Alzheimer's Disease Prevention Trial with Estrogens

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PREPARE: Preventing Postmenopausal Alzheimer's Disease with Replacement Estrogen.

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Bench to Bedside September 29, 2004

PREPARE

Preventing Memory Loss & Alzheimer's Disease

Thanking my collaborators

- **Neill Graff-Radford**
- **Peter Rabins**
- **Karen Bell**
- **Howard Andrews**
- **Wei Yann Tsai**
- **Diane Jacobs****

And all of the site PI and their staff

PREPARE

Preventing Memory Loss & Alzheimer's Disease

- **Randomized, double-blind, placebo controlled multi-center trial of HRT to:**
  - **Prevent AD**
  - **Prevent memory decline**
- **5 year study (Jan 2002 modification)**
- **65 years and older**
- **Family history of AD in a first degree relative**
- **No history of CHD, DVT or Breast CA**

Neuropsychological Test Battery

- Memory
  - Selective Reminding Test (12 item; 6 trials; 15-min delay)
  - WMS-R Visual Reproduction Test (Immed. & 30-min delay)
- Orientation
  - 10 items (time & place) from MMS
- Abstract Reasoning
  - WAIS-R Similarities
- Language
  - Boston Naming Test (15 item)
  - Letter & Category Fluency
- Attention
  - WAIS-R Digit Symbol
  - Letter & Shape Cancellation
- Motor Speed
  - Grooved Pegboard

Alzheimer's Disease Prevention Trial with Estrogens

Neuropsychological Exclusion Criteria

If T-score for either

- SRT total recall or
- SRT long term recall is < 35

AND

T-score for either

- SRT delayed recall or
- SRT delayed recognition is < 35

Then participant is excluded.

Alzheimer's Disease Prevention Trial with Estrogens
Neuropsychological Triggers for Physician Evaluation

Trigger A

- Same is exclusion criteria

Trigger B

- T-score for either SRT total recall or SRT long term recall is < 40

AND

- T-score for either SRT delayed recall or SRT delayed recog. is < 40

AND

- There is evidence of decline from baseline (raw score)

Then participant is referred to a "dementia expert".

PREPARE vs WHI/WHMS
Similarities

- **Similar medication regimen and stratification:**
  - **Prempro or Premarin**
  - **Stratification to treatment based on uterine status**

PREPARE vs WHI/WHMS

Differences

- Selected population with family history
- Planned for a smaller sample
- Screened for intact cognitive function
- Cognitive change and dementia were primary outcome.
- Other outcomes reflected side effect, not clinical benefit
- Selected against cardiac disease

PREPARE:
Historical Context

- The Prepare study was the first NIA sponsored primary prevention trial for dementia and memory loss.
- It capitalized on the epidemiological and basic science findings of estrogen and used some of the design features of WHI/WHMS
- The doubt about the benefits of estrogen in (cardiac disease) was present even before the first subject was enrolled.

PREPARE

Where we stand

- All subjects are off medication
- DSMB review requested evaluation of breaking the blind: Value of blinded follow-up for 5 yrs vs. Participant need to know.
- Statistical advice acknowledged low power but also acknowledged limited value to participants knowing treatment status.
- Recommended continuing the blind
- Current DSMB decision to permit continued blind study

PREPARE

What we can hope to learn

- **Using cognitively healthy cohort**
  - **Tells us about incident MCI**
  - **True change rate on truly intact individuals**
  - **May permit separation of aging vs dementing changes**
- **Modeling the epidemiological data**
  - **Measure effect after stopping**
- **Feasibility for family history as an enrichment strategy**

Baseline Cohort

Subject Characteristics

N	466
Mean Age	72.7 (5.1)
Education	14.2 (3.1)
Race/Ethnicity (%)	
White	80.7
Black	12.9
Hispanic	4.7
MMS Score	28.8 (1.5)

PREPARE

Preventing Memory Loss & Alzheimer's Disease

- 28 % have had a hysterectomy
- 41% have never taken estrogen in the past
- MMSE score = 28.8 $\pm$ 1.5
- Beck Depression score = 4.9 $\pm$ 3.7
- Apolipoprotein E 4
  - Any: 29.6%
  - Homozygote: 2.2%

Neuropsychological Assessment

Baseline Scores -- Memory Measures

	Raw Score Mean (SD)		T-score Mean (SD)	
Selective Reminding Immed. Recall (max. 72)	46.5	(8.4)	49.5	(11.0)
Selective Reminding LTR (Storage) (max. 72)	35.3	(12.8)	49.3	(11.8)
Selective Reminding Delayed Recall (max. 12)	7.4	(2.3)	49.6	(10.3)
Selective Reminding Delayed Recog. (max. 12)	11.7	(0.8)	50.5	(7.6)
Visual Reproduction - Immed. Recall (max. 41)	29.8	(7.3)	n/a	
Visual Reproduction - Delayed Recall (max. 41)	23.1	(9.7)	n/a	

