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

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

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.”

• “Vascular risk may complement imaging biomarkers in assessing risk of prospective cognitive decline in preclinical Alzheimer disease.”
  Liesz, 10.1126/science.aay2720
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

**STUDY POPULATION**

- 9361 elderly participants

**INTERVENTION**

- Intensive blood pressure control (systolic bp <120 mmHg)
- Standard blood pressure control (systolic bp <140 mmHg)

**OUTCOME**

- Improved blood pressure control
- Reduced risk of Mild Cognitive Impairment (MCI)

**CASES OF MCI PER 1000 PERSON-YEARS**

- Standard ctrl: 18.3
- Intensive ctrl: 14.6

**CASES OF MCI/PROBABLE DEMENTIA PER 1000 PERSON-YEARS**

- Standard ctrl: 24.1
- Intensive ctrl: 20.2

**Hazard Ratio**

- MCI: 0.81 (95% CI 0.69 to 0.95)
- Probable dementia: 0.85 (95% CI 0.74 to 0.97)

**MEAN BLOOD PRESSURE**

- Intensive: 121.6 vs. 134.8 (95% CI 120.8 to 122.3 vs. 134.1 to 133.6 mmHg)

**LIMITATION:**

Study terminated early due to cardiovascular benefit
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.

**Randomization**

Age 75+ without CVD, dementia or disability (N = 20,000)

Atorvastatin 40mg

Placebo

(4 year follow-up)

Survival w/o dementia or persisting disability

CV composite (CV death, MI, HF, Stroke/TIA) or MCI/dementia
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
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

Dear, would you please come over and scratch my back—and tie my shoes. Bring more chips, too.
## Classification of physical activity based on intensity levels

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

*Based on 2011 Compendium of Physical Activities¹
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

Beachu et al. CJASN. 2015 Jul 7;10(7):1145-53
<table>
<thead>
<tr>
<th></th>
<th>↑ 2 min/hr of light activity duration HR (95% CI, p)**</th>
<th>↑ 2 min/hr of MVPA duration HR (95% CI, p)***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entire cohort</td>
<td>0.67 (0.48, 0.93, p = 0.02)</td>
<td>0.80 (0.42, 1.51, p = 0.46)</td>
</tr>
<tr>
<td>CKD subgroup</td>
<td>0.59 (0.35, 0.98, p = 0.04)</td>
<td>0.46 (0.09, 2.45, p = 0.34)</td>
</tr>
</tbody>
</table>

*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
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

<table>
<thead>
<tr>
<th>Visit (Month)/Activity</th>
<th>Within 3 months of Randomization</th>
<th>Month 12</th>
<th>Month 36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activity monitor training/education</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wearing of activity monitor for 7 days</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Completing wear time diary for 7 days</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Sedentary Behavior Questionnaire</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
OPENING OUR MINDS: BROADENING THE DEFINITION OF ‘SYMPTOMATIC’ ATRIAL FIBRILLATION

BENJAMIN A. STEINBERG, MD, MHS, FACC, FHRS
ASSOCIATE PROFESSOR OF MEDICINE
CLINICAL CARDIAC ELECTROPHYSIOLOGY
UNIVERSITY OF UTAH HEALTH SCIENCES CENTER

@ba_steinberg
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.

MarketScan and Thomson Reuters Medicare Databases, 2009
Olmsted County Data, 2006 (assuming a continued increase in AF incidence)
Olmsted County Data, 2006 (assuming no further increase in AF incidence)
ATRIA Study Data, 2000

Patients with AF (millions)
Year

ATRIA = Anticoagulation and Risk Factors in Atrial Fibrillation.
## SYMPTOMS ≠ ARRHYTHMIA

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

<table>
<thead>
<tr>
<th></th>
<th>ECG +AT/AF (n=114)</th>
<th>ECG –AT/AF (n=391)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient “Yes” (n=107)</td>
<td>72</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>11.68</td>
<td>11.70</td>
</tr>
<tr>
<td>Patient “No” (n=389)</td>
<td>42</td>
<td>356</td>
</tr>
<tr>
<td></td>
<td>6.76</td>
<td>7.59</td>
</tr>
</tbody>
</table>

AF Symptom Score (mean), p<0.001

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
## AF & COGNITION

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

## AF & COGNITION: META-ANALYSIS

<table>
<thead>
<tr>
<th>Condition</th>
<th>Studies (n)</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF &amp; cognitive impairment with or without stroke</td>
<td>14</td>
<td>1.40</td>
<td>1.19–1.64</td>
</tr>
<tr>
<td>AF &amp; dementia</td>
<td>8</td>
<td>1.38</td>
<td>1.22–1.56</td>
</tr>
<tr>
<td>AF &amp; cognitive impairment</td>
<td>9</td>
<td>1.50</td>
<td>1.18–1.91</td>
</tr>
<tr>
<td>AF &amp; cognitive impairment independent of stroke</td>
<td>10</td>
<td>1.34</td>
<td>1.13–1.58</td>
</tr>
<tr>
<td>AF and cognitive impairment after stroke</td>
<td>7</td>
<td>2.70</td>
<td>1.82–4.00</td>
</tr>
</tbody>
</table>


POTENTIAL MECHANISMS: AF & COGNITION

- The timing, use, and efficacy of anticoagulation is critical
- Micro and Macro Emboli/Bleeds
- Disruptions of blood/brain barrier/Cytotoxicity
- Cellular Apoptosis Cytotoxicity Volume Loss

Mediators
- Inflammation, Oxidative Stress, Vascular Disease, Genetic Risks

Rhythm, Rate, and Cerebral Perfusion Strategies May Impact Risk
- Cerebral Hypoperfusion
- Arteriolar Hypotension Capillary Hypertension
- Cellular Apoptosis Cytotoxicity Volume Loss

AF & STROKE (& COGNITION)

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

Are "Silent" Strokes Really Silent?

