

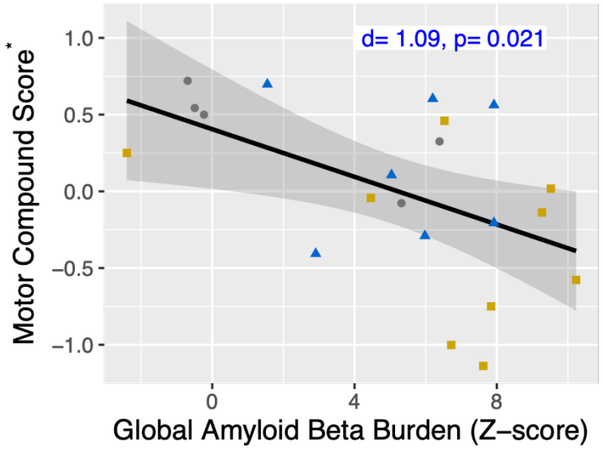
Shared interests in core resources of proposed Pepper Center

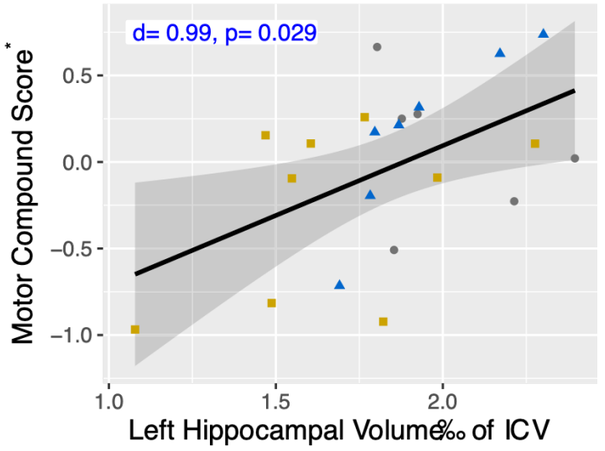
- Clinical Core: expanded and longitudinal participant database including cognitive and functional status

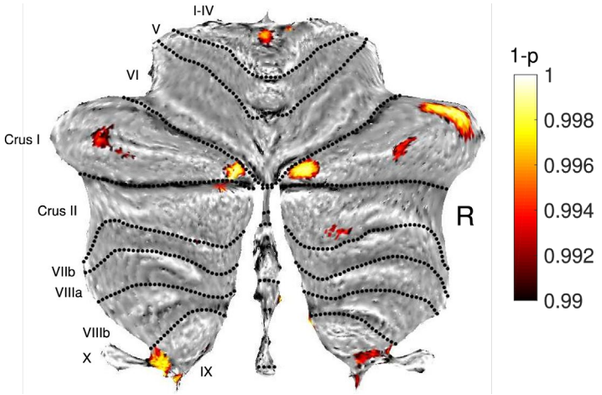
Motor Behavioral Profile Scores as Biomarkers for Alzheimer's Disease

Muscle Strength	Motor Speed	Fine Motor Skill	Coordination	Gait	Balance	Motor Learning	Drawing
							
Hand Dynamometer	Computerized Finger Tapping Test	Computerized Archimedes Spiral Test	Purdue Pegboard Test	Preferred and Maximum Speed + TUG + Dual Task	Romberg Balance Test w. Eyes Open + Closed	Computerized Implicit Sequence Learning Test	Trail Making Test A









Supported by: K01AG073578

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HUNTSMAN MENTAL HEALTH INSTITUTE UNIVERSITY OF UTAH

HEALTH UNIVERSITY OF UTAH

MOCO LAB

Areas for collaboration

- Exercise Physiology / Kinesiology:
  Setting up exercise interventions aiming at improving motor function
- Cognitive Neurology:
  Further determination of key aspects of comorbid movement disorders in MCI/AD
- Radiology:
  Quantification of cerebrovascular pathology
  (ASL, automated quantification of WML and microbleeds, phase contrast imaging for total CBF)

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HUNTSMAN MENTAL HEALTH INSTITUTE UNIVERSITY OF UTAH

HEALTH UNIVERSITY OF UTAH

MOCO LAB

Pepper Center Support

- Clinical Core:
  Recruitment of participants: a) healthy older adults; b) individuals with pre-symptomatic AD pathology and those with ADRD
- Data and Biomarker Core:
  Repurposing biomarker and imaging data (repositories), development/application of machine learning algorithms

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HUNTSMAN MENTAL HEALTH INSTITUTE UNIVERSITY OF UTAH

HEALTH UNIVERSITY OF UTAH

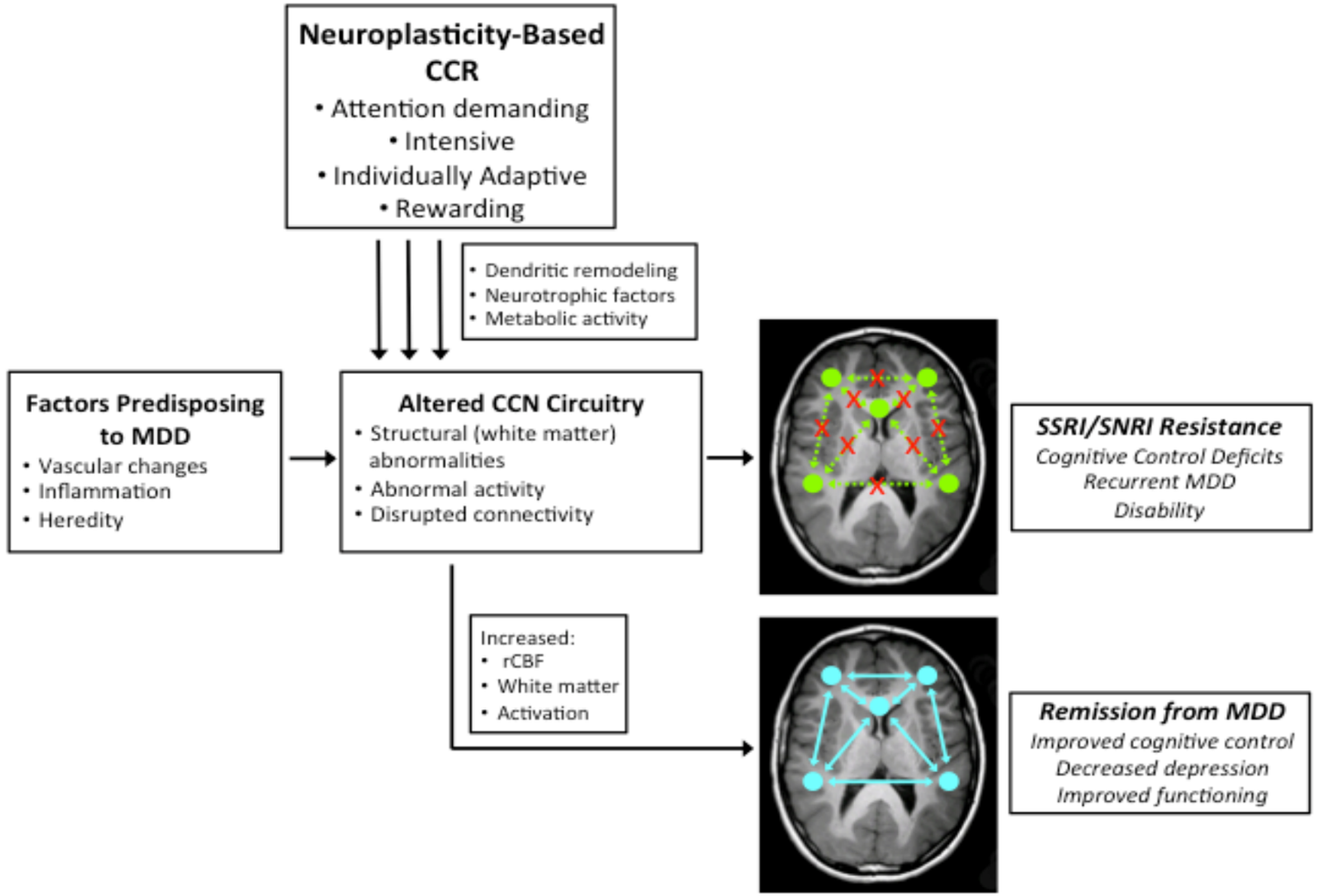
MOCO LAB

Plasticity-Based Digital Interventions for Major Depression and Cognitive Impairment

Sarah Shizuko Morimoto, Psy.D.
Associate Professor
Department of Population Health Sciences

HEALTH
UNIVERSITY OF UTAH

NEUROBIOLOGICAL MODEL OF NEUROFLEX: GRAPHICAL ABSTRACT



PRINCIPLES OF NEUROFLEX:

PLASTICITY IN AN AGING BRAIN Requires:

- Selection of specific, clinically-relevant network.
- Extensive practice/activation of network
- "Bottom up" + "top down" modules
- ↑ Neurotransmission associated with reward (Bao et al, 2001; Mahncke et al; 2006)

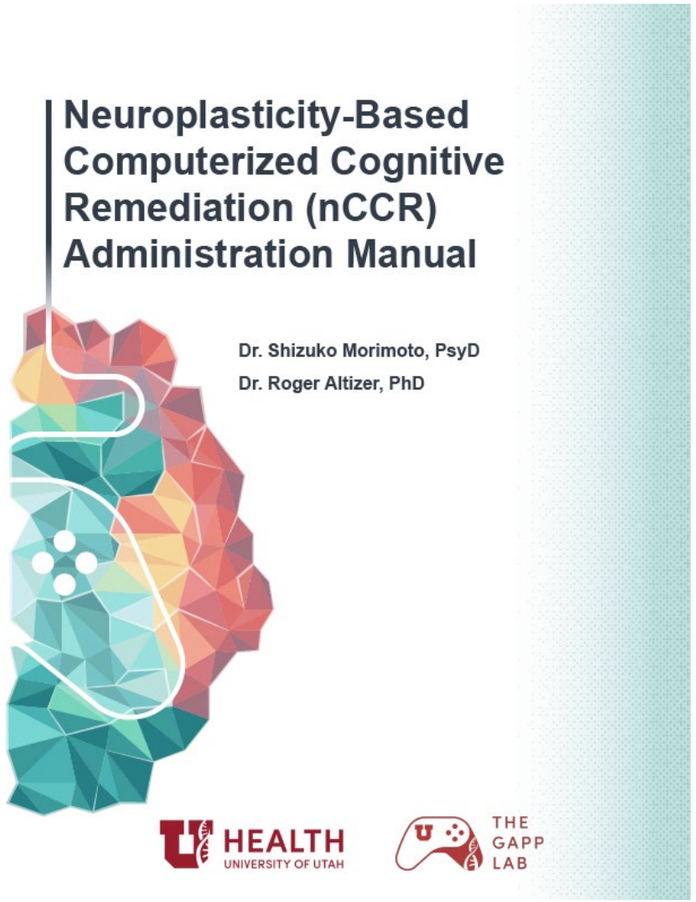
PARADIGMS ENGAGE CCN WITH SENSORY, MOTOR, AND COGNITIVE TASKS THAT ARE:

- Increasingly challenging
- Dynamic difficulty adjusted
- "Layered"
- Attention demanding
- Immediately rewarding (Bao et al, 2001; Bao et al, 2004;Mahncke et al; 2006)

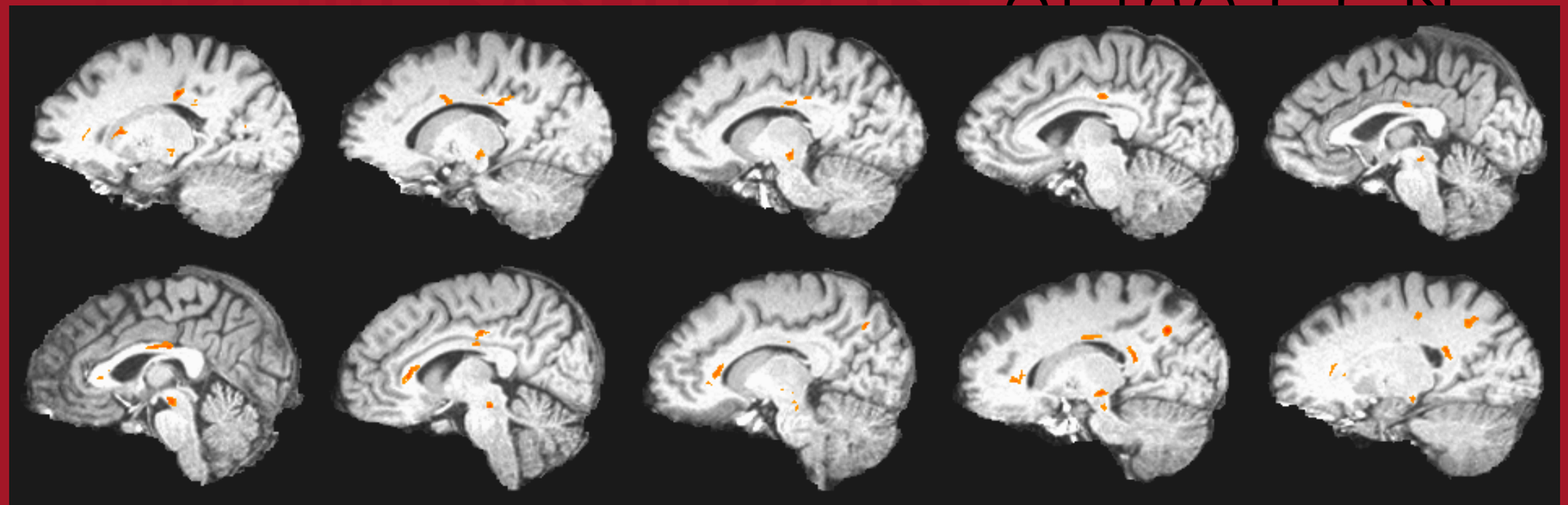
NEUROFLEX IS A **DIGITAL SOLUTION** DEVELOPED TO TREAT THE SPECIFIC **COGNITIVE DEFICITS** THAT PREDICT POOR CLINICAL OUTCOMES IN DEPRESSION.

IT IS:

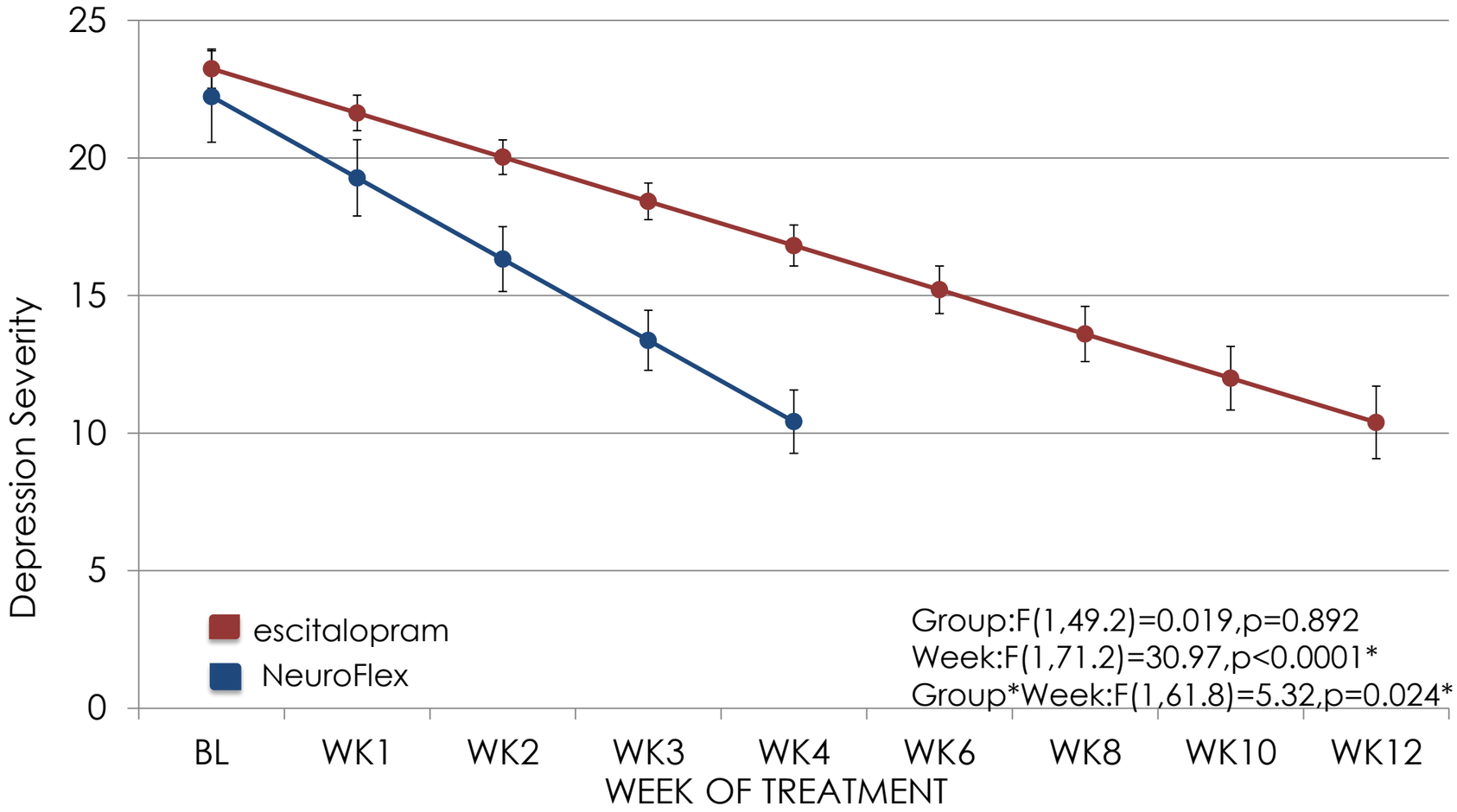
- Short (4 weeks)
- Efficacious For Mood *and* Cognition
- Easily Disseminated
- Cost Effective



