WHIMS
The Women's Health Initiative Memory Study

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

- Support provided by:
  - Wyeth pharmaceuticals (initial WHIMS)
  - NHLBI
  - NIA

WHIMS Specific Aims

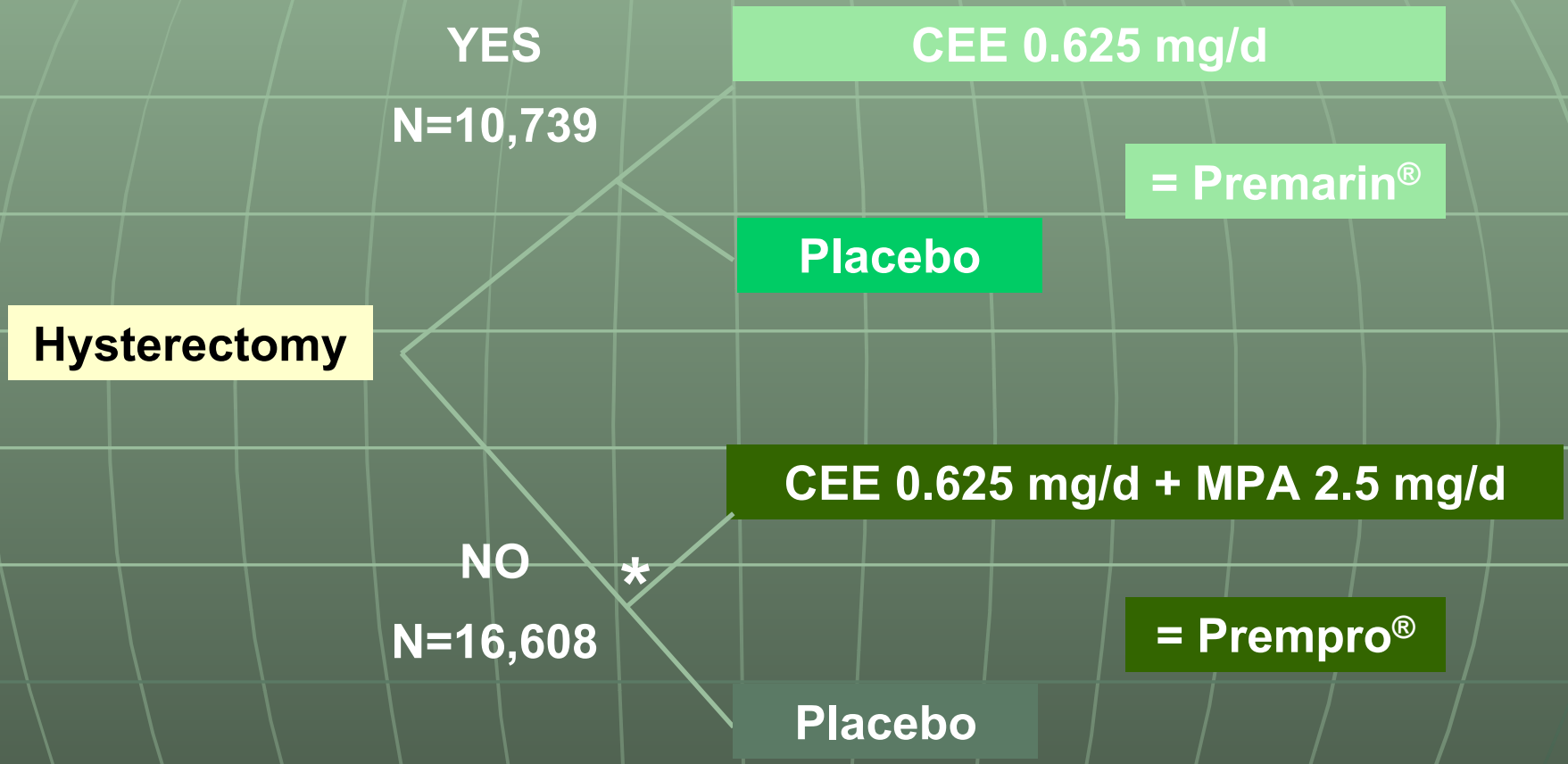
- PRIMARY: Does HT (E + P and E-alone) reduce incidence of:
  - Dementia (any cause)?
  - Dementia caused by Alzheimer disease (AD)?
- SECONDARY:
  - Improve global cognition?
  - Improve MCI?
  - Slow progression of disease?

