Brain & Hormone Therapy

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Why do more Women than Men have Alzheimer's disease??

- Women live longer than men?
  - In some rural, developing areas, the sex difference in longevity is reversed, & AD-sex ratio is also reversed.
  - After control for the sex-longevity effect, epid. St. yet still showed a sex difference in AD.
- The mortality rate of AD in NH
  - men 54% : women 33%
- Men get more VaD?
  - masking early AD sx.
- Low level of education?
- Hormones?
  - Testosterone & Estrogen

성호르몬?

- 정말 성호르몬이 맞는가?
  - 남녀 모두에게 존재
  - 생식기에만 작용하나?
  - 난소나 고환에서만 생성되나?

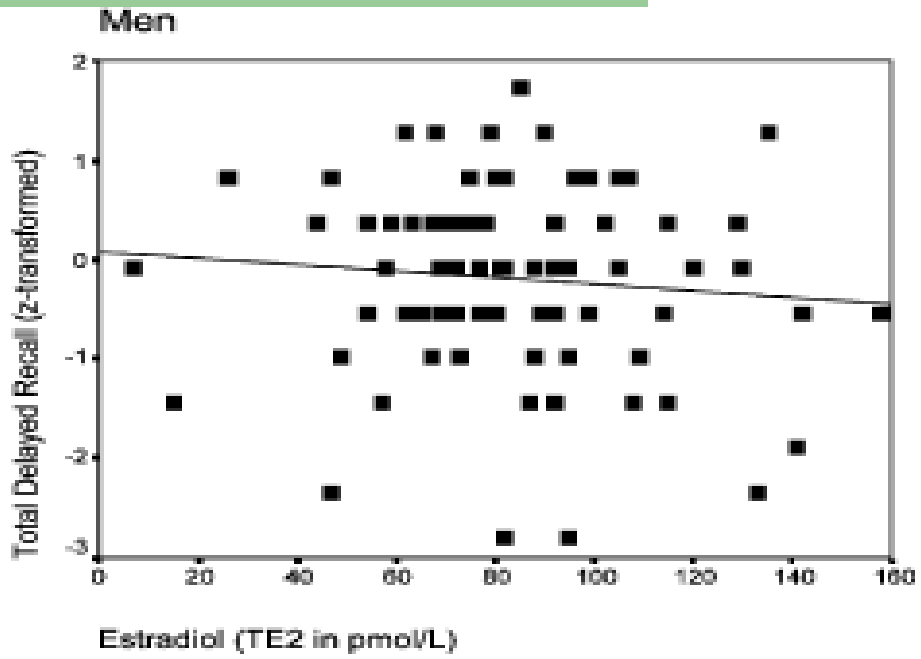
E2 & TT in different cognitive domains in the healthy elderly

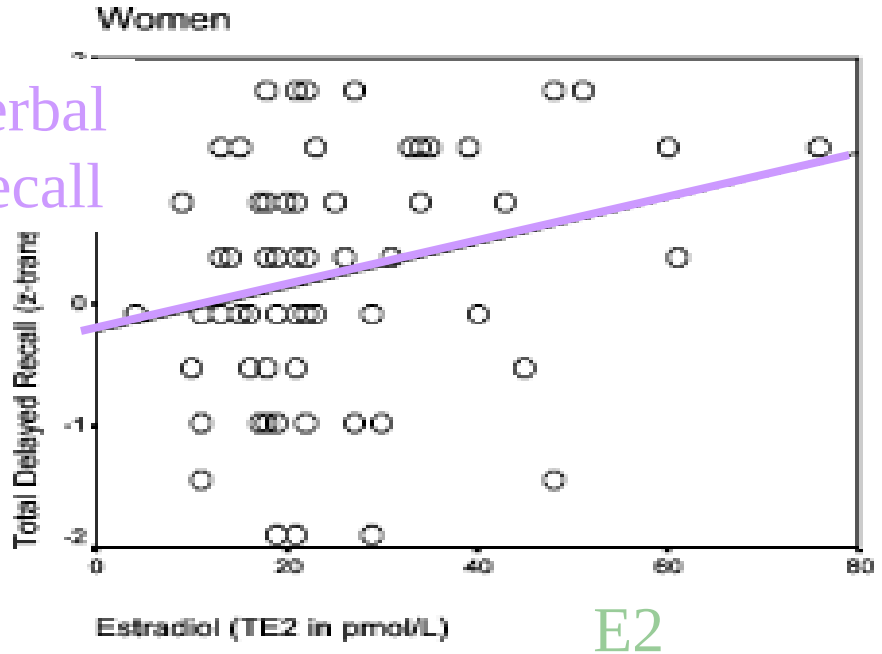
- Psychoneuroendocrinology. 2004
- Methods
  - 145 non-demented elderly volunteers
  - aged 61-91 years