- NeuroFlex is Designed To Be a



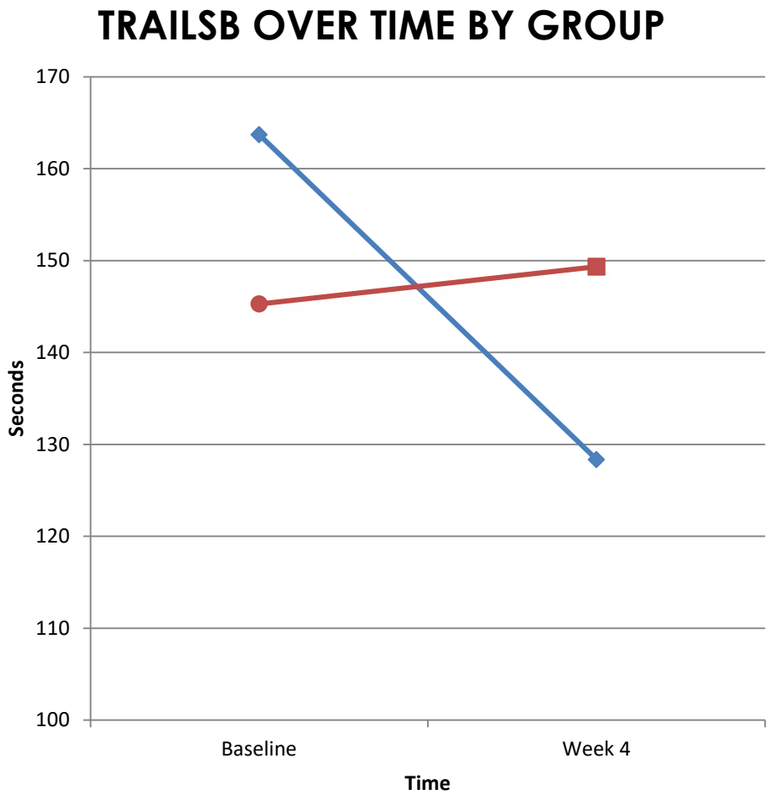
PILOT TRIAL: MIXED MODELS : NEUROFLEX VS. ESCITALOPRAM

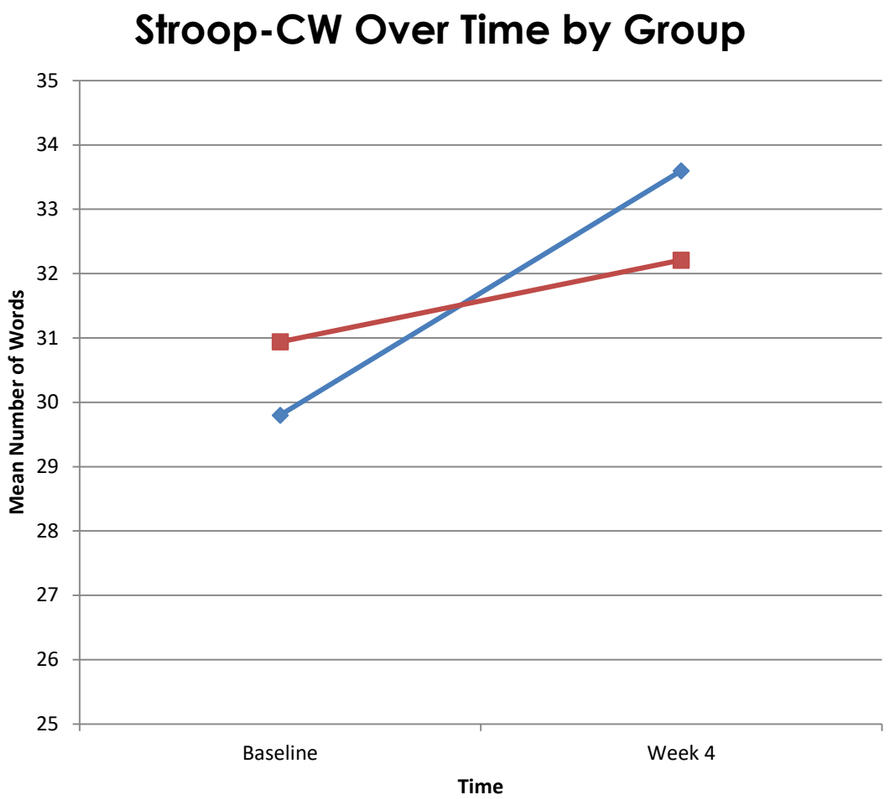


Remission

*Morimotoet.al., *Nature Communications*, 2014

PILOT TRIAL: EFFECT ON COGNITIVE CONTROL





escitalopram

NeuroFlex

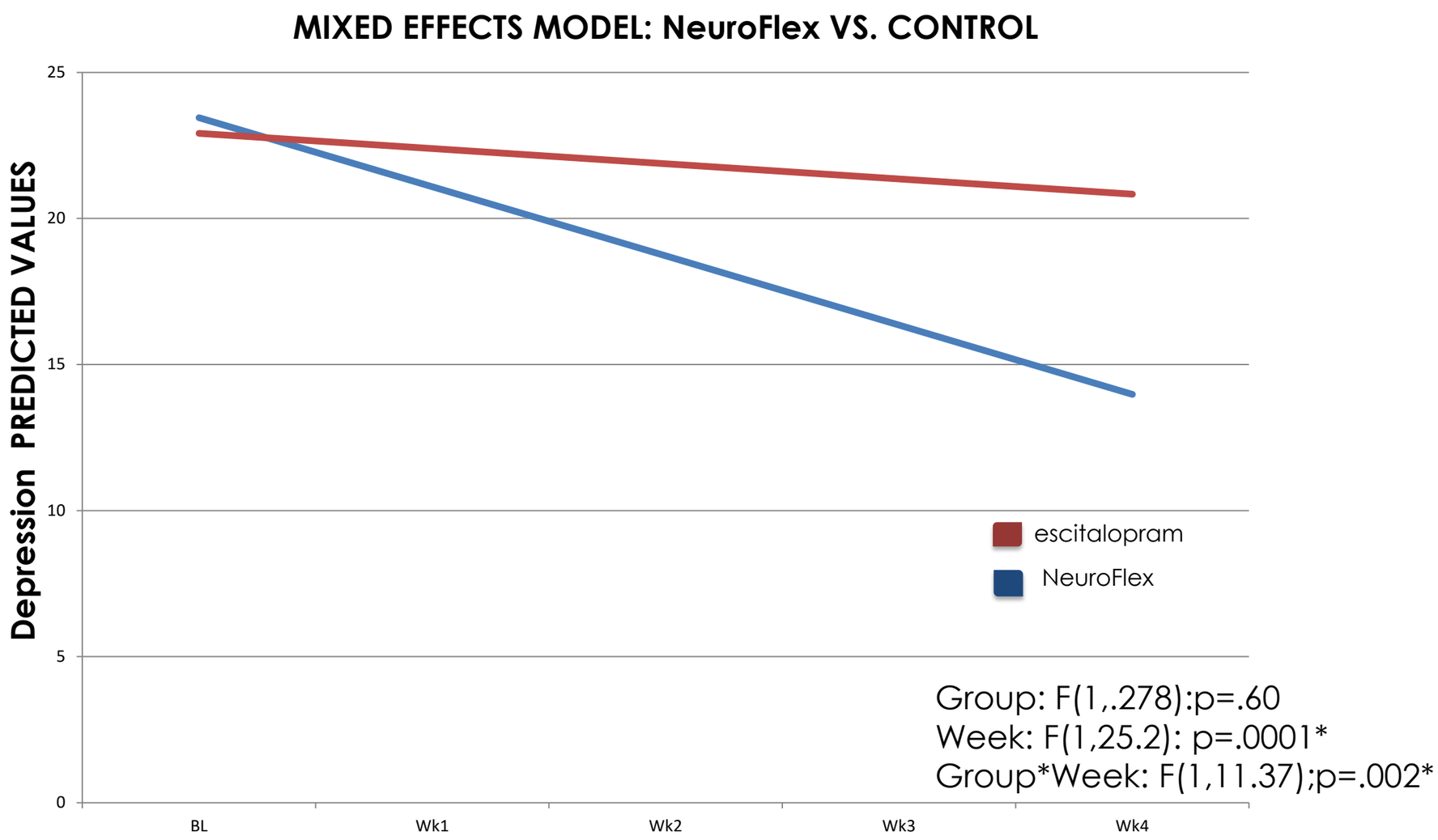
t=2.28,DF=41,**p=0.027***

t=1.86,DF=41,**p=0.103**

*Morimoto et. Al., *Nature Communications*, 2014

RANDOMIZED, DOUBLE-BLIND, CONTROLLED TRIAL: MOOD

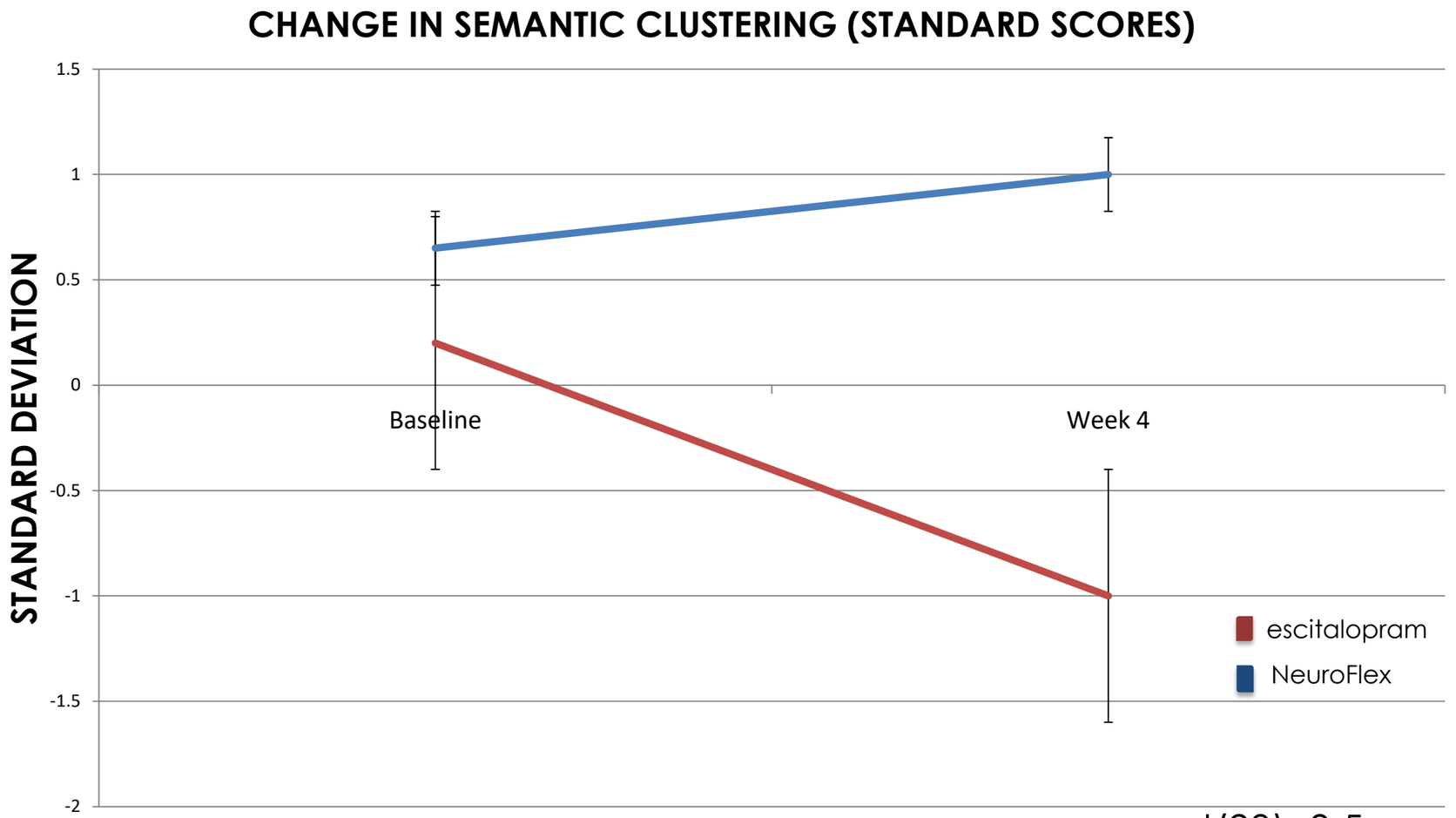
PI: MORIMOTO (K23 MH 095830)



*Morimoto et. Al *Am. J. of Geri Psych*. 2020

RCT: COGNITIVE CONTROL DEFICITS

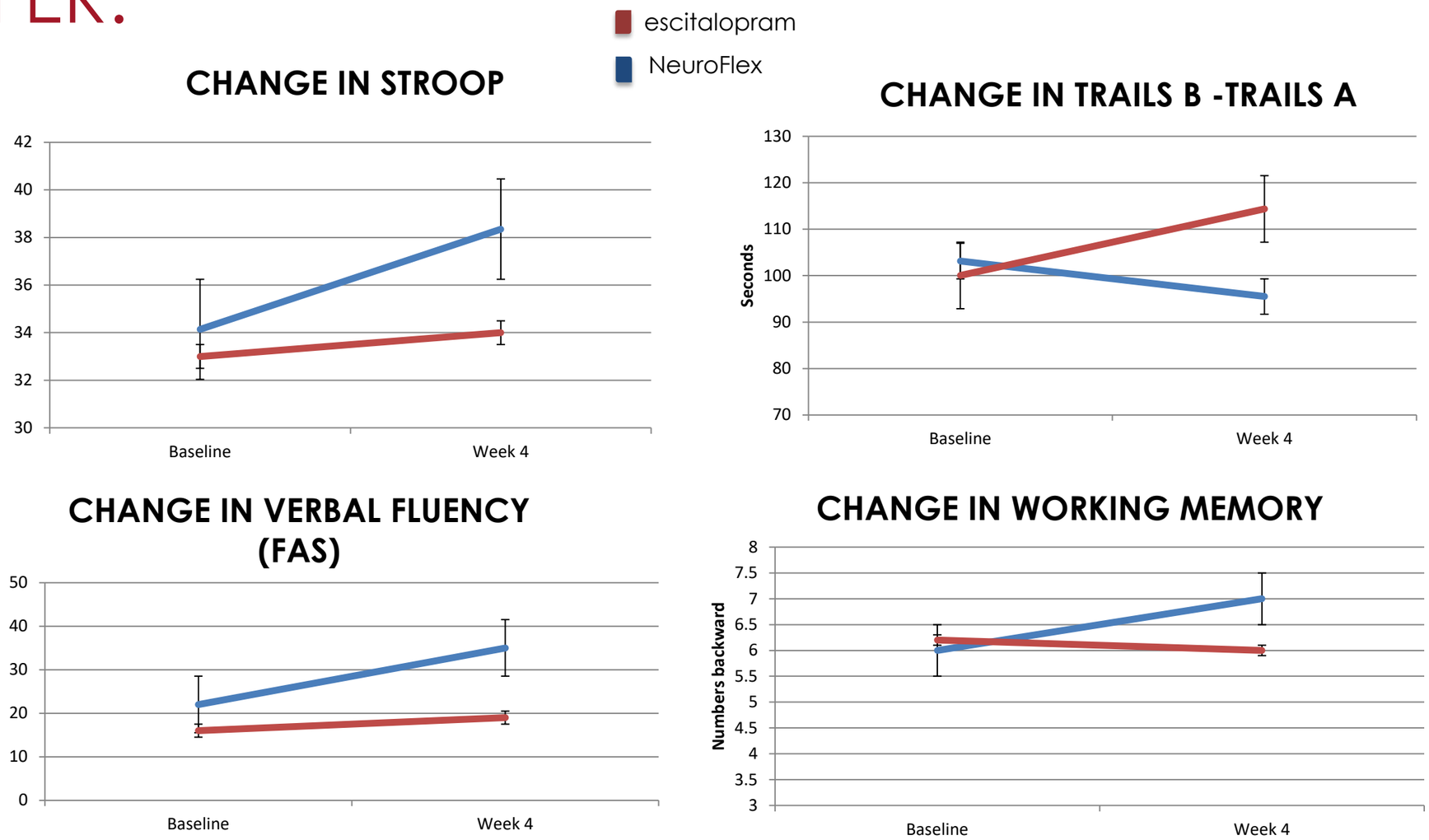
PI: MORIMOTO (K23 MH 095830)



t(28)=9.5 ; p=.006*

*Morimoto et. Al *Am. J. of Geri Psych*. 2020

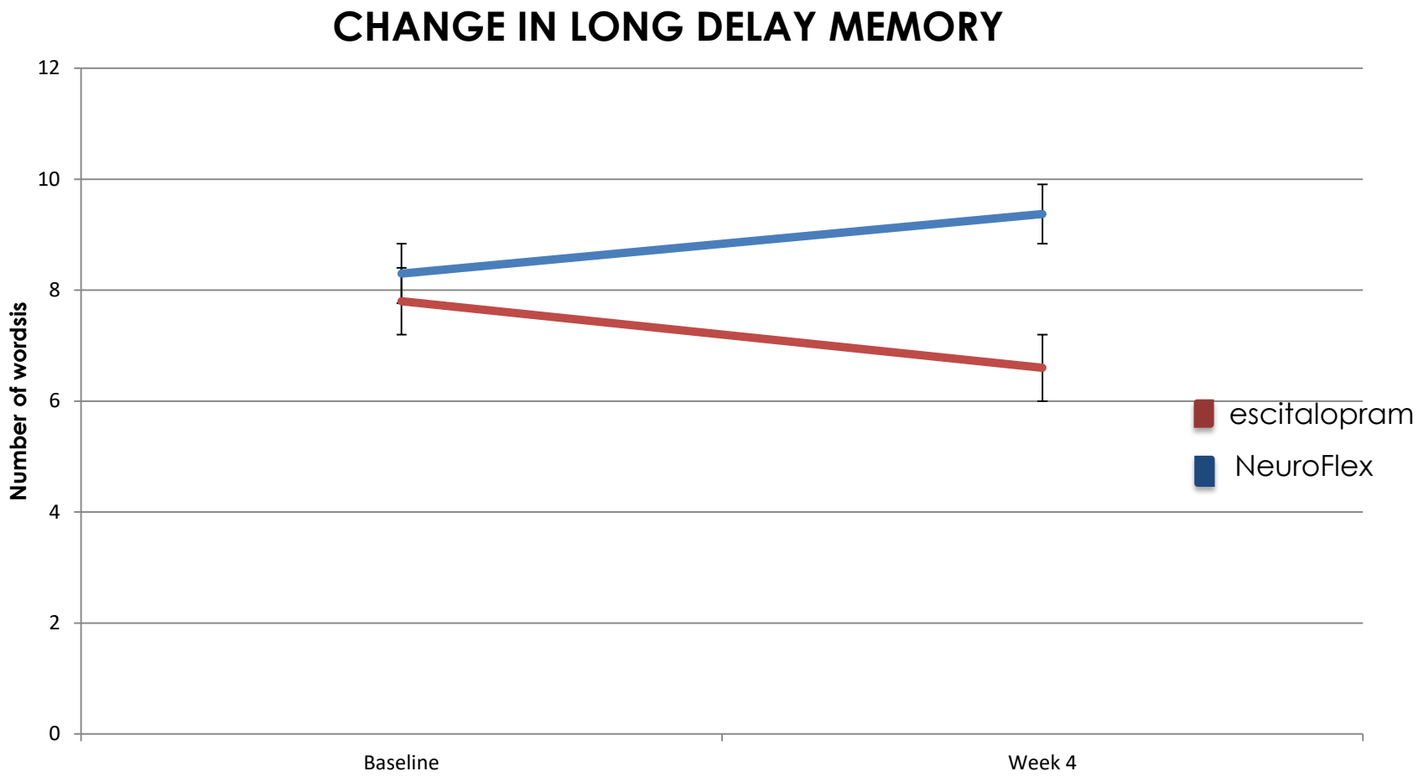
TARGET COGNITIVE FUNCTIONS AND TRANSFER:



*Morimoto, Gunning et al.,AJGP 2020

STROOP: t(26)-3.00; p=.007*; TRAILS: t(28)2.97; p=.007*
FAS: t(28)2.38; p=.03* DIGITS B: t(26)2.59;p=.02*

