Multi-Domain Trials
Diet, Exercise and Neurocognition

Institute of Medicine
Committee on the Public Health Dimensions of Cognitive Aging
Irvine, California
June 9, 2014

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Disclosure Information

No Conflicts of Interest
Key Issues

• When to intervene?
• On Whom to intervene?
• What interventions?
• What outcomes?
Hypothetical Course of An Individual’s Aging Brain

Cognitive Function

Age-Associated Memory Impairment

MCI or CIND

Alzheimer’s Disease

Prevention

Treatment

Time
On Whom Do We Intervene?

• Healthy older adults
• Adults vulnerable to dementia
  – MCI
  – CIND
  – Medical comorbidities (e.g., hypertension or cardiovascular disease, pulmonary disease)
• Patients with dementia
  – AD
  – Vascular dementia
What (Non-pharmacologic) Interventions?

• Physical Activity/Exercise
• Diet
• Cognitive training
• Combination (i.e., Multi-domain)
  – Exercise and Diet
  – Exercise and Cognitive Training
  – Diet and Cognitive Training
Non-Pharmacological Interventions

• Physical Activity
  – Aerobic (walking / jogging / running)
  – Strength Training (weight lifting)
  – Stretching / Toning

• Dietary Supplementation
  – Antioxidants (vitamins A/C/E), Flavanoids
  – Omega $n-3/n-6$ fatty acids
  – B6 / B12 / Folate

• Dietary Modification
  – DASH diet
  – Mediterranean Diet
  – Caloric Restriction

• Cognitive Training

• Combined “Multi-domain” Interventions
Multi-Domain Interventions: Evidence from Observational and Interventional Studies

- Exercise + Nutrition
- Nutrition + Supplements
- Exercise + Cognitive retraining
- Nutrition + Cognitive retraining
Physical Activity, Diet, and Alzheimer Disease
(Scarmeas et al, JAMA. 2009;302(6):627-637)

• Prospective cohort of 1,880 community-dwelling elders without dementia living in New York
• Standardized neurological and neuropsychological measures administered every 1.5 years from 1992 to 2006
• Exercise measured from self-report (GODIN)
• 61-item Food Frequency Questionnaire
• Outcome: time to incident Alzheimer Disease
Physical Activity, Diet, and Alzheimer Disease
(Scarmeas et al, JAMA. 2009;302(6):627-637)

• 282 cases over M=5.4 yrs
• Greater physical activity associated with reduced risk of AD
  – ‘Some’ physical activity: 29-41% reduced risk
  – ‘Much’ physical activity: 37-50% reduced risk
• MeDi alone reduced risk of AD:
  – 32-40% reduced risk among most adherent
• High physical activity and high MeDi combined had greatest risk reduction
### Multidomain Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>n</th>
<th>Intervention</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>SimA</td>
<td>Germany</td>
<td>375</td>
<td>CT/EX</td>
<td>9 mo</td>
</tr>
<tr>
<td>Fabre</td>
<td>France</td>
<td>32</td>
<td>CT/EX</td>
<td>2 mo</td>
</tr>
<tr>
<td>SHARP-P</td>
<td>US</td>
<td>73</td>
<td>CT/EX</td>
<td>4 mo</td>
</tr>
<tr>
<td>De Jong</td>
<td>Netherlands</td>
<td>130</td>
<td>Diet/EX</td>
<td>17 wk</td>
</tr>
<tr>
<td>Cetin et al.</td>
<td>Turkey</td>
<td>57</td>
<td>Vit E/EX</td>
<td>6 mo</td>
</tr>
<tr>
<td>van Uffelen</td>
<td>Netherlands</td>
<td>152</td>
<td>Vit B/EX</td>
<td>12 mo</td>
</tr>
<tr>
<td>MAX</td>
<td>US</td>
<td>126</td>
<td>CT/EX</td>
<td>12 wk</td>
</tr>
<tr>
<td>ENCORE</td>
<td>US</td>
<td>144</td>
<td>Diet/EX</td>
<td>4 mo</td>
</tr>
</tbody>
</table>
Results