남녀 인지기능 하부영역 차이

n=66
n=79

Hogervorst E. Psychoneuroendo 2004

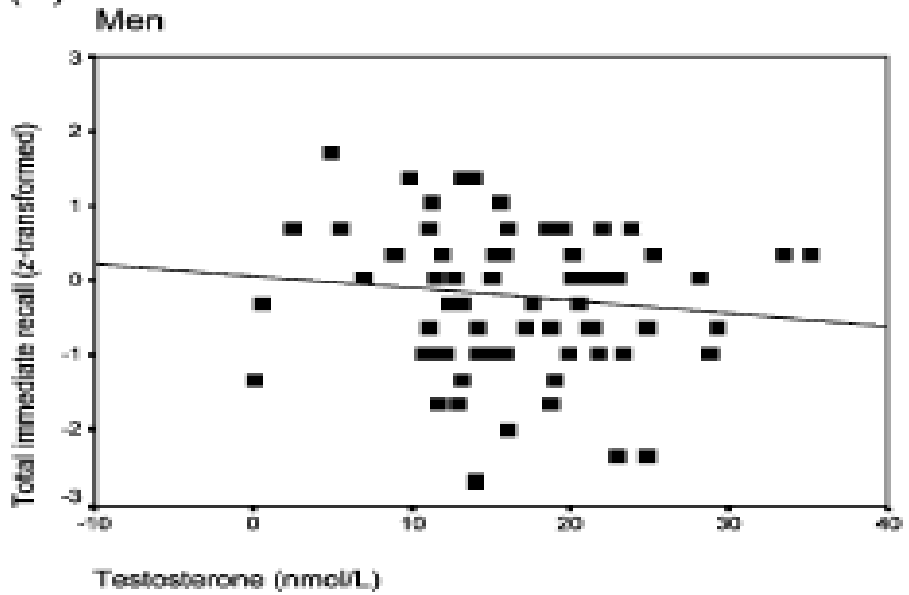