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

What were we thinking? Remember when. . . A quick reality check

- We thought HT both prevented AD *and* slowed its progression – regardless of women's "underlying neuronal health status"
- Women were initiating HT – many for the first time – all the way into their 70s
- Placebo controlled trials of HT were considered unethical because we "already knew HT was beneficial"

WHI Hormone Program Design



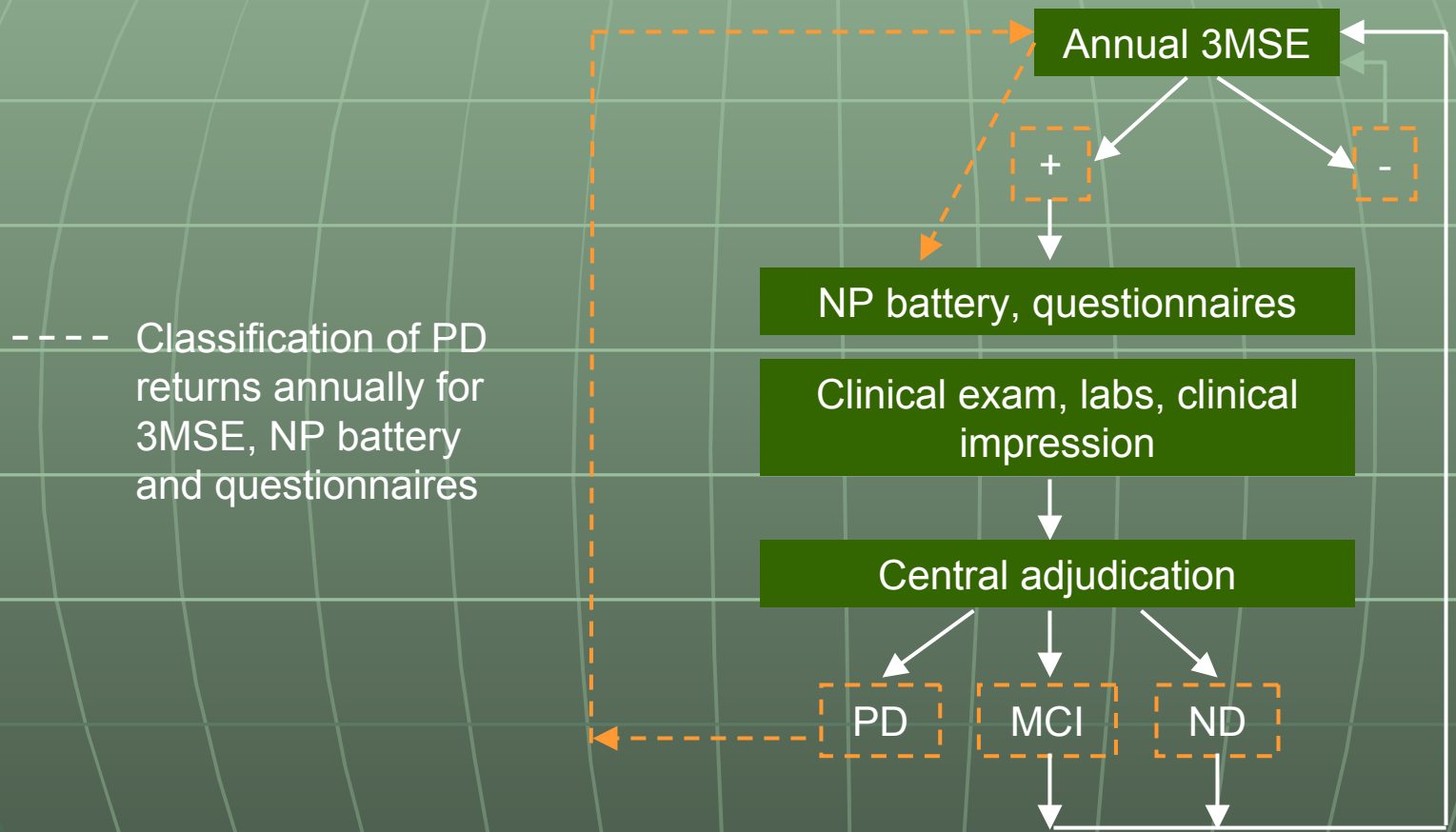
CEE=conjugated equine estrogen; MPA=medroxyprogesterone acetate.
*Initially: CEE only (n=331), CEE + MPA, or placebo.
(CEE only was subsequently converted to CEE + MPA).
WHI Study Group. *Control Clin Trials*. 1998;19:61-109.

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.

