WHIMS
The Women's Health Initiative Memory Study

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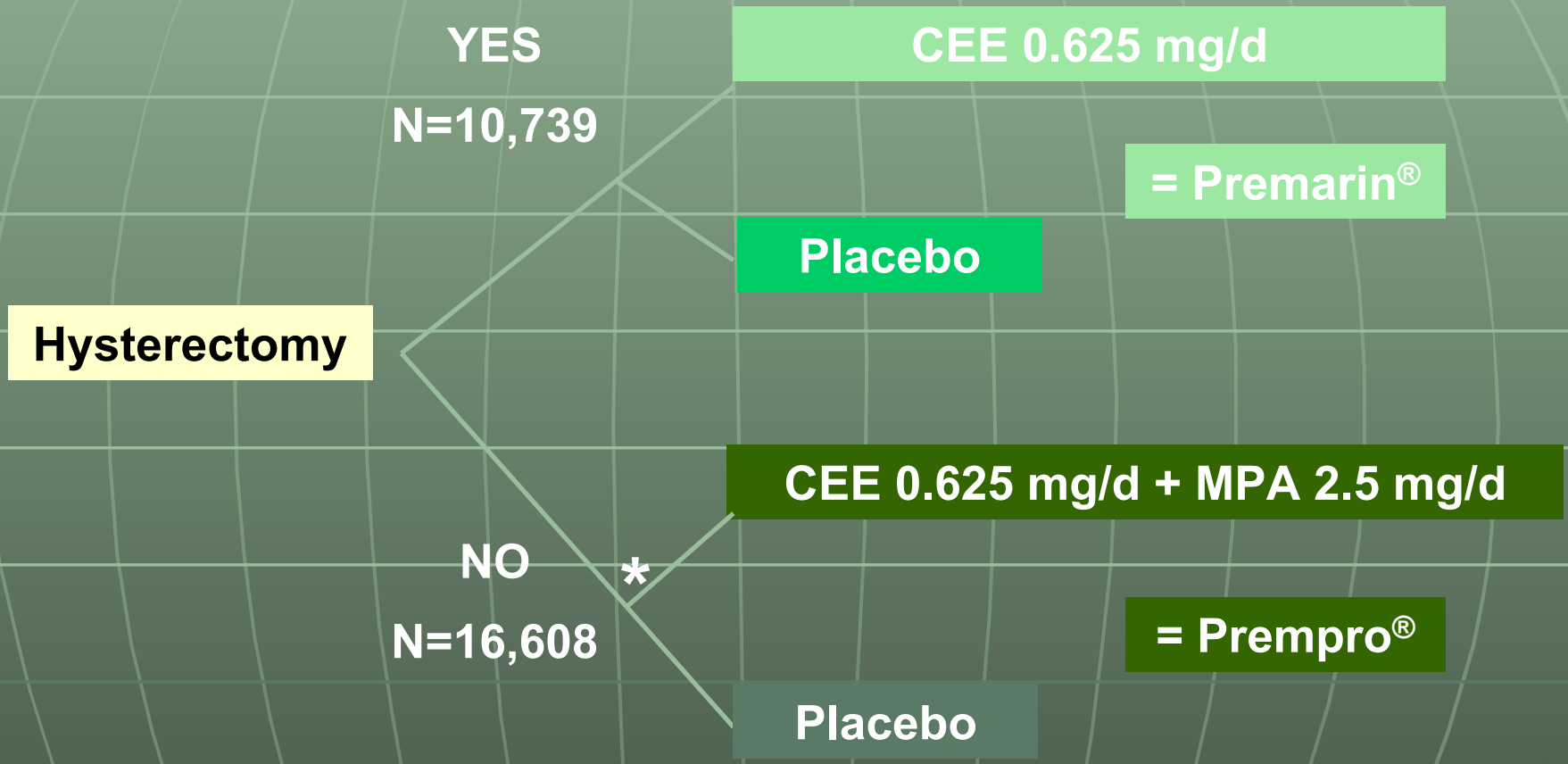
WHI/MS Clinic staff
WHI/MS Participants
WHIMS External Advisors

WHIMS Specific Aims

- PRIMARY: Does HT (E + P and E-alone) reduce incidence of:
  - Dementia (any cause)?
  - Dementia caused by Alzheimer disease (AD)?
  - Mild cognitive impairment?
- SECONDARY: Does HT improve global cognition?

Shumaker SA, et al. *Control Clin Trials*. 1998;19:604-621.