N=466

Neuropsychological Assessment

Baseline Scores -- Non-Memory Measures

	Raw Score Mean (SD)	T-score Mean (SD)
Orientation items from MMS (max. 10)	9.7 (0.6)	50.8 (9.4)
WAIS-R Similarities (max. 28)	20.0 (4.7)	53.0 (9.6)
Boston Naming Test (15 item) (max. 15)	14.6 (0.9)	52.9 (8.3)
Letter Fluency (max. 180)	39.3 (12.8)	48.9 (10.9)
Category Fluency (max. 180)	58.4 (12.6)	51.9 (11.0)
WAIS-R Digit Symbol (max. 93)	43.6 (12.1)	n/a
Letter Cancellation Rate (range 1-240 sec.)	3.9 (3.5)	48.3 (8.3)
Shape Cancellation Rate (range 1-240 sec.)	3.8 (1.8)	51.4 (7.9)
Grooved Pegboard		
Dominant Hand (max. 240 sec.)	100.9 (33.1)	n/a
Non-dominant Hand (max. 240 sec.)	112.0 (37.3)	n/a

N=466

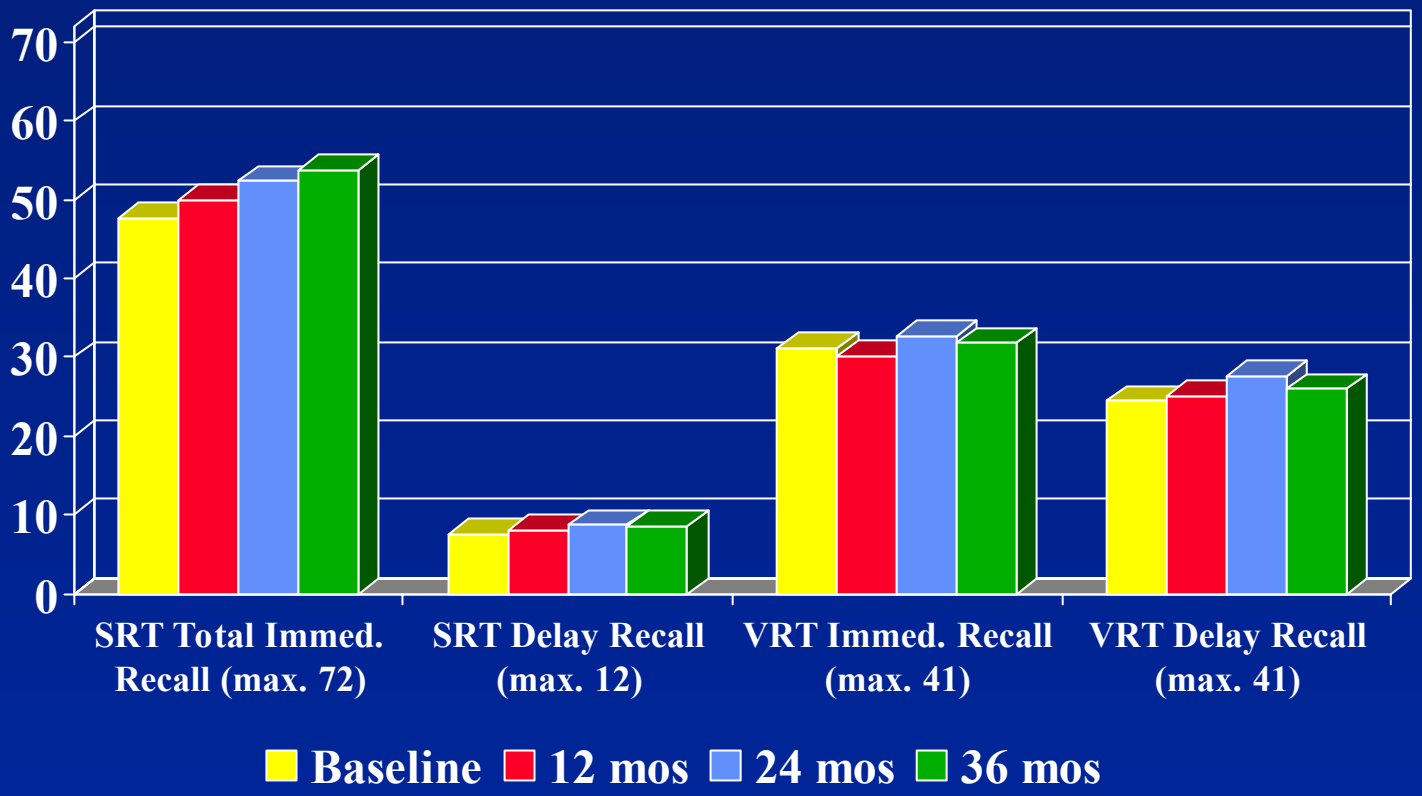
Memory Functioning Over Time

Subject Characteristics

	Baseline	12-mos	24 mos	36 mos
N	466	273	136	55
Mean Age	72.7 (5.1)	72.8 (5.3)	72.2 (5.1)	71.4 (4.3)
Education	14.2 (3.1)	14.2 (3.2)	14.3 (3.0)	13.8 (2.3)
Race/Ethnicity (%)				
White	80.7	82.1	83.8	94.5