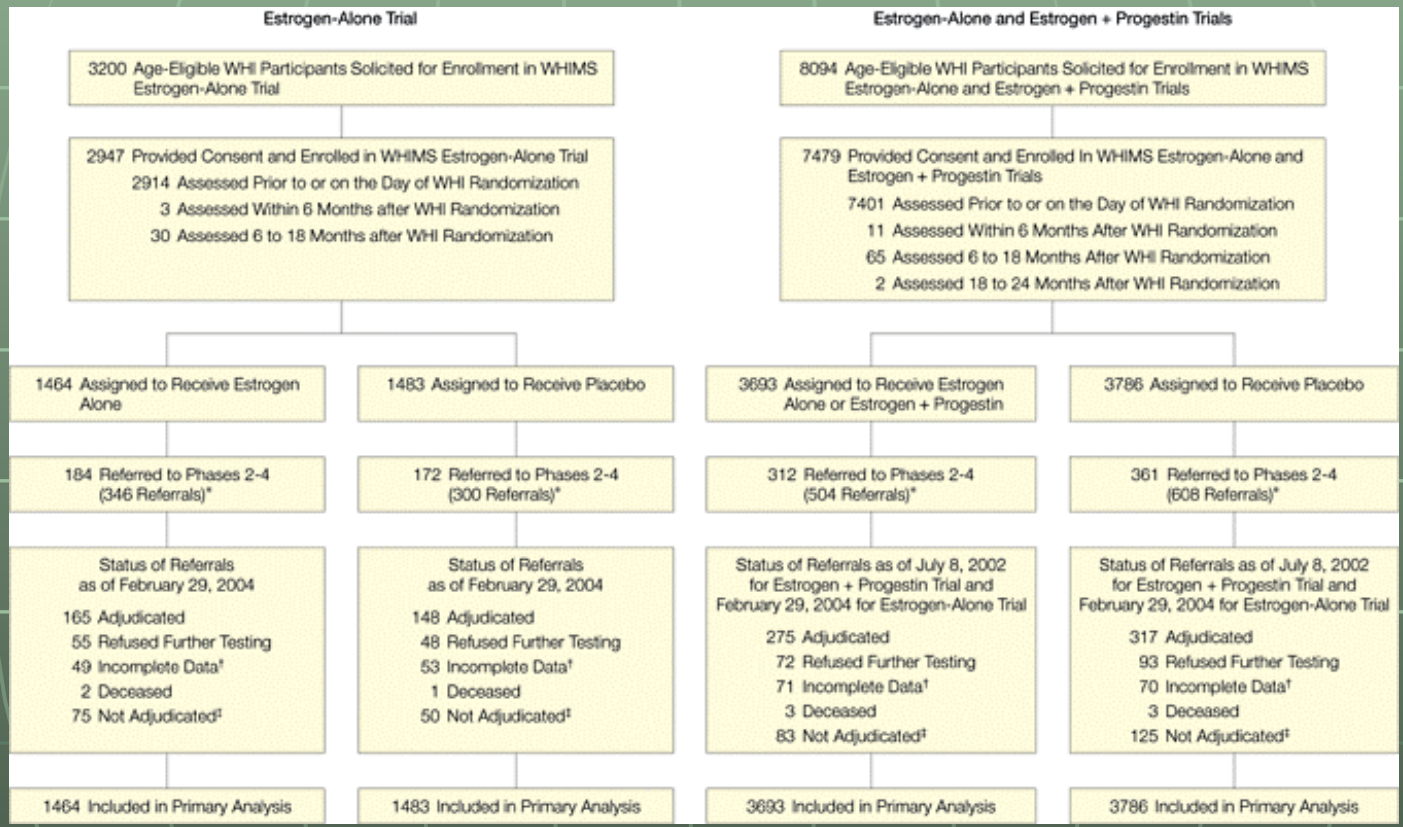
WHIMS Methodology



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

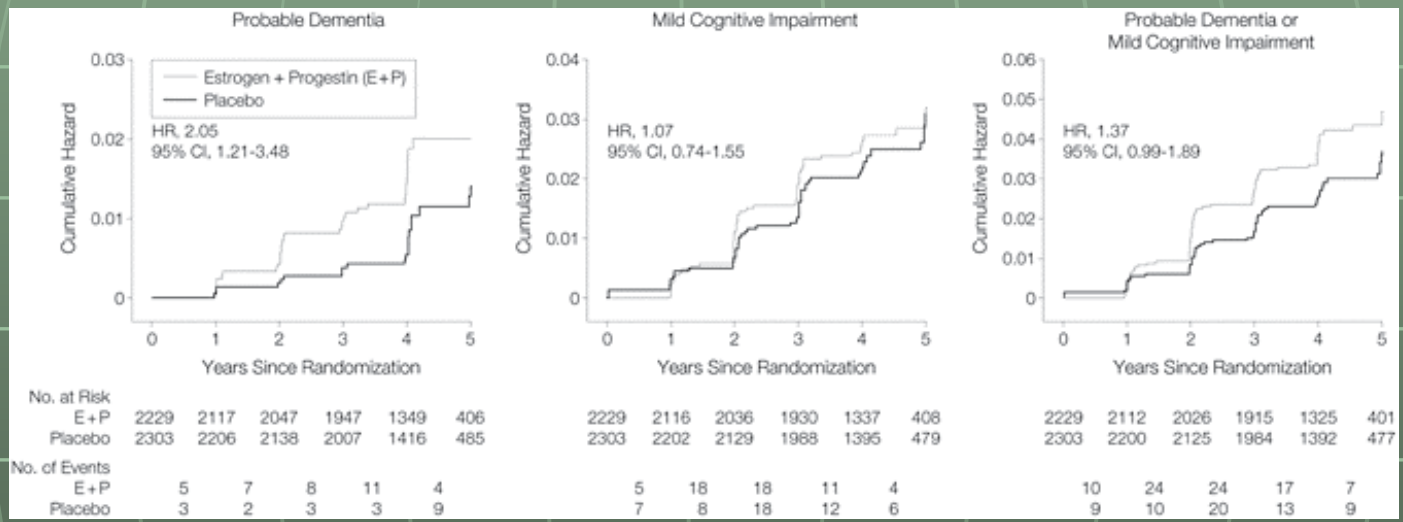
WHIMS: Selected Data