Different Viewpoints/Perspectives

Patients with Atrial Fibrillation (>65 years)

Clinical Stroke/TIA Symptoms at 2 years

Brain MRI at 2 Years

2.3% Incidence

5.5% Incidence

2.4x Increase

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
CEREBROVASCULAR RESERVE IN AF (CANINE)

A

Pre-Pharmacological Challenge Imaging
Time = 1 min

Diamox Injection
Time = 2 min

Post-Pharmacological Challenge Imaging
Time = 15 min

Decreased Perfusion
Increased Perfusion

B

Changes in Average Cerebrovascular Reserve in the Gray and White Brain Matter

<table>
<thead>
<tr>
<th></th>
<th>Gray Matter Reserve Blood Flow</th>
<th>White Matter Reserve Blood Flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>50</td>
<td>40</td>
</tr>
<tr>
<td>3 Month</td>
<td>-10</td>
<td>-20</td>
</tr>
<tr>
<td>6 Month</td>
<td>-15</td>
<td>-30</td>
</tr>
</tbody>
</table>

Zenger B...Bunch TJ. JACC EP. In Revision.
SUMMARY: AF & COGNITION

• Causal relationship beyond stroke
  – Mechanism 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
AF ABLATION IN HF: NOT EVERYONE WINS

HETEROGENEITY OF TREATMENT EFFECTS

A Average Treatment Effect Assessed in a Heterogeneous Population

Estimation of average treatment effect

- = expected to derive benefit from treatment
- = expected to have an equivocal response
- = expected to be harmed by treatment
- = response in the "average"

B Identification of Heterogeneous Responses to Treatment

Segregation of patient population based on treatment response

- = expected to derive benefit from treatment
- = expected to have an equivocal response
- = expected to be harmed by treatment

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\(^3\)
We have very little knowledge of the effects of concussions in older adults

<table>
<thead>
<tr>
<th>Young adults ≠ Older adults</th>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Balance</th>
<th>Established Relationship with Falls in Older Adults</th>
<th>Established Consequence of mTBI in Young Adults</th>
<th>Established Consequence of mTBI in Older Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Self-Report</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Clinical Measure</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Objective Measure</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<table>
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<tr>
<th>Cognition</th>
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<tbody>
<tr>
<td>Patient Self-Report</td>
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<tr>
<td>Clinical Measure</td>
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<tr>
<td>Objective Measure</td>
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<table>
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<tr>
<th>Mood</th>
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<tbody>
<tr>
<td>Patient Self-Report</td>
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<tr>
<td>Clinical Diagnosis</td>
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<tr>
<th>Autonomic</th>
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<tbody>
<tr>
<td>Patient Self-Report</td>
</tr>
<tr>
<td>Clinical Measure</td>
</tr>
<tr>
<td>Objective Measure</td>
</tr>
</tbody>
</table>

**Legend:**
- **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.

Funding Support

Neuromechanics & Applied Locomotion Lab

Improving Care for People with Concussion

Motor Control

Neuroscience

Neuro-psychology

Athletic Training

Biostatistics

Implementation Science

Psychology

Geriatrics

Engineering

Rehabilitation Science

Neuroscience

Motor Control

Biomechanics
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.

### Hazard Ratio

**OVERALL**
- Hazard Ratio: 0.93
- Pinteraction: NS

**With MCI**
- Hazard Ratio: 0.97
- Pinteraction: NS

**Without MCI**
- Hazard Ratio: 0.75
- Pinteraction: NS

**Intensive Arm**
- Hazard Ratio: 1.17
- Pinteraction: 0.007

**Standard Arm**
- Hazard Ratio: 0.61

### Demographic Factors

- **Age <75 yrs**
  - Hazard Ratio: 0.98
- **Age ≥75 yrs**
  - Hazard Ratio: 0.81
- **Male**
  - Hazard Ratio: 0.90
- **Female**
  - Hazard Ratio: 0.99
- **Black**
  - Hazard Ratio: 1.11
- **Non-Black**
  - Hazard Ratio: 0.84

### Median Follow-up
- 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.

Hazard Ratio (95% CI)
0.76 (0.66 - 0.87)
4.8 years of median follow-up (95% CI, 4.7-4.8 years)
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
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

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
- Rachel Hess
- Brandon Bellows
- Jordan King
- Paul Muntner
- Ambarish Pandey
- Daichi Shimbo
- Alfred Cheung
- Katie Derington
- Alex Zheutlin
- Josh Jacobs
- Ransmond Berchie

- Jordy Cohen
- April Mohanty
- Andrew Moran
- Bill Weintraub
- Aisha Langford
- Calvin Colvin
- Rick Kittles
- Lynn Jorde
- Dan Scharfstein
- Zach Marcum
- Daniel Addo

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- NIA R01AG065805 (PI)
- NIA R01AG074989 (MPI)

JHS Participants
REGARDS Participants
SPRINT Participants
SPRINT Coordinating Center
SPRINT Research Group
- Investigators
- Staff
NHLBI, NIA, and NINDS Support
There is one more thing...