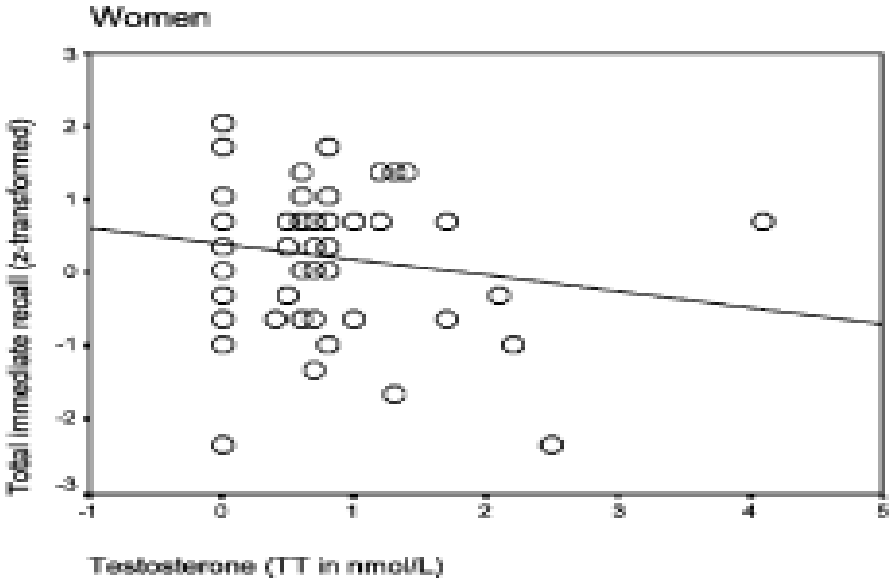


Verbal Recall

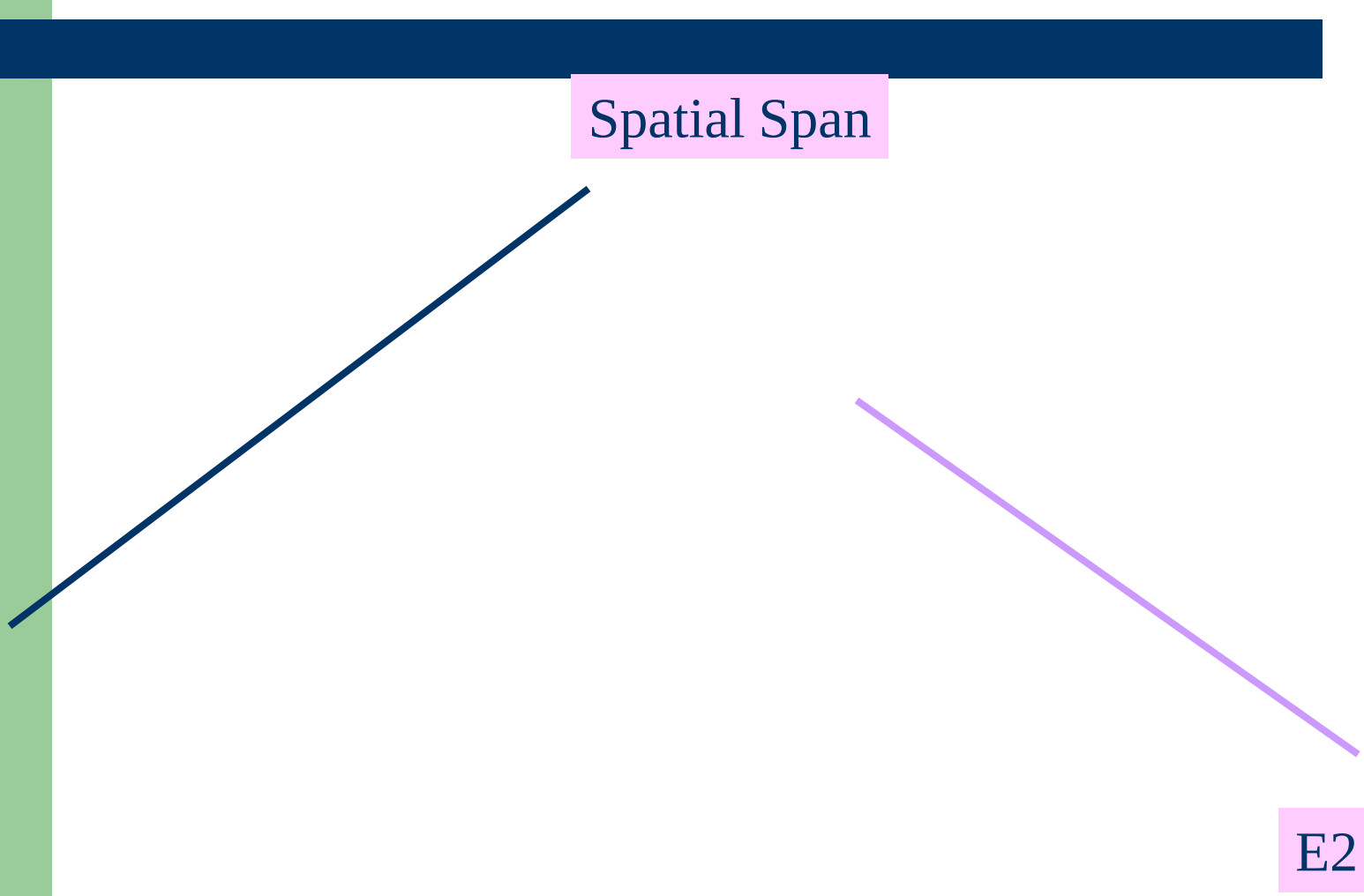
E2

(b)