Black	12.9	12.5	12.5	1.8
Hispanic	4.7	4.4	2.9	3.6
MMS Score	28.8 (1.5)	28.8 (1.4)	28.7 (1.6)	28.9 (1.3)

Memory Scores

36-month follow-up



N=55

Baseline Cohort

Subject Characteristics by Hysterectomy

	No Hysterectomy	Hysterectomy
N	312	161
Mean Age	72.7 (5.1)	72.9 (5.2)
Education**	14.5 (3.0)	13.7 (3.1)
Race/Ethnicity (%)		
White	81.1	80.1
Black	12.2	14.3
Hispanic	5.1	3.7
MMS Score	28.9 (1.5)	28.8 (1.5)

Neuropsychological Assessment

Baseline Scores -- Memory Measures
By Hysterectomy

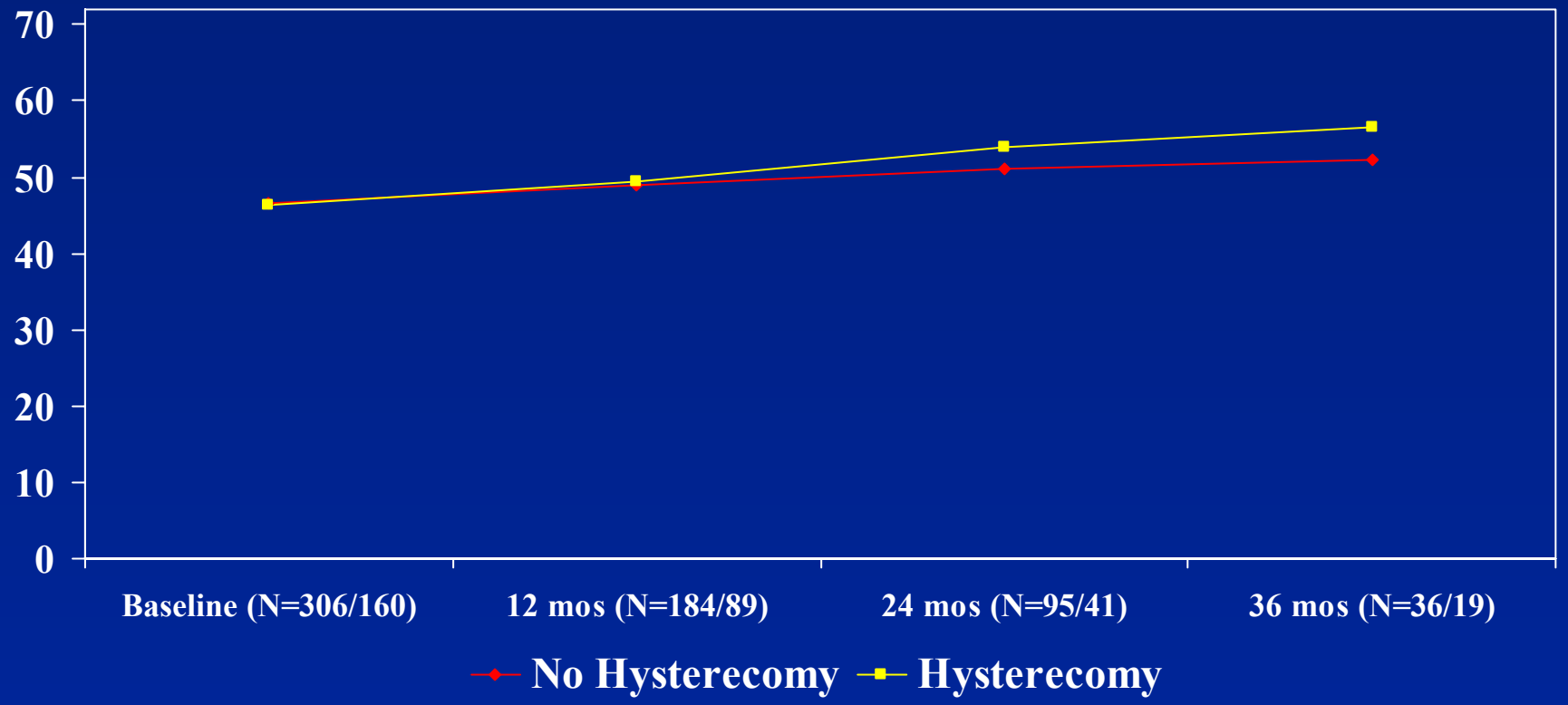
	No Hysterectomy		Hysterectomy	
Selective Reminding Immed. Recall (max. 72)	46.5	(8.7)	46.4	(7.8)
Selective Reminding LTR (Storage) (max. 72)	35.3	(13.1)	35.2	(12.5)
Selective Reminding Delayed Recall (max. 12)	7.4	(2.3)	7.4	(2.4)
Selective Reminding Delayed Recog. (max. 12)	11.7	(0.8)	11.6	(0.9)
Visual Reproduction - Immed. Recall (max. 41)	30.0	(7.2)	29.5	(7.5)
Visual Reproduction - Delayed Recall (max. 41)	23.1	(9.9)	23.1	(9.4)