FAR TRANSFER TO NON-TARGET COGNITIVE FUNCTIONS: NEUROFLEX VS. CONTROL



*Morimoto, Gunning et al.,AJGP 2020

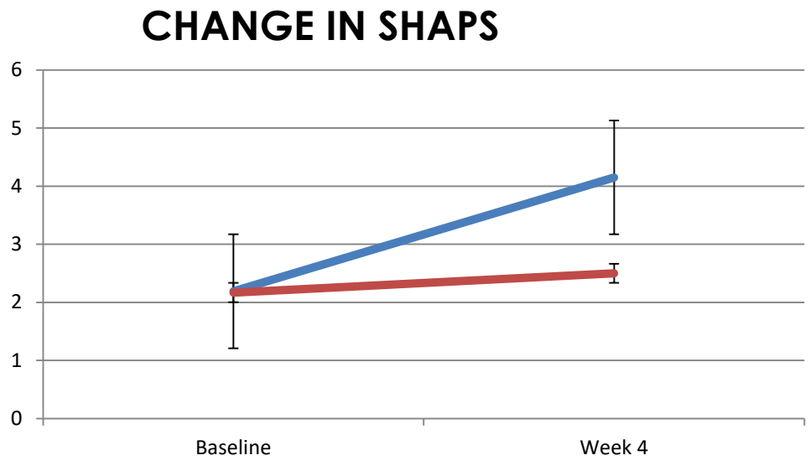
t(28)=2.84; p=.03*

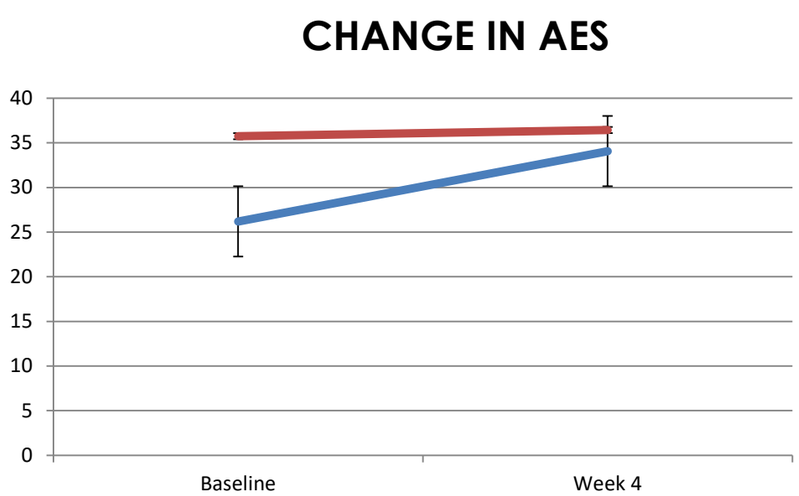
NEUROFLEX IMPROVES **FUNCTIONING** (VS. CONTROL)

ANHEDONIA: t(28)2.63;p=.014*

APATHY: t(28)1.89;p=.07*

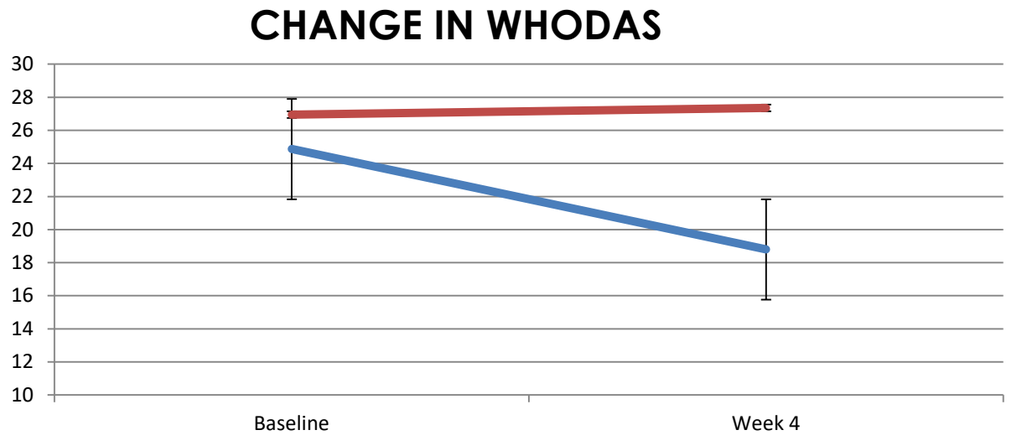
DISABILITY: t(28)2.45;p=.021*





escitalopram

NeuroFlex



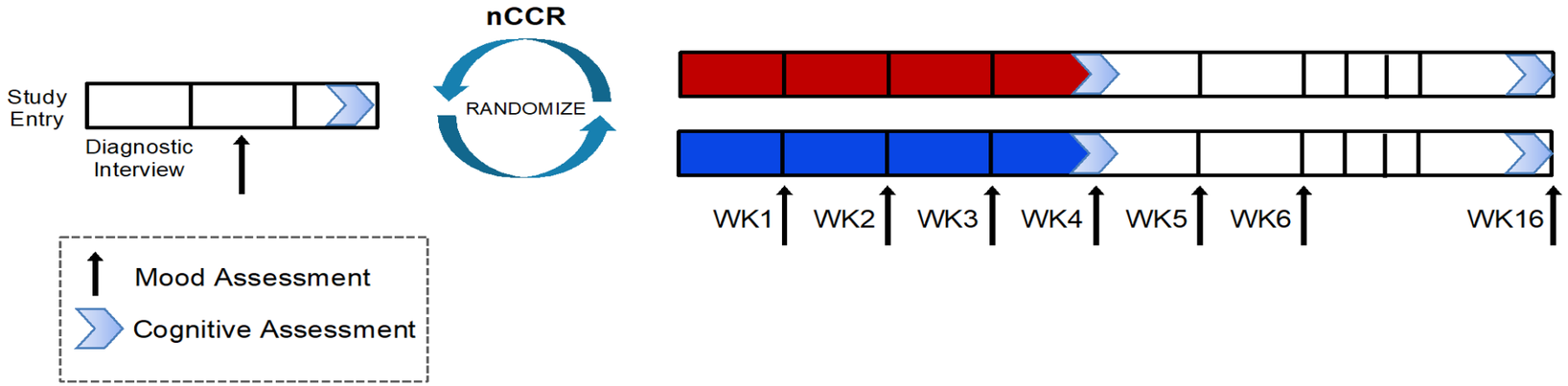
*Morimoto, Gunning et al.,AJGP 2020

NEUROFLEX **EFFECT SIZES**

	Baseline	Week4	statistic	pvalue	d
MADRS			F(1,61.8)=11.37	**.002***	**-.64**
Neuroflex	25.7(8.9)	13.2(5.9)			
Control	25.6(8.2)	18.9(8.0)			
WHODAS			t(28)2.98	**.006***	**-1.17**
Neuroflex	23.87(9.4)	18.8(5.4)			
Control	25.9(9.0)	27.3(8.1)			
StroopCW			t(26)-2.97	**.007***	**-1.21**
Neuroflex	34.4(9.3)	36.4(8.7)			
Control	33.4(9.4)	34.0(9.5)			
TrailsB			t(28)2.2	**.04***	**-.86**
Neuroflex	157.6(101.2)	140.9(102.4)			
Control	150.6(96.2)	158.0(80.2)			
DigitSpan			t(26)2.56	**.02***	**-1.08**
Neuroflex	6.1(2.2)	7.0(2.4)			
Control	6.9(2.2)	6.9(1.7)			
SemanticClus. (StandardScore)	SS	SS	t(26)=-3.12	**.006***	**1.39**
Neuroflex	.56(1.7)	.96(1.5)			
Control	.2(0.9)	-1.0(.85)			
VerbalMemory			t(24)=2.84	**.03***	**-.97**
Neuroflex	8.1(3.8)	9.6(4.9)			
Control	7.8(4.5)	6.6(3.8)			
DesignFluency Switch			t(28)=1.16	.26	**
Neuroflex	5.8(2.6)	6.2(1.3)			
Control	5.9(1.9)	6.0(1.6))			
FAS			t(28)=2.27	**.03***	**-.99**
Neuroflex	34.8(17.2)	41.9(16.4)			
Control	40.3(16.7)	41.0(16.3)			

R01 MH126051 – MULTI-SITE CONFIRMATORY EFFICACY RCT

- $7.5 M Budget
- 5 YR ITERATIVE EFFICACY TRIAL
- SECOND SITE – U of Connecticut
- 250 Treatment Resistant Depressed
- FULL REMOTE Capability
- Pts on a stable dose or OFF SSRI/SNRI



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FUNDING

R01 MH126051 (Morimoto)

K 23 MH 095830 (Morimoto)

UL1TR000457 (Morimoto)

Wheeler Foundation (Morimoto)

UU Development Council (Morimoto)

R01 MH065653 (Alexopoulos)

P30 MH68638 (Alexopoulos)

T32 MH19132 (Alexopoulos)

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HEALTH
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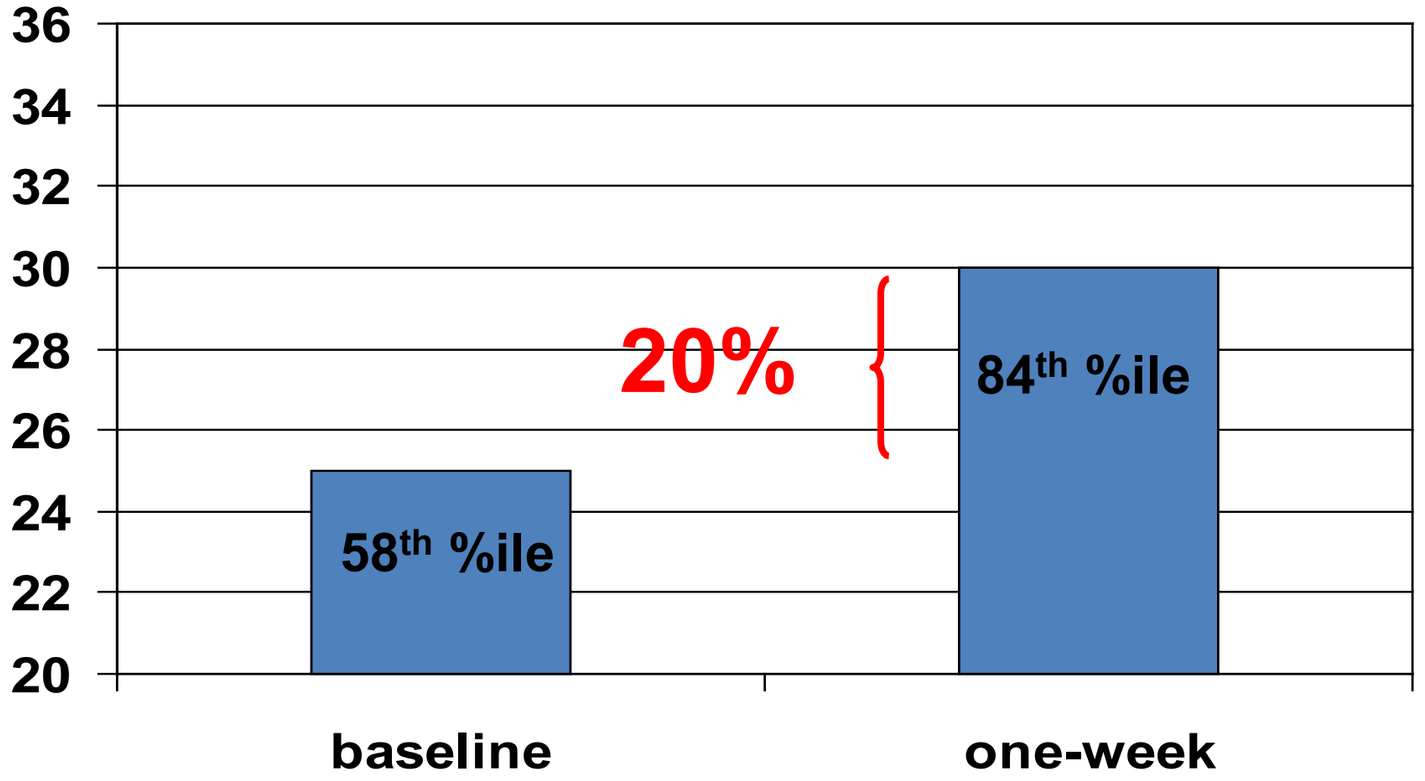
HOW DO YOU GET TO CARNEGIE HALL? PRACTICE, PRACTICE, PRACTICE!

KEVIN DUFF, PH.D.

CENTER FOR ALZHEIMER'S CARE, IMAGING AND RESEARCH (CACIR)

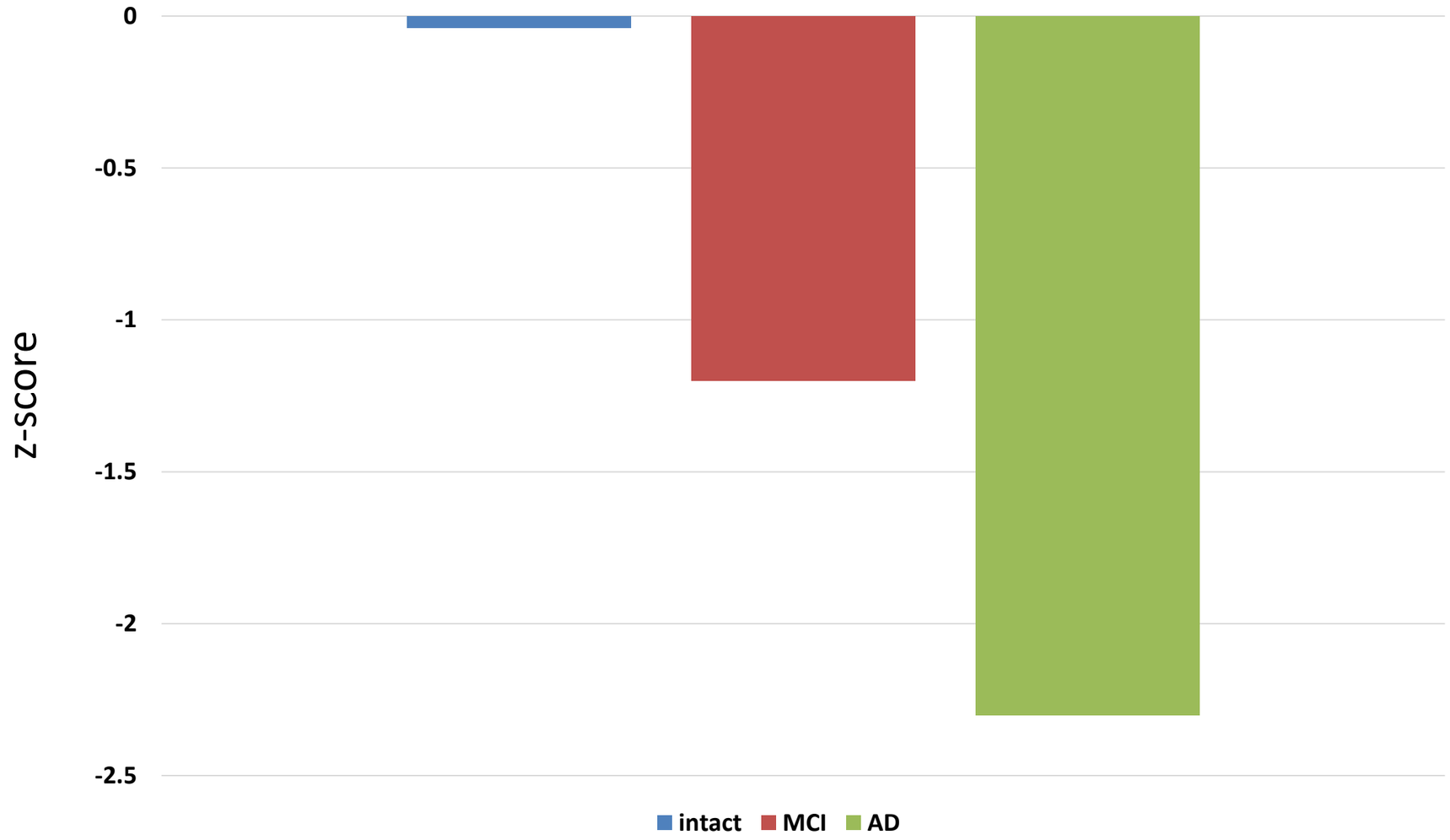
DEPARTMENT OF NEUROLOGY, UNIVERSITY OF UTAH

- Practice effects are improvements in cognitive test scores due to repeated exposure to the same/similar test materials
- Largely considered error



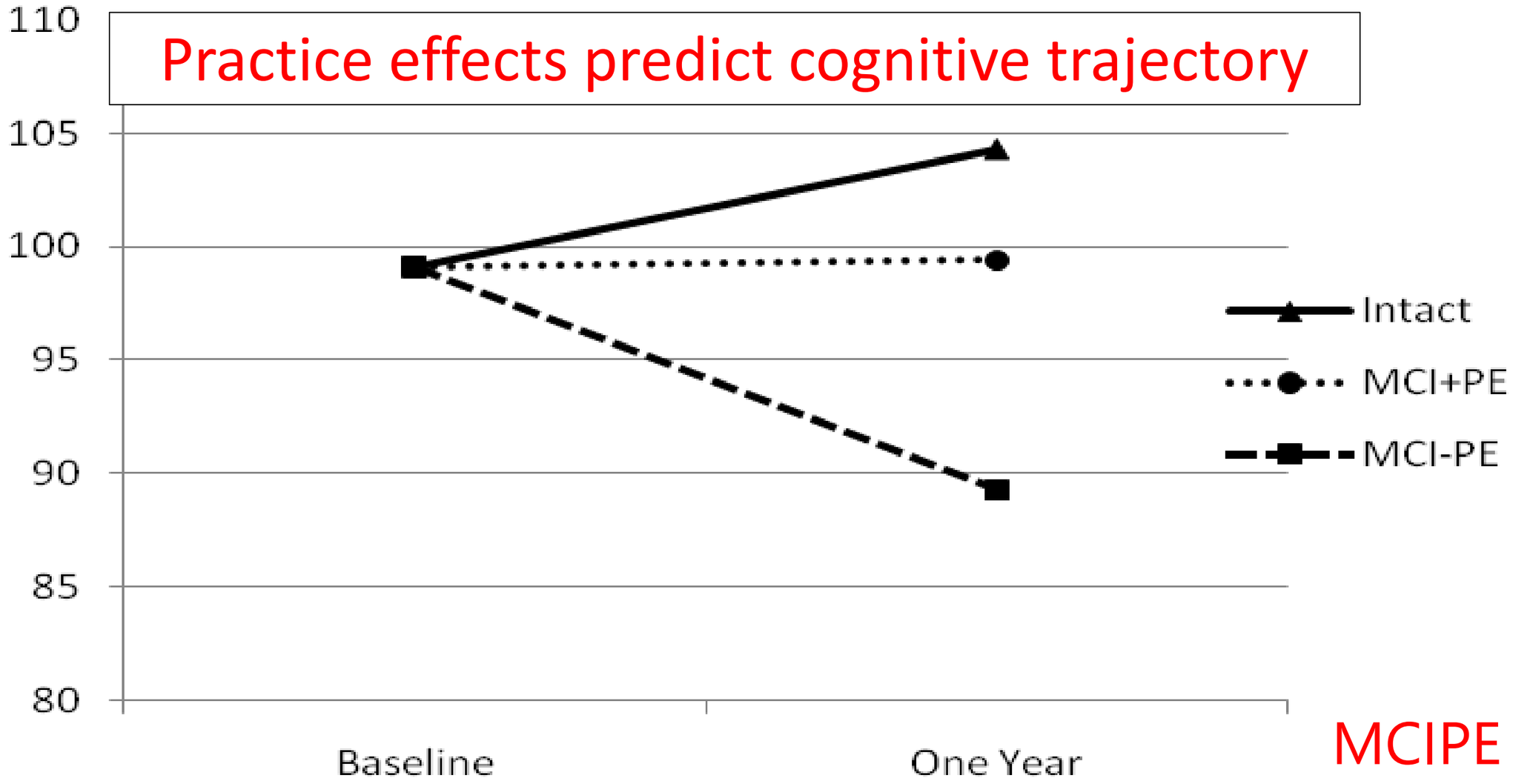
HVLT-R Total Recall in healthy elders

Practice effects are reduced in impaired samples



APPE
Amyloid Positivity & Practice Effects

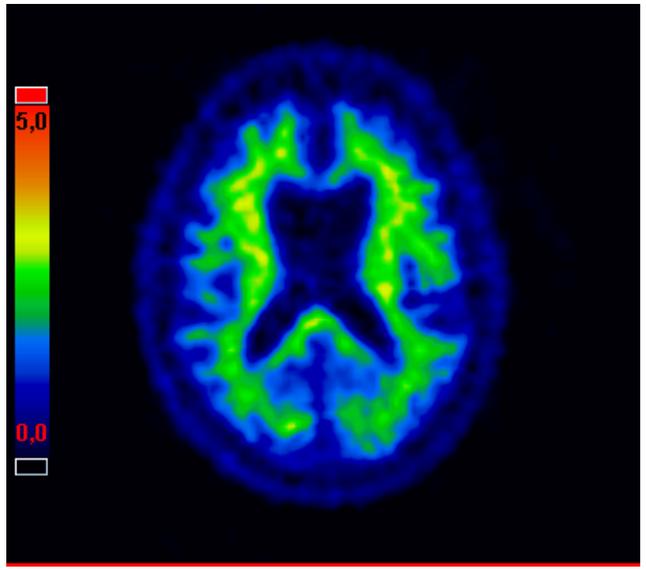
Practice effects predict cognitive trajectory