	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

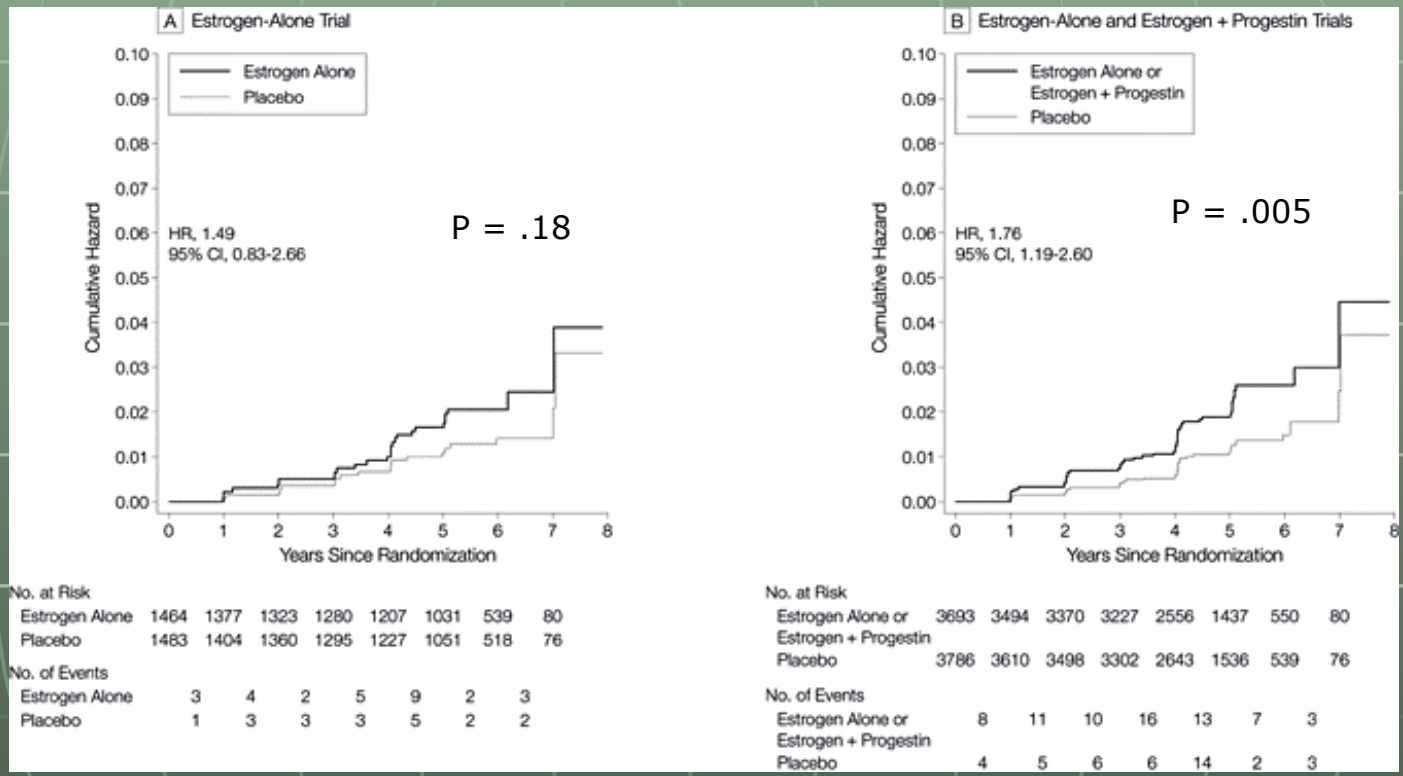
P = .01 P = .72 P = .06



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