E2 & Spatial span in the elderly



Testosterone & Speed of performance in the elderly

Speed of information

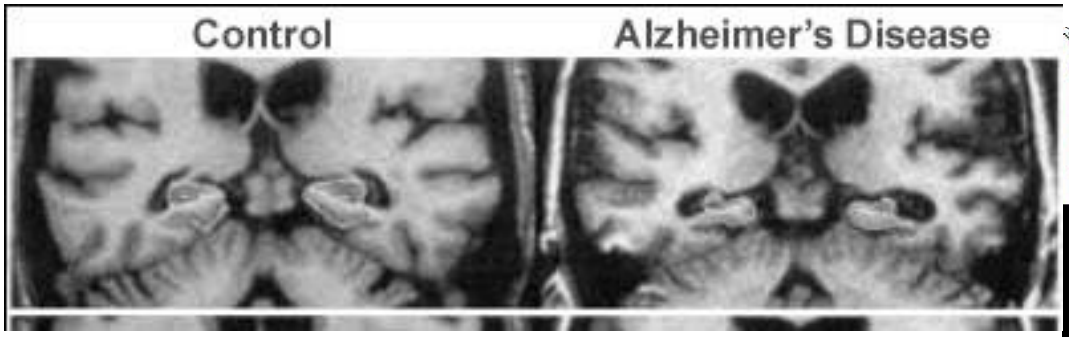
T

인지기능의 남녀차이 정리

- 여성
  - verbal recall
  - 에스트로겐
    - 언어 기억력와 관련
    - 시공간 능력과 부정적 상관(?)
- 남성
  - naming
  - 테스토스테론
    - 정보처리속도와 관련

Effects of Testosterone on Behavioral & Neural Systems

- Hippocampus
  - High concentrations of androgen receptors.
  - Spatial learning & memory in the rats
    - Administration of T to females during critical periods of development enhances spatial learning
    - Castration in males impairs maze learning



Neural Effects of Testosterone

- an early organizational effect
  - on the development of the hypothalamus, the cerebral cortex, and the hippocampus.
- Physiological effects
  - Neuroprotective & Neurotrophic factor
  - Eg
    - Prevent NMDA excitotoxicity in hippocampal neurons
    - Increase NGF levels in the hippocampus
    - Inhibit the expression of amyloid
      - Suppression of T for Tx of prostate ca => x 2 inc. of plama amyloid concentration

Relationship b/w Testosterone & Human Cognitive Function

- Enhanced visuo-spatial performance in females exposed prenatally to excess androgens
- ↓ Spatial performance in young male hypogonadism
- **An Inverted U-shaped relationship b/w T & spatial cognition in young adults**
- Language-related measures (**Verbal fluency**)
  - **No relationship to T**.
- 결) In young adults, spatial cognition as the domain of cognitive function : most sensitive to T.

The association between endogenous free testosterone and cognitive performance: A population-based study in 35 to 90 year-old men and women