WHI Hormone Program Design



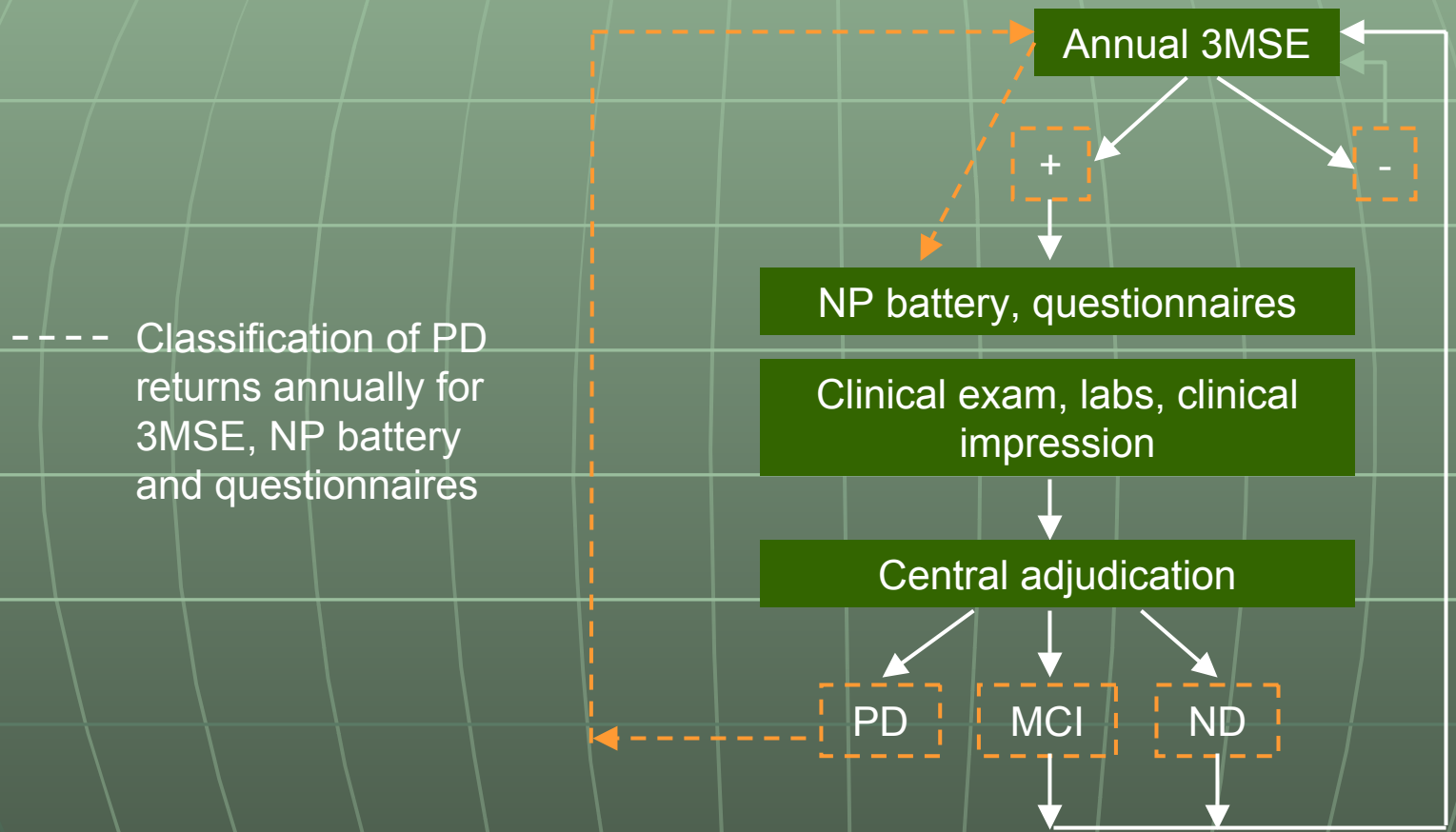
CEE=conjugated equine estrogen; MPA=medroxyprogesterone acetate.
*Initially: CEE only (n=331), CEE + MPA, or placebo.
(CEE only was subsequently converted to CEE + MPA).
WHI Study Group. *Control Clin Trials*. 1998;19:61-109.

WHIMS

- Approximately 7,500 non-demented women aged 65-80 years with and without a uterus
- 39 clinical centers and WHI CCC

Shumaker SA, et al. *Control Clin Trials*. 1998;19:604-621.