JAMA

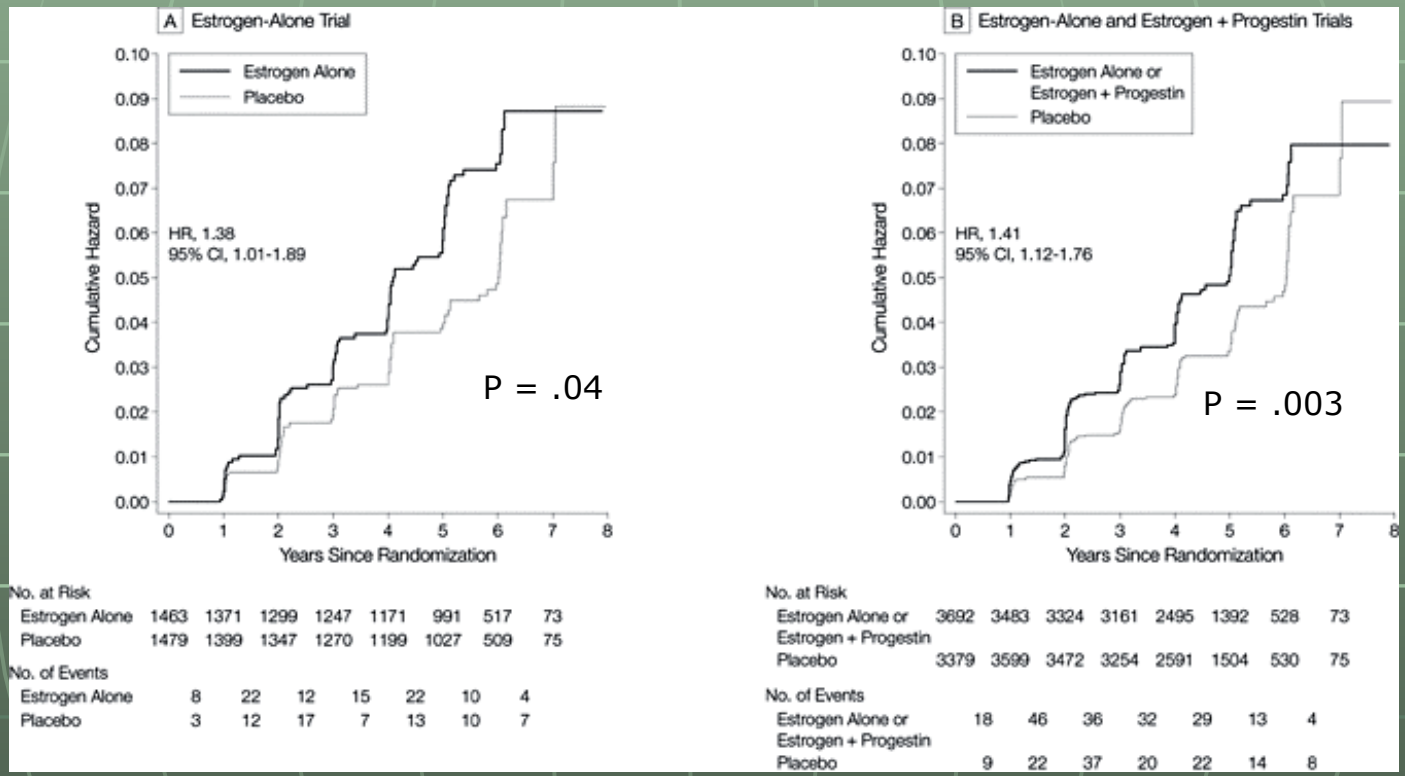
Times to Probable Dementia for Women Taking Estrogen Alone vs Placebo or Estrogen and Estrogen + Progestin Combined vs Placebo