• No Benefit—3 studies
• Some (generally modest) benefit--5 studies
  – SimA: improved psychomotor performance, reduced dementia symptoms
  – Fabre: improved memory
  – van Uffelen: improved Digit Symbol for women
  – Cetin: shortened P3 latency
  – ENCORE: improved executive functioning, memory and learning measures
Van Uffelen (2008)

- 179 patients
  - Adults age 70-80 with MCI
- 2 x 2 design
  - Vit B/Placebo
  - EX/non-aerobic activity
- 23% of patients lost to follow-up
- Fitness not assessed
- Baseline activity levels high (e.g., EX > 3x/wk)
• Neither the walking program nor Vit B supplementation improved cognition

• No difference in Mini Mental State Examination (MMSE) scores between the active intervention and placebo controls

• Adherence problematic
  o 38% dropout of EX
  o Median adherence = 63% of EX sessions
  o Only 18 women (45%) attended >75% of EX sessions

Figure 1. Median MMSE scores for (A) walking program compared to placebo activity program and (B) vitamin B pill compared to placebo pill groups. No significant difference in MMSE scores was observed between intervention and placebo groups. Higher score indicates better performance.
- Women taking Vit B scored better on Digit Symbol Substitution Test (DSST) compared to placebo
- No effect for men
- EX x Vit B interaction not examined; insufficient power to examine benefit of combining Vit B with EX
Reasons for Inconsistent Findings

- Small sample sizes
- Diverse patient samples (Healthy, MCI, etc.)
- Concurrent therapies
- Dissimilar or unspecified exercise interventions
- Different measures of neurocognition
- Changes in physical fitness/diet small or not assessed

- Methodological issues
  - Blinding of outcome ratings
  - Intention to treat analysis
  - Cherry pick results
  - Control groups
Examples of Multidomain Exercise and Diet Trials and Neurocognition

- **ENCORE Study**
  - RCT of 144 patients with high blood pressure
  - 3 group design
  - BP and cardiovascular biomarkers
  - Neurocognition

- **ENLIGHTEN Study**
  - Ongoing trial of 160 patients with CIND
  - 2 by 2 design
  - Neurocognitive functioning
  - CVD biomarkers and transition to dementia
ENCORE Purpose

• Primary
  – Examine the effects of DASH diet alone and combined with exercise and caloric restriction on blood pressure

• Secondary
  – Examine effects of DASH diet alone and combined with exercise and caloric restriction on CVD biomarkers

• Tertiary
  – Examine effects of diet and exercise and neurocognitive functioning
Study Population

• Overweight but otherwise generally healthy adults with above-optimal blood pressure

• Inclusion criteria
  – Age > 35 years
  – BMI 25-40 kg/m²
  – Sedentary (not engaged in regular exercise)
  – BP 130-159/85-99 mmHg

• Exclusion criteria
  – Treatment with antihypertensive medication
  – Secondary hypertension
  – Cardiac disease, diabetes, or chronic kidney disease
  – Dementia
Outcome measures

• Primary outcome measure
  – Resting blood pressure

• Secondary outcome measures
  – Ambulatory blood pressure
  – Vascular stiffness (pulse wave velocity)
  – Endothelial function (flow-mediated dilation)
  – Left ventricular mass (echocardiography)
  – Baroreflex sensitivity

• Tertiary outcome measures
  – Neurocognition
  – QoL
ENCORE Study Design

- Screening
- Baseline Assessments
- DASH Diet
- DASH Diet + Behavioral Weight Loss
- Usual care
- Post Intervention Assessments

Timepoints:
- Screening: 3 weeks
- Baseline Assessments: 1 week
- DASH Diet: 16 weeks
- DASH Diet + Behavioral Weight Loss: 16 weeks
- Usual care: 16 weeks
- Post Intervention Assessments: 1 week
Interventions