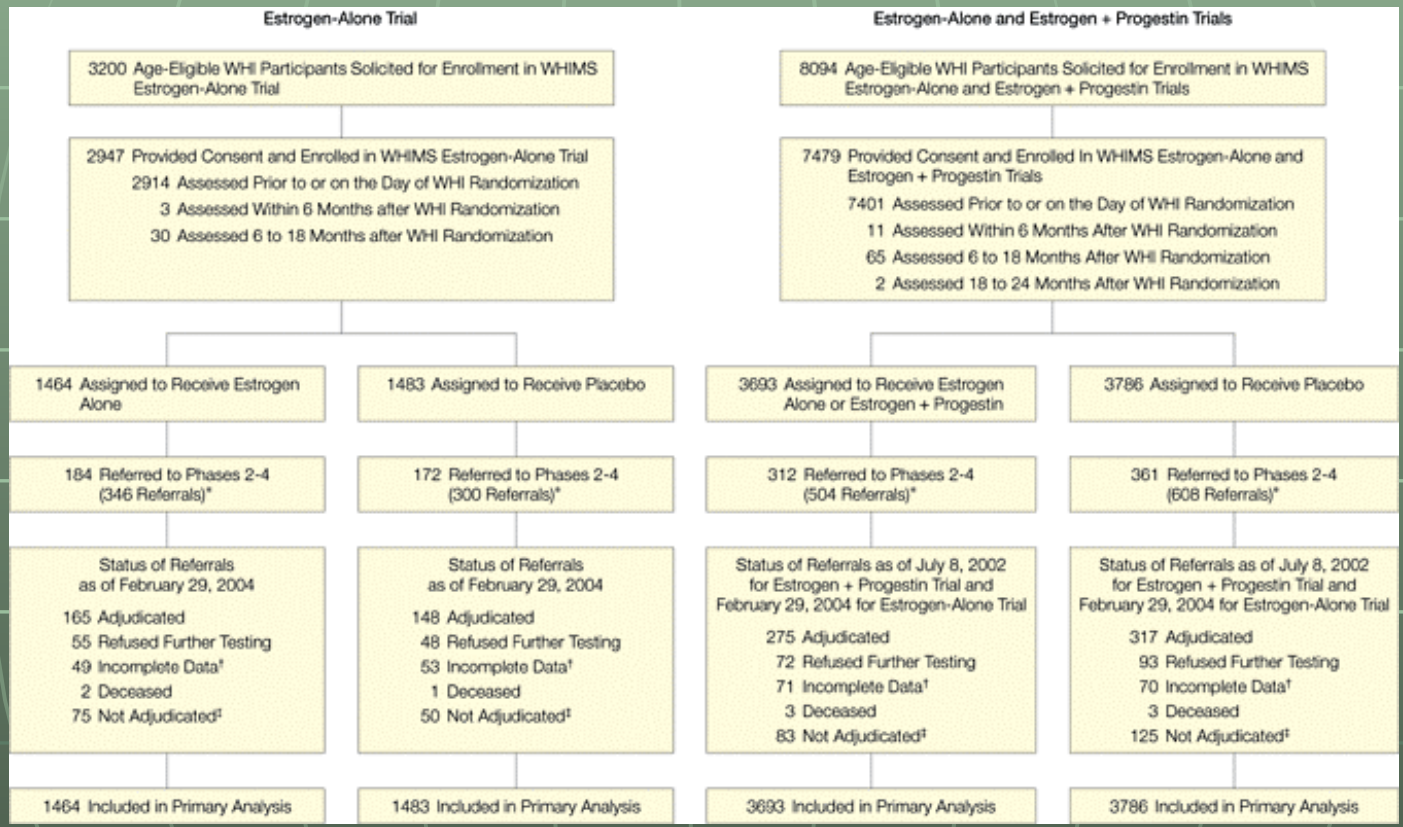
WHIMS Methodology



NP=neuropsychological; PD=probable dementia; MCI=mild cognitive impairment; ND=no dementia.

Shumaker SA, et al. *JAMA*. 2003;289:2651-2662.

Flow of Participants Through the WHIMS Estrogen-Alone Trial and the Combined Estrogen-Alone and Estrogen + Progestin Trials



Shumaker, S. A. et al. JAMA 2004;291:2947-2958.

JAMA

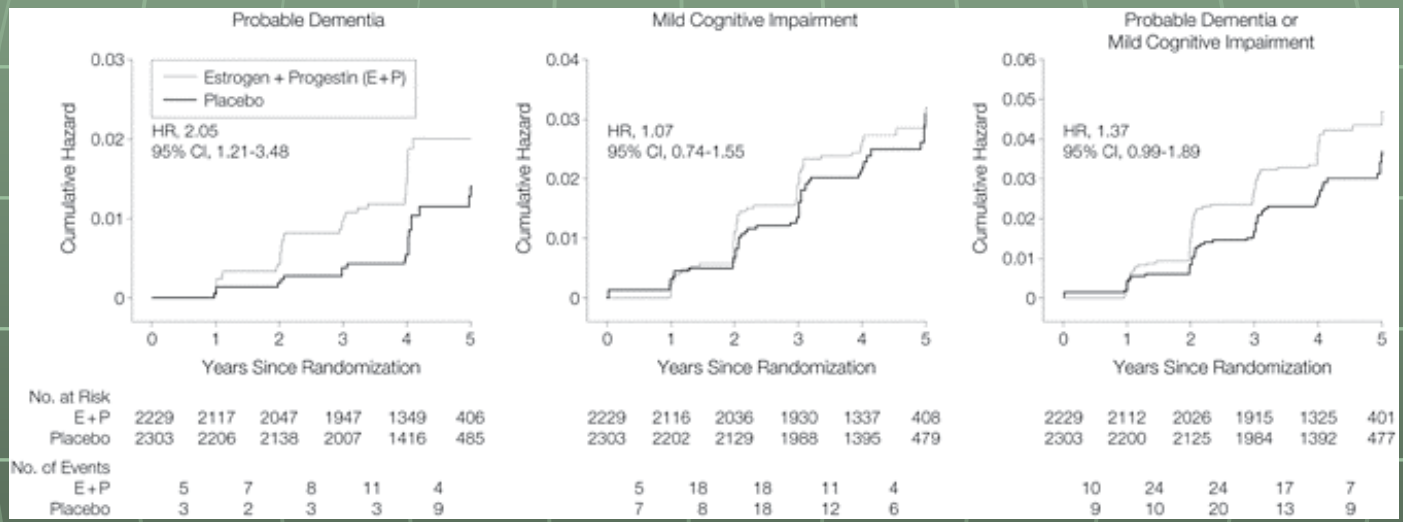
WHIMS: Selected Results

	E+P	Placebo	E-alone	Placebo
N	2229	2303	1464	1483
% 65-69 yr	47	47	44	45
% 70-74 yr	35	36	38	35
≥ 75	18	17	18	21
Mean yr. follow-up	4.01	4.06	5.16	5.20
# dementia cases	40	21	28	19
Rate per 10,000 per-yr	45	22	37	25
# MCI cases	56	55	76	58

Shumaker, S. A. et al. JAMA 2004;291:2947-2958.