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

JAMA

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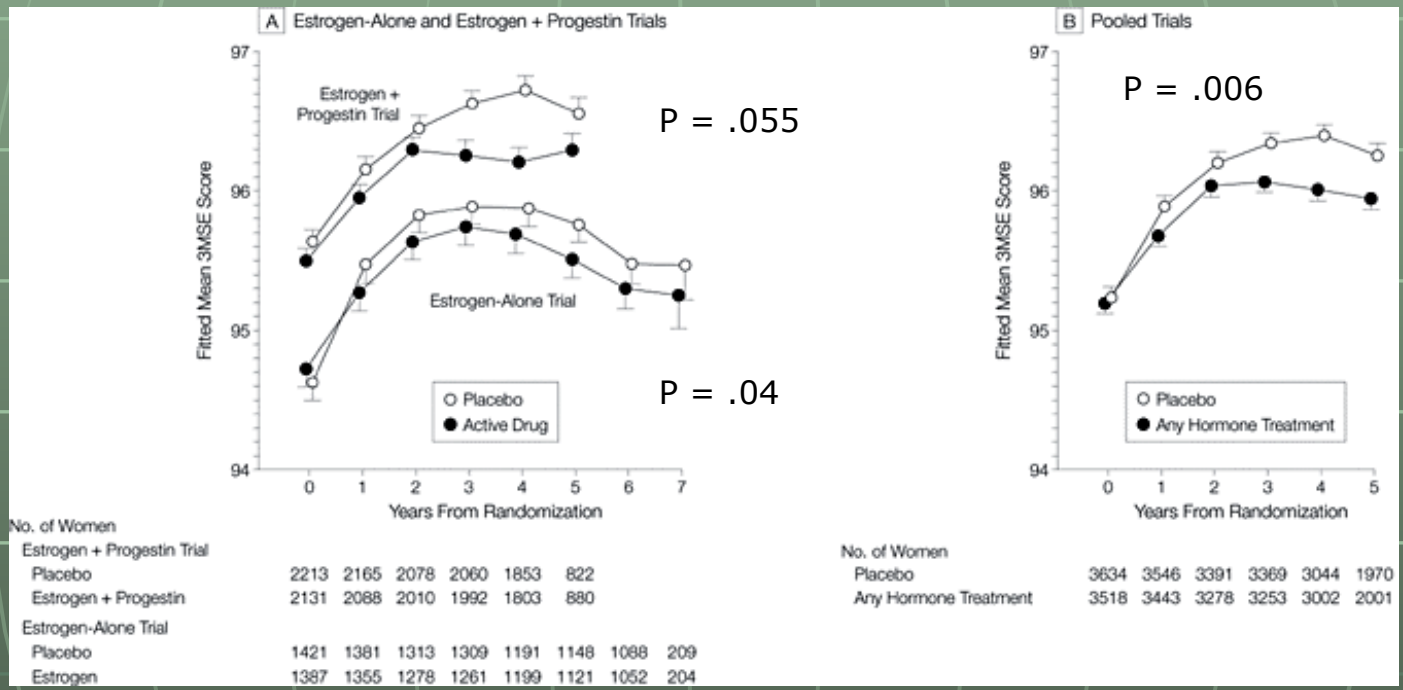
Fitted Mean Modified Mini-Mental State Examination Scores for Estrogen-Alone and Estrogen Plus Progestin Trials and Pooled Trials



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

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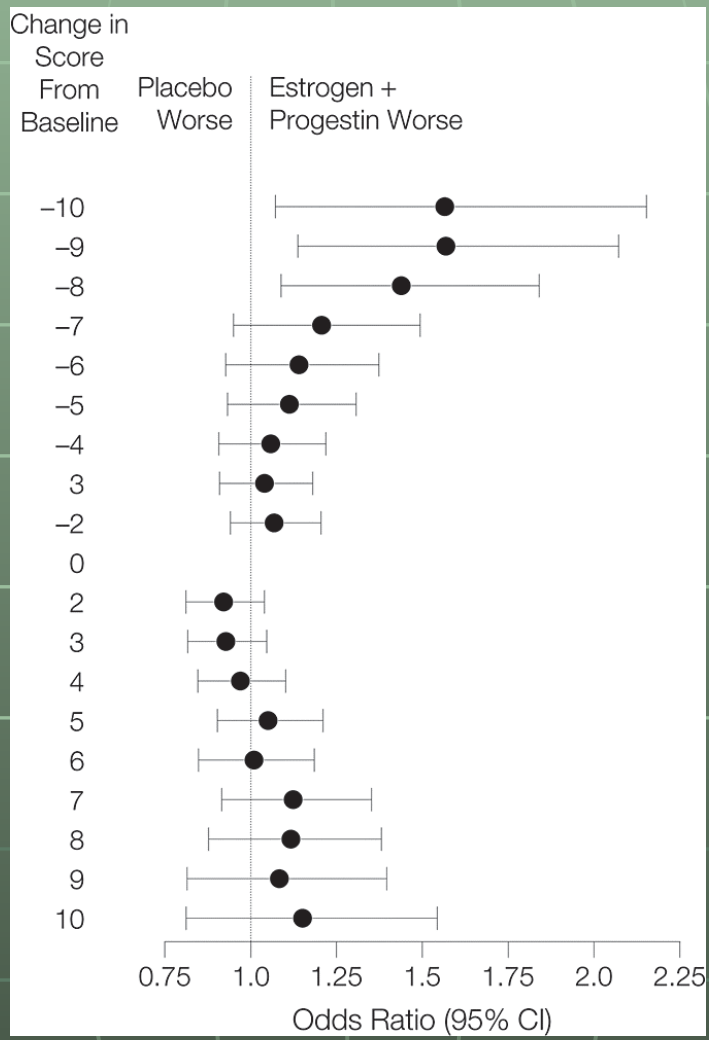
Odds Ratio (95% Confidence Intervals) for Various Magnitudes of Modified Mini-Mental State Examination Score Changes From Baseline (Across All Follow-up Visits): Estrogen Plus Progestin vs Placebo



