

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

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April 17, 2019

Women 's Health Research Day



Disclosures

- Nothing to disclose

Women's Health Initiative Memory Study (1995-present)

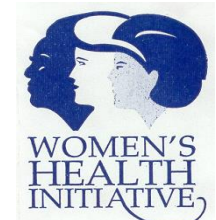
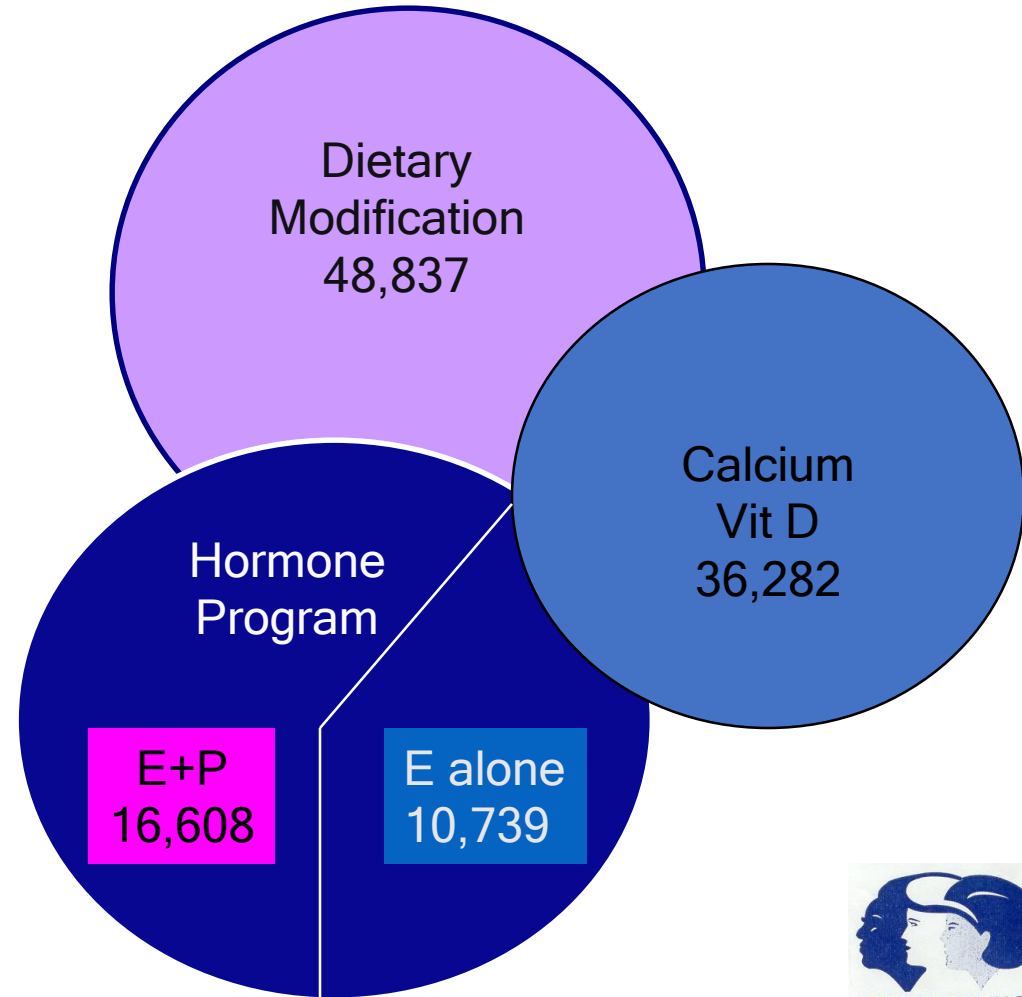
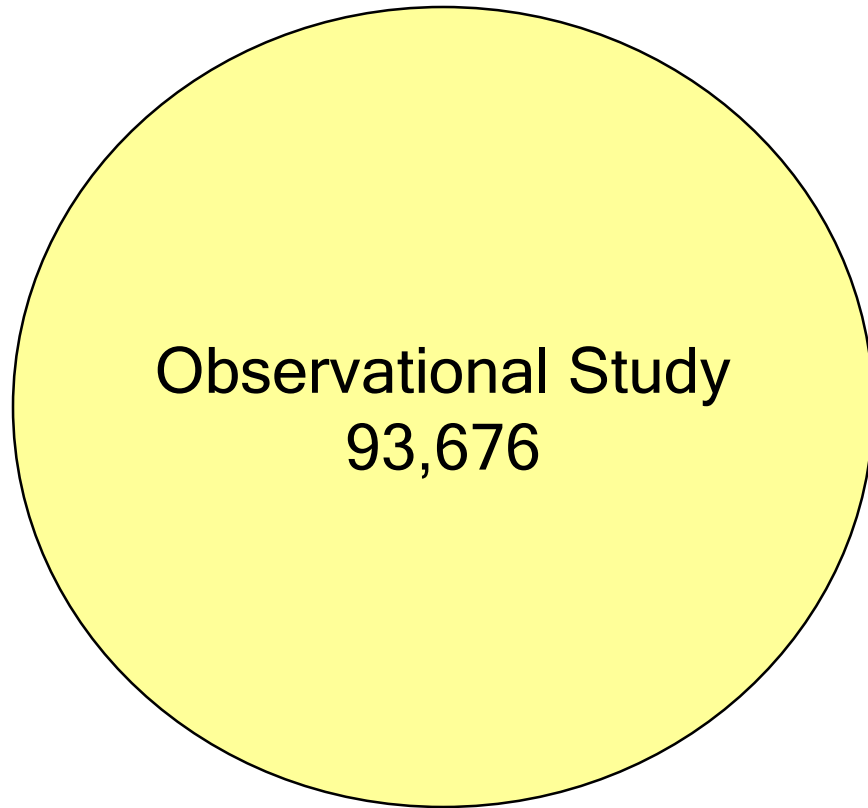