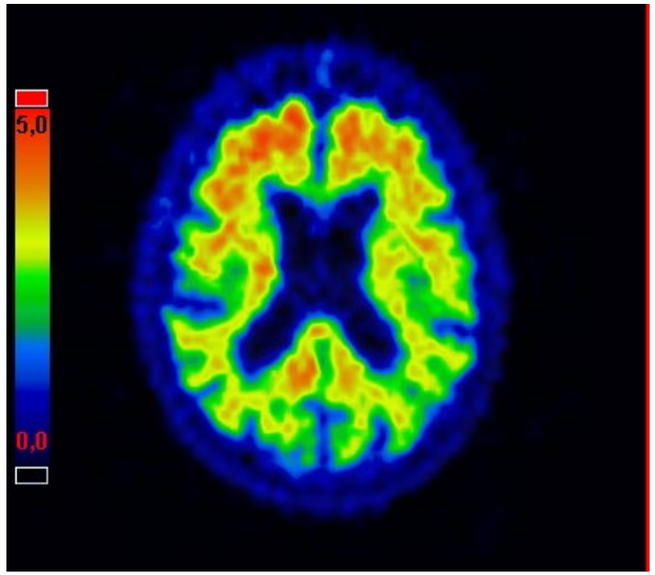
MCIPE

Duff et al. (2011)

Practice effects predict disease pathology



Little amyloid deposition
High practice effects



High amyloid deposition
Low practice effects

- Odds ratio of having a positive amyloid scan was **13.7 times higher** if the individual had low practice effects compared to high practice effects

APPE
Amyloid Positivity & Practice Effects

Duff et al. (2014)

HEALTH
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PE = BIOMARKER IN PRECLINICAL DEMENTIA

PE = COGNITIVE RESILIENCE

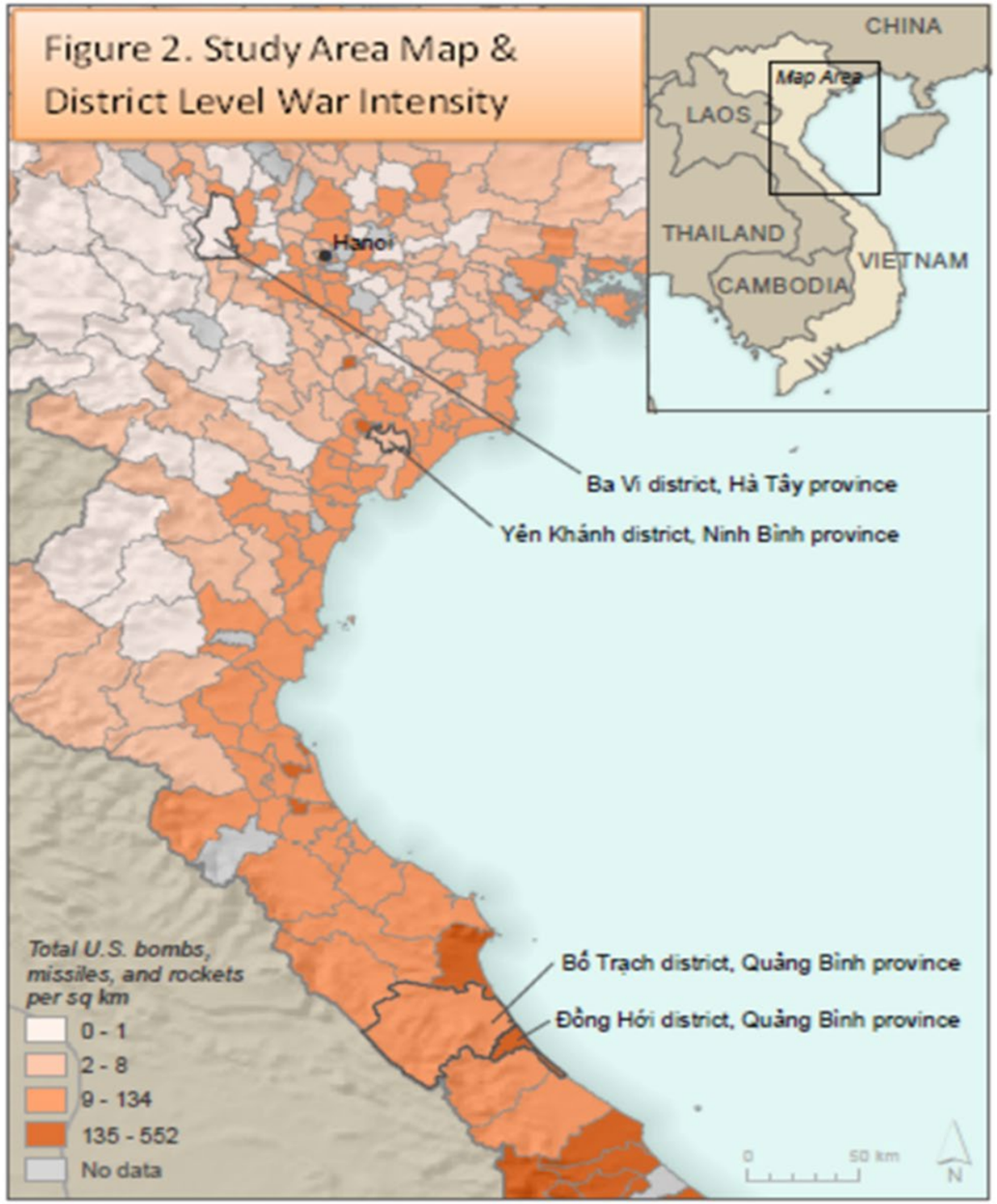
Cognitive Function & ADRD Risk in the Context of Early Life Wartime Stress Exposures

Kim Korinek, Department of Sociology & The Asia Center, University of Utah

Presentation for Center on Aging Retreat, May 25, 2022

Vietnam Health & Aging Study, 2018 (www.vhas.utah.edu)

- In-person interview & biomarker data collection (N=2,447, age 60+) in northern Viet Nam
  - 'American War' cohort – teens/young adults in 1965-75
  - Multi-stage probability sampling; purposive selection of 4 districts → differential exposure to bombing, wartime stress
  - Wave I (Summer 2018) & Wave II (Summer 2021, 2022); ~12% attrition due to mortality, loss to follow-up
- Omnibus survey; early life & wartime stressors, self-reports of health status, cognitive performance tests (MMSE, CSI-D)
- Biomarker collection (venous blood, hair, anthropometrics) in full sample to assess disease risk; physiological & cognitive aging



The "long arm of war" and cognitive health in low- and middle-income countries (LMICS)

- Alzheimer's Disease (AD) & other neuro disorders, are a global epidemic & substantial share of disease burden in LMICs
- Research on AD's experiential & environmental correlates in LMICs is sparse
- Armed conflict: "environment" of "extreme, violent nature" with clusters of stressors that may accelerate aging[1]
- Benign & adverse life course exposures (e.g., death in family) affect AD risk, in part via "cognitive reserve"[2,3,4]
- Stressed nutritional environments in conflict-affected LMICs underlie deficiencies/illnesses that heighten ADRD[5]

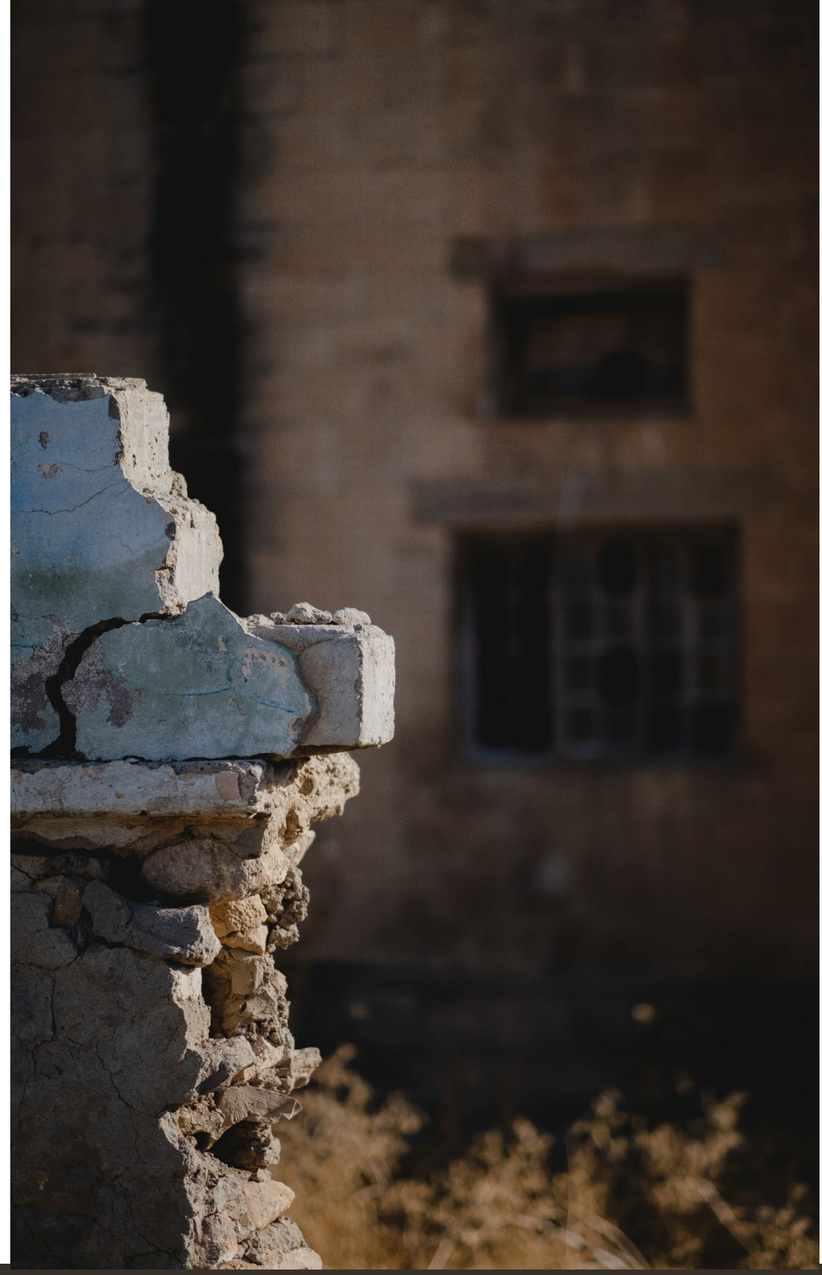


Figure 1. MMSE Cognitive Score by Respondent Age, VHAS 2018

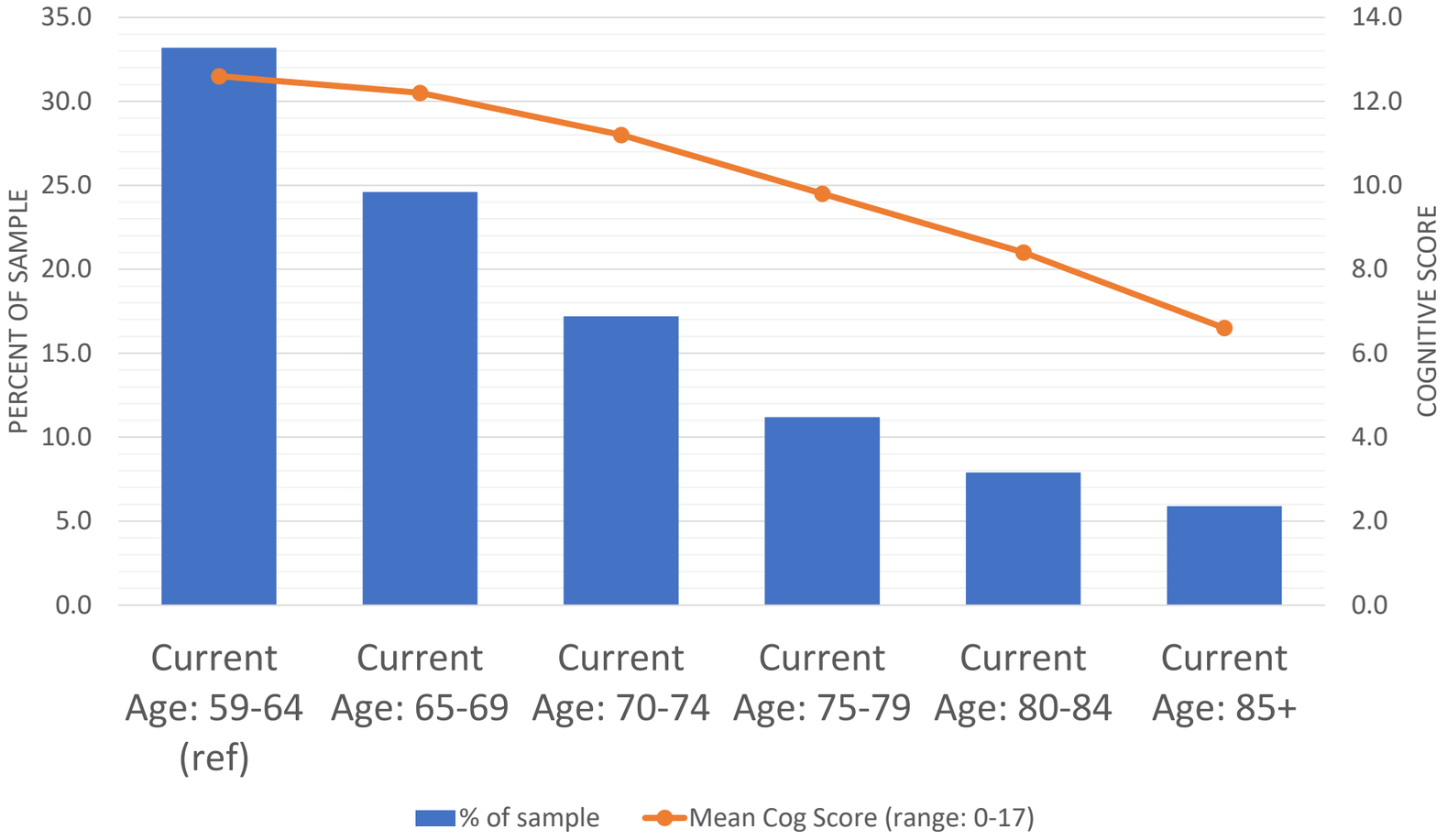


Figure 2. MMSE Cognitive Score by Nutrition/Food Insecurity Covariates, VHAS 2018