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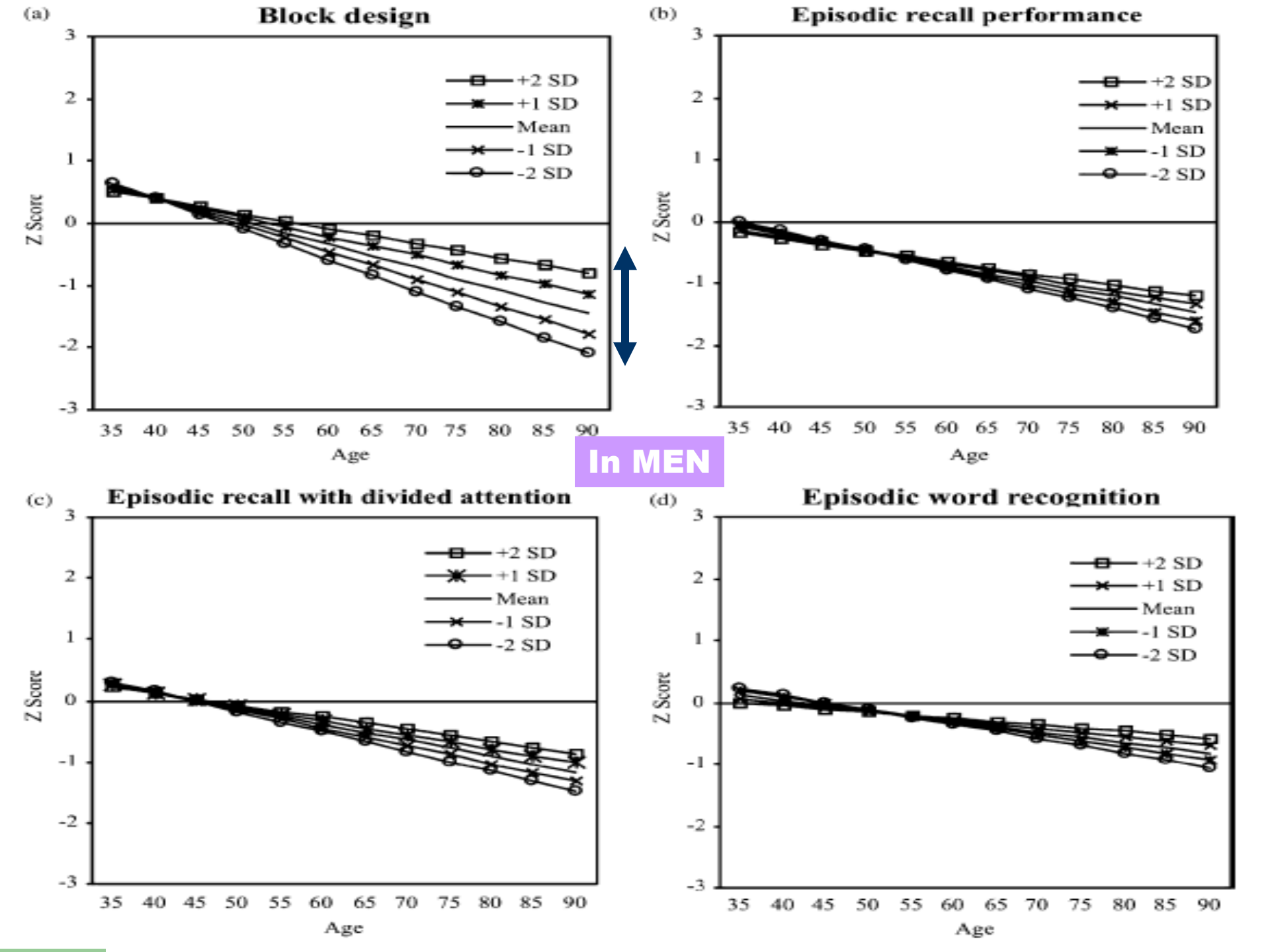
KEYWORDS
Hormones;
Testosterone;
Sex differences;
Cognition;
Visuospatial abilities;
Memory

Summary The relationship between testosterone (T) and cognition has yielded conflicting evidence, showing both positive and negative influences of T on cognitive performance. The association between free testosterone (FT) and cognition was revisited in a large population-based sample of 1276 women and 1107 men (35–90 years of age), assessed individually on visuospatial, verbal fluency, semantic, and episodic memory tasks. For men, higher FT levels were associated with better visuospatial abilities, semantic memory, and episodic memory, with greater positive influence with increasing age. Statistical covariates included age, education, and select medications. For women, FT was negatively associated with verbal fluency, semantic memory, and episodic memory, although only verbal fluency was significant at conventional alpha levels. These results support the claim that FT exerts sex-specific influences on cognitive performance.

