Highlights from 25 Years of the Women’s Health Initiative Memory Study (WHIMS)

Steve Rapp, PhD for the WHIMS Team
Professor
Departments of Psychiatry & Behavioral Medicine and Social Science & Health Policy
Wake Forest School of Medicine
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Women ‘s Health Research Day
Disclosures

• Nothing to disclose
Women’s Health Initiative Memory Study (1995-present)

Sally Shumaker, PhD
Wake Forest
Women’s Health Initiative

Observational Study
93,676

Clinical trials

Dietary Modification
48,837

Calcium
Vit D
36,282

Hormone Program

E+P
16,608

E alone
10,739
WHIMS Clinical Centers

Portland, OR
Sacramento, CA
Reno, NV
Oakland, CA
Stanford, CA
Los Angeles, CA
Orange, CA
San Diego, CA
Tucson, AZ
Honolulu, HI
San Antonio, TX
Houston, TX
Gainesville, FL
Birmingham, AL
Atlanta, GA
Memphis, TN
Pittsburgh, PA
Cincinnati, OH
Columbus, OH
Memphis, TN
Minneapolis, MN
Milwaukee, WI
Madison, WI
Chicago, IL
Pittsburgh, PA
Cincinnati, OH

Clinical Center
Minority Clinical Center
WHIMS Study Design (65-79 yrs. of age)

Hysterectomy

- Women who had no uterus at start of study
  - Ended: 2/29/04

- Women who had a uterus at start of study
  - N=4,532
  - Ended: 7/9/02

  YES
  - Conjugated equine estrogen (CEE) 0.625 mg/d
  - Placebo

  NO
  - CEE 0.625 mg/d + medroxyprogesterone acetate (MPA) 2.5 mg/d
  - Placebo
WHIMS Study Design (cont’d.)

**Primary Outcome:**
- Probable Dementia (PD)

**Secondary Outcomes:**
- Combined PD + Mild Cognitive Impairment (MCI)
- Global Cognitive Function

HT Trial Design = 7 years

HT trials stopped early due to harm

Average Follow-up 5.2 years

Average Follow-up 4.1 years

Primary Outcome: Probable Dementia (PD)

Secondary Outcomes:
- Combined PD + Mild Cognitive Impairment (MCI)
- Global Cognitive Function
WHIMS Suite of Studies 1996-2019

WHIMS N=7,479

WHIMS Extension N=4,174

WHIMS MRI-1 N=1,403

WHIMS MRI-2 N=1,193

WHIMS ECHO N=3,939

WHISCA N=2,302

WHISCA Extension N=1,230

WHIMS-Younger N = 2,550
WHIMS Methodology (1996/98-2008)

1. Annual administration of global cognitive measure (Modified Mini Mental State Exam)
2. If triggered, full neuropsychiatric eval, neurocognitive test battery, proxy interview, labs, CT at local clinic
3. Central adjudication of No Cognitive Impairment, MCI or probable Dementia
4. Repeat steps 1-3 unless adjudicated PD
WHIMS-ECHO Methodology (2009-present)

1. **Annual** administration of validated telephone **cognitive battery**
2. If triggered, administration of Dementia Questionnaire to proxy
3. **Central adjudication of No Cognitive Impairment, MCI or probable Dementia**
4. Repeat steps 1-3 unless adjudicated PD
5. If deceased, administer DQ to proxy
WHIMS Hypotheses

Does random assignment to conjugated equine estrogen (with and without progesterone) reduce the incidence of Dementia/Mild Cognitive Impairment and reduce global cognitive decline in postmenopausal women (>65 years old) compared to placebo?
HT is associated with an increased incidence of Dementia and Any Impairment (Dementia+Mild Cognitive Impairment)

Mean Duration of Trials:
CEE+MPA: 4.2 yrs; CEE-Alone: 5.4 yrs

HT is associated with poorer global cognitive function

Did the adverse effect of HT continue after the trial ended?

Assignment > 65 years of age at enrollment to HT was associated with small broad-based decrements in global cognitive function and several domain-specific cognitive functions that persist.

Does HT adversely affect the brain?

**CEE with and without MPA was associated with small but significant decrements in hippocampal and frontal regions**


A widespread pattern of significant volume loss was detected in women undergoing HT mainly in the anterior cingulate and adjacent medial frontal gyrus, and the orbitofrontal cortex using voxel-based morphometry


**CEE did not affect rates of decline in brain volumes or increases in brain lesion volumes in the 4.7 years following the end of HT trial.**

Coker et al Neurology 2014;82:427-434
HT Associated with Smaller Total Brain Volume Among Women with Cognitive Impairment

HT Differentially Affects Brain Volumes and Risk of Dementia for Women With Diabetes

‘Window of Opportunity’ Hypothesis:
Does exposure to HT close to the menopausal transition affect the risk of cognitive decline and impairment?

“CEE-based therapies produced no overall sustained benefit or risk to cognitive function when administered to women aged 50 to 55 years.”