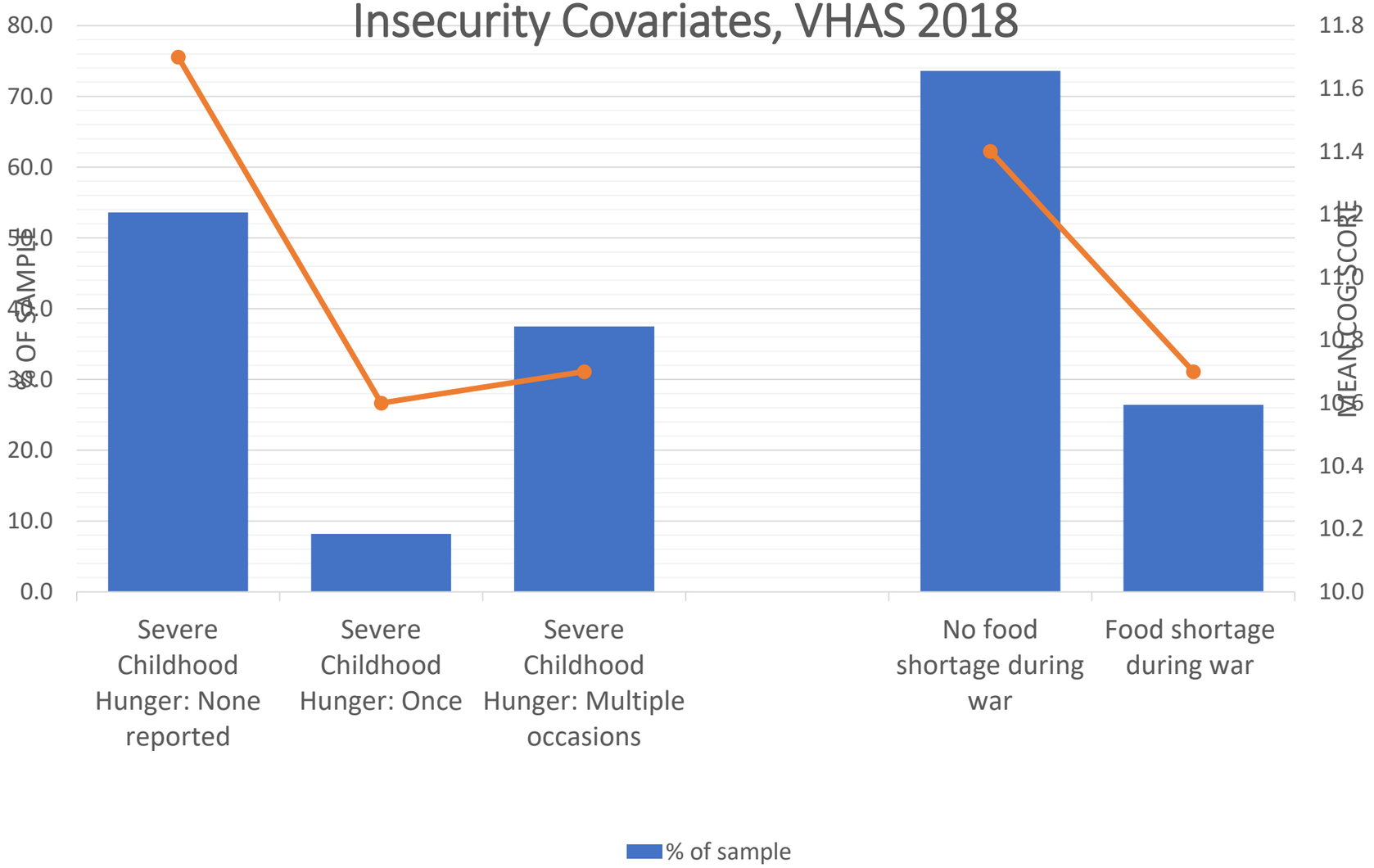


Figure 3. MMSE Cognitive Score by War Stress Exposure Covariates, VHAS 2018

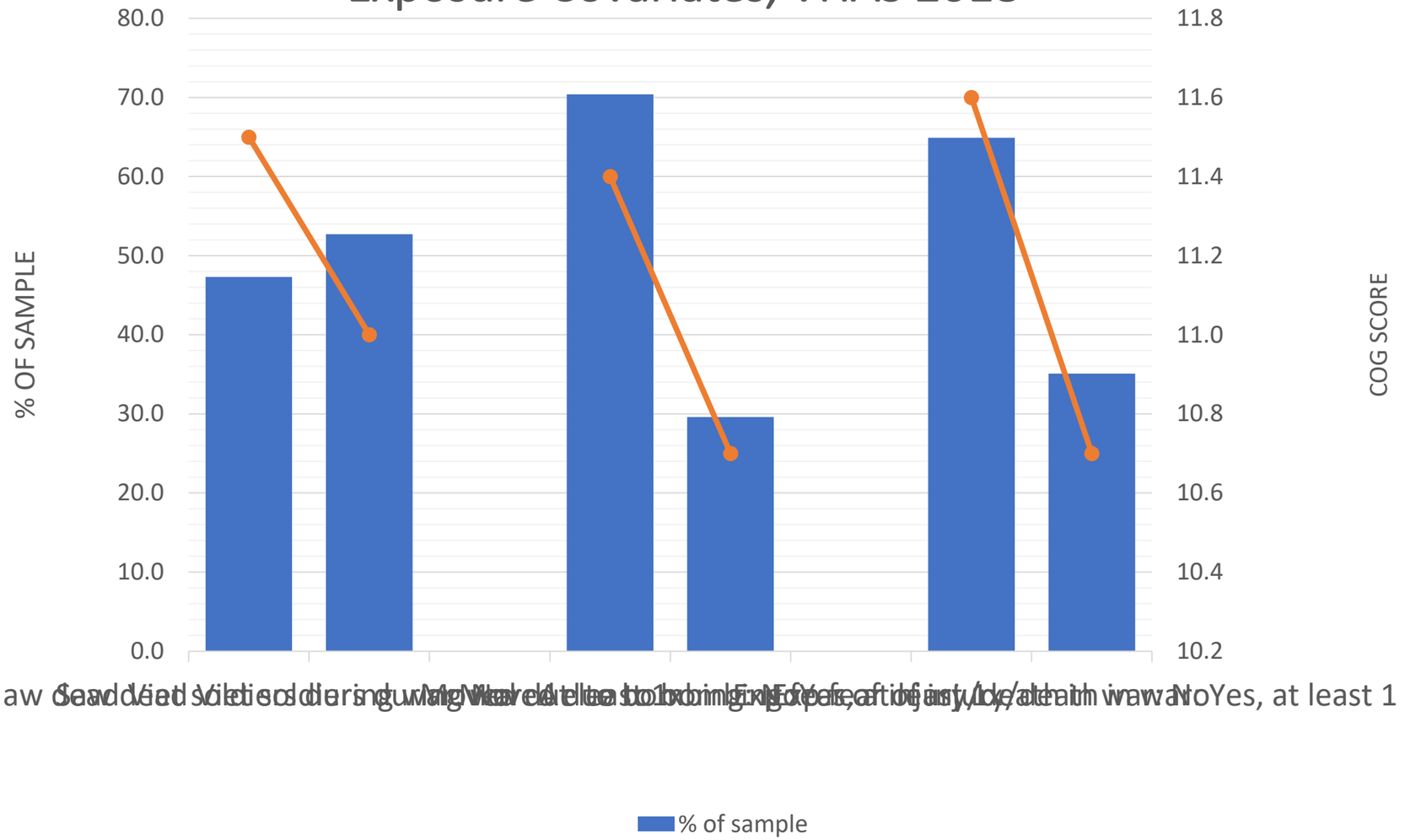


Figure 4. MMSE Cognitive Score by Recent PTSD Symptoms, VHAS 2018

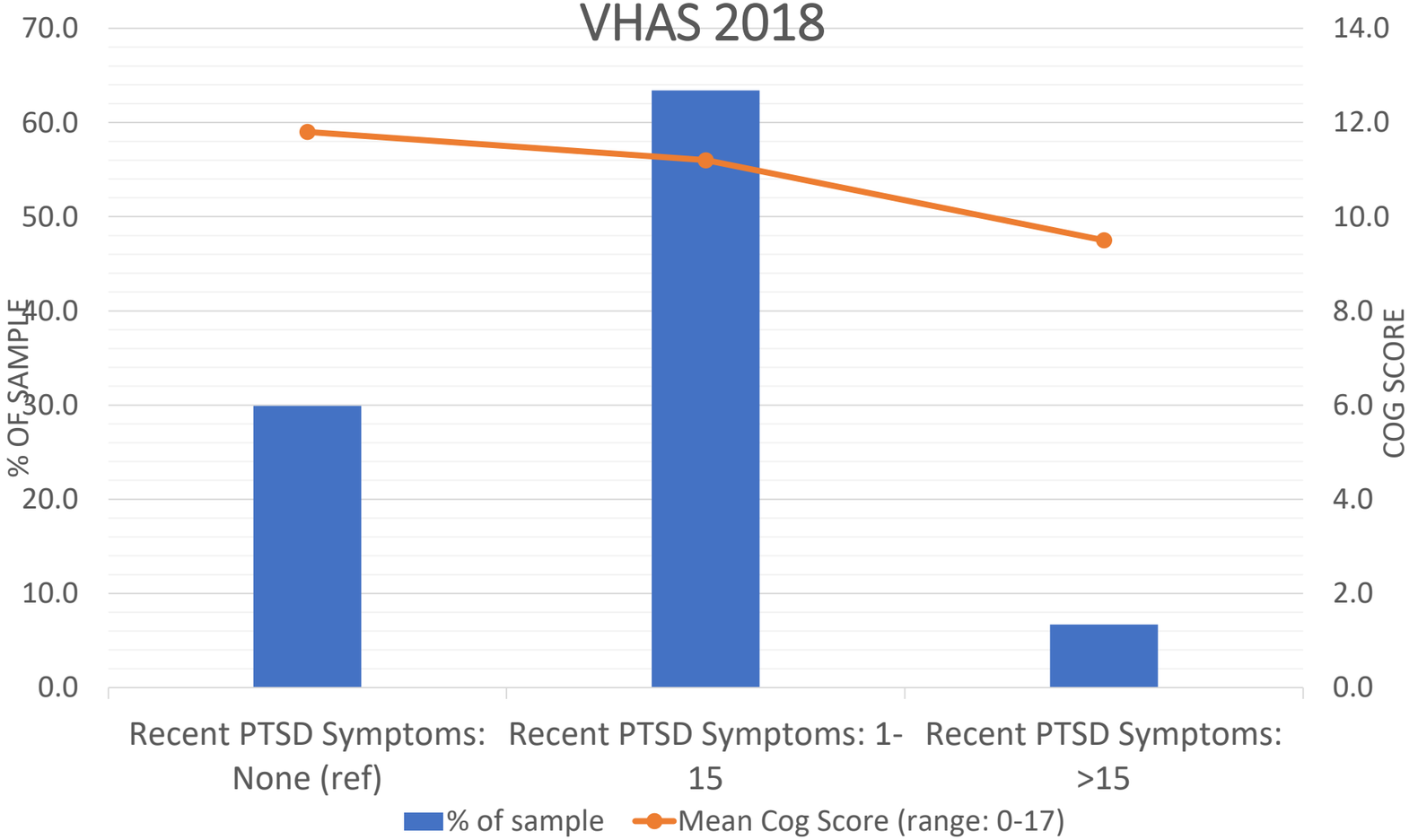


Table 1. Survey-adjusted Poisson Regression Results: Modified MMSE Cognitive Score, Vietnamese Older Adults 60+

	Model A	Model B	Model C
Nutrition/food insecurity covariates	b	b	b
Experience of Severe Childhood Hunger: Only once (Ref: None reported)	-0.050+	-0.051+	-0.048
Experience of Severe Childhood Hunger: Multiple occasions (Ref: None reported)	-0.031*	-0.032*	-0.028+
Experienced weakness/illness due to food shortage during war	-0.030+	-0.031+	-0.023
Weight Status: Presently Underweight (BMI <=18.5) (ref: Normal or overweight)	-0.054*	-0.053*	-0.049*
War-related stressor covariates			
Family member deaths due to war (Count)	-0.009	-0.009	-0.005
Saw dead or seriously injured civilians during war at least once (Ref: never)	-0.005	-0.007	0.005
Saw dead/seriously injured Vietnamese soldiers during war at least once (ref: never)	-0.016	-0.033+	-0.030*
Moved due to bombing during war at least once (ref: never)	0.008	0.008	0.003
Experienced fear of being injured or killed during war at least once (ref: never)	-0.023	-0.024	-0.008
Experienced exposure to agent orange (self-reported) at least once (Ref: never)	0.005	-0.003	0.015
Combat covariates			
Engaged in combat patrols during war at least once (ref: Never)		0.042*	0.045*
Had a friend shot near them in battle at least once (ref: never)		0.009	0.015
PTSD covariate			
Recent PTSD symptoms (count)			-0.005**
Health Status Covariates			
CVD Conditions (Count)			-0.014*
Elevated A1c level (ref: normal)			-0.063**
Physical exercise: Infrequently (Less than weekly) (ref: never)			0.035*
Physical exercise: Frequently (Daily/almost daily) (ref: never)			0.074***
Psychosocial covariates			
Recent stressful life events (count)			-0.022**
Family-based emotional support index (reverse coded)			-0.038+
N	2135	2135	2135

+ p<=.10; * p<=.05; ** p<=.01; *** p<=.001

Vietnam Health and Aging Study, NIA ADRD Supplement (2021-22)

Specific Aims:

a) Implement and validate a survey-based cognitive test (Community Screening Instrument for Dementia, CSI-D) to measure cognitive impairment and dementia within a sample of Vietnamese older adults;

b) Develop and test the properties of a modified blood-based biomarker panel for ADRD;

c) While adjusting for established risk factors, analyze associations among early-life war exposures and biological and cognitive performance assessments of ADRD. Focal war exposures include combat and associated forms of violence; environmental adversities including severe food shortage; and contact with Agent Orange.

NIA ADRD Supplement – Proposed Data Collection & Analyses

- **Sample:** Stratified random subsample of VHAS Wave II participants (N=450); strata defined by war-stress exposure severity, gender & military service
- **Implement additional cognitive performance test, CSI-D**
- **Assay blood-based biomarkers for ADRD Risk/Screening**
  - O'Bryant et al. ADRD proteomic biomarker profile[6,7,8]
  - Homocysteine & life course malnutrition/helminths[9,10]
- **Analysis plans:**
  - Validation/replication of O'Bryant et al proteomic profiles & CSI-D
  - Examine life course stress, malnutrition & disease environment correlates of ADRD risk; longitudinal analysis of cognitive decline in context of early life & recent life event stressors

Acknowledgements

- VHAS is funded by a grant from the National Institutes of Health/National Institute on Aging (R01-AG052537).
- Research Partners:
  - Hanoi Medical University, Viet Nam
  - Mount Saint Vincent University, Halifax, Nova Scotia
  - National University of Singapore
  - Center for Studies in Demography and Ecology, University of Washington.

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HEALTH
UNIVERSITY OF UTAH

KAREN SCHLIEP, PHD MSPH

Assistant Professor
Family and Preventive Medicine

Research Interests

Predicting dementia from health records

Models evaluated with nested cross-validation yielded an AUC of 72% for dementia, 69% sensitivity and 64% specificity.

AUCs higher for AD versus related dementia and using multiple data sources.

	Electronic Health Record Data Source			
	All	Medicare	Inpatient	Outpatient
	Area under the curve (sensitivity, specificity)			
Dementia	0.72 (0.69, 0.64)	0.68 (0.64, 0.62)	0.66 (0.56, 0.64)	0.66 (0.66, 0.59)
Alzheimer's Disease	0.70 (0.62. 0.68)	0.69 (0.64, 0.65)	0.67 (0.61, 0.64)	0.67 (0.59, 0.64)
Related Dementia	0.61 (0.53, 0.64)	0.62 (0.55, 0.59)	0.60 (0.41, 0.60)	0.53 (0.52, 0.53)

KEY FEATURES among 2000 evaluated:

Age at baseline
Hypertension
Chronic kidney disease
Heart failure
Pulmonary disease
Atrial fibrillation
Vascular disease
Fibromyalgia, chronic pain
Fatigue
Anemia
Gastrointestinal disorders

GSA 2021 ANNUAL SCIENTIFIC MEETING
Disruption to Transformation: Aging in the "New Normal"

Sex differences in dementia risk

Schliep *et al. Biology of Sex Differences* (2022) 13:16
https://doi.org/10.1186/s13293-022-00425-3

Biology of Sex Differences

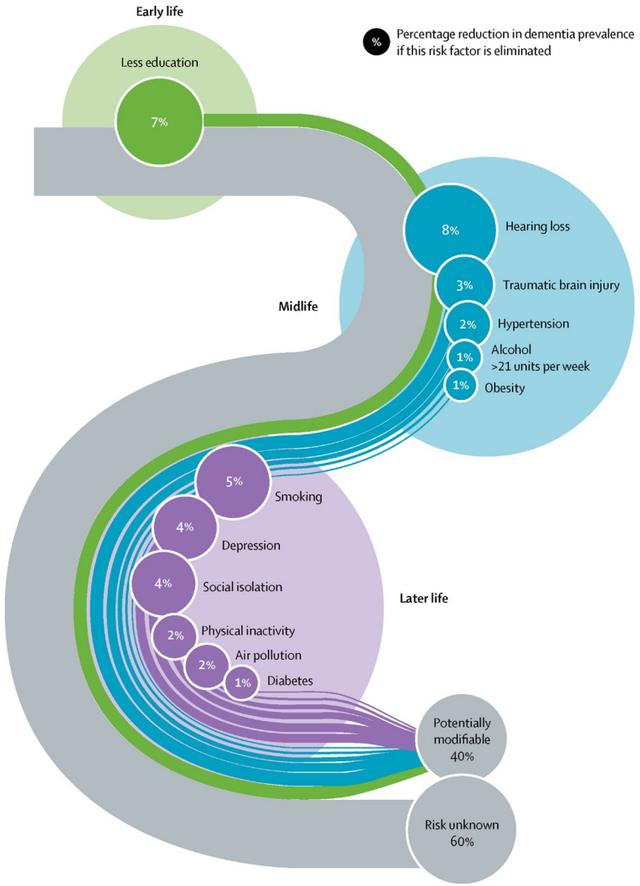
RESEARCH Open Access

Overall and sex-specific risk factors for subjective cognitive decline: findings from the 2015–2018 Behavioral Risk Factor Surveillance System Survey

Karen C. Schliep[1], William A. Barbeau[2], Kristine E. Lynch[3,4], Michelle K. Sorweid[5], Michael W. Varner[6], Norman L. Foster[7] and Fares Qeadan[2,8*]

Table 4 Adjusted modifiable risk factors for subjective cognitive decline in U.S. adults aged 45 years and older, 2015–2018

Risk factor	Adj RR[1] (95% CI[2])	Prevalence (%)	Communality[3] (%)	Adj PAF[4] (%)	Weighted Adj PAF[5] (%)
All adults					
Limited education[a]	1.12 (0.99–1.26)	4.78	66.19	0.59	0.20
Deafness[b]	2.01 (1.82–2.19)	9.66	39.81	8.87	2.96
Social isolation[c]	2.46 (2.15–2.77)	52.38	70.97	43.28	14.44
Depression[d]	3.12 (2.95–3.29)	18.76	56.15	28.47	9.50
Smoking[e]	1.20 (1.12–1.27)	15.46	64.26	2.97	0.99
Physical inactivity[f]	1.32 (1.25–1.39)	30.76	39.83	8.92	2.98
Obesity[g]	1.14 (1.08–1.19)	32.97	59.06	4.32	1.44
Hypertension[h]	1.28 (1.20–1.36)	50.99	57.99	12.57	4.20
Diabetes[i]	1.28 (1.21–1.35)	17.76	57.65	4.78	1.59
			Overall[6]	74.13	38.30
Women					
1 Limited education[a]	1.18 (0.97–1.38)	4.49	58.99	0.79	0.26
Deafness[b]	2.09 (1.79–2.38)	7.46	48.90	7.50	2.44
Social isolation[c]	2.48 (2.07–2.89)	55.70	69.20	45.21	14.72
Depression[d]	3.26 (3.01–3.50)	22.92	57.33	34.08	11.09
Smoking[e]	1.29 (1.18–1.40)	14.41	65.83	4.00	1.30
Physical inactivity[f]	1.32 (1.23–1.42)	32.25	41.35	9.45	3.07
Obesity[g]	1.14 (1.06–1.22)	32.08	64.84	4.37	1.42
Hypertension[h]	1.26 (1.15–1.37)	49.57	58.25	11.33	3.69
Diabetes[i]	1.32 (1.22–1.42)	16.73	59.35	5.10	1.66
			Overall[6]	76.81	39.65
Men					
Limited education[a]	1.05 (0.87–1.24)	5.11	26.67	0.28	0.11
Deafness[b]	1.93 (1.68–2.17)	12.22	20.30	10.16	3.86
Social isolation[c]	2.47 (1.98–2.96)	47.68	71.96	41.20	15.66
Depression[d]	3.23 (2.94–3.51)	13.94	39.75	23.68	9.00
Smoking[e]	1.11 (1.01–1.22)	16.68	50.75	1.86	0.71
Physical inactivity[f]	1.32 (1.22–1.42)	29.03	35.75	8.50	3.23
Obesity[g]	1.13 (1.04–1.21)	33.93	48.34	4.14	1.58
Hypertension[h]	1.32 (1.20–1.44)	52.63	57.98	14.44	5.49
Diabetes[i]	1.24 (1.14–1.34)	18.95	54.94	4.37	1.66
			Overall[6]	71.68	41.30



Livingston et al, Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet. 2020 Aug 8;396(10248):413-446. doi: 10.1016/S0140-6736(20)30367-6. Epub 2020 Jul 30. PMID: 32738937; PMCID: PMC7392084.

Reproductive health and future dementia

Women with, versus without HDP, had a 1.4 fold higher hazard for dementia. >40% of the effect could be explained by mid-life hypertension or stroke.