Angiotensinogen

(+)

Angiotensin-I

(+)

Angiotensin-II

(+)

Angiotensin-(1-7)

(-)

Angiotensin-IV

(-)

Renin

(-)

ACE1

(+)

ACE inhibitors

(-)

Beta-blockers

Calcium channel blockers, non-dihydropyridine

AT1R

AT2R

MasR

AT4R (IRAP)

Thiazide diuretics
Calcium channel blockers, dihydropyridine

ARBs

AT2R/AT4R stimulating antihypertensives

AT2R/AT4R inhibiting antihypertensives

Agonism = bad

Agonism = good
Funding & Acknowledgements

• **Principal 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**
  – R01 HL117323 (Multi-PI: Muntner/Shimbo/Ogedegbe) – JHS-HWG
  – R01 NR01889 (Baron, PI)
  – R01 HL157439 (King, PI)
Central
Thank you to my team!
Primary outcome results

Part I: ARBs vs. ACEIs

Results

4.9 years median follow-up
SENSITIVITY ANALYSES

• 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

<table>
<thead>
<tr>
<th></th>
<th>Standard arm</th>
<th>Intensive arm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-Hispanic White</td>
<td>Non-Hispanic Black</td>
</tr>
<tr>
<td>Unique participants, n</td>
<td>2451</td>
<td>1306</td>
</tr>
<tr>
<td>Participant-visits, n</td>
<td>13704</td>
<td>7364</td>
</tr>
<tr>
<td>Overall Prevalence, % (95% CI)</td>
<td>12.7 (12.0,13.5)</td>
<td>10.6 (9.0,12.4)</td>
</tr>
<tr>
<td>12 Month Prevalence, % (95% CI)</td>
<td>10.8 (8.3,13.9)</td>
<td>10.5 (7.3,15.0)</td>
</tr>
<tr>
<td>36 Month Prevalence, % (95% CI)</td>
<td>10.1 (6.8,14.8)</td>
<td>5.3 (2.5,11.1)</td>
</tr>
<tr>
<td>Adjusted OR (95% CI)</td>
<td>1 (Reference)</td>
<td>0.83 (0.73,0.94)</td>
</tr>
</tbody>
</table>

§Adjusted OR (95% CI)

|                      | 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) | 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

### Part I: ARBs vs. ACEIs

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Actions</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT₁</td>
<td>Vasoconstriction, increase sodium retention, suppress renin secretion,</td>
<td>Vessels, brain, heart, kidney, adrenal gland,</td>
</tr>
<tr>
<td></td>
<td>increase endothelin secretion, increase vasopressin release, activate</td>
<td>and nerves</td>
</tr>
<tr>
<td></td>
<td>sympathetic activity, promote myocyte hypertrophy, stimulate vascular</td>
<td></td>
</tr>
<tr>
<td></td>
<td>and cardiac fibrosis, increase myocardial contractility, induce</td>
<td></td>
</tr>
<tr>
<td></td>
<td>arrhythmias, stimulate plasminogen activator inhibitor 1, and stimulate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>superoxide formation</td>
<td></td>
</tr>
<tr>
<td>AT₂</td>
<td>Antiproliferation/inhibition of cell growth, cell differentiation, tissue</td>
<td>Adrenal gland, heart, brain, myometrium, fetus,</td>
</tr>
<tr>
<td></td>
<td>repair, apoptosis, vasodilation (NO mediated?), kidney and urinary tract</td>
<td>and injured tissues</td>
</tr>
<tr>
<td></td>
<td>development, control of pressure/natriuresis, stimulate renal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>prostaglandins, and stimulate renal bradykinin and NO</td>
<td></td>
</tr>
<tr>
<td>AT₃</td>
<td>Unknown</td>
<td>Neuroblastoma cells in amphibians</td>
</tr>
<tr>
<td>AT₄</td>
<td>Renal vasodilator; stimulate plasminogen activator inhibitor 1</td>
<td>Brain, heart, vessels, lungs, prostate, adrenal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>gland, and kidney</td>
</tr>
</tbody>
</table>
### Part II: Therapeutic Inertia

<table>
<thead>
<tr>
<th>Model</th>
<th>Odds ratio (95% CI)</th>
<th>Non-Hispanic White</th>
<th>Non-Hispanic Black</th>
<th>Hispanic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>1 (Reference)</td>
<td>0.89 (0.84, 0.95)</td>
<td>1.00 (0.91, 1.11)</td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td>1 (Reference)</td>
<td>0.92 (0.86, 0.99)</td>
<td>1.01 (0.90, 1.12)</td>
<td></td>
</tr>
<tr>
<td>Model 3</td>
<td>1 (Reference)</td>
<td>0.85 (0.79, 0.92)</td>
<td>1.00 (0.90, 1.13)</td>
<td></td>
</tr>
<tr>
<td>Model 4</td>
<td>1 (Reference)</td>
<td>0.88 (0.82, 0.96)</td>
<td>1.08 (0.97, 1.22)</td>
<td></td>
</tr>
<tr>
<td>Model 5</td>
<td>1 (Reference)</td>
<td>0.89 (0.82, 0.97)</td>
<td>0.98 (0.86, 1.13)</td>
<td></td>
</tr>
</tbody>
</table>

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?

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

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

<table>
<thead>
<tr>
<th>Drug (Active Metabolite)</th>
<th>AT&lt;sub&gt;1&lt;/sub&gt; Receptor Affinity, nmol/L</th>
<th>Bioavailability, %</th>
<th>Food Effect</th>
<th>Active Metabolite</th>
<th>Half-Life, h</th>
<th>Protein Binding, %</th>
<th>Dosage, mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losartan (EXP 3174)</td>
<td>IC&lt;sub&gt;50&lt;/sub&gt;, 20</td>
<td>33</td>
<td>No</td>
<td>Yes</td>
<td>2 (6–9)</td>
<td>98.7 (99.8)</td>
<td>50–100</td>
</tr>
<tr>
<td>Valsartan</td>
<td>IC&lt;sub&gt;50&lt;/sub&gt;, 2.7</td>
<td>25</td>
<td>Yes, −40%</td>
<td>No</td>
<td>9</td>
<td>95</td>
<td>80–320</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>IC&lt;sub&gt;50&lt;/sub&gt;, 1.3</td>
<td>70</td>
<td>No</td>
<td>No</td>
<td>11–15</td>
<td>90*</td>
<td>150–300</td>
</tr>
<tr>
<td>Candesartan cilexetil</td>
<td>(TCV 116)</td>
<td>...</td>
<td>No</td>
<td>Yes</td>
<td>3.5–4</td>
<td>...</td>
<td>4–16 (32)</td>
</tr>
<tr>
<td>(CV11974)</td>
<td>K&lt;sub&gt;i&lt;/sub&gt;, 0.6</td>
<td>42</td>
<td></td>
<td></td>
<td>3–11</td>
<td>99.5</td>
<td></td>
</tr>
<tr>
<td>Telmisartan</td>
<td>K&lt;sub&gt;i&lt;/sub&gt;, 3.7</td>
<td>43</td>
<td>No</td>
<td>No</td>
<td>24</td>
<td>&gt;99</td>
<td>40–80</td>
</tr>
<tr>
<td>Eprosartan</td>
<td>IC&lt;sub&gt;50&lt;/sub&gt;, 1.4–3.9</td>
<td>15</td>
<td>No†</td>
<td>No</td>
<td>5–7</td>
<td>98</td>
<td>400–800</td>
</tr>
</tbody>
</table>

Values are mean or range. K<sub>i</sub> 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)

CV mortality
MI
Stroke
Heart Failure
ESKD
Hyperkalemia
Acute kidney failure
New onset diabetes

Favors ARBs
Favors ACE inhibitors
Pooled relative risk (with 95% CI)

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

Cardiovascular events
MI
Stroke
Heart Failure
ESKD
Hyperkalemia
Acute kidney failure
New onset diabetes

Favors ARBs
Favors ACE inhibitors
Hazard ratio (with 95% CI)
### META-ANALYSIS OF RCTS- COMPARATIVE EFFECTS OF ARBS VS ACEIS ON CVD OUTCOMES

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo</th>
<th>CCBs</th>
<th>ACE inhibitors</th>
<th>β-blockers</th>
<th>Diuretics</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARBs</td>
<td>0.60 ± 0.18 (P = 0.02)</td>
<td>0.57 ± 0.24 (P = 0.06)</td>
<td>0.47 ± 0.17 (P = 0.04)</td>
<td>0.67 ± 0.18 (P = 0.01)</td>
<td>0.54 ± 0.19 (P = 0.04)</td>
</tr>
<tr>
<td>CCBs</td>
<td>0.02 ± 0.19 (P = 0.91)</td>
<td>–</td>
<td>–0.11 ± 0.22 (P = 0.65)</td>
<td>0.10 ± 0.17 (P = 0.58)</td>
<td>–0.03 ± 0.24 (P = 0.89)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>0.13 ± 0.17 (P = 0.49)</td>
<td>–</td>
<td>0.21 ± 0.15 (P = 0.23)</td>
<td>–</td>
<td>0.07 ± 0.17 (P = 0.70)</td>
</tr>
<tr>
<td>β-blockers</td>
<td>–0.08 ± 0.13 (P = 0.59)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–0.13 ± 0.19 (P = 0.50)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>0.06 ± 0.17 (P = 0.76)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

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).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Comparison group</th>
<th>Placebo</th>
<th>CCBs</th>
<th>ACE inhibitors</th>
<th>β-blockers</th>
<th>Diuretics</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARBs</td>
<td>Placebo</td>
<td>0.60 ± 0.18 (P = 0.02)</td>
<td>0.57 ± 0.24 (P = 0.06)</td>
<td>0.47 ± 0.17 (P = 0.04)</td>
<td>0.67 ± 0.18 (P = 0.01)</td>
<td>0.54 ± 0.19 (P = 0.04)</td>
</tr>
<tr>
<td>CCBs</td>
<td>Placebo</td>
<td>0.02 ± 0.19 (P = 0.91)</td>
<td>-</td>
<td>-0.11 ± 0.22 (P = 0.65)</td>
<td>0.10 ± 0.17 (P = 0.58)</td>
<td>-0.03 ± 0.24 (P = 0.89)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>Placebo</td>
<td>0.13 ± 0.17 (P = 0.48)</td>
<td>-</td>
<td>0.21 ± 0.15 (P = 0.23)</td>
<td>0.07 ± 0.17 (P = 0.70)</td>
<td></td>
</tr>
<tr>
<td>β-blockers</td>
<td>Placebo</td>
<td>-0.08 ± 0.13 (P = 0.59)</td>
<td>-</td>
<td>-</td>
<td>-0.13 ± 0.19 (P = 0.50)</td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>Placebo</td>
<td>0.06 ± 0.17 (P = 0.76)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

AMONG THOSE WITH THERAPEUTIC INERTIA, HOW MUCH WAS THEIR BLOOD PRESSURE ABOVE GOAL ON AVERAGE?
AMONG THOSE WITH THERAPEUTIC INERTIA, HOW MUCH WAS THEIR BLOOD PRESSURE ABOVE GOAL ON AVERAGE?
# COGNITIVE OUTCOME ASCERTAINMENT IN SPRINT

## Part I: Pharmacoepi Methods

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

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

**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

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

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
Central Auditory Dysfunction as a Harbinger of Alzheimer Dementia

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

Hearing Loss and Cognition in the Baltimore Longitudinal Study of Aging

Frank R. Lin
Johns Hopkins University
Luigi Ferrucci, E. Jeffrey Metter, Yang An, Alan B. Zonderman, and Susan M. Resnick
National Institute on Aging, Baltimore, Maryland

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 Parham-Helzer, PhD; Suzanne Satterfield, MD; DePPE, Yihua N. Auyunyan, PhD; Luigi Ferrucci, MD, PhD; Eleanor M. Simonick, 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

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
9% of modifiable risk of Alzheimer disease attributed to hearing loss.
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

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

<table>
<thead>
<tr>
<th>Cognitive domain</th>
<th>Verbal stimuli/responses</th>
<th>Visual stimuli/responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple attention</td>
<td>Digit Span</td>
<td>Spatial Span</td>
</tr>
<tr>
<td>Sustained attention</td>
<td>Stroop Color Word Test</td>
<td>d2 Test of Attention</td>
</tr>
<tr>
<td>Learning and memory</td>
<td>HVLT-R</td>
<td>BVMT-R</td>
</tr>
<tr>
<td>Executive functioning</td>
<td>Hayling Sentence Completion Test</td>
<td>Trail Making Test Part B</td>
</tr>
</tbody>
</table>
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
Sensory Integration for Navigation:  
*Effects of Age and Sensory Impairment*

Sarah Creem-Regehr  
Department of Psychology  
University of Utah
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?
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 auditory 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

<table>
<thead>
<tr>
<th>Muscle Strength</th>
<th>Motor Speed</th>
<th>Fine Motor Skill</th>
<th>Coordination</th>
<th>Gait</th>
<th>Balance</th>
<th>Motor Learning</th>
<th>Drawing</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Hand Dynamometer" /></td>
<td><img src="image2" alt="Computerized Finger Tapping Test" /></td>
<td><img src="image3" alt="Computerized Archimedes Spiral Test" /></td>
<td><img src="image4" alt="Purdue Pegboard Test" /></td>
<td><img src="image5" alt="Preferred and Maximum Speed + TUG + Dual Task" /></td>
<td><img src="image6" alt="Romberg Balance Test w. Eyes Open + Closed" /></td>
<td><img src="image7" alt="Computerized Implicit Sequence Learning Test" /></td>
<td><img src="image8" alt="Trail Making Test A" /></td>
</tr>
</tbody>
</table>

- **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

vincent.koppelmans@utah.edu  @VKoppeolmans
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)

vincent.koppelemans@utah.edu   @VKoppelemans
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
Plasticity-Based Digital Interventions for Major Depression and Cognitive Impairment
Sarah Shizuko Morimoto, Psy.D.
Associate Professor
Department of Population Health Sciences
NEUROBIOLOGICAL MODEL OF NEUROFLEX: GRAPHICAL ABSTRACT

**Neuroplasticity-Based CCR**
- Attention demanding
- Intensive
- Individually Adaptive
- Rewarding

**Factors Predisposing to MDD**
- Vascular changes
- Inflammation
- Heredity

**Altered CCN Circuitry**
- Structural (white matter) abnormalities
- Abnormal activity
- Disrupted connectivity

**SSRI/SNRI Resistance**
Cognitive Control Deficits
Recurrent MDD
Disability

**Remission from MDD**
Improved cognitive control
Decreased depression
Improved functioning

- Dendritic remodeling
- Neurotrophic factors
- Metabolic activity

- Increased:
  - rCBF
  - White matter
  - Activation
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
IN ADDITION TO TREATING COGNITIVE DEFICITS:

• NeuroFlex is Designed To Be a CIRCUIT-BASED PROBE of the CCN.
PILOT TRIAL: MIXED MODELS: NEUROFLEX VS. ESCITALOPRAM

*Morimoto et al., Nature Communications, 2014

**Depression Severity vs. Week of Treatment**

- **Group**: F(1,49.2) = 0.019, p = 0.892
- **Week**: F(1,71.2) = 30.97, p < 0.0001*
- **Group*Week**: F(1,61.8) = 5.32, p = 0.024*

* Remission
PILOT TRIAL: EFFECT ON COGNITIVE CONTROL

TRAILS B OVER TIME BY GROUP

Baseline  | Week 4
---|---
Seconds
100 | 150
110 | 160
120 | 170

Stroop-CW Over Time by Group

Baseline  | Week 4
---|---
Mean Number of Words
25 | 35
26 | 34
27 | 33
28 | 32
29 | 31
30 | 30
31 | 29
32 | 28
33 | 27
34 | 26
35 | 25

$t=2.28, \text{DF}=41, p=0.027^*$

$t=1.86, \text{DF}=41, p=0.103$

*Morimoto et. Al., Nature Communications, 2014*
RANDOMIZED, DOUBLE-BLIND, CONTROLLED TRIAL: MOOD
PI: MORIMOTO (K23 MH 095830)

MIXED EFFECTS MODEL: NeuroFlex VS. CONTROL

- Group: F(1,278); p = .60
- Week: F(1, 25.2); p = .0001*
- Group*Week: F(1, 11.37); p = .002*

**RCT: COGNITIVE CONTROL DEFICITS**

**PI: MORIMOTO (K23 MH 095830)**

---

**CHANGE IN SEMANTIC CLUSTERING (STANDARD SCORES)**

![Graph showing change in semantic clustering](chart.png)

**Baseline**  
**Week 4**

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

---

*Morimoto et. Al Am. J. of Geri Psych. 2020*
TARGET COGNITIVE FUNCTIONS AND TRANSFER:

CHANGE IN STROOP

CHANGE IN TRAILS B - TRAILS A

CHANGE IN VERBAL FLUENCY (FAS)

CHANGE IN WORKING MEMORY

*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

**CHANGE IN LONG DELAY MEMORY**

![Graph showing change in long delay memory](image)

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

*Morimoto, Gunning et al., AJGP 2020*
## NEUROFLEX EFFECT SIZES

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week4</th>
<th>statistic</th>
<th>pvalue</th>
<th>d</th>
</tr>
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<tbody>
<tr>
<td>MADRS</td>
<td>F(1,61.8)=11.37</td>
<td>.002*</td>
<td>-.64</td>
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<tr>
<td>Neuroflex</td>
<td>25.7(8.9)</td>
<td>13.2(5.9)</td>
<td></td>
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<tr>
<td>Control</td>
<td>25.6(8.2)</td>
<td>18.9(8.0)</td>
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<tr>
<td>WHODAS</td>
<td>t(28)=2.98</td>
<td>.006*</td>
<td>-1.17</td>
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</tr>
<tr>
<td>Neuroflex</td>
<td>23.87(9.4)</td>
<td>18.8(5.4)</td>
<td></td>
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</tr>
<tr>
<td>Control</td>
<td>25.9(9.0)</td>
<td>27.3(8.1)</td>
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<tr>
<td>StroopCW</td>
<td>t(26)=-2.97</td>
<td>.007*</td>
<td>-1.21</td>
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<tr>
<td>Neuroflex</td>
<td>34.4(9.3)</td>
<td>36.4(8.7)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Control</td>
<td>33.4(9.4)</td>
<td>34.0(9.5)</td>
<td></td>
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<tr>
<td>TrailsB</td>
<td>t(28)=2.2</td>
<td>.04*</td>
<td>-.86</td>
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<tr>
<td>Neuroflex</td>
<td>157.6(101.2)</td>
<td>140.9(102.4)</td>
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<td></td>
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<tr>
<td>Control</td>
<td>150.6(96.2)</td>
<td>158.0(80.2)</td>
<td></td>
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<td></td>
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<tr>
<td>DigitSpan</td>
<td>t(26)=2.56</td>
<td>.02*</td>
<td>-1.08</td>
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<tr>
<td>Neuroflex</td>
<td>6.1(2.2)</td>
<td>7.0(2.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>6.9(2.2)</td>
<td>6.9(1.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SemanticClus. (StandardScore)</td>
<td>SS</td>
<td>SS</td>
<td>t(26)=-3.12</td>
<td>.006*</td>
<td>1.39</td>
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<tr>
<td>Neuroflex</td>
<td>.56(1.7)</td>
<td>.96(1.5)</td>
<td></td>
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</tr>
<tr>
<td>Control</td>
<td>.2(0.9)</td>
<td>-1.0(0.85)</td>
<td></td>
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<tr>
<td>VerbalMemory</td>
<td>t(24)=2.84</td>
<td>.03*</td>
<td>-.97</td>
<td></td>
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</tr>
<tr>
<td>Neuroflex</td>
<td>8.1(3.8)</td>
<td>9.6(4.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>7.8(4.5)</td>
<td>6.6(3.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DesignFluency Switch</td>
<td>t(28)=1.16</td>
<td>.26**</td>
<td></td>
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<tr>
<td>Neuroflex</td>
<td>5.8(2.6)</td>
<td>6.2(1.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>5.9(1.9)</td>
<td>6.0(1.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAS</td>
<td>t(28)=2.27</td>
<td>.03*</td>
<td>-.99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuroflex</td>
<td>34.8(17.2)</td>
<td>41.9(16.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>40.3(16.7)</td>
<td>41.0(16.3)</td>
<td></td>
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</tr>
</tbody>
</table>
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
COLLABORATORS AND FUNDING

MORIMOTO NEUROTHERAPEUTICS LAB
- Sarah E Cote, M.S.
- Annalisa Adams, M.A.
- Bruno Porras-Garcia, Ph.D.
- Tina Hyunn

MEDICAL SCHOOL OF SOUTHEAST UNIVERSITY, NANJING
- Jiachang Liu, M.D., Ph.D.

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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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- George S. Alexopoulos, M.D.
- Faith M. Gunning, Ph.D.
- Glen Prusky, Ph.D.
- Willie Hu, B.S.E, M.D.
- Juliana Nitis, M.D.
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.

HVLTR Total Recall in healthy elders:
- Baseline: 58th %ile
- One-week: 84th %ile

20%
Practice effects are reduced in impaired samples
Practice effects predict cognitive trajectory

Duff et al. (2011)
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.

Duff et al. (2014)
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

Current Age: 59-64 (ref)
Current Age: 65-69
Current Age: 70-74
Current Age: 75-79
Current Age: 80-84
Current Age: 85+

% of sample
Mean Cog Score (range: 0-17)
Figure 2. MMSE Cognitive Score by Nutrition/Food Insecurity Covariates, VHAS 2018
Figure 3. MMSE Cognitive Score by War Stress Exposure Covariates, VHAS 2018

aw dead Viet soldiers during war: No
Saw dead Viet soldiers during war: At least 1x
Moved due to bombing: No
Moved due to bombing: Yes, at least 1x
Exp fear of injury/death in war: No
Exp fear of injury/death in war: Yes, at least 1
Recent PTSD Symptoms:
None (ref)
Recent PTSD Symptoms: 1-15
Recent PTSD Symptoms: >15

Figure 4. MMSE Cognitive Score by Recent PTSD Symptoms, VHAS 2018
<table>
<thead>
<tr>
<th></th>
<th>Model A</th>
<th>Model B</th>
<th>Model C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nutrition/food insecurity covariates</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Experience of Severe Childhood Hunger: Only once (Ref: None reported)</td>
<td>-0.050+</td>
<td>-0.051+</td>
<td>-0.048</td>
</tr>
<tr>
<td>Experience of Severe Childhood Hunger: Multiple occasions (Ref: None reported)</td>
<td>-0.031*</td>
<td>-0.032*</td>
<td>-0.028+</td>
</tr>
<tr>
<td>Experienced weakness/illness due to food shortage during war</td>
<td>-0.030+</td>
<td>-0.031+</td>
<td>-0.023</td>
</tr>
<tr>
<td>Weight Status: Presently Underweight (BMI &lt;=18.5) (ref: Normal or overweight)</td>
<td>-0.054*</td>
<td>-0.053*</td>
<td>-0.049*</td>
</tr>
<tr>
<td><strong>War-related stressor covariates</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family member deaths due to war (Count)</td>
<td>-0.009</td>
<td>-0.009</td>
<td>-0.005</td>
</tr>
<tr>
<td>Saw dead or seriously injured civilians during war at least once (Ref: never)</td>
<td>-0.005</td>
<td>-0.007</td>
<td>0.005</td>
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<tr>
<td>Saw dead/seriously injured Vietnamese soldiers during war at least once (ref: never)</td>
<td>-0.016</td>
<td>-0.033+</td>
<td>-0.030*</td>
</tr>
<tr>
<td>Moved due to bombing during war at least once (ref: never)</td>
<td>0.008</td>
<td>0.008</td>
<td>0.003</td>
</tr>
<tr>
<td>Experienced fear of being injured or killed during war at least once (ref: never)</td>
<td>-0.023</td>
<td>-0.024</td>
<td>-0.008</td>
</tr>
<tr>
<td>Experienced exposure to agent orange (self-reported) at least once (Ref: never)</td>
<td>0.005</td>
<td>-0.003</td>
<td>0.015</td>
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<tr>
<td><strong>Combat covariates</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Engaged in combat patrols during war at least once (ref: Never)</td>
<td>0.042*</td>
<td>0.045*</td>
<td></td>
</tr>
<tr>
<td>Had a friend shot near them in battle at least once (ref: never)</td>
<td>0.009</td>
<td>0.015</td>
<td></td>
</tr>
<tr>
<td><strong>PTSD covariate</strong></td>
<td></td>
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<tr>
<td>Recent PTSD symptoms (count)</td>
<td>-0.005**</td>
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<tr>
<td><strong>Health Status Covariates</strong></td>
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<tr>
<td>CVD Conditions (Count)</td>
<td>-0.014*</td>
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<tr>
<td>Elevated A1c level (ref: normal)</td>
<td>-0.063**</td>
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<tr>
<td>Physical exercise: Infrequently (Less than weekly) (ref: never)</td>
<td>0.035*</td>
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<tr>
<td>Physical exercise: Frequently (Daily/almost daily) (ref: never)</td>
<td>0.074***</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Psychosocial covariates</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recent stressful life events (count)</td>
<td>-0.022**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family-based emotional support index (reverse coded)</td>
<td>-0.038+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>2135</td>
<td>2135</td>
<td>2135</td>
</tr>
</tbody>
</table>

+ 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.
REFERENCES


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.

<table>
<thead>
<tr>
<th>Electronic Health Record Data Source</th>
<th>All</th>
<th>Medicare</th>
<th>Inpatient</th>
<th>Outpatient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Area under the curve (sensitivity, specificity)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dementia</td>
<td>0.72</td>
<td>0.68</td>
<td>0.66</td>
<td>0.66</td>
</tr>
<tr>
<td></td>
<td>(0.69, 0.64)</td>
<td>(0.64, 0.62)</td>
<td>(0.56, 0.64)</td>
<td>(0.66, 0.59)</td>
</tr>
<tr>
<td>Alzheimer’s Disease</td>
<td>0.70</td>
<td>0.69</td>
<td>0.67</td>
<td>0.67</td>
</tr>
<tr>
<td></td>
<td>(0.62, 0.68)</td>
<td>(0.64, 0.65)</td>
<td>(0.61, 0.64)</td>
<td>(0.59, 0.64)</td>
</tr>
<tr>
<td>Related Dementia</td>
<td>0.61</td>
<td>0.62</td>
<td>0.60</td>
<td>0.53</td>
</tr>
<tr>
<td></td>
<td>(0.53, 0.64)</td>
<td>(0.55, 0.59)</td>
<td>(0.41, 0.60)</td>
<td>(0.52, 0.53)</td>
</tr>
</tbody>
</table>

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
Sex differences in dementia risk


Karen C. Schliep1, William A. Barbeau1, Kristine E. Lynch1,4, Michelle K. Sorweid1, Michael W. Vaner1, Norman L. Foster1 and Fares Qadan1,6

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

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.

<table>
<thead>
<tr>
<th></th>
<th>All-cause Dementia</th>
<th>Vascular Dementia</th>
<th>Alzheimer’s Disease</th>
<th>Other Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of Women; Adjusted Hazard Ratio (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDP</td>
<td>827</td>
<td>1.37 (1.26, 1.50)</td>
<td>55</td>
<td>1.64 (1.19, 2.26)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>178</td>
<td>1.04 (0.87, 1.24)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>594</td>
<td>1.49 (1.34, 1.65)</td>
</tr>
<tr>
<td>No HDP</td>
<td>1596</td>
<td>1.00</td>
<td>97</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>410</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1098</td>
<td>1.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Direct Effect</th>
<th>Indirect Effect</th>
<th>% Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adjusted Hazard Ratio (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.40 (1.37, 1.43)</td>
<td>1.09 (1.06, 1.12)</td>
<td>24%</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>1.40 (1.37, 1.44)</td>
<td>1.08 (1.06, 1.11)</td>
<td>32%</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1.38 (1.36, 1.42)</td>
<td>1.07 (1.03, 1.10)</td>
<td>20%</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.27 (1.25, 1.29)</td>
<td>1.20 (1.18, 1.23)</td>
<td>49%</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>1.38 (1.32, 1.38)</td>
<td>1.14 (1.11, 1.17)</td>
<td>35%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.21 (1.19, 1.24)</td>
<td>1.14 (1.12, 1.17)</td>
<td>46%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1.38 (1.35, 1.41)</td>
<td>1.10 (1.08, 1.13)</td>
<td>27%</td>
</tr>
<tr>
<td>Depression</td>
<td>1.49 (1.40, 1.57)</td>
<td>1.02 (0.96, 1.08)</td>
<td>6%</td>
</tr>
</tbody>
</table>

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
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
Thanks!
karen.schliep@utah.edu
@schliepy
https://medicine.utah.edu/dfpm/research/life-course-epi
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)

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.

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

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)

<table>
<thead>
<tr>
<th>Blood flow measurement</th>
<th>Univariable linear regression</th>
<th>Multivariable linear regression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \beta )</td>
<td>( P )</td>
</tr>
<tr>
<td>TOF artery length</td>
<td>0.605</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>SNAP artery length</td>
<td>0.520</td>
<td>(0.004)</td>
</tr>
<tr>
<td>ASL CBF</td>
<td>0.526</td>
<td>(0.003)</td>
</tr>
<tr>
<td>PC CBF</td>
<td>0.480</td>
<td>(0.008)</td>
</tr>
<tr>
<td>WMH volume</td>
<td>-0.178</td>
<td>0.355</td>
</tr>
</tbody>
</table>

^aFor one subject, the systolic blood pressure was not available. Therefore, the same size for Model 1 and Model 2 was 28.

^bModel 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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Brain Infarct Volume (N=33) (Ipsilateral)</th>
<th>Brain Infarct Volume (N=33) (Whole Brain)</th>
<th>MoCA (N=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r*</td>
<td>P-value</td>
<td>r*</td>
</tr>
<tr>
<td>Mean NWI</td>
<td>0.26</td>
<td>0.048</td>
<td>0.14</td>
</tr>
<tr>
<td>Mean WT</td>
<td>0.23</td>
<td>0.076</td>
<td>0.24</td>
</tr>
<tr>
<td>Max WT</td>
<td>0.31</td>
<td>0.017</td>
<td>0.25</td>
</tr>
<tr>
<td>Calcium % volume</td>
<td>-0.14</td>
<td>0.29</td>
<td>-0.24</td>
</tr>
<tr>
<td>LRNC % volume</td>
<td>0.29</td>
<td>0.029</td>
<td>0.34</td>
</tr>
<tr>
<td>IPH % volume</td>
<td>0.25</td>
<td>0.062</td>
<td>0.29</td>
</tr>
</tbody>
</table>

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

Baseline & Follow-up (1 year)

TOF

Baseline | Follow-up

Black Blood SNAP → Bright Blood SNAP → Tracing → Labeling

Whole brain CBF + iSNAP T1-w Image → GM CBF → Territory GM CBF → Database
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

Chun Yuan, Ph.D.
Professor, Radiology and Imaging Sciences
Adjunct Professor, Biomedical Engineering and Biomedical Informatics