Cumulative Hazards Ratios for a Diagnosis of Probable Dementia and Mild Cognitive Impairment for Women on Estrogen + Progestin

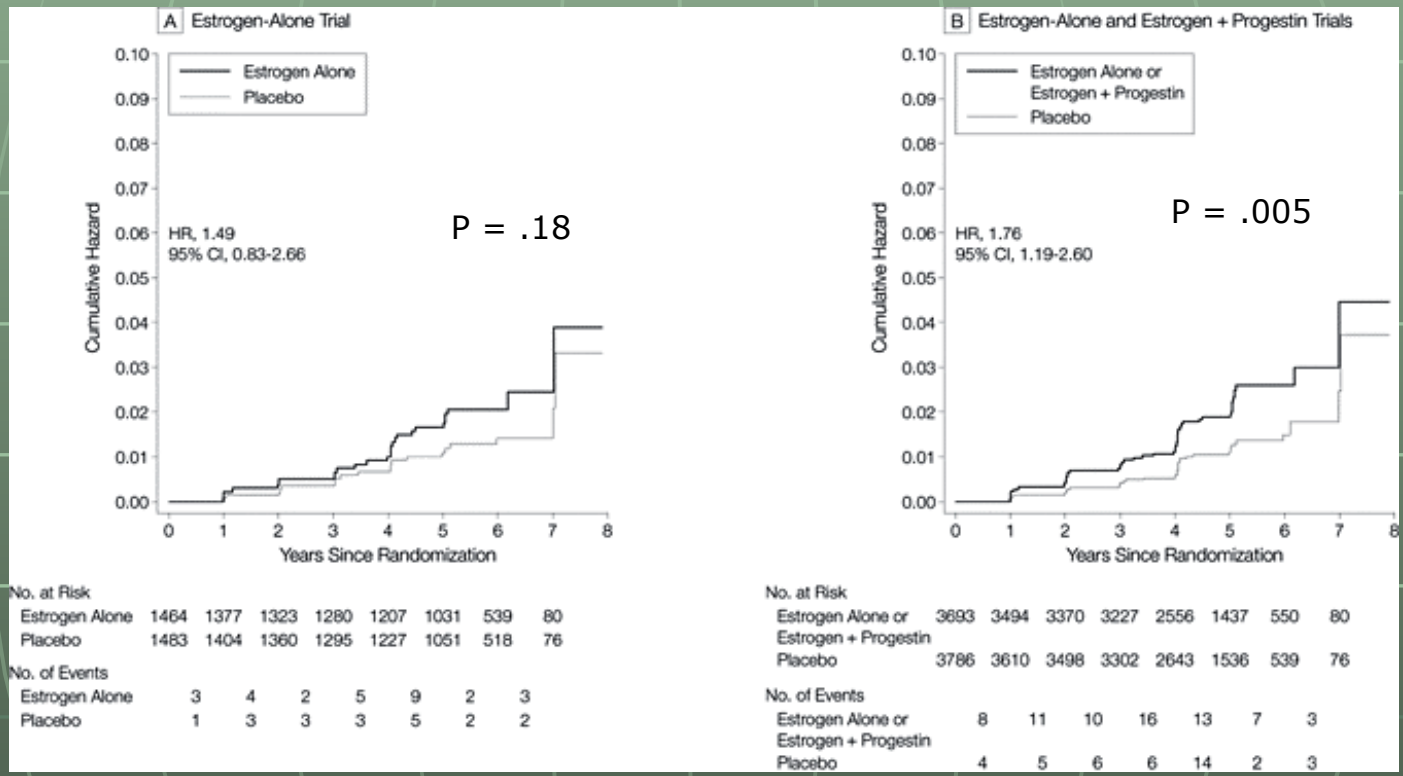
P = .01 P = .72 P = .06



Shumaker, S. A. et al. JAMA 2003;289:2651-2662.

JAMA

Times to Probable Dementia for Women Taking Estrogen Alone vs Placebo or Estrogen and Estrogen + Progestin Combined vs Placebo



Shumaker, S. A. et al. JAMA 2004;291:2947-2958.