	All-cause Dementia		Vascular Dementia		Alzheimer's Disease		Other Dementia	
	Number of Women; Adjusted Hazard Ratio (95% CI)							
HDP	827	1.37 (1.26, 1.50)	55	1.64 (1.19, 2.26)	178	1.04 (0.87, 1.24)	594	1.49 (1.34, 1.65)
No HDP	1596	1.00	97	1.00	410	1.00	1098	1.00

	Direct Effect	Indirect Effect	% Mediated
	Adjusted Hazard Ratio (95% CI)		
Myocardial infarction	1.40 (1.37, 1.43)	1.09 (1.06, 1.12)	24%
Ischemic heart disease	1.40 (1.37, 1.44)	1.08 (1.06, 1.11)	22%
Heart failure	1.38 (1.35, 1.42)	1.07 (1.03, 1.10)	20%
Stroke	1.27 (1.25, 1.29)	1.20 (1.18, 1.23)	49%
Chronic kidney disease	1.35 (1.32, 1.38)	1.14 (1.11, 1.17)	35%
Hypertension	1.21 (1.19, 1.24)	1.14 (1.12, 1.17)	46%
Anxiety	1.38 (1.35, 1.41)	1.10 (1.08, 1.13)	27%
Depression	1.49 (1.40, 1.57)	1.02 (0.96, 1.08)	6%

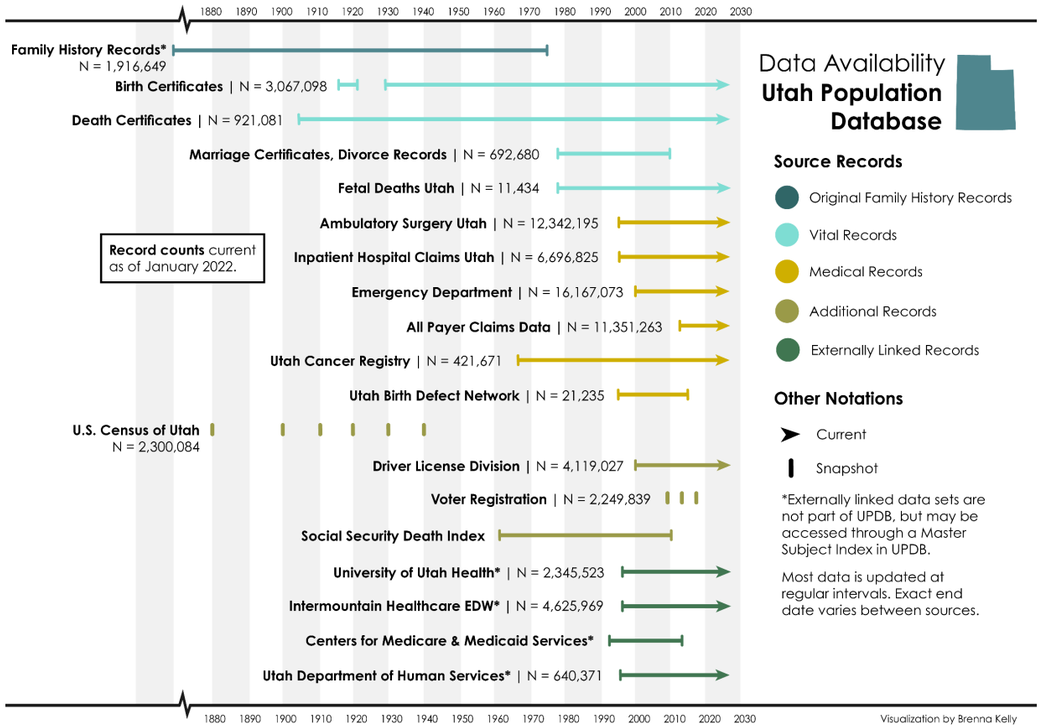
Hazard ratio models adjusted for maternal 5-year age groups, year of childbirth (within 1 year), and parity (1, 2, 3, 4, ≥5) at the time of the index pregnancy.

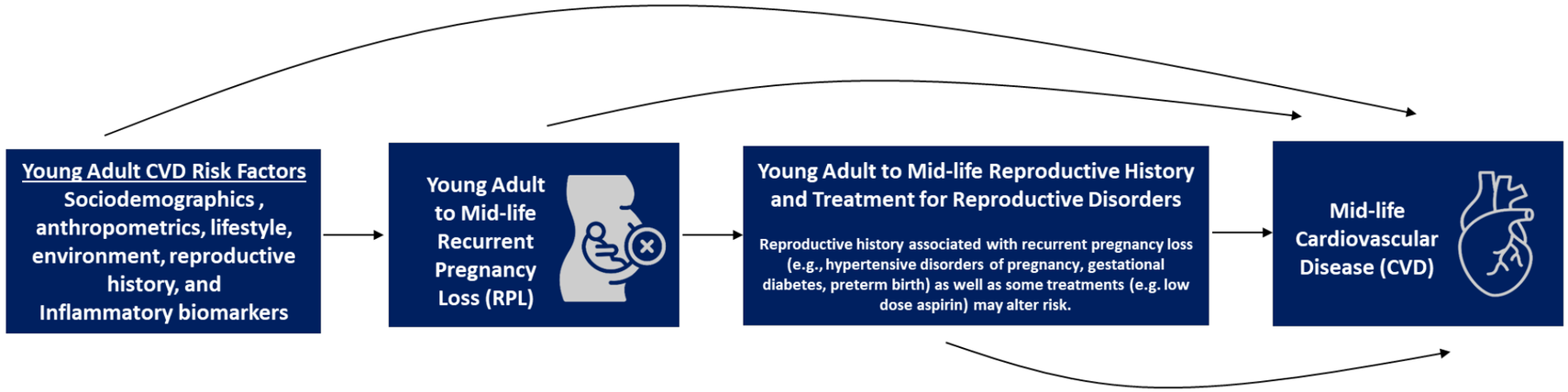
GSA 2021 ANNUAL SCIENTIFIC MEETING

Disruption to Transformation: Aging in the "New Normal"

Areas for collaboration

Lifecourse epidemiology leveraging UPDB and nested research studies





Pepper Center

BENEFIT TO MY RESEARCH?

- **Clinical core:** Potential for retrospective study on reproductive health and cognitive resilience
- **Data and biomarker core:** Underlying predisposition vs reproductive events themselves cause for dementia. Novel measures of cardiometabolic risk factors and expertise on CVD and dementia outcomes.
- **Caregiver core:** Ability to support data capture of exposures and outcomes of interest

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https://medicine.utah.edu/dfpm/research/life-course-epi

HEALTH
UNIVERSITY OF UTAH

Thanks!

Novel Metrics of Brain Dynamics in Alzheimer's Disease

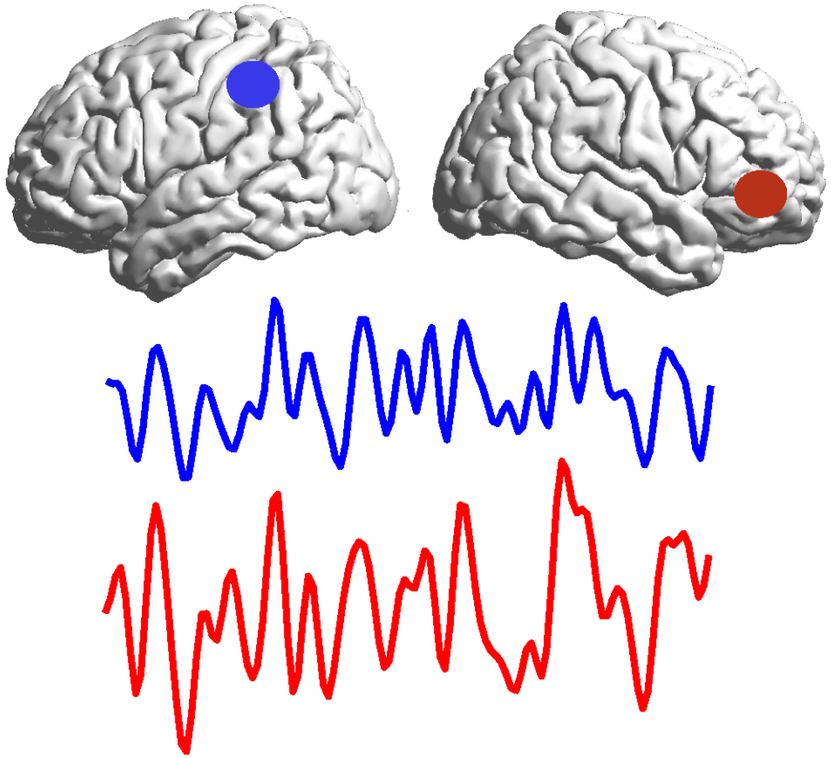
Jace King, MBA, PhD
Research Assistant Professor
Radiology & Imaging Sciences

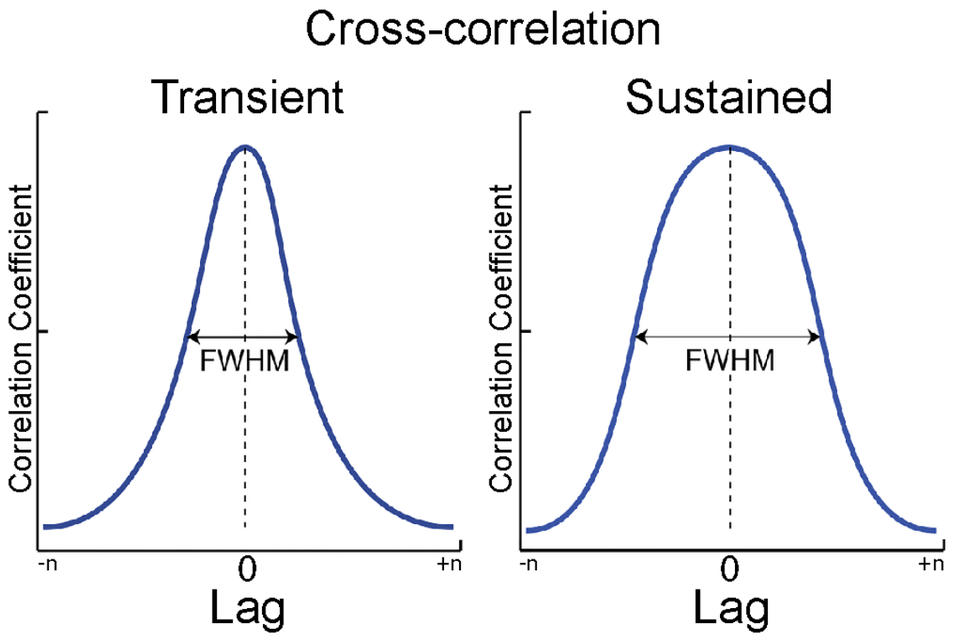
RESEARCH INTERESTS

- Brain Network Laboratory
  - Multimodal neuroimaging (MRI, fMRI, DTI)
  - Autism spectrum disorder
  - Brain effects of cannabinoids
  - Alzheimer's disease

- Novel metrics of brain dynamics in Alzheimer's disease
  - Longitudinal analysis of neuroimaging and neuropsychological data

NOVEL METRICS – SUSTAINED CONNECTIVITY





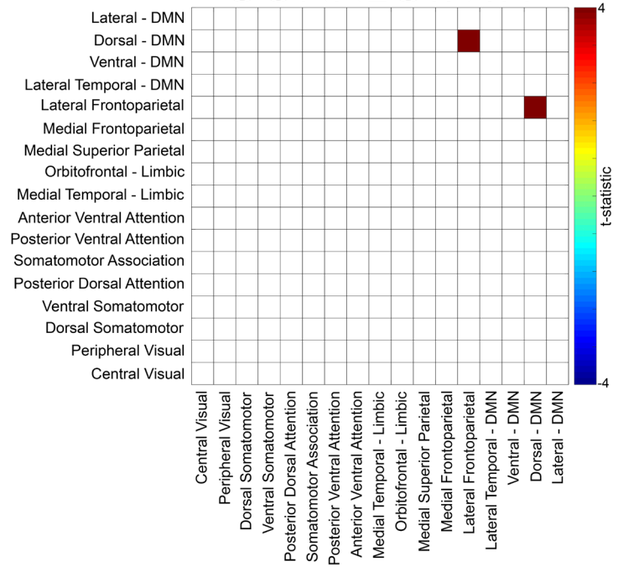
SUSTAINED CONNECTIVITY IS ASSOCIATED WITH COGNITIVE DECLINE

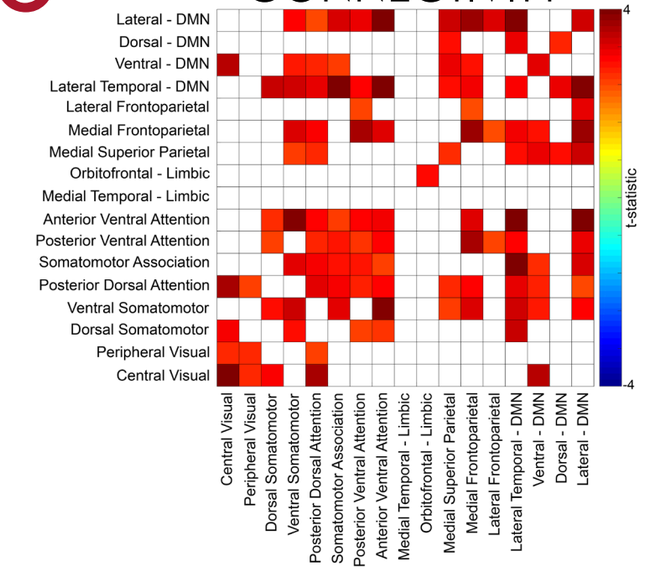
FUNCTIONAL CONNECTIVITY

VS

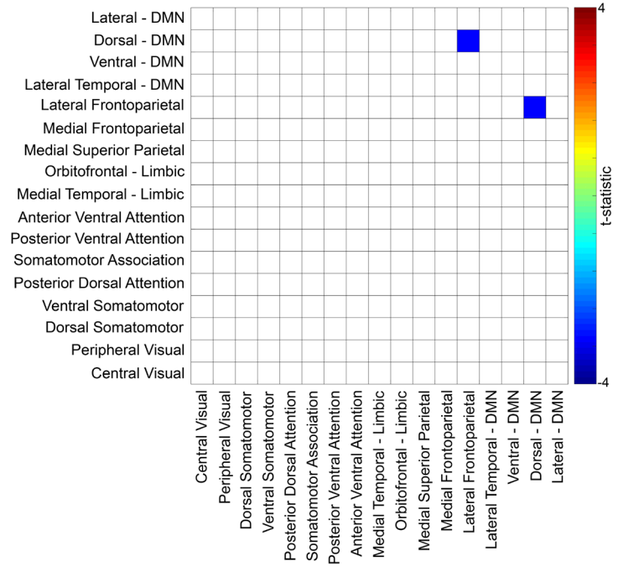
SUSTAINED CONNECTIVITY

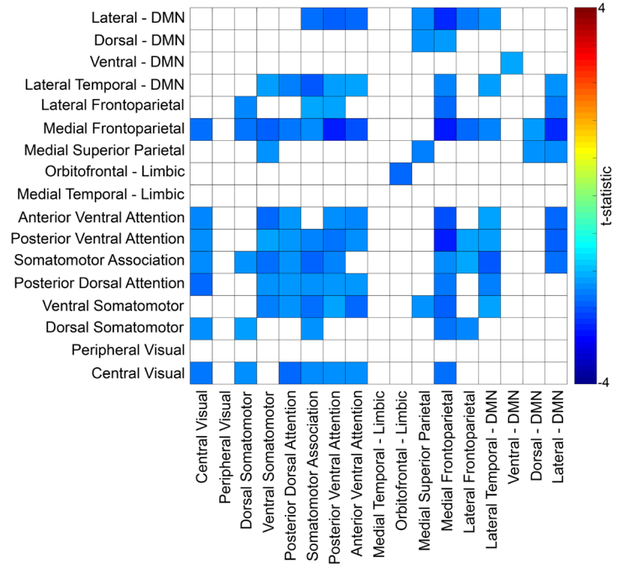
ACROSS GROUP





RBANS TOTAL SCORE





IDENTIFYING AREAS FOR COLLABORATION

- What I can offer
  - Imaging before/during/after intervention
  - Image analysis
  - Neuropsychological assessment
- What I would benefit from
  - Recruitment (participant registry)
  - Data management
  - Study design/analysis advice

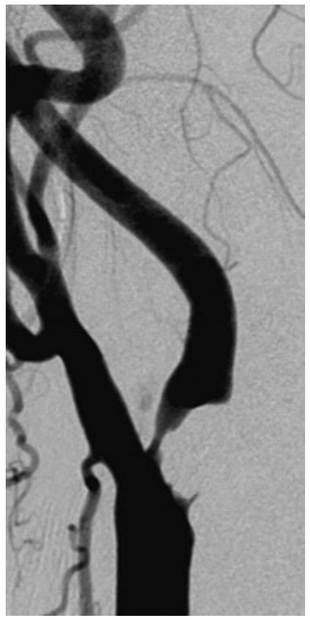
Human Brain Vascular Imaging and Quantitative Analysis

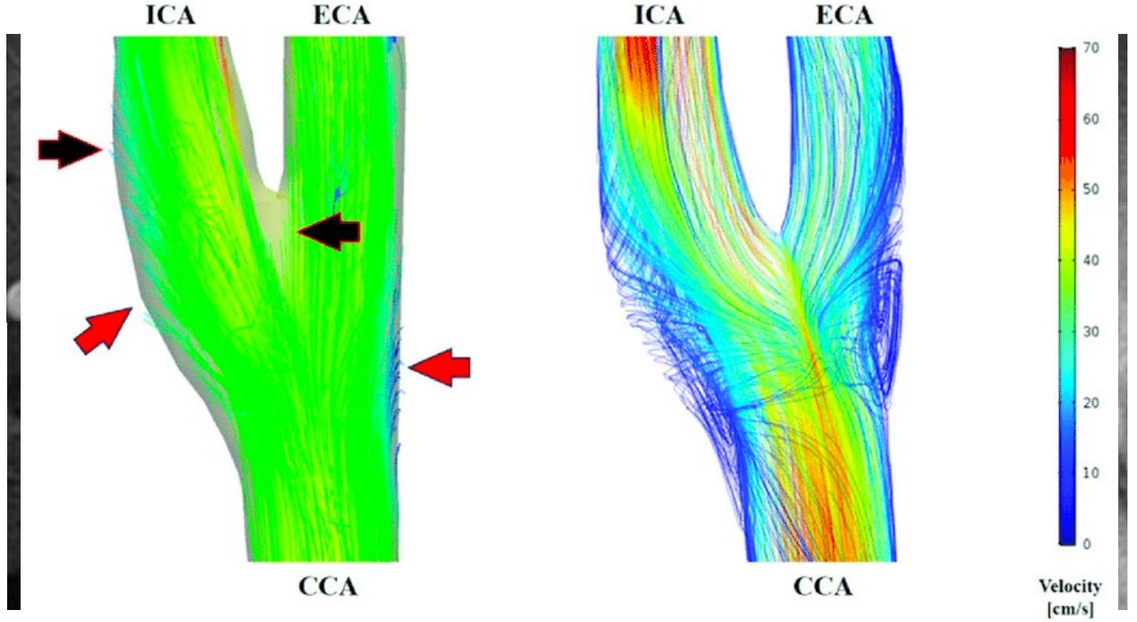
Chun Yuan, Ph.D.