Sally Shumaker, PhD
Wake Forest

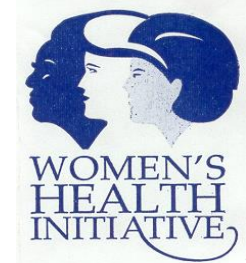
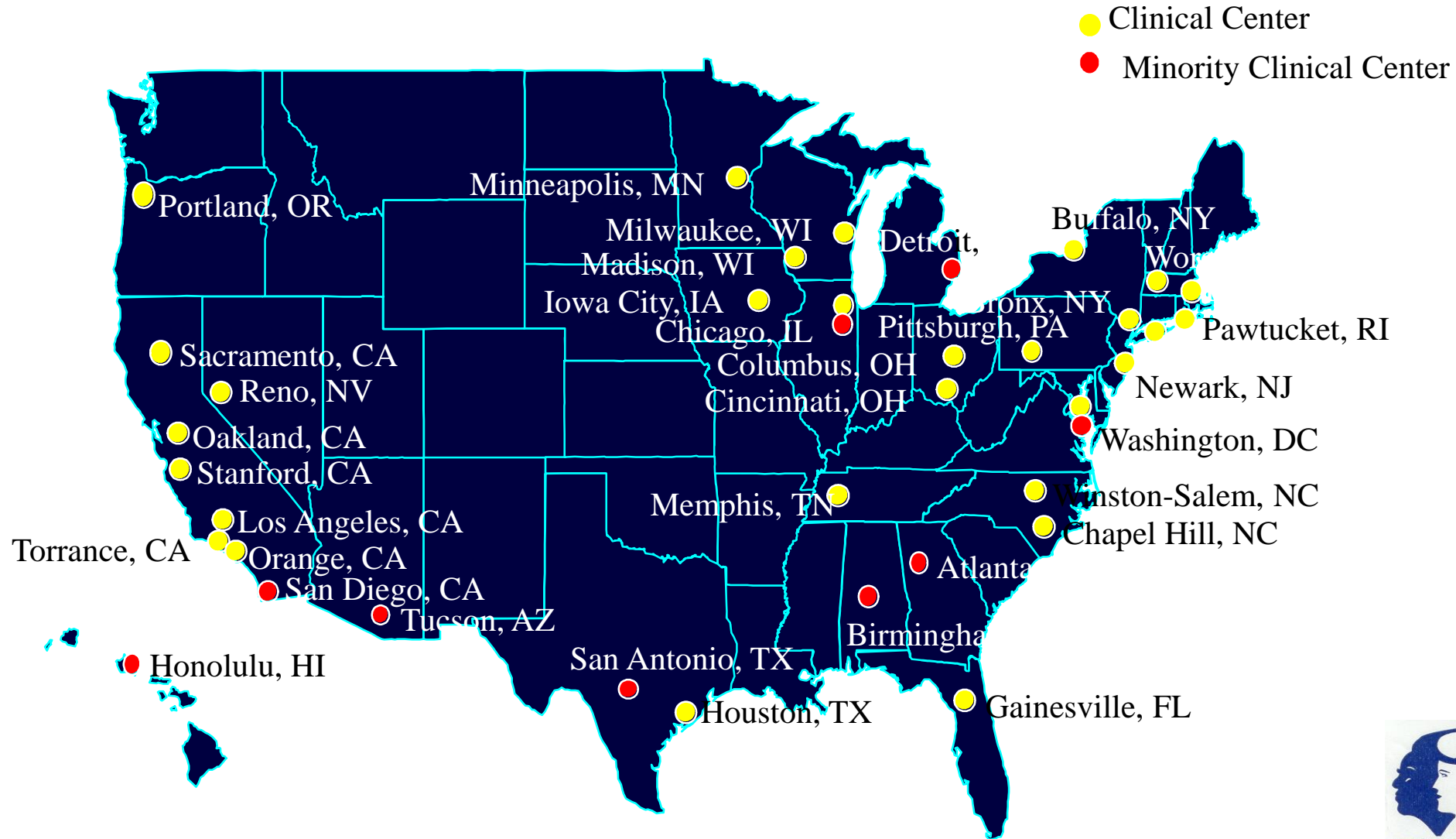