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

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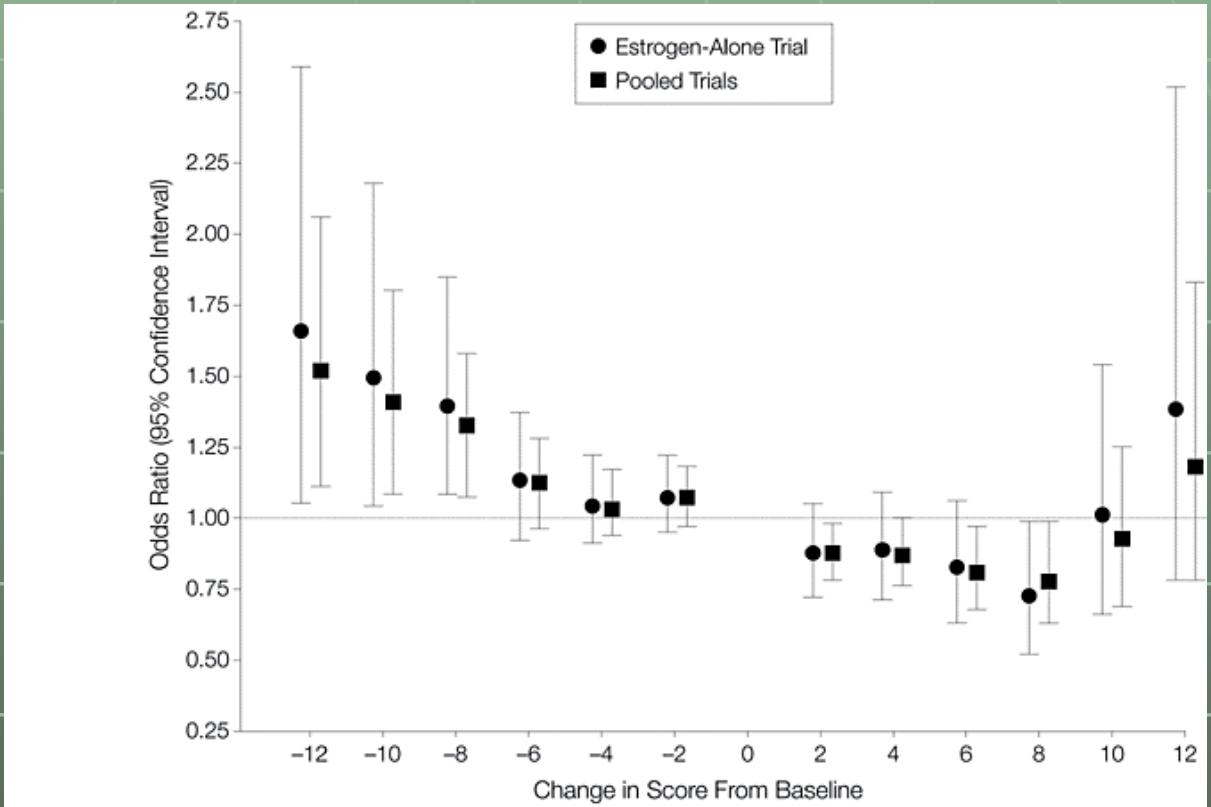
Distribution of Changes in Modified Mini-Mental State Examination Scores From Baseline Between the Estrogen-Alone and Pooled Trials



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?
- Is this risk accumulative and/or sustained over time?
- What effect does *cessation* of HT have on cognition and risk of dementia?