Professor, Radiology and Imaging Sciences

Adjunct Professor, Biomedical Engineering and Biomedical Informatics

Vascular Imaging Has Evolved Over Time



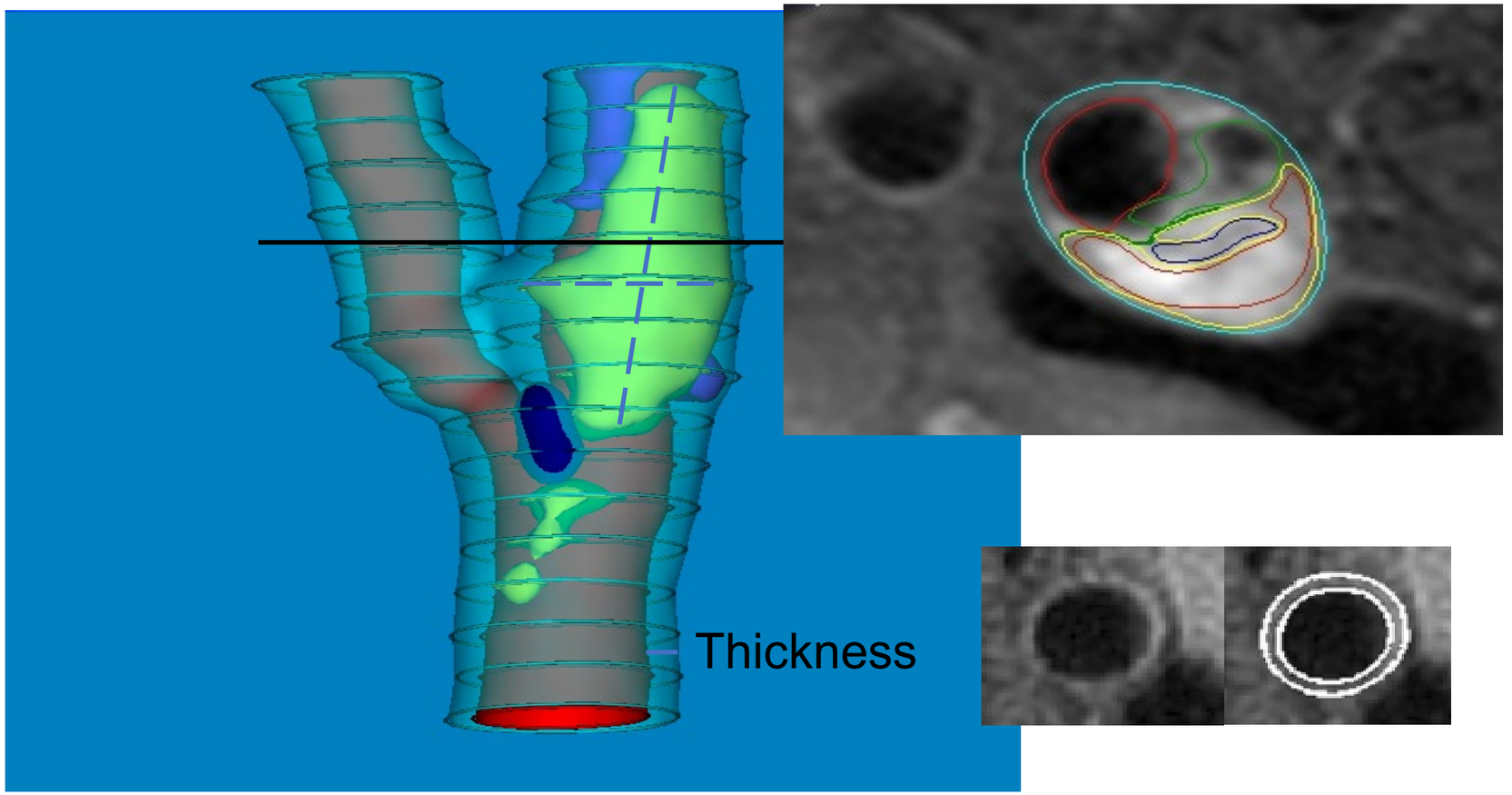


Key I — From luminal stenosis to vessel wall imaging

Key II — From vulnerable plaque imaging to blood flow to vessel wall compliance

Vessel Wall and Atherosclerosis – Quantitative Analysis

- Wall thickness
- AREA
  - LUMEN
  - WALL
  - NECROTIC CORE
  - HEMORRHAGE
  - CALCIFICATIONS
- VOLUME
  - PLAQUE
  - COMPONENTS

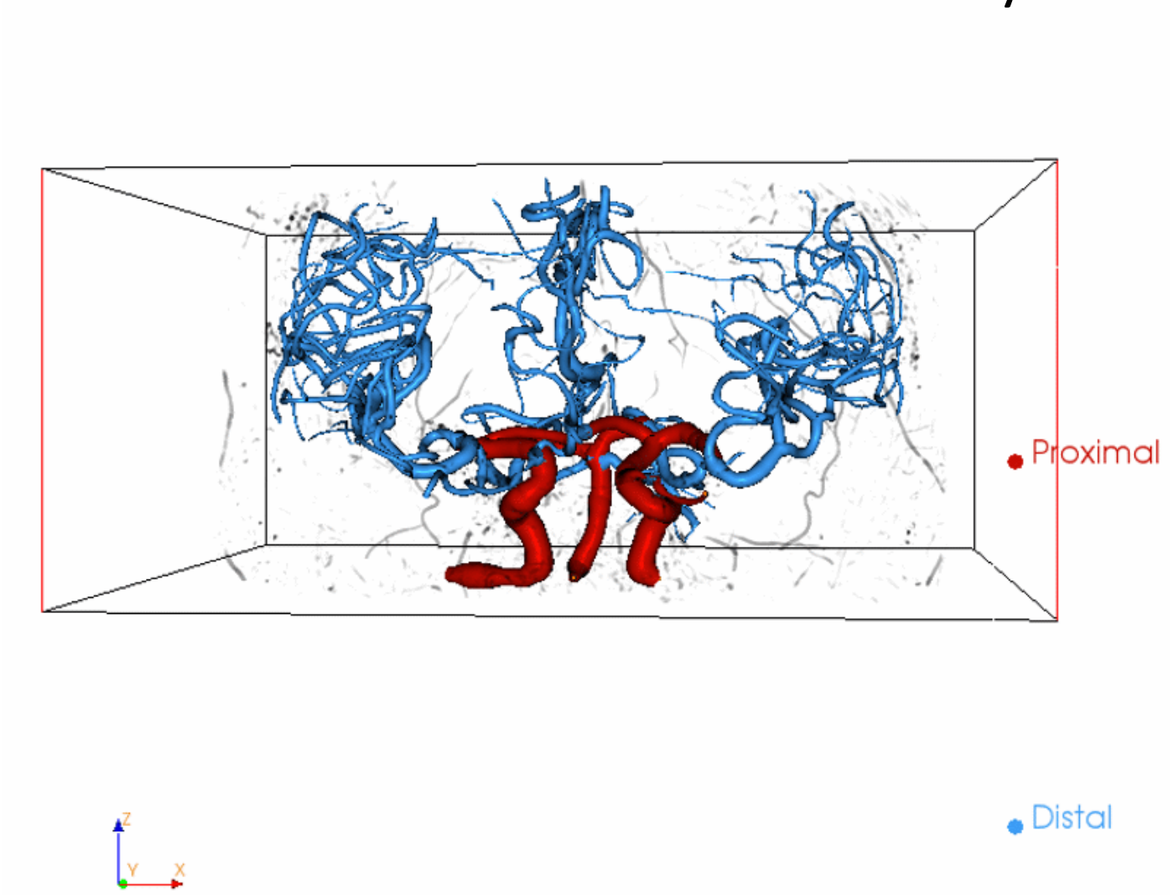


2DCASCADE

Kerwin, et al. TMRI, 2007

Quantitative Vascular Map
intraCranial artery features extraction (iCafe)

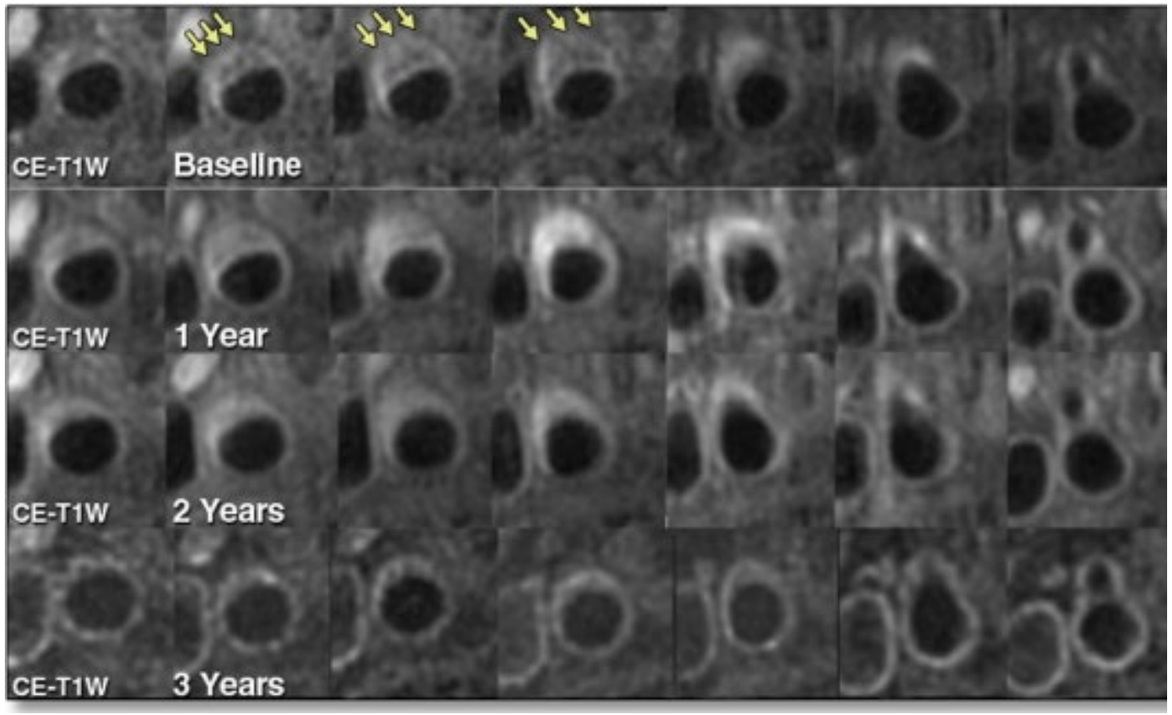
Combined lumen and wall analysis



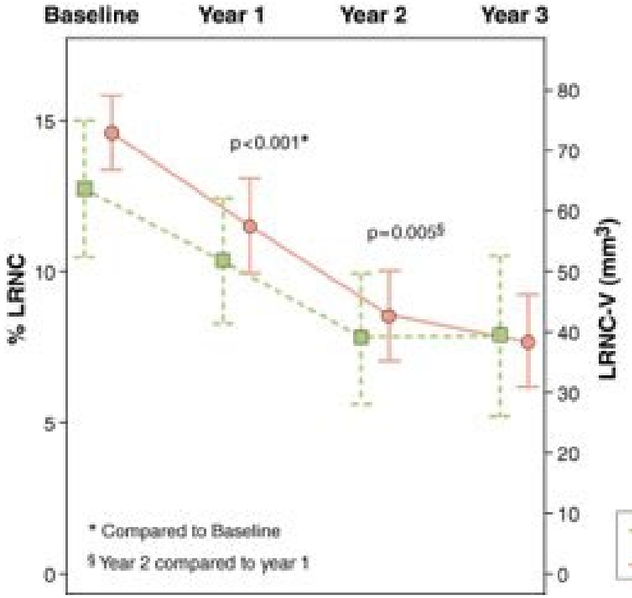
Chen L, et al. MRM, 2017

Plaque Changes over Time: Impact of Lipid Depletion Treatment Atorvastatin (CPC)

N = 33 subjects on intensive lipid therapy that included atorvastatin (10-80 mg/day)

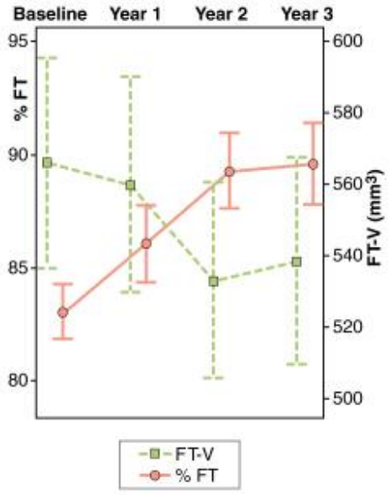


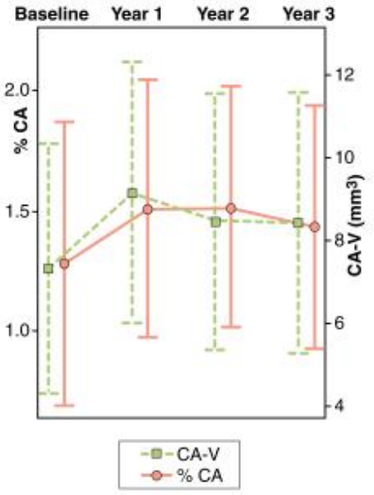
Zhao et al., *JACC Cardiovasc Imaging,* 2011;4:977-86
CPC: Carotid Plaque Composition by MRI During Lipid-Lowering

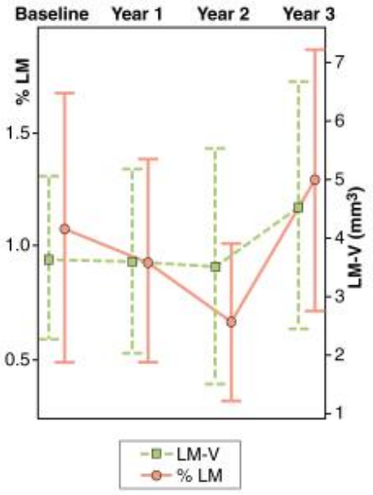


Plaque lipid depletion is observed after 1 year of treatment and continues in the second year. Regression in overall plaque burden was observed primarily at locations with a LRNC, and its time course follows plaque lipid depletion.

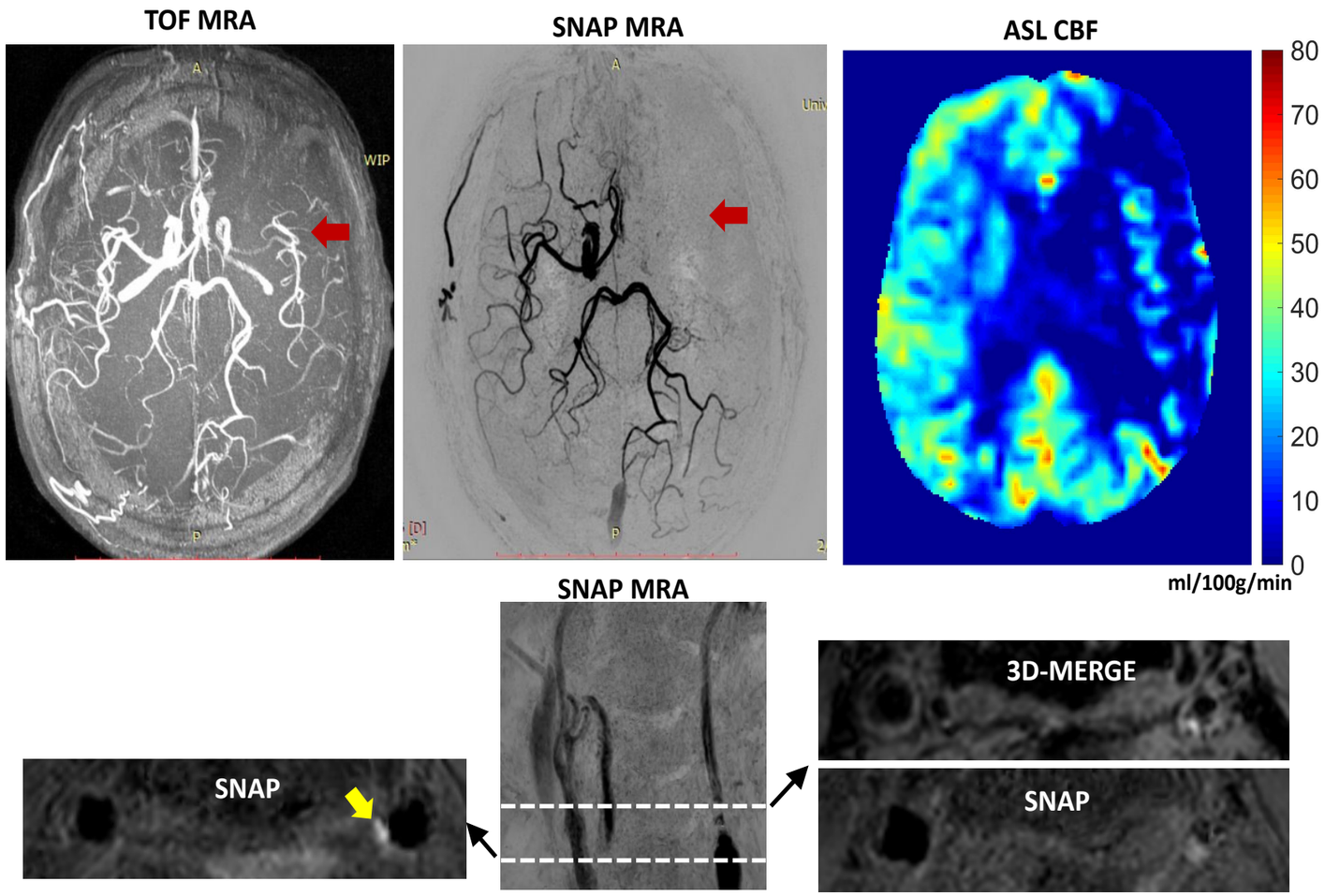
Green squares: volume
Pink circle: wall %



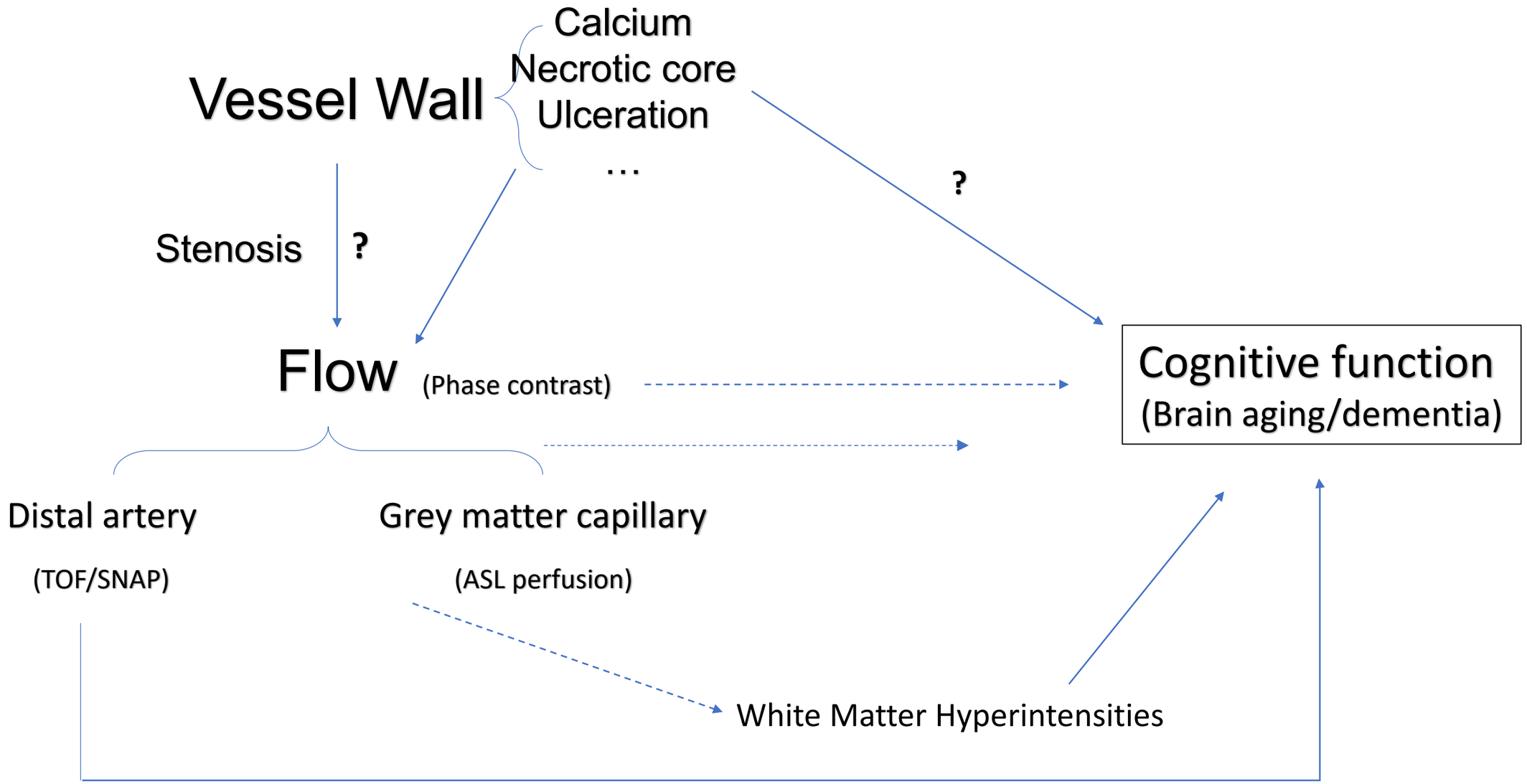




Cerebral Blood Flow, Vessel Wall, Brain Function



- Opportunity to study mechanisms of
  - Vascular disease progression
  - Flow in large, small artery and tissue level
  - Impact in both brain aging and chronic disease development


Vessel Wall
Calcium
Necrotic core
Ulceration
…
Stenosis
?
?
Flow
(Phase contrast)
Cognitive function
(Brain aging/dementia)
Distal artery
(TOF/SNAP)
Grey matter capillary
(ASL perfusion)
White Matter Hyperintensities

Can conditions of blood flow and vessel wall in medium-to-large arteries predict cognitive function?