Women's Health Initiative

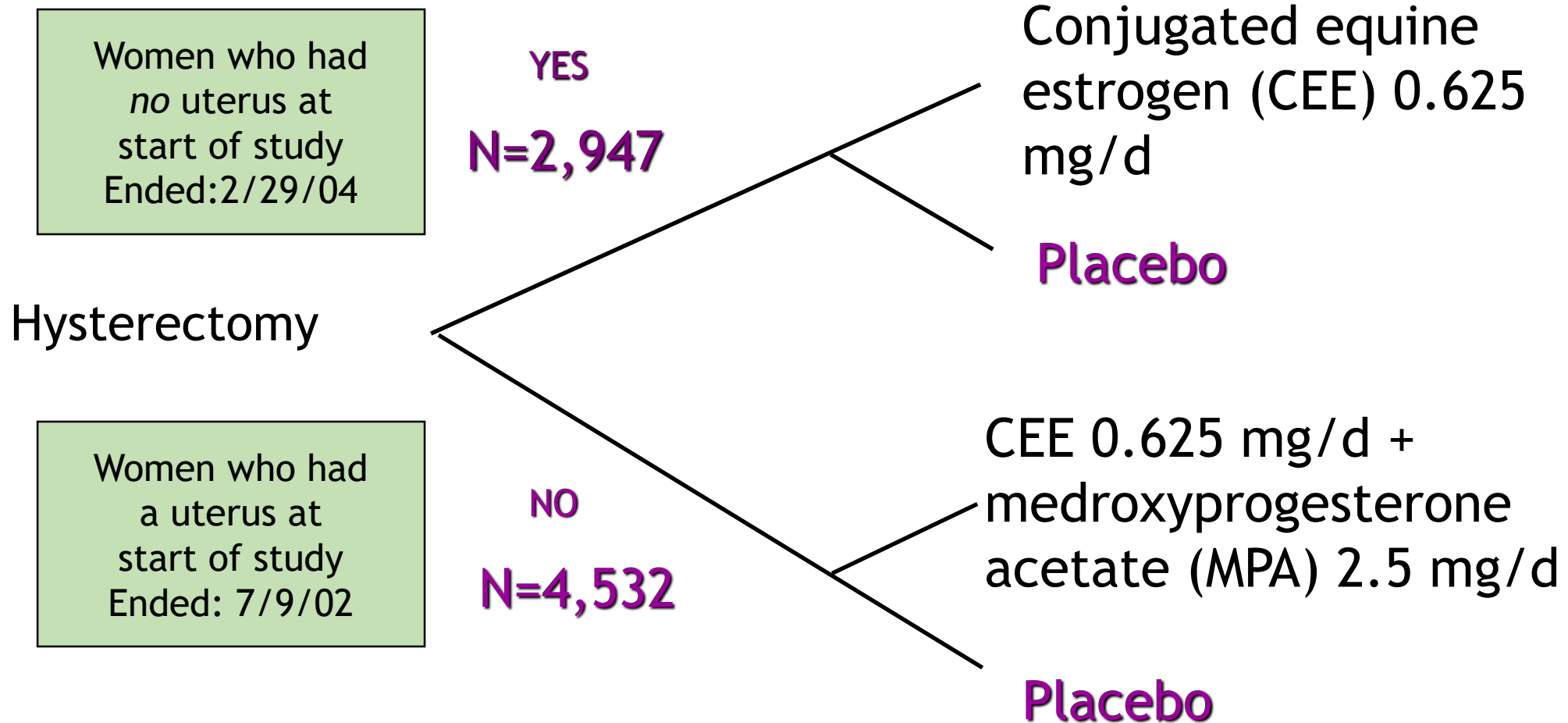
Clinical trials



WHIMS Clinical Centers



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



WHIMS Study Design (cont'd.)