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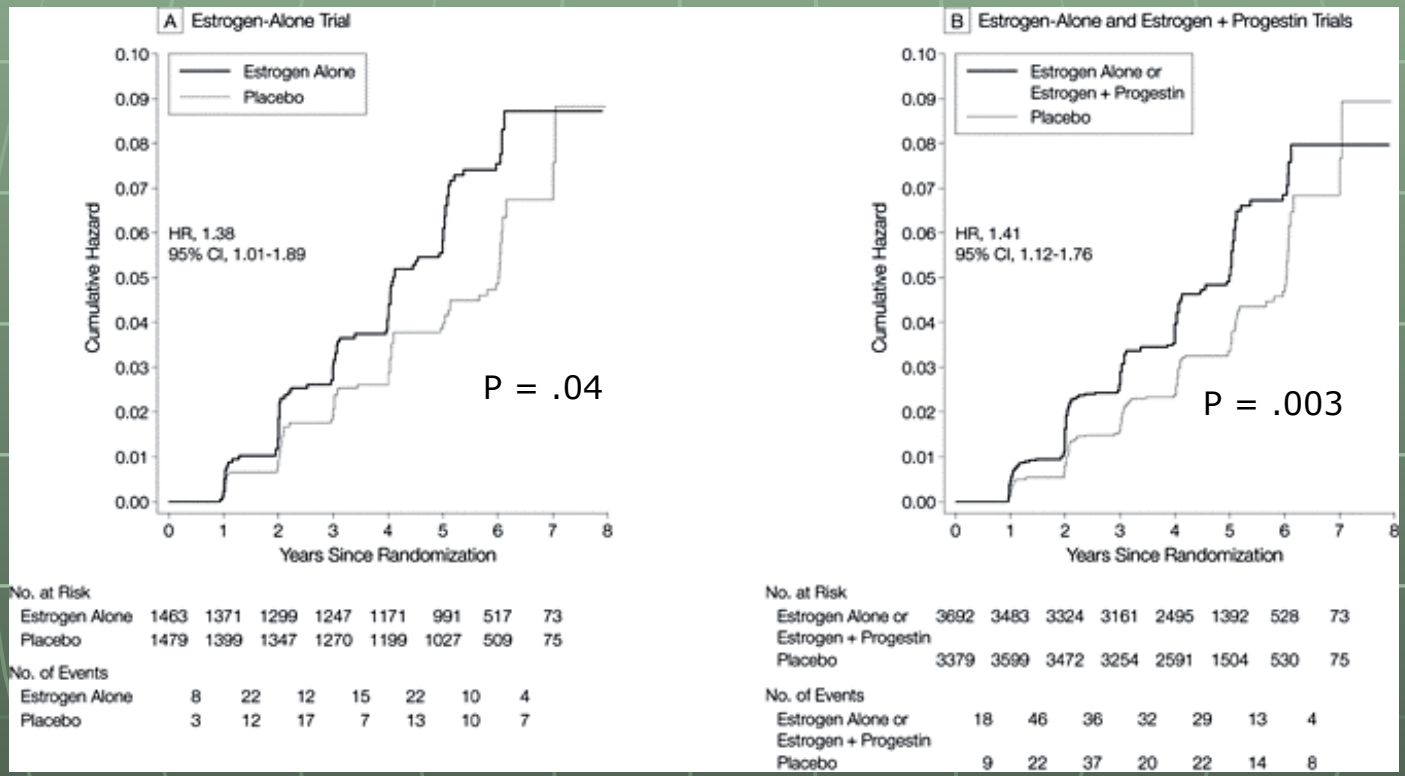
Times to the First Occurrence of the Composite End Point of Probable Dementia or Mild Cognitive Impairment for Women Taking Estrogen Alone vs Placebo or Estrogen and Estrogen + Progestin Combined vs Placebo



Shumaker, S. A. et al. JAMA 2004;291:2947-2958.