Neuropsychological Assessment

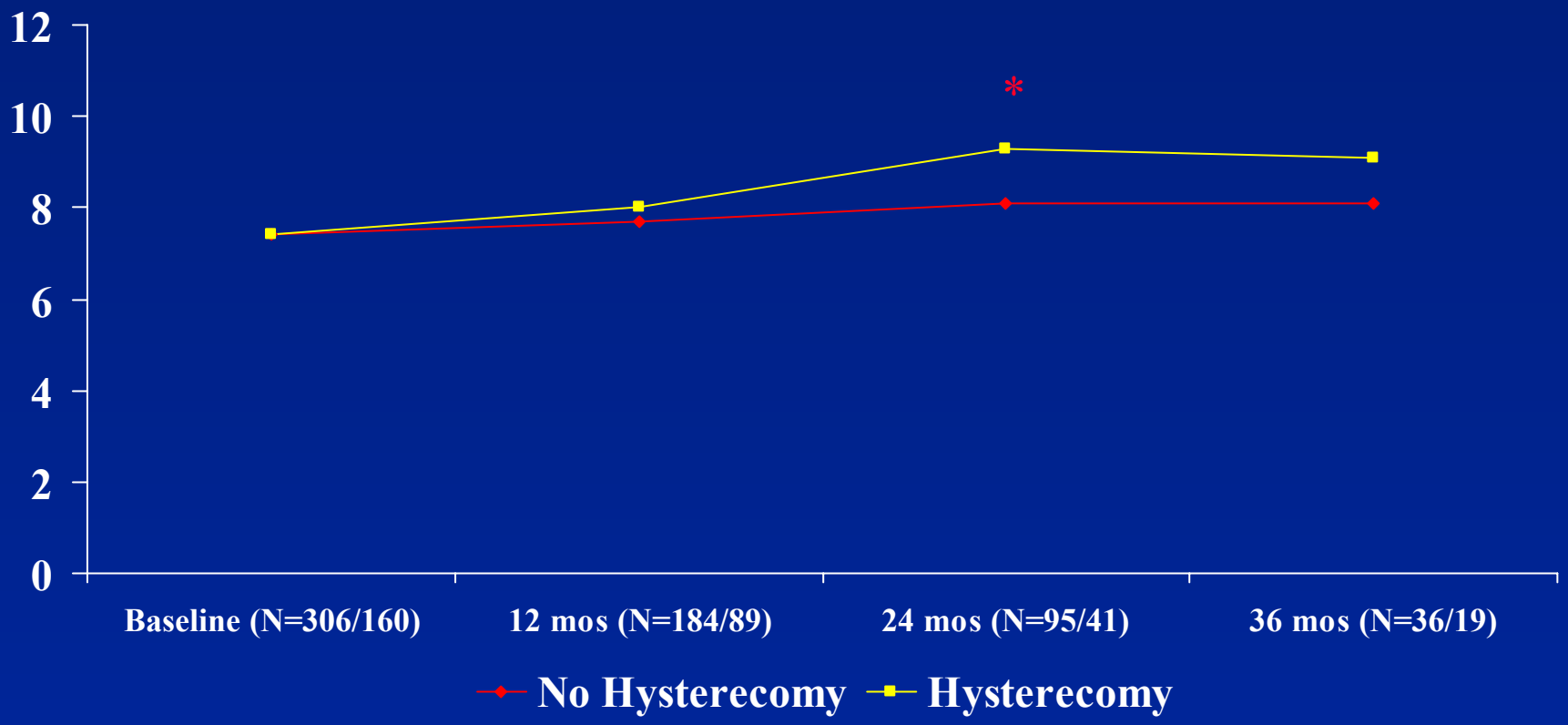
Baseline Scores -- Non-Memory Measures by Hysterectomy