7,479

HT Trial Design = 7 years

HT trials stopped early
due to harm

Primary Outcome:

- Probable Dementia (PD)

Secondary Outcomes:

- Combined PD + Mild Cognitive Impairment (MCI)
- Global Cognitive Function

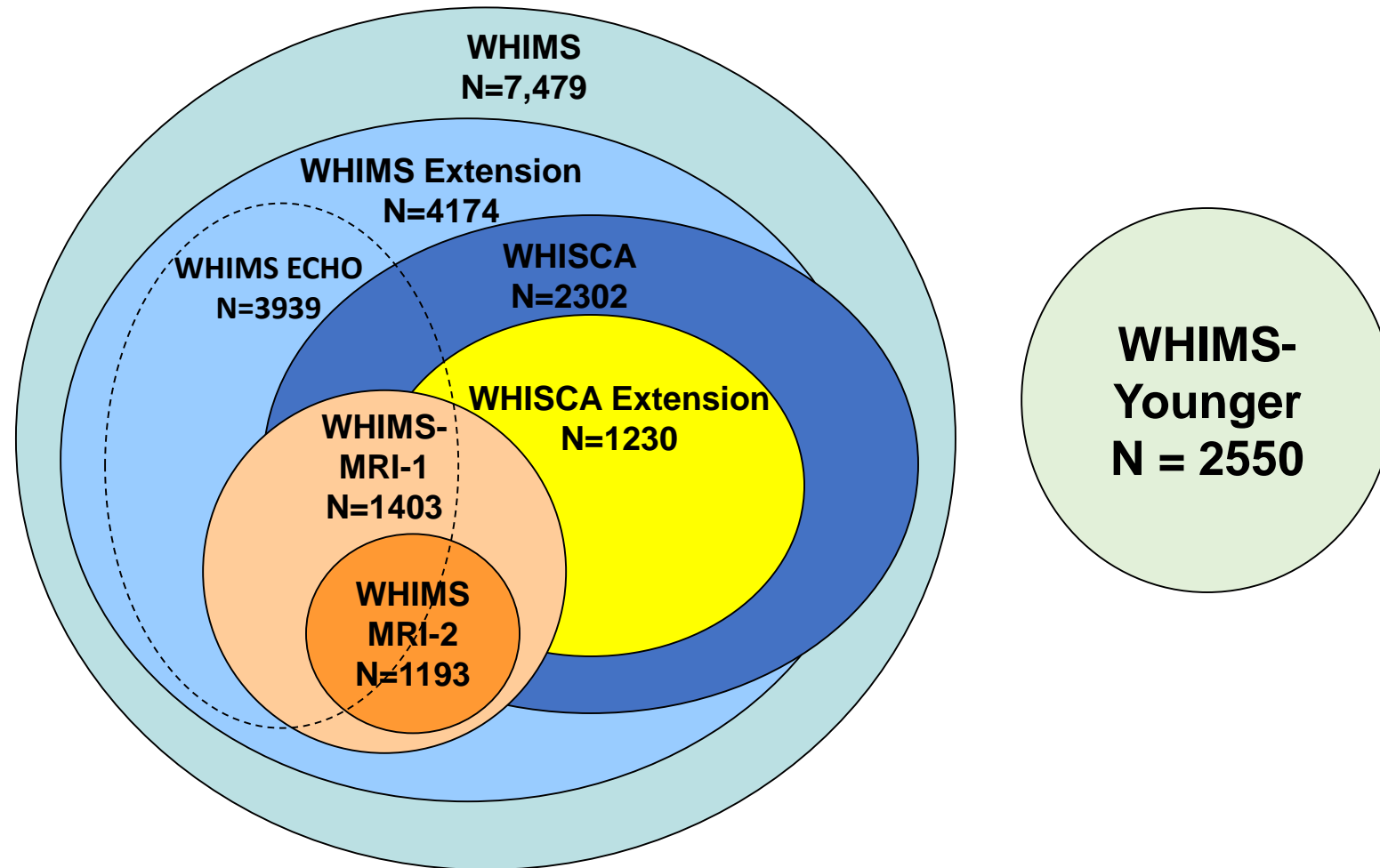
**E-alone
(CEE)
2947**

**Average
Follow-up
5.2 years**

**E+P
(CEE+MPA)
4532**

**Average
Follow-up 4.1
years**

WHIMS Suite of Studies 1996-2019



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)