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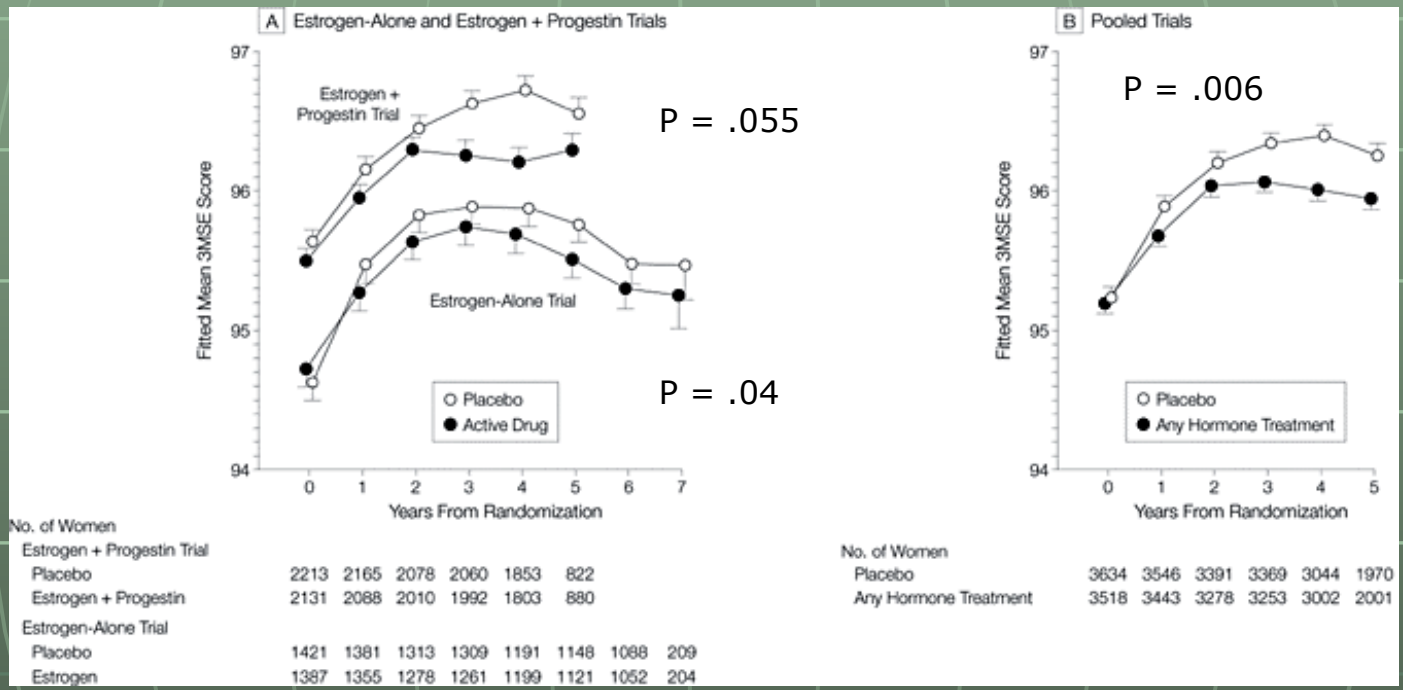
Fitted Mean Modified Mini-Mental State Examination Scores for Estrogen-Alone and Estrogen Plus Progestin Trials and Pooled Trials



Espeland, M. A. et al. JAMA 2004;291:2959-2968.

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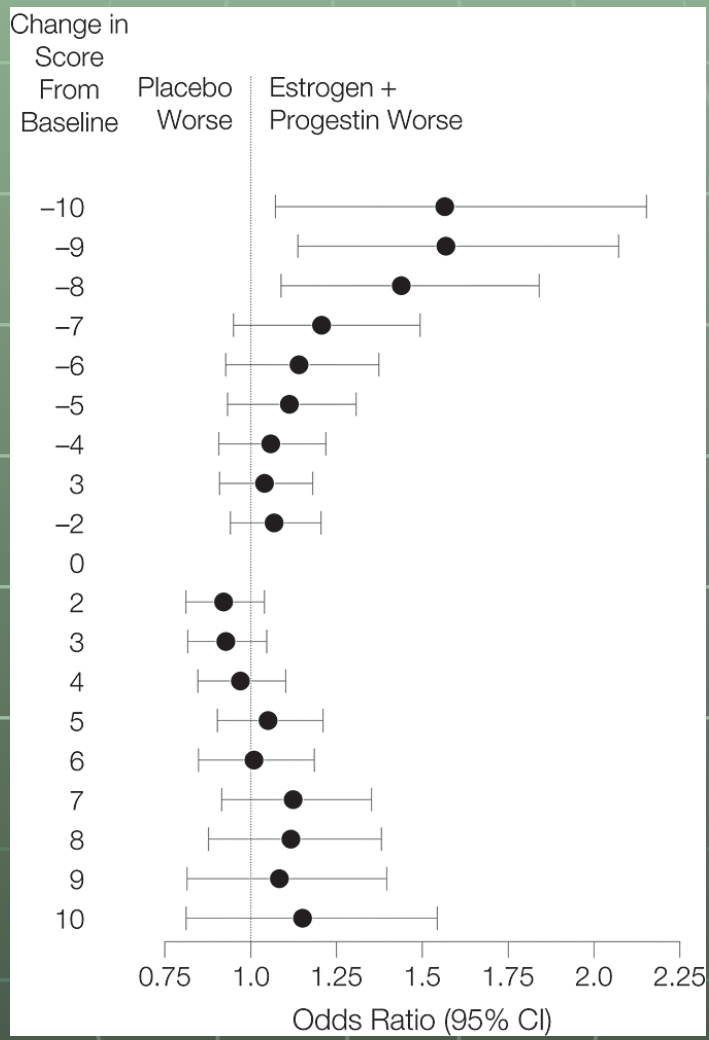
Odds Ratio (95% Confidence Intervals) for Various Magnitudes of Modified Mini-Mental State Examination Score Changes From Baseline (Across All Follow-up Visits): Estrogen Plus Progestin vs Placebo



Rapp, S. R. et al. JAMA 2003;289:2663-2672.