	No Hysterectomy	Hysterectomy
Orientation items from MMS (max. 10)	9.7 (0.6)	9.7 (0.6)
WAIS-R Similarities (max. 28)	20.2 (4.6)	19.5 (4.9)
Boston Naming Test (15 item) (max. 15)*	14.6 (1.0)	14.8 (0.7)
Letter Fluency (max.180)	40.0 (12.6)	37.9 (13.2)
Category Fluency (max.180)	58.6 (12.8)	58.0 (12.3)
WAIS-R Digit Symbol (max. 93)	43.9 (12.4)	42.9 (11.3)
Letter Cancellation Rate (range 1-240 sec)	4.1 (4.3)	3.7 (1.0)
Shape Cancellation Rate (range 1-240 sec)	3.7 (1.4)	3.8 (2.5)
Grooved Pegboard		
Dominant Hand (max. 240 sec.)	100.5 (34.4)	101.6 (30.7)
Non-dominant Hand (max. 240 sec.)	110.8 (37.1)	114.4 (37.7)

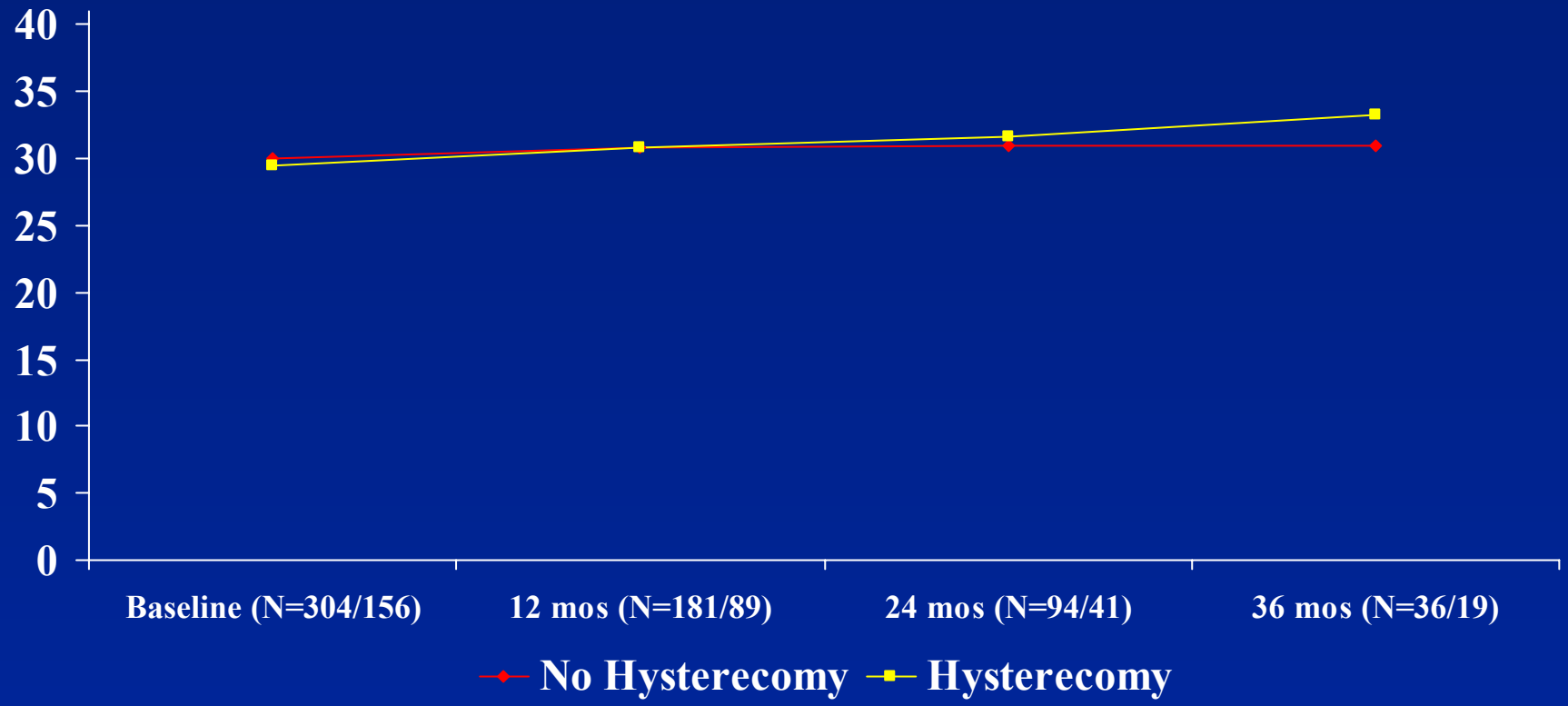
SRT Total Recall Over Time by Hysterectomy