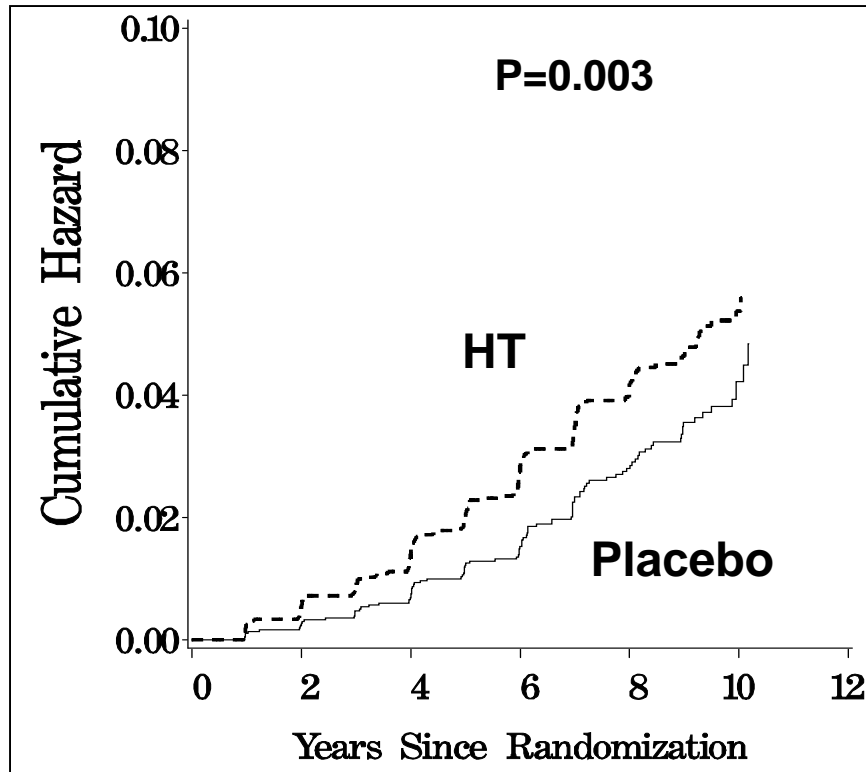
1. Annual administration of validated telephone cognitive battery
2. If triggered, administration of Dementia Questionnaire to proxy
3. Central adjudication of No Cognitive Impairment, MCI or probable Dementia
4. Repeat steps 1-3 unless adjudicated PD
5. If deceased, administer DQ to proxy

WHIMS Hypotheses

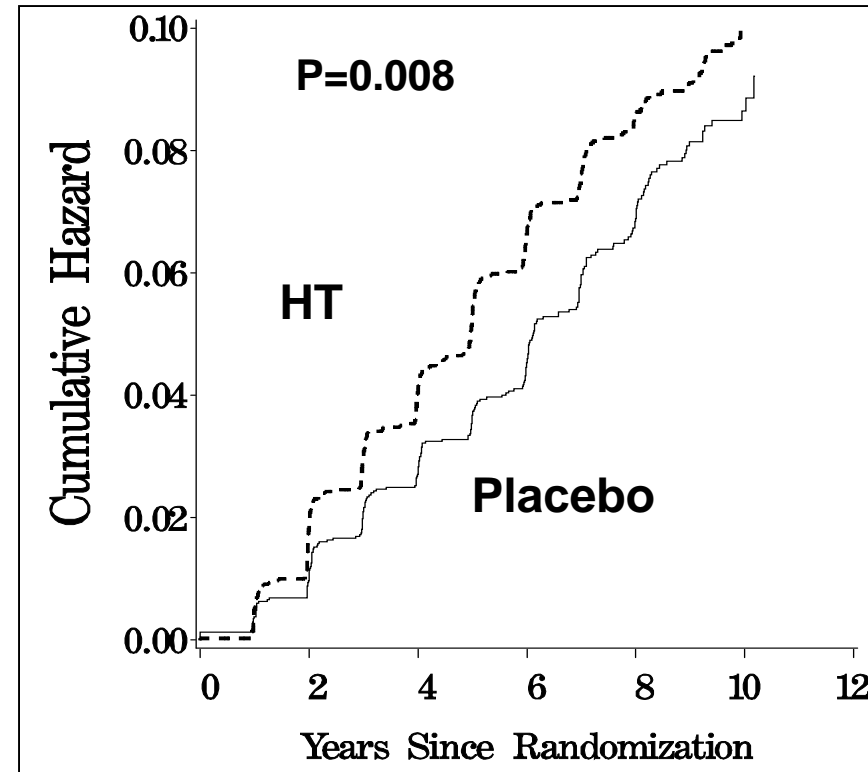
Does random assignment to conjugated equine estrogen (with and without progesterone) reduce the incidence of Dementia/Mild Cognitive Impairment and reduce global cognitive decline in postmenopausal women (>65 years old) compared to placebo?