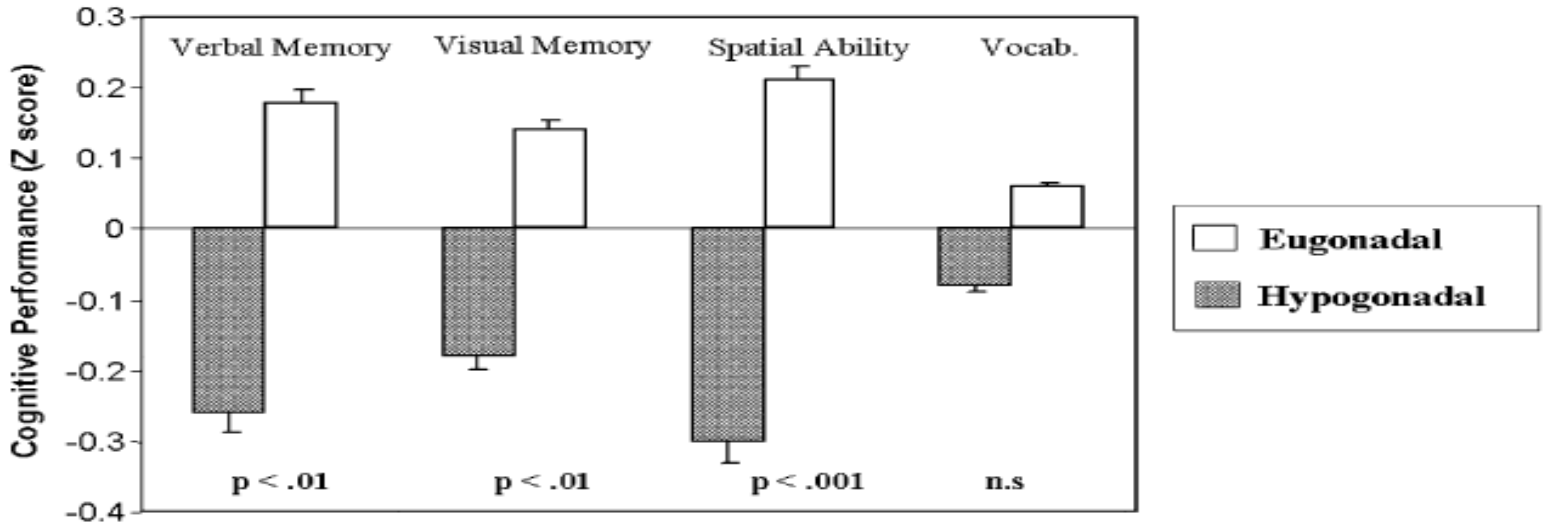
Psychoneuroendocrinology

- In Women (1276명)
  - Verbal components 우세
    - word comprehension / recognition, verbal fluency, recall,
  - Negative correlation with FT
    - Verbal fluency
- In Men (1107명)
  - Block design (visuospatial abilities) 우세
  - Positive Correlation with FT
    - Block design, recall
  - Positive influence (older > younger men)


(a)
Block design
(b)
Episodic recall performance
(c)
Episodic recall with divided attention
(d)
Episodic word recognition
+2 SD
+1 SD
Mean
-1 SD
-2 SD
Z Score
Age
3
2
1
0
-1
-2
-3
35 40 45 50 55 60 65 70 75 80 85 90
In MEN

Testosterone & Cognition in Older Men

- Longitudinal St. (Moffat SD, 2002)
  - BLSA
  - 407 men aged 50 to 91 years
  - F/U for 10 years
  - Results
    - Free T. was ass. with higher scores visual & verbal memory and visuospatial functions and with a reduced rate of decline in visual memory.
    - No relations b/w T. & verbal knowledge, general mental status, or depressive symptoms