Espeland et al, JAMA Internal Medicine, 2013;173(15):1429-1436
Cardiovascular disease and risk of cognitive decline

Over 8.4 years of follow-up among women with CVD, the risk of cognitive decline…

- 29%
- 45% increased risk for women w hx of Angina
- Doubled risk w hx of MI

Among women without CVD....
- Hypertension increased risk of cognitive decline
- Diabetes increased risk of cognitive decline

Among women with CVD
- Diabetes increased risk of cognitive decline

Haring, et al J Am Heart Assoc 2013;2:e000369
In women >65 yr free of CVD, those with lower baseline cognitive function and faster decline in global cognitive function were at greater risk for incident CVD, CVD death and all-cause mortality

Hypertension, cognitive function and the brain

BP at WHI baseline was strongly related to amount of white matter lesion volume 8 years later. Women with HTN (>140/90 mm Hg) had more white matter lesion volume in most brain regions, esp. the frontal lobe.

Is obesity associated with poorer cognitive and poorer brain health in older women?

*Worse cognitive performance is associated with all-cause weight loss in older women*

Driscoll et al, Obesity, 2011;19:1595-1600

*Obesity predicted less brain atrophy and lower ischemic lesion loads.*

Is diet associated with cognitive impairment?

Over an average of 9.7 yrs., higher Dietary Inflammatory Index score was associated with greater cognitive decline and earlier onset of cognitive impairment

Retinopathy, cognitive function and the brain

Presence of retinopathy was associated with poorer cognitive function (3MS) over 10-yr. follow-up and greater ischemic volumes in total brain and parietal lobe.

Haan et al, Neurology, 2012;78:942-949
Air pollution, the brain and cognitive decline

Residing in places with fine particulate matter exceeding EPA standards increased the risks for global cognitive decline and all-cause dementia respectively by 81% and 92%, with stronger adverse effects in APOE ε4/4 carriers.


Greater particulate matter exposure was associated with smaller WM and GM volumes

Chen et al, Ann Neurol 2015;78:466-476
Casanova et al Front in Human Neurosci, 2016;10.495
WHIMS Innovations

**Telephone administration of cognitive tests and questionnaires in older women is reliable and valid**

Rapp et al, J Amer Geri Soc, 2012;60:1616-1623

**Supplemental Case Ascertainment Protocol, a proxy-based interview reduced biases in estimated incidence rates and risk factor relationships**


**Using machine learning approach applied to ADNI imaging and cognitive data, Alzheimer’s Disease Pattern Similarity Scores distinguished well between women with and without cognitive impairment in WHIMS cohort**

Casanova et al PLoS One, 2013;8:e77949
Opportunities to Collaborate in WHIMS, WHI

Resources

• Large cohorts (WHI, WHIMS and many ancillary studies)
• Deep phenotyping
• Genotyping
• Bio specimens
• Imaging studies

Opportunities

• Propose papers
• Propose ancillary studies
• WHI Extension 2020-2025
• WHIMS 2021-?
WHIMS Team

• Sally Shumaker, PhD
• Mark Espeland, PhD
• Steve Rapp, PhD
• Laura Coker, PhD
• Claudine Legault, PhD
• Sarah Gaussoin, MS
• Maggie Dailey, PhD
• Dan Beavers, PhD
• Bev Snively, PhD
• Iris Leng, PhD
• Kate Hayden, PhD
• Leslie Vaughan, PhD
• Ramon Casanova, PhD
• Laura Baker, PhD
• Katie Garcia, MS
• Mark Brown, MS
• Darrin Harris, BS
• Julia Robertson, BS
• Patricia Hogan, MS
• Beverly Jones, MD
• John Absher, MD
• Valerie Wilson, MD

NIA
• Susan Resnick, PhD

WHIMS Staff
• Debbie Pleasants
• Cheryl Summerville
• Sonya Ashburn
• Debbie Booth
• Doris Clark
• Ashley Lentz
• Heather Dailey
• Brad Caudle
• Debbie Allen
• Gina Miller
• Josh Evans
• Debbie Felton
• Pam Nance

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Related Ancillary Studies

• *Cocoa Supplement and Multivitamin Outcomes Study in the Mind* (COSMOS-MIND; Laura Baker PI)

• *Women’s Health Initiative Sleep Hypoxia Effects on Resilience* (WHISPER; Laura Baker PI)

• *Investigating the Biology of Cognitive Resilience in WHIMS “APOE ε4 Escapees”* (Susan Resnick, PI)
Thank you
Cognitive Studies Timeline

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<thead>
<tr>
<th>Study/Extension</th>
<th>Start</th>
<th>End</th>
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<tr>
<td>WHIMS (E+P), n=4,532</td>
<td>5/96</td>
<td>7/02</td>
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<tr>
<td>WHIMS (E-alone), n=2,947</td>
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<td>4/04</td>
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<td>WHISCA, n=2,302</td>
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<td>WHIMS Extension, (E+P &amp; E-alone), n=4,174</td>
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