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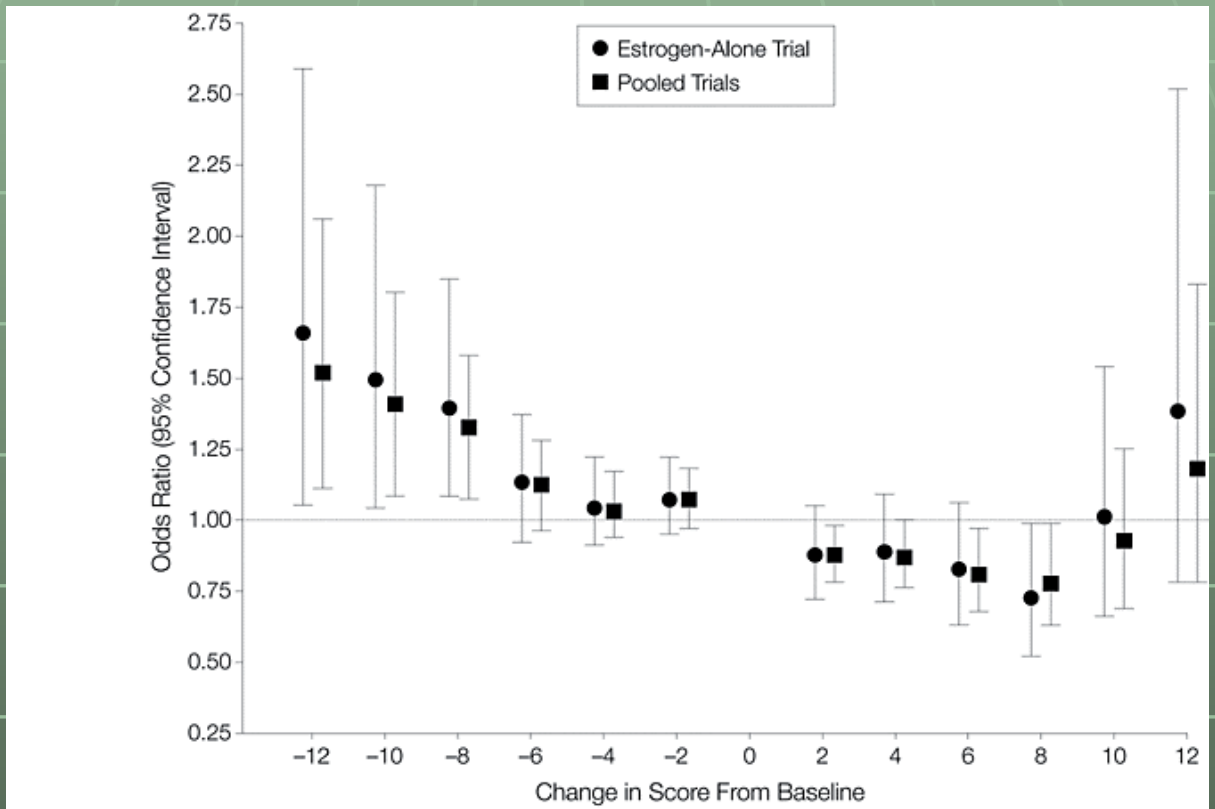
Distribution of Changes in Modified Mini-Mental State Examination Scores From Baseline Between the Estrogen-Alone and Pooled Trials



No. of Women												
Estrogen-Alone Trial												
Placebo	42	64	111	211	405	699	912	544	321	176	84	37
Estrogen	54	77	123	217	400	697	863	510	285	138	73	36
Pooled Trials												
Placebo	74	113	209	422	866	1666	2186	1211	658	339	159	65
Any Hormone Therapy	108	151	258	446	864	1667	2049	1141	610	307	152	70

Espeland, M. A. et al. JAMA 2004;291:2959-2968.

JAMA

Questions raised by WHIMS results:

- What mechanism(s) might account for the increased risk of dementia?
- What effect does cessation of HT have on cognition and risk of dementia?
- Are dementia and MCI more prevalent among WHIMS decedents and women on limited follow-up?
- Is a*mnestic* MCI more prevalent among women receiving HT vs. placebo?

Resources within WHIMS

- Large population of women followed for extended period
- Well-characterized clinically, demographically and cognitively w/repeated cognitive measures
- Excellent data on hormone exposure over time
- Well-trained, and certified staff

Implications of WHIMS: Where do we go from here?

- Further Analyses w/in the current WHIMS data set
  - Increasing precision on MCI
  - Enhancing outcomes ascertainment
  - The MRI Study
- WHIMS Extension – what else will we learn?
- Other possible new WHIMS studies
- Limitations of WHIMS
- The "perfect study" and ethical limitations

Precision in MCI Assessment

- WHIMS dataset provides unique opportunity to re-examine MCI and its predictive validity
- Potential for developing the elusive and more cost-effective surrogate endpoint needed to test
  - New treatments for dementia
  - Validity of other surrogates

WHIMS and MCI: Further "explorations"

- MCI data available for re-classification
- Modeling various classifications w/r to
  - Possible differential treatment effects
  - Association with primary outcome

Is a*mnestic* MCI more prevalent among women receiving HT vs. placebo?

- WHIMS: risk of MCI not related to HT
- 10-15% MCIs convert to dementia each year.(Artero et al. Acta Psychiatr Scand 2003; 390-393; Petersen et al. Arch Neurol 1999; 56:303-308)
- Amnestic MCI subtype associated with other risk factors (Lopez et al., Arch Neurol 2003; 1394-1399)
- Does HT affect risk of Amnestic MCI subtype?

Enhancing Outcomes Ascertainment

Are dementia and MCI more prevalent among WHIMS decedents and women on 'proxy only' follow-up?