Harman SM. BLSA. J Clin Endocrinol Metab 2001

Decline in Visual Memory

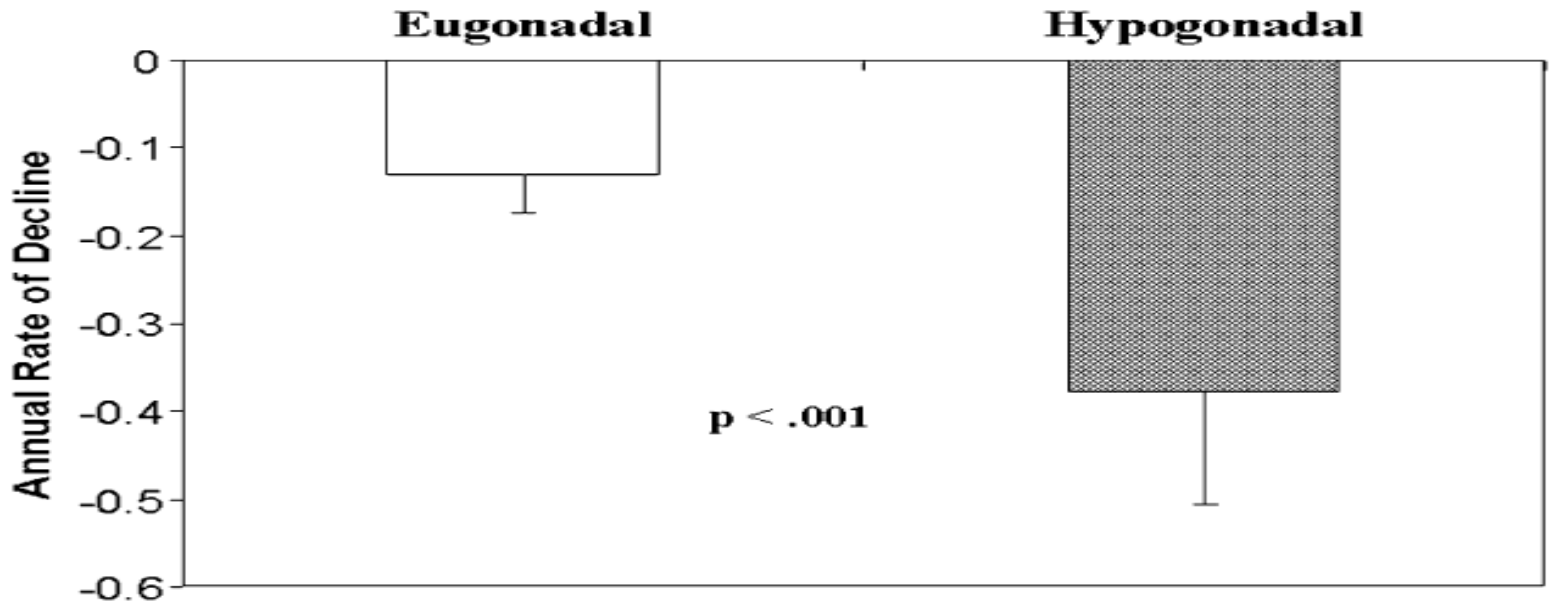


FIGURE 2. Annual rate of decline in visual memory as a function of hypogonadal or eugonadal status. Men classified as hypogonadal had a steeper rate of decline in visual memory than did eugonadal men.

Harman SM. BLSA. J Clin Endocrinol Metab 2001

Q) A Marker or a Causative Factor ?

Low T. level in age-related cognitive decline

The decreased androgen levels in AD could be a consequence rather than a cause of the disease.

Degenerative brain change in AD => hypothalamic-pituitary-gonadal axis function

Neuroimaging Study

- Neuroimaging Study with PET
  - Men with higher free T. had increased blood flow in the hippocampus bilaterally.
- Physiological explanation for the possible beneficial effects of free T. on cognitive function.

Free T & Risk for AD in Older Men

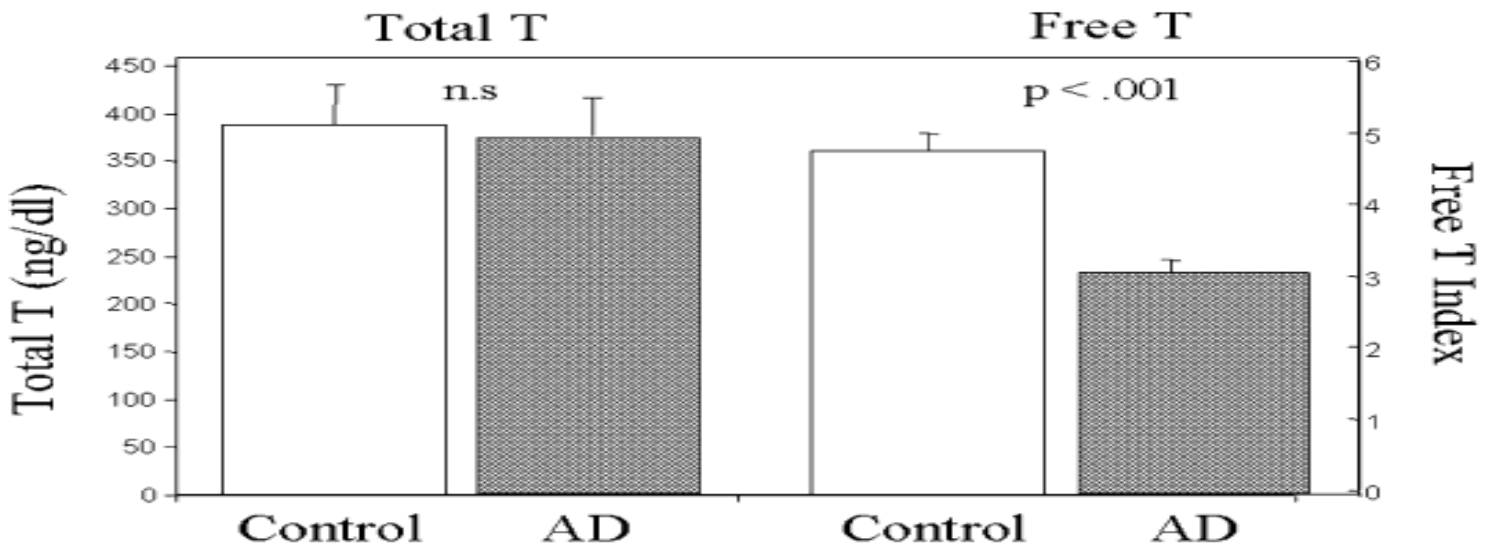


FIGURE 4. Mean total testosterone (T) and mean free T levels in individuals diagnosed with AD and non-demented controls. There was no difference between AD patients and controls in total T, but we observed significantly lower free T levels in patients with AD than in controls. There was an approximately 10% reduced risk for AD for each unit increase in free T.