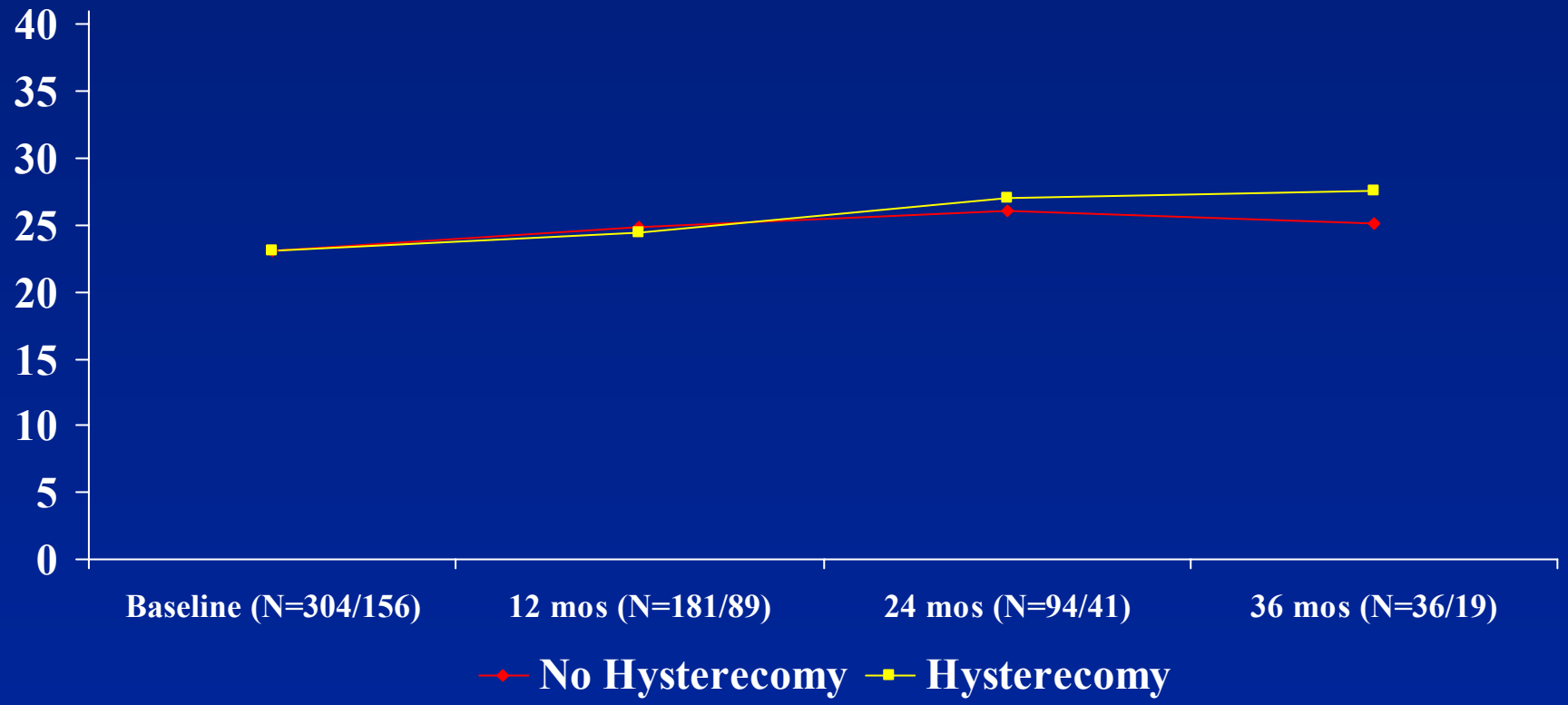
SRT Delayed Recall Over Time by Hysterectomy