• Subjects were randomized to one of three interventions for 16 weeks:
  – DASH diet alone
    • 2-week feeding period plus weekly group sessions
    • Diet designed to maintain weight
  – DASH diet plus behavioral weight management program
    • DASH diet plus weekly sessions to implement cognitive behavioral weight loss program
    • Supervised exercise three times weekly
  – Usual Care
    • Maintain weight and usual dietary and activity patterns
Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>DASH + WM (N=49)</th>
<th>DASH Alone (N = 46)</th>
<th>Usual Care (N = 49)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>52.3 (10)</td>
<td>51.8 (10)</td>
<td>52.0 (10)</td>
</tr>
<tr>
<td><strong>Gender: Female (%)</strong></td>
<td>69</td>
<td>63</td>
<td>69</td>
</tr>
<tr>
<td><strong>Ethnicity: Caucasian (%)</strong></td>
<td>69</td>
<td>50</td>
<td>59</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>33.5 (4.4)</td>
<td>32.8 (3.4)</td>
<td>33.0 (3.9)</td>
</tr>
<tr>
<td><strong>Systolic BP (mmHg)</strong></td>
<td>139 (8)</td>
<td>138 (9)</td>
<td>138 (10)</td>
</tr>
<tr>
<td><strong>Diastolic BP (mmHg)</strong></td>
<td>86 (7)</td>
<td>86 (6)</td>
<td>86 (6)</td>
</tr>
</tbody>
</table>

Values are mean (SD) unless otherwise specified
Subject Retention and Adherence

• Drop-outs: 4
  – 3 in DASH + WM
  – 1 in Usual Care
• DASH dietary class attendance: 92%
• Exercise session attendance: 90%
• Exercise with target HR range: 94%
Weight

Adjusted means after treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Adjusted Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual Care</td>
<td>230 lbs</td>
</tr>
<tr>
<td>DASH Alone</td>
<td>210 lbs</td>
</tr>
<tr>
<td>DASH + WM</td>
<td>190 lbs</td>
</tr>
</tbody>
</table>

Treatment v Usual Care: p < .001
DASH + WM v DASH Alone: p < .001
## Dietary Intake

<table>
<thead>
<tr>
<th></th>
<th>DASH + WM N=49</th>
<th>DASH Alone N = 46</th>
<th>Usual Care N = 49</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fruit servings/day</td>
<td>4.0</td>
<td>3.7</td>
<td>2.6</td>
</tr>
<tr>
<td>Vegetable servings/day</td>
<td>5.5</td>
<td>5.6</td>
<td>2.6</td>
</tr>
<tr>
<td>Dairy servings/day</td>
<td>1.8</td>
<td>1.9</td>
<td>0.9</td>
</tr>
<tr>
<td>% Fat calories</td>
<td>26</td>
<td>28</td>
<td>37</td>
</tr>
<tr>
<td>Calorie (kcal)</td>
<td>1648</td>
<td>1962</td>
<td>2095</td>
</tr>
</tbody>
</table>

Values are medians unless otherwise specified.
Aerobic Capacity

Adjusted means after treatment

Peak VO₂

Treadmill Time

Treatment v Usual Care: p < .001
DASH + WM v DASH Alone: p < .001
Resting Blood Pressure
Adjusted means after treatment

Systolic

Diastolic

Treatment v Usual Care: p < .001
DASH + WM v DASH Alone: p = .023

Treatment v Usual Care: p < .001
DASH + WM v DASH Alone: p = .048
Resting Blood Pressure
Change in Blood Pressure from Baseline

<table>
<thead>
<tr>
<th>Condition</th>
<th>Systolic</th>
<th>Diastolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual Care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DASH Alone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DASH + WM</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Change in BP (mmHg)
Autonomic Function

Adjusted Means After Treatment

Baroreflex Sensitivity

Treatment v Usual Care: \( p = .216 \)
DASH + WM v DASH Alone: \( p = .047 \)
Vascular stiffness and endothelial function

Adjusted Means After Treatment

Pulse Wave Velocity

- Treatment v Usual Care: p = .002
- DASH + WM v DASH Alone: p = .033

Flow-Mediated Dilation

- Treatment v Usual Care: p < .059
- DASH + WM v DASH Alone: p = .989
Left ventricular mass index

Adjusted Means After Treatment

Treatment v Usual Care: $p = .202$
DASH + WM v DASH Alone: $p = .016$
Assessment of Cognitive Performance

• Executive Function-Memory Learning (EFML)
  – Semantic Fluency (items in a category: 1-min)
  – Controlled Oral Word Association Test (COWAT) (words starting with the same letter: 1-min each section, 3 sections)
  – Stroop Test (reading speed for words, colors, and color-words)
  – Trail Making Test (B & A) (connect the dots with numbers [A] and letters and numbers [B])
  – Digit Span forwards and backwards (remembering a string of #'s)
  – Verbal Paired Associates