FT 1U 증가 => AD 위험도 10% 감소

Moffat SD, Neurology 2004

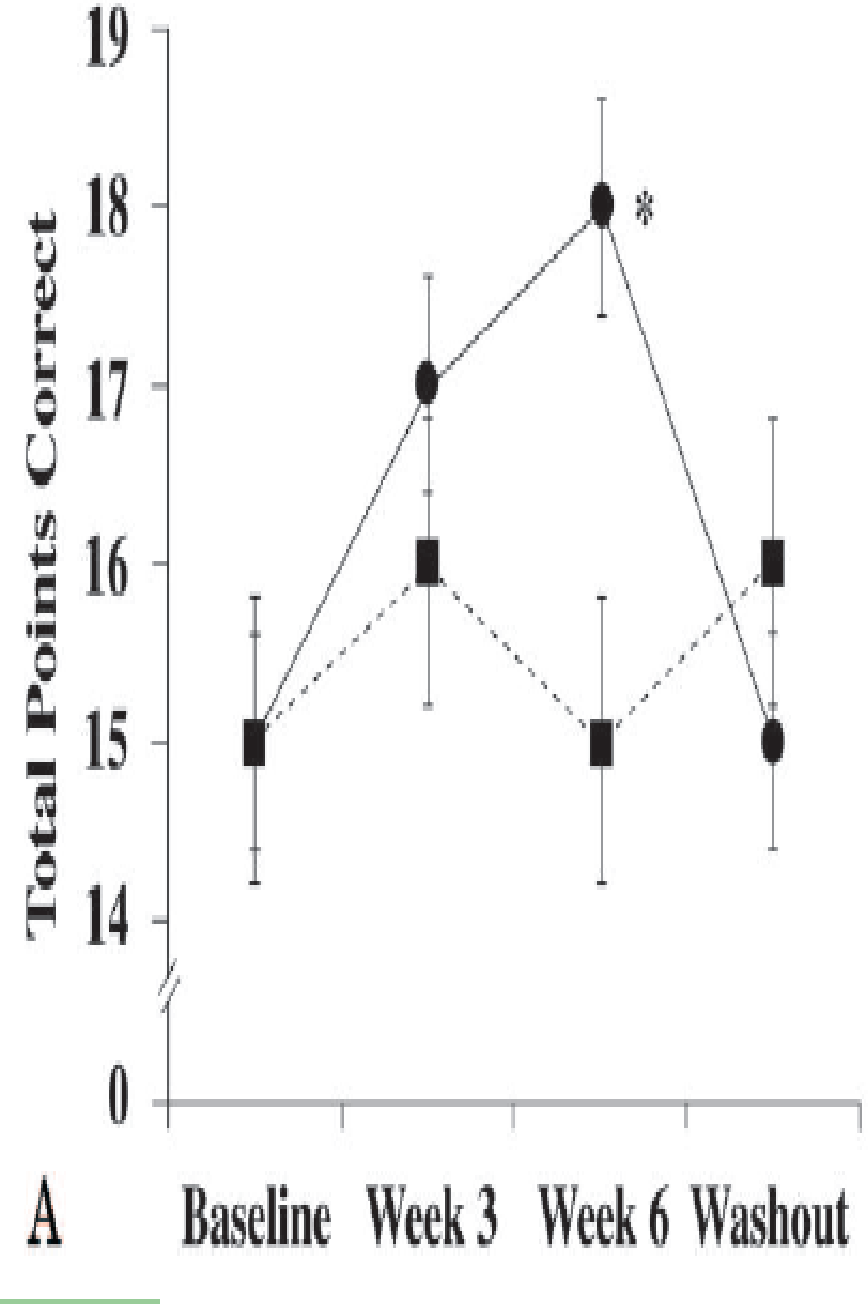
Q) Global or Specific Domain of Cognitive Function?