VRT Immediate Recall Over Time by Hysterectomy



VRT Delayed Recall Over Time by Hysterectomy



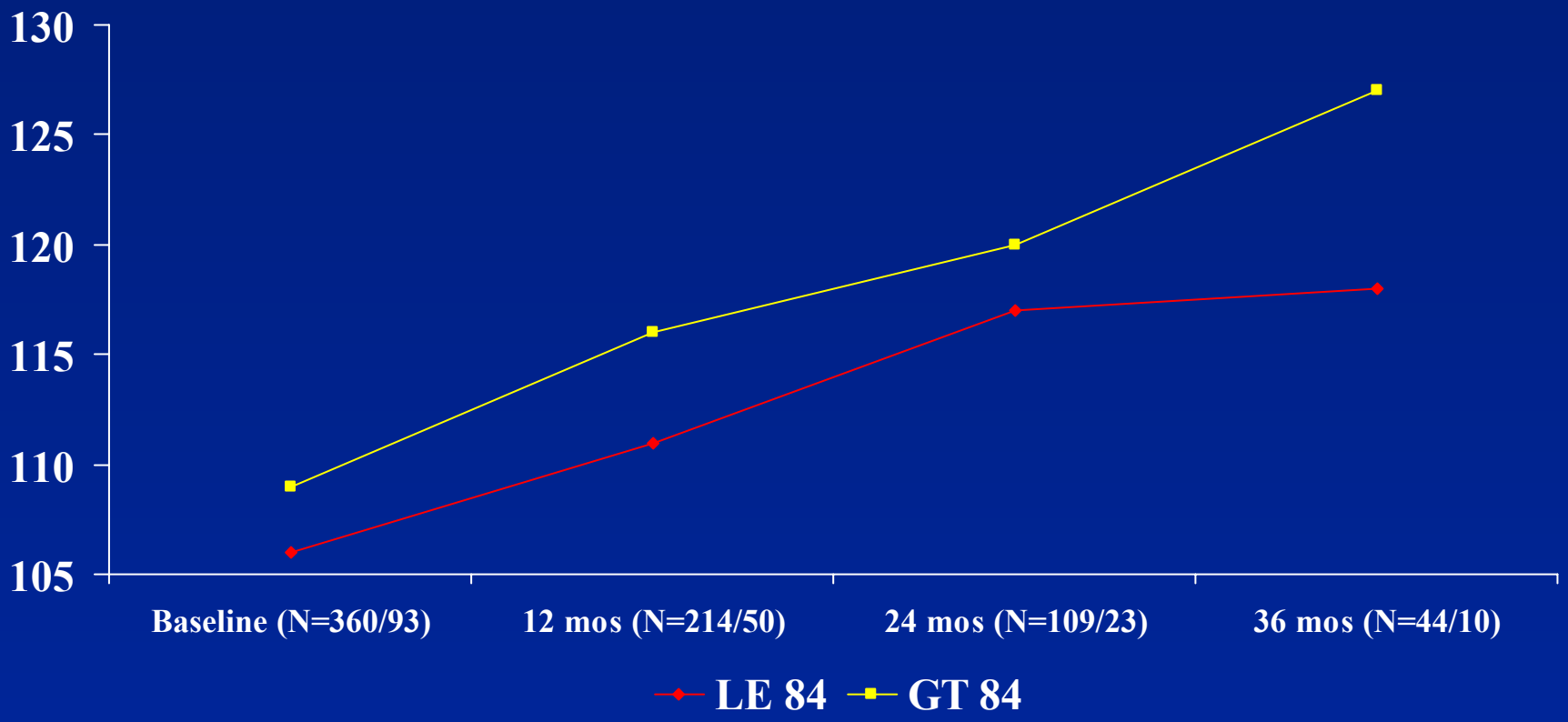
PREPARE:
Defining Family History

- A first degree relative with memory loss, senility, Alzheimer's disease.
  - 58% had AD
- Confidence in Dx: Made by MD, specialist or autopsy
  - 56% had MD or better (N=255)
  - (N=157)
- Age of onset in relative:
  - 7.1 % before age 65
  - 21% age 85 and up

PREPARE:
Confidence in DX and Cognition

- Demographics (age, education, ethnicity):
  - Higher education in Dx by MD or better (p=0.043) no other differences.
- Cognition:
  - Significant difference only in VRT
  - Dx by MD: 1.57 improvement
  - NO MD: 1.26 decline
  - Result remains significant after education adjustment

Memory Composite Score Over Time by Dementia Onset in Relative



Summary of Observations

- Selection for cognitive health may identify a population without prodromal disease.
- Hysterectomy status may change cognitive function.
- The age of onset of dementia in relatives may affect rate of cognitive change.

The Challenge

"Yes, I've learned from my mistakes. I've learned if you call them 'missed opportunities' you get in less trouble."