> To explore the associations of intracranial artery length measured from TOF-MRA or SNAP-MRA with global cognitive function

> To compare the associations with cognitive function between different brain blood flow measuring techniques

- **29 subjects with carotid atherosclerotic disease**

- **Brain MR imaging**
  - ✓ 3D TOF
  - ✓ 3D SNAP
  - ✓ 3D arterial spin labeling (ASL)
  - ✓ 3D Phase contrast (PC)
  - ✓ 2D FLAIR (for quantifying white matter hyperintensities)

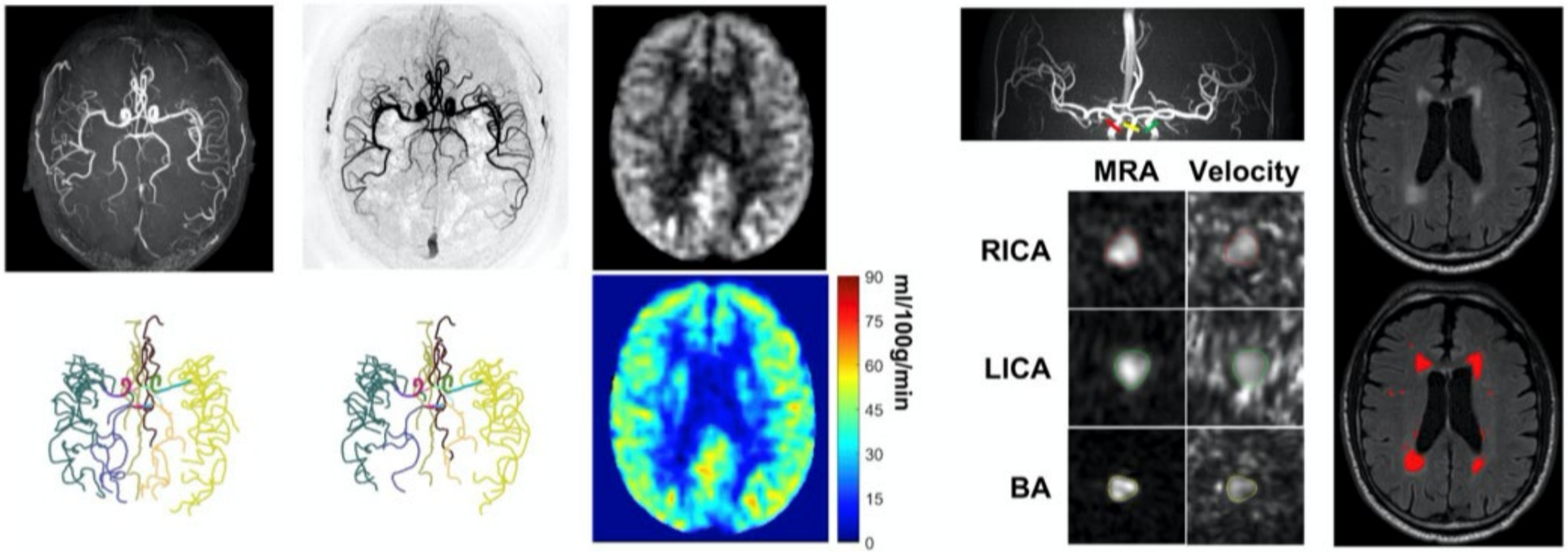
- **Global cognition was assessed using Montreal Cognitive Assessment (MoCA)**

Supported by NIH RO1 supplementary

Can conditions of blood flow and vessel wall in medium-to-large arteries predict cognitive function?

Baseline

TOF **SNAP** **ASL CBF** **3D PC** **FLAIR**



+ MoCA Test

Z Chen et al. Sci. Rep. in press, 2022

Can conditions of blood flow and vessel wall in medium-to-large arteries predict cognitive function?

Baseline result

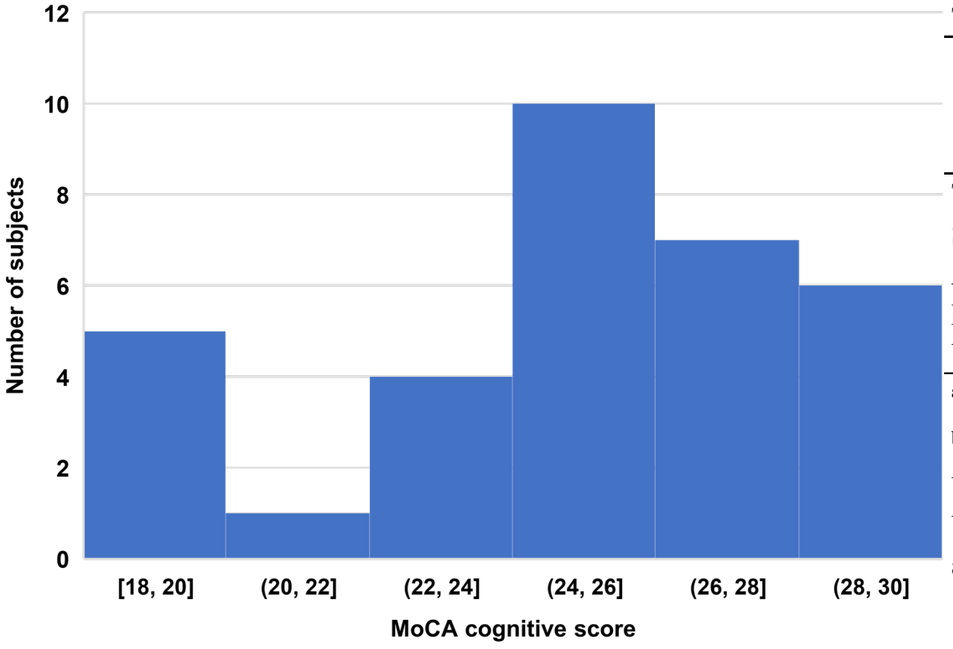


Table 2. Associations of different brain blood flow measurements, WMH volume with MoCA score (N=29[a])

Blood flow measurement	Univariable linear regression			Multivariable linear regression					
				Model 1[b]			Model 2[b]		
	β	*P*	*adjusted R²*	*β*	*P*	*adjusted R²*	*β*	*P*	*adjusted R²*
TOF artery length	0.605	**<0.001**	0.343	0.511	**0.003**	0.497	0.515	**0.003**	0.477
SNAP artery length	0.520	**0.004**	0.244	0.410	**0.040**	0.383	0.443	**0.038**	0.363
ASL CBF	0.526	**0.003**	0.250	0.309	0.097	0.341	0.329	0.097	0.316
PC CBF	0.480	**0.008**	0.202	0.352	**0.046**	0.377	0.427	**0.032**	0.372
WMH volume	-0.178	0.355	-0.004	-0.018	0.923	0.256			

[a]For one subject, the systolic blood pressure was not available. Therefore, the same size for Model 1 and Model 2 was 28.

[b]Model 1 was adjusted for age, use of antihypertensive drug and systolic blood pressure; Model 2 was Model 1 plus adjustment for WMH volume.

WMH: white matter hyperintensity; MoCA: Montreal cognitive assessment; TOF: time-of-flight; SNAP: simultaneous non-contrast angiography and intraplaque hemorrhage; ASL: arterial spin labeling; CBF: cerebral blood flow; PC: phase contrast

Can conditions of blood flow and vessel wall in medium-to-large arteries predict cognitive function?

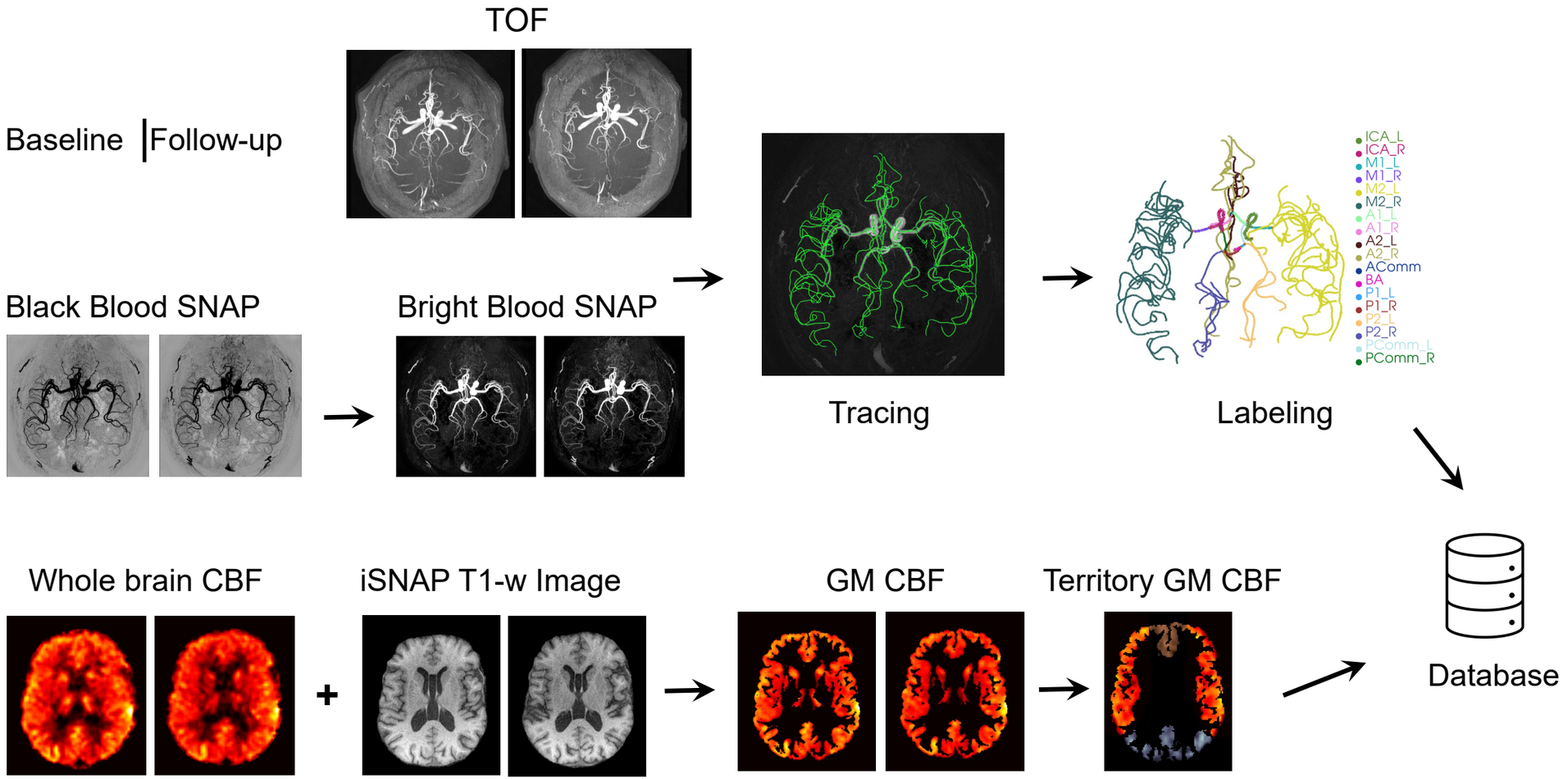
Table 3: Correlation of carotid morphology and composition with brain lesions and MoCA

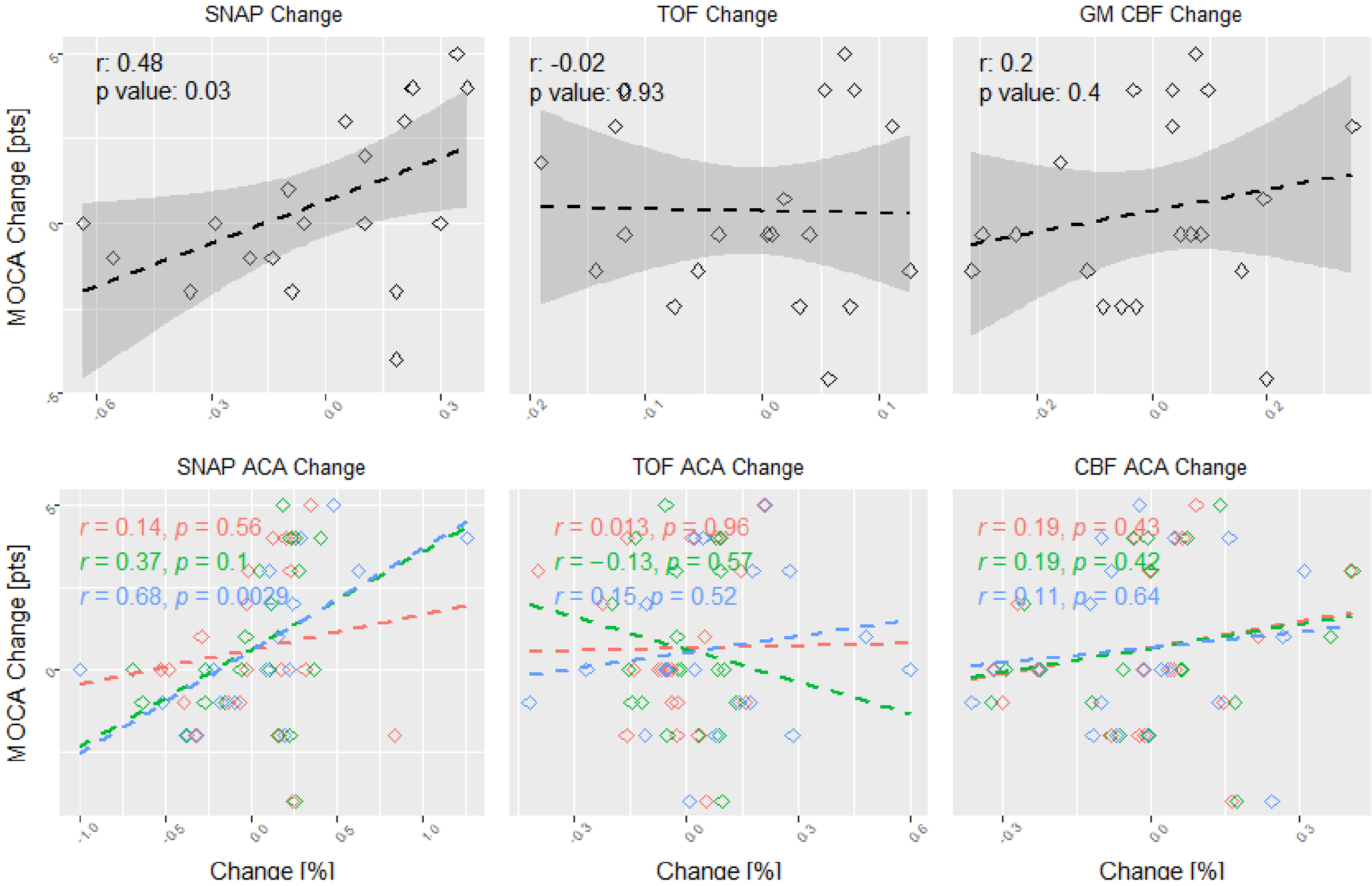
	Brain Infarct Volume (N=33) (Ipsilateral)		Brain Infarct Volume (N=33) (Whole Brain)		MoCA (N=32)	
Variable	**r***	**P-value**	**r***	**P-value**	**r***	**P-value**
Mean NWI	0.26	**0.048**	0.14	0.44	-0.18	0.32
Mean WT	0.23	***0.076***	0.24	0.18	-0.11	0.53
Max WT	0.31	**0.017**	0.25	0.16	0.09	0.62
Calcium % volume	-0.14	0.29	-0.24	0.17	-0.36	**0.046**
LRNC % volume	0.29	**0.029**	0.34	0.053	-0.07	0.69
IPH % volume	0.25	***0.062***	0.29	0.10	-0.10	0.60

* Spearman's rank correlation coefficient. NWI: normalized wall index, WT: wall thickness, LRNC: lipid-rich necrotic core, IPH: intraplaque hemorrhage. Significant p-values bolded, trending p-values bolded and italicized.

Can conditions of blood flow and vessel wall in medium-to-large arteries predict cognitive function?

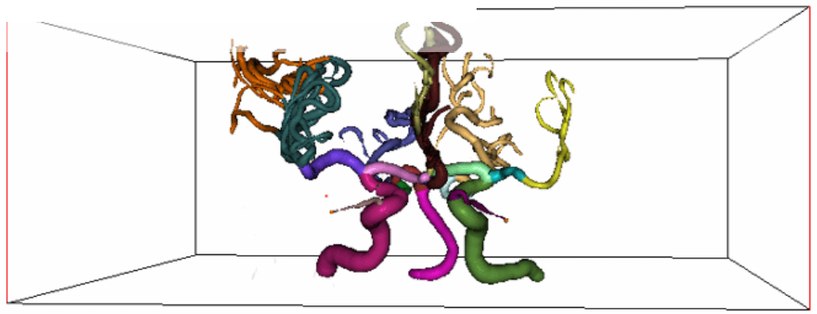
Baseline & Follow-up (1 year)

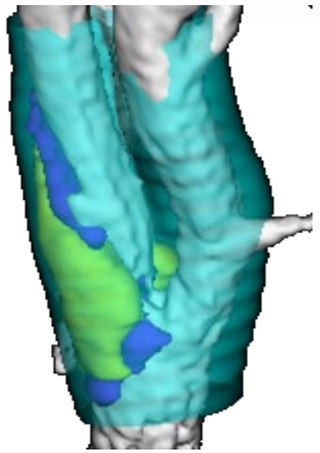




Zhang K, et al. ISMRM, 2022

Summary: Quantitative Vascular MRI Imaging's Role





A series of quantitative tools has been developed

- **Imaging sequences**
- **iCafe**
- **CASCADE – MOCHA (with new NIH funding)**
- **Quantitative measurements (3D map)**

Can be used to monitor cholesterol lowering treatment

Maybe linked to other brain maps of anatomy, function, and oxygen consumption

Can be used to study vascular health in different populations

Acknowledgements

- Vascular Imaging Lab
  - U. of Washington

- NHLBI
- NINDS

Q & A

Thank You

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