SCAP (Supplemental Case Ascertainment Protocol)

- Phone interview of proxy (friend or family member) for 'at risk' women:
  - Deceased WHIMS ppts (~700)
  - Women who have missed recent annual visits (~200)
- *Dementia Questionnaire* administered by certified interviewers at WHIMS CCC
- WHIMS central adjudication process

WHIMS MRI

Summary of Relevant WHI and WHIMS Findings

- WHI reported that both E-alone and E+P increased risk of stroke
- WHIMS reported that treatment with E+P doubled the incidence of probable dementia, and significantly increased the composite endpoint of probable dementia and/or MCI (Shumaker 2003)
- WHIMS women assigned to E-alone were also at increased risk for probable dementia and MCI

Background and Significance Rationale for the WHIMS-MRI Study

- Stroke is the 3rd leading cause of death in the United States
- Subclinical (silent) CVD is substantially more prevalent than clinical CVD and begins in middle age
- Hormone Therapy increases the risk of clinical stroke in women 65 years and older (WHI, 2002; Wassertheil-Smoller, 2002; WHI, 2004)

Rationale For Assessing Relationship Between HT and Predictors of Cognitive Endpoints

WHIMS-MRI is based on the following paradigm:

- the increase in clinical stroke associated with HT will also result in a significant increase in SCIs (primarily subcortical and small vessel disease); and increased WMG lesions
- This pathology is associated with an increased risk for all-cause dementia

WHMS-MRI: Overall Objective

- The overall objective of the WHIMS-MRI Study is to mount a cross-sectional MRI study in approximately 1450 women previously enrolled in the Women's Health Initiative Memory Study (WHIMS) to evaluate the impact of HT on Subclinical Neurological Pathology.

WHIMS MRI:
Primary Objective

- To establish whether the prevalence of silent infarcts, detected by a standard MRI protocol, is increased among women who had been assigned to HT, relative to placebo during the WHIMS clinical trials.

WHIMS MRI:
Secondary Objectives

- Contrast the relative effects of prior assignment of estrogen alone on the prevalence of silent infarcts with those associated with estrogen plus progestin therapy.
- Establish whether the prevalence of white matter grade (WMG) abnormalities and estimates of hippocampal, ventricular, and whole brain volumes vary between women assigned to HT versus placebo

WHIMS MRI:
Secondary Objectives (contd.)

- Examine whether the increased risk of probable dementia and minor cognitive impairment (MCI) associated with HT is conveyed through the development of vascular and/or white matter abnormalities.
- Examine whether sub-clinical abnormalities on MRI predict conversion from MCI to dementia.
- Examine whether a dose-response relationship exists between duration of exposure to HT and sub-clinical abnormalities.

WHIMS-MRI Inclusion Criteria

- Any WHIMS participant, regardless of
  - Prior adherence during WHIMS/WHISCA
  - Current cognitive status
  - Participation in WHI-Extension and/or WHIMS Extension
- Both E-Alone and E+P trials
- Fully informed consent to participate and to allow data sharing (HIPAA)

Timeline

- WHIMS recruitment: 5/96 to 12/99
- WHIMS E+P termination: 7/02
  - Mean on-trial follow-up: 4.0 yrs
  - 4-year E+P adherence: 50%
- WHIMS E-Alone termination: 2/04
  - Mean on-trial follow-up: 5.2 yrs
  - 5-year E-alone adherence: 46%
- WHIMS-MRI scans: 9/04-12/05

What else can we learn from WHIMS?

What effect does cessation of HT have on cognition and risk of dementia?

- WHIMS Extension Study
  - Continue annual assessments (3MS) and neuroclinical evaluations and case ascertainment
  - PRIMARY OBJECTIVE: Determine effect of ***cessation*** of HT on cognition and incidence of dementia and MCI.

Other Opportunities with WHIMS Cohort

- Identification and assessment of other hypothesized mechanisms for treatment effects
- Further sub-analyses of existing data; "drilling down" into data
- Analyses w/WHISCA data
- Future behavior-based intervention studies

Other Opportunities with WHIMS Paradigm: A look at the younger WHI women

- Strengths
  - Unique cohort
  - Well-characterized population
  - Diverse population
  - Trained and certified staff in cognitive measures
  - Simplified outcomes ascertainment (SCAP)
- Weaknesses
  - No baseline cognitive assessments
  - Differential drop-out rates over time

Questions WHIMS Cannot Answer

- Effects of hormone therapy on cognitive decline and dementia initiated in the younger (peri-menopausal) woman
- Effects of alternative hormone therapies
  - Dosages
  - Types
  - Mode of administration

The Perfect RCT on the effects of HT on dementia

- Women randomized peri-menopausally w/no prior hormone exposure
- Thorough baseline assessment of neurological health (neuropsych assessment and imaging)
- Long-term follow-up w/"hard" (non-surrogate) outcome
- Range of treatment types, dosages, and modes of administration

Constraints

- Resources
  - Number of women required
  - Selecting the appropriate treatments now that will remain relevant years from now
  - Years of follow-up required
- Ethics
  - Other negative outcomes associated w/hormone therapy – true cost-benefit analysis