PREPARE

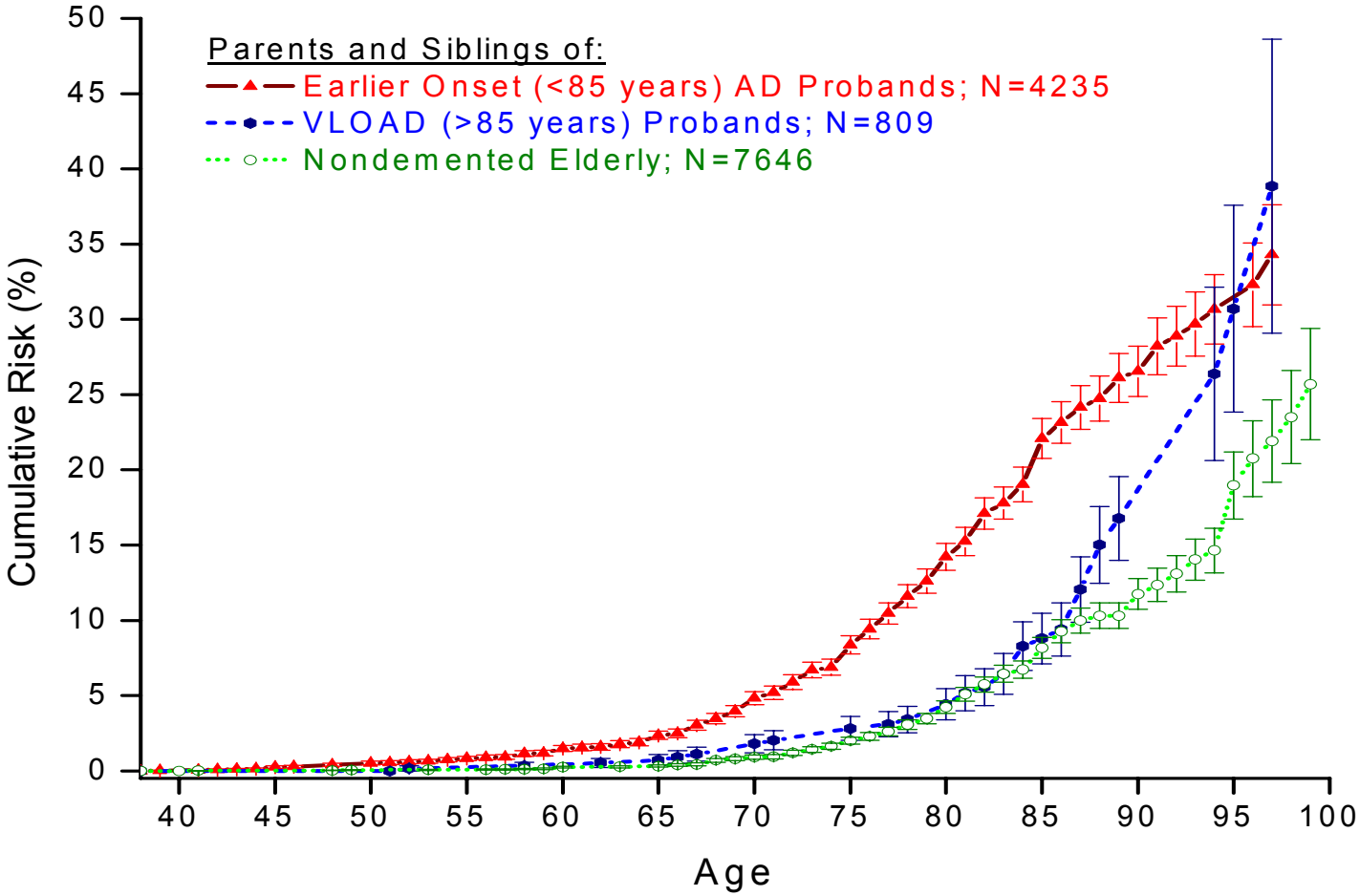
Preventing Memory Loss & Alzheimer's Disease

- 28 % have had a hysterectomy
- 41% have never taken estrogen in the past
- MMSE score = 28.8 $\pm$ 1.5
- Beck Depression score = 4.9 $\pm$ 3.7
- Apolipoprotein E 4
  - Any: 29.6%
  - Homozygote: 2.2%
- 4.8 %worsening with 168 person yrs of follow up

Outcomes

- 6 cases of "trigger" at 12 months of a total of 105 cases who had annual visit
- 1 was triggered at 24 months with a total of 36 in the data base.
- None were deemed to have dementia
- Annual rate of decline (with only one year): 4.9%

Cumulative Risk of AD in Relatives of VLOAD, Earlier Onset AD, and Nondemented Elderly



Silverman et al., Arch Gen Psych, 2003