HT is associated with an increased incidence of Dementia and Any Impairment (Dementia+Mild Cognitive Impairment)

Probable Dementia



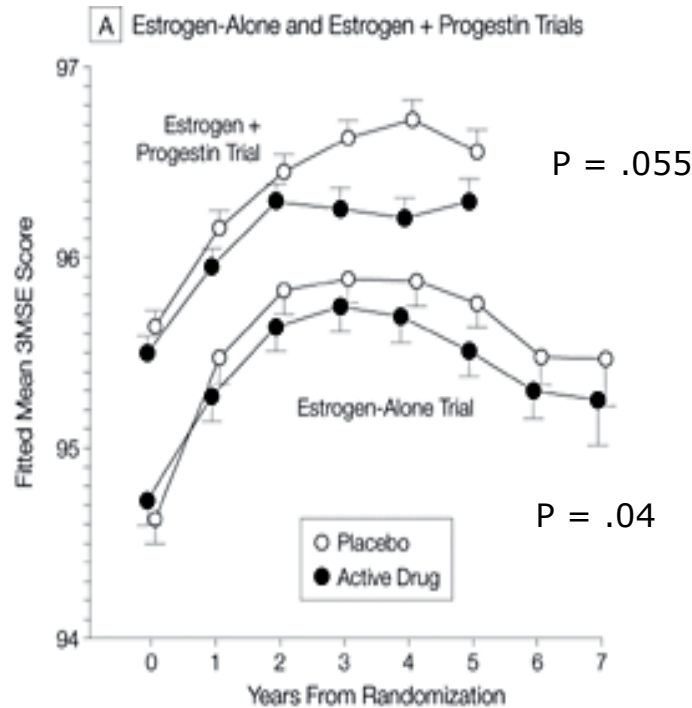
Any Impairment



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

Shumaker, et al. JAMA 2003;7:217-23.
Shumaker, et al. JAMA 2004;291:2947-58.

HT is associated with poorer global cognitive function



No. of Women

Estrogen + Progestin Trial

Placebo

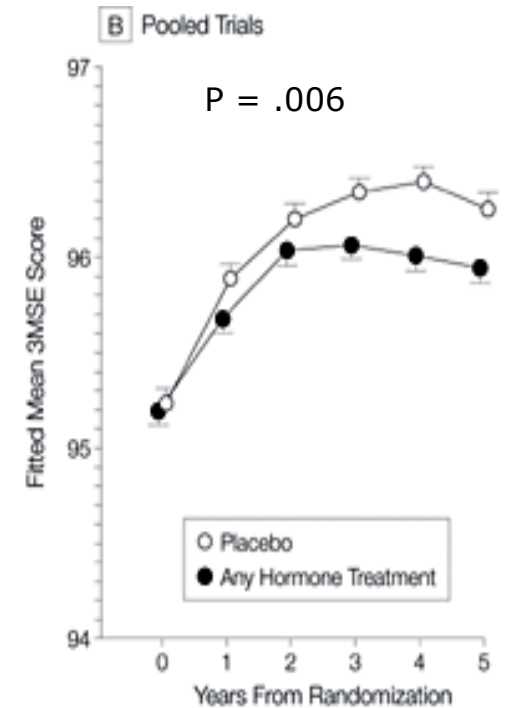
Estrogen + Progestin

Estrogen-Alone Trial

Placebo

Estrogen

2213	2165	2078	2060	1853	822		
2131	2088	2010	1992	1803	880		
1421	1381	1313	1309	1191	1148	1088	209
1387	1355	1278	1261	1199	1121	1052	204



No. of Women

Placebo

Any Hormone Treatment

3634	3546	3391	3369	3044	1970
3518	3443	3278	3253	3002	2001

Rapp SR, et al. JAMA 2003;289:2663-2672
Espeland MA, et al. JAMA 2004;291:2959-2968.

JAMA

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.

Espeland, et al, J Amer Geri Soc, 2010; 58:1263-1271

Espeland, et al, J Gerontol Med Sci, 2017;72:838-845

Does HT adversely affect the brain?

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

Resnick et al, Neurology, 2009;72:135-142

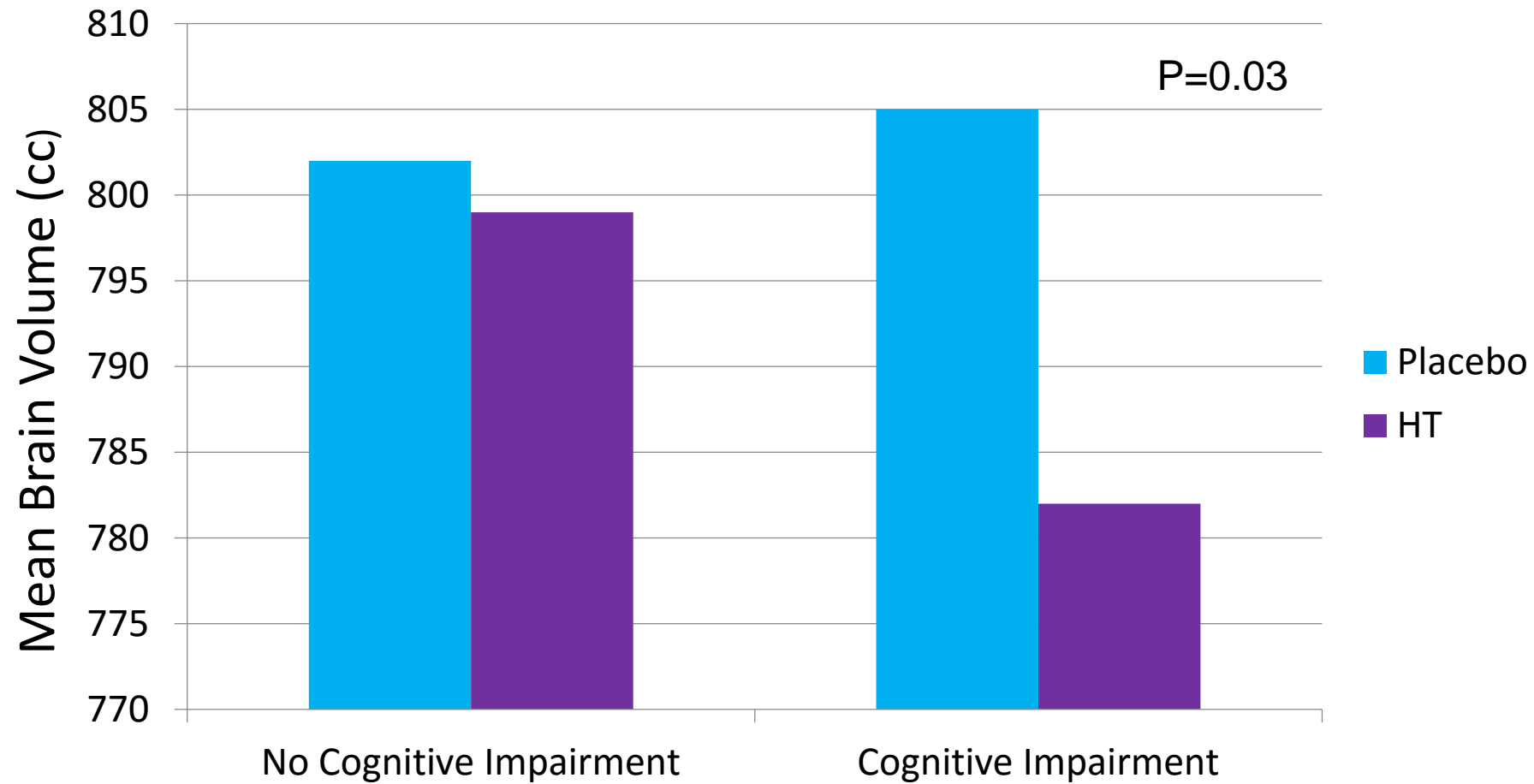
A widespread pattern of significant volume loss was detected in women undergoing HT mainly in the anterior cingulate and adjacent medial frontal gyrus, and the orbitofrontal cortex using voxel-based morphometry

Zhang, T. et al PLoS ONE,2011;11:e0150834

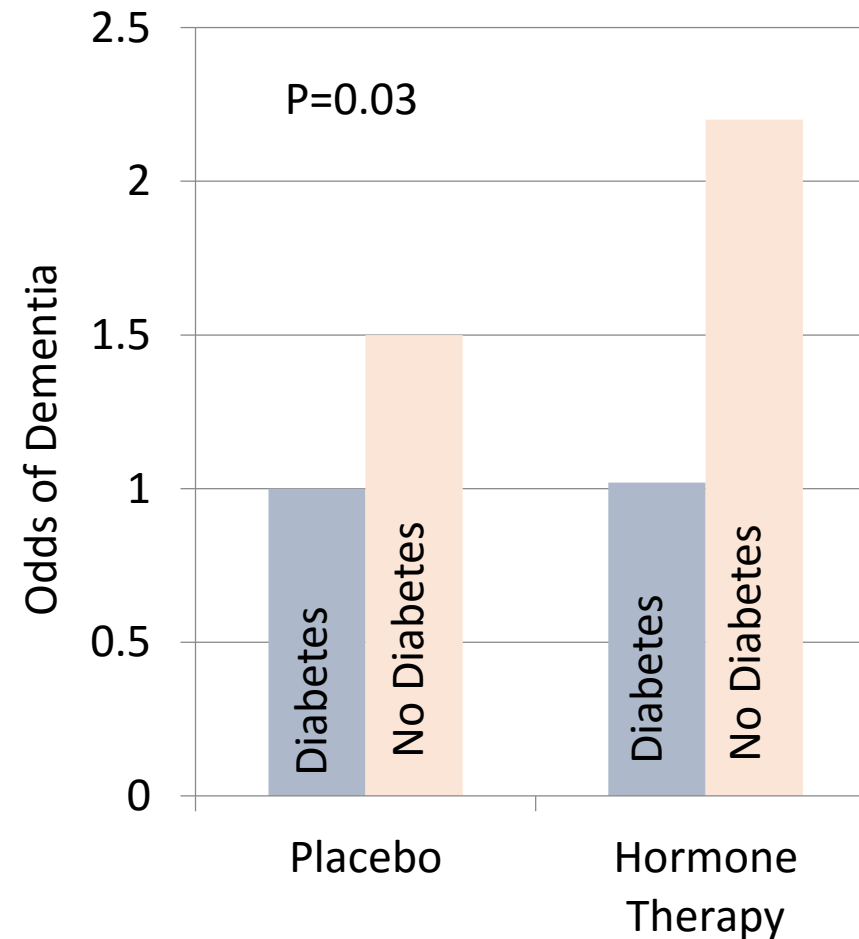
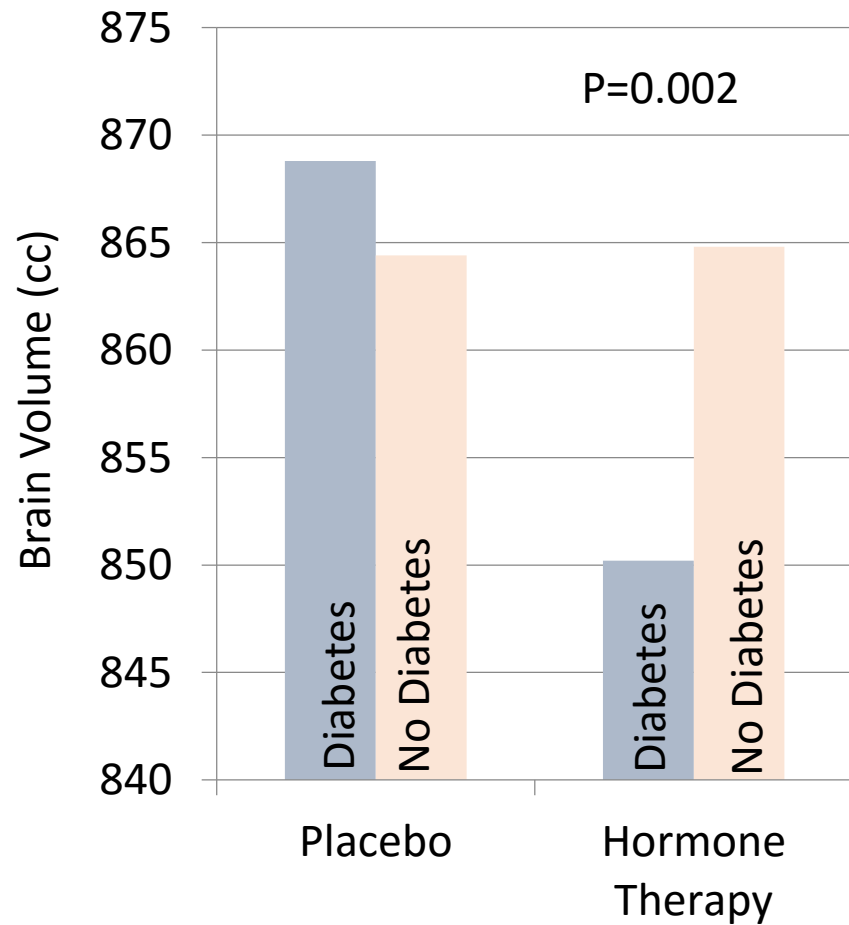
CEE did not affect rates of decline in brain volumes or increases in brain lesion volumes in the 4.7 years following the end of HT trial.

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



Espeland, et al. *Diabetes Care* 2015;38:2316-24.

Espeland, et al. *Neurology* 2015;29;85:1131-8.

‘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

Does cognitive decline predict CVD, mortality?

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

Leng et al, J Gerontol A Biol Sci Med Sci, 2018;73:779-785

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 ($\geq 140/90$ mm Hg) had more white matter lesion volume in most brain regions, esp. the frontal lobe.

Kuller et al, J Clin Hypertension, 2010;12:203-212

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.

Driscoll et al, *J Gerontol Med Sci*, 2016;71:1216-1222

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

Hayden, K. et al, *Alzheimer's Dementia*, 2017;13:1187-1196

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.

Cacciottolo M, et al., Transl Psychiatry. 2017 Jan 7(1):e1022

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

Gaussoin et al Int J Geri Psychiatry, 2012;27:205-214.

*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

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WHIMS ECHO and WHIMS-Y are supported by the National Institute of Aging (HHSN271-2011-00004C). The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services. Wyeth Pharmaceuticals;



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 ϵ 4 Escapees"** (Susan Resnick, PI)

Thank you

A large, vibrant pink brushstroke graphic that sweeps across the center of the slide, partially overlapping the text.

WHIMS
Women's Health Initiative Memory Study

Cognitive Studies Timeline