Potential of WHIMS to Address Critical Questions

- Large, heterogeneous population of women followed for extended period
- Well-characterized clinically, demographically and cognitively w/repeated cognitive measures
- Excellent data on hormone exposure over time—as well as other "confounding" therapies
- Well-trained, and certified staff

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

MCI: Limitations and Promise

- WHIMS: risk of MCI alone 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?

Precision in MCI Assessment

- WHIMS dataset provides unique opportunity to develop more sensitive and specific operational definitions of MCI subtypes w/potential to:
  - Test possible differential treatment effects on MCI subtypes (e.g. amnesic)
  - Determine association of MCI with primary outcome—increase predictive validity of MCI
- The psychometric refinement of MCI, coupled with further MCI/HT analyses have the potential for producing a cost-effective surrogate endpoint needed to test
  - New treatments for dementia
  - Validity of other surrogates (e.g. imaging techniques)

Enhancing Outcomes Ascertainment in WHIMS

- Development & testing of the supplemental case ascertainment protocol (SCAP)
  - 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

Potential of SCAP

- Enhances number of cases of MCI and dementia and, therefore, statistical power for further analyses
- Can use WHIMS data set to advance psychometric properties (e.g. predictive validity) of SCAP – an alternative (and more efficient) cognitive testing protocol for large OS and RCT
- Cognitive decline and dementias take women out of RCTs selectively – valid SCAP provides mechanism for addressing inherent de-selection bias
- Provides potential opportunity to assess effects of HT on cognitive decline/dementia in "younger" WHI women

The WHIMS MRI Study

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 (WHI, 2002; Wassertheil-Smoller, 2002; WHI, 2004)

WHMS-MRI: Overall Objective

- 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
- WHIMS E-Alone termination, 2/04; Mean on-trial follow-up, 5.2 yrs
- 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

- Identification and assessment of other hypothesized mechanisms for treatment effects
- Association of biomarkers w/MCI; dementias
- Further sub-analyses of existing data; "drilling down" into data
- Analyses w/WHISCA data & Co-STAR

Another opportunity with WHIMS *Paradigm*: Testing the effects of HT on cognition in the younger WHI women

- Strengths
  - Committed cohort of participants
  - Well-characterized population w/r to HT exposure, clinical status over time, demographics, etc.
  - Diverse population
  - Trained and certified staff on cognitive measures
  - Strong cognitive assessment protocol in place
  - Simplified outcomes ascertainment (SCAP)
- Weaknesses
  - No baseline cognitive assessments
  - Differential drop-out rates over time
  - Priority of this type of analysis among competing priorities w/in WHI -- resources

Questions WHIMS Cannot Answer

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

Challenges to the "perfect" HT/cognition RCT:

- When do we randomize – pre-, peri-, post menopausal
  - If AD is pre-clinically present for up to 15 years prior to diagnosis – just how far back do we go?
- *IF* HT promotes cognitive health in the neurologically in tact woman – and promotes decline and dementia in the neurologically "damaged" woman, then:
  - How do we guarantee the neurological health of our baseline cohort?
  - How do we know when this neurologically in tact cohort becomes damaged and the potential benefit crosses to harm – that is, how long do we "treat" women?
- How long would we have to follow a younger cohort to reliably assess treatment effects on "hard" (non-surrogate) outcomes?

Challenges to the "perfect" HT/cognition RCT, cont. . .

- How many factors would we have to vary to be confident we captured the full range of potential beneficial therapies: dose (2-3) X mode (2-3) X menopausal stage (3) X drug (2) X continuous vs cyclical (2) . . . . Etc.
- How long will our current choices be relevant – how can we be confident that secular trends, new HT formulations, and/or new non-hormonal treatments won't make our choices irrelevant before the study is done?
- Resources
  - Number of women required
  - Cost
- Ethics – we can't ignore the known risks associated w/HT – even in younger women
  - Evidence of presumed benefit must be substantially stronger than is currently the case to offset risks – regardless of how small that risk may appear to be

Finally. . . .

- If we accept the hypothesis that HT exacerbated underlying, pre-existing disease in the WHIMS women – what would we predict for rates of transitioning to dementia?
  - What is the prevalence of sub-clinical dementia in women the WHIMS baseline cohort?
  - What is the effect size expected for accelerating the dementia disease process? And, therefore,
  - How many cases of dementia should we have seen?