• Psychomotor Speed
  – Digit Symbol Substitution Test
  – Ruff 2 & 7
ENCORE Results

EFML = Executive Function, Memory, and Learning. Smith et al, 2010
Executive function

- DASH + WM exhibited greater improvements in
  - Stroop
  - Trail Making Test
  - Verbal Paired Associates

Compared to DASH-A and UC
Psychomotor Speed

- DASH –A and DASH+WM perform better on Ruff 2 & 7 Test compared to UC
- But not on Digit Symbol
Mediators

- **DASH + WM**
  - Effects on EFML mediated by improved peak VO$_2$
    - Sobel $Z_{101} = 2.14$, $P = .032$
  - Effects on Psychomotor Speed associated with improved peak VO$_2$ and reduced weight
  - After accounting for improved peak VO$_2$, weight mediation remained significant
    - Sobel $Z_{101} = 2.21$, $P = .027$

- **DASH – A**
  - Mediators of Psychomotor Speed improvement unclear

Smith et al, 2010
Exercise and Nutritional Interventions for cognitive and cardiovascular Health ENhancement
Improved Cognitive Function

Improved Arterial Stiffness

Lower Blood Pressure

Improved Endothelial Function

Exercise & Diet

Reduced Inflammation

Improved Insulin Resistance

Improved Lipid Profile

Reduced CVD Risk
Study Design

- Screening
- Baseline Assessments
  - Exercise
  - DASH Diet
  - Combined EX / DASH
  - Health Education Control
- Post-treatment Assessments
- 18-month Follow-up Assessment

Timeline:
- 1-2 Days
- 2-3 Days
- 6 Months
- 2-3 Days
- 1 Day
Inclusion criteria

- Male or female outpatients $\geq 55$ and sedentary
- Presence of cardiac disease
  - $>2$ CVD risk factors
    - Sedentary PLUS HTN, diabetes, high lipids, smoking, or family history OR
  - History of CHD: MI, CABG, PVD, or documented CHD
    - Sedentary
- Cognitive performance consistent with CIND
  - MoCA score 19-25
  - Or $< 12$ on a lexical fluency test (letter F)
  - Or $< 15$ on animal naming test
ENLIGHTEN

• Exclusion criteria
  – Actively exercising
  – Significant neurological disease
    • Hx of stroke, Parkinson’s, Huntington's, PSP, brain tumor, NPH, seizure disorder, MS, or history of head trauma with persistent neurological deficits
  – Current psychosis or severe depression
  – History of alcohol or substance abuse/dependence within last two years
  – History of schizophrenia
  – Systemic illness or unstable medical condition that would interfere with compliance
CVD Risk Assessment

• Clinic Blood Pressure & Weight
• Vascular Assessment
  – Brachial Artery Flow-Mediated Dilation
  – Arterial Stiffness
  – Carotid Artery Intima-Media Thickness
• Inflammation
  – C-Reactive Protein, IL-6
• Genetic Biomarkers
  – APOE
Neurocognitive Assessments

- **Language**
  - Controlled Oral Word Association Test
  - Animal Naming Test

- **Memory / Learning**
  - Hopkins Verbal Learning Test
  - Complex Figure Test

- **Executive Function / Attention**
  - Digit Symbol Substitution Test
  - Digit Span Test
  - Trail Making Test
  - Stroop Test
  - Ruff 2&7 Test

*Modification of battery recommended by Neuropsychological Working Group for vascular cognitive disorders*
Summary

• Lifestyle interventions show some promise for improving neurocognitive functioning
• Synergistic effects of combining interventions not well-established
• Methodological quality of most studies is fair-poor.
• Lack of common assessments of neurocognition and different lifestyle interventions make direct comparisons difficult between studies.
Recommendations

• Establish a common ‘core’ neurocognitive battery used across investigative teams
• Define optimal interventions
  – Exercise
  – Diet/Nutritional supplements
  – Cognitive retraining/Mental Activity
• Determine appropriate controls
• Consider multi-center trials targeting specific patient groups
“Well, I see my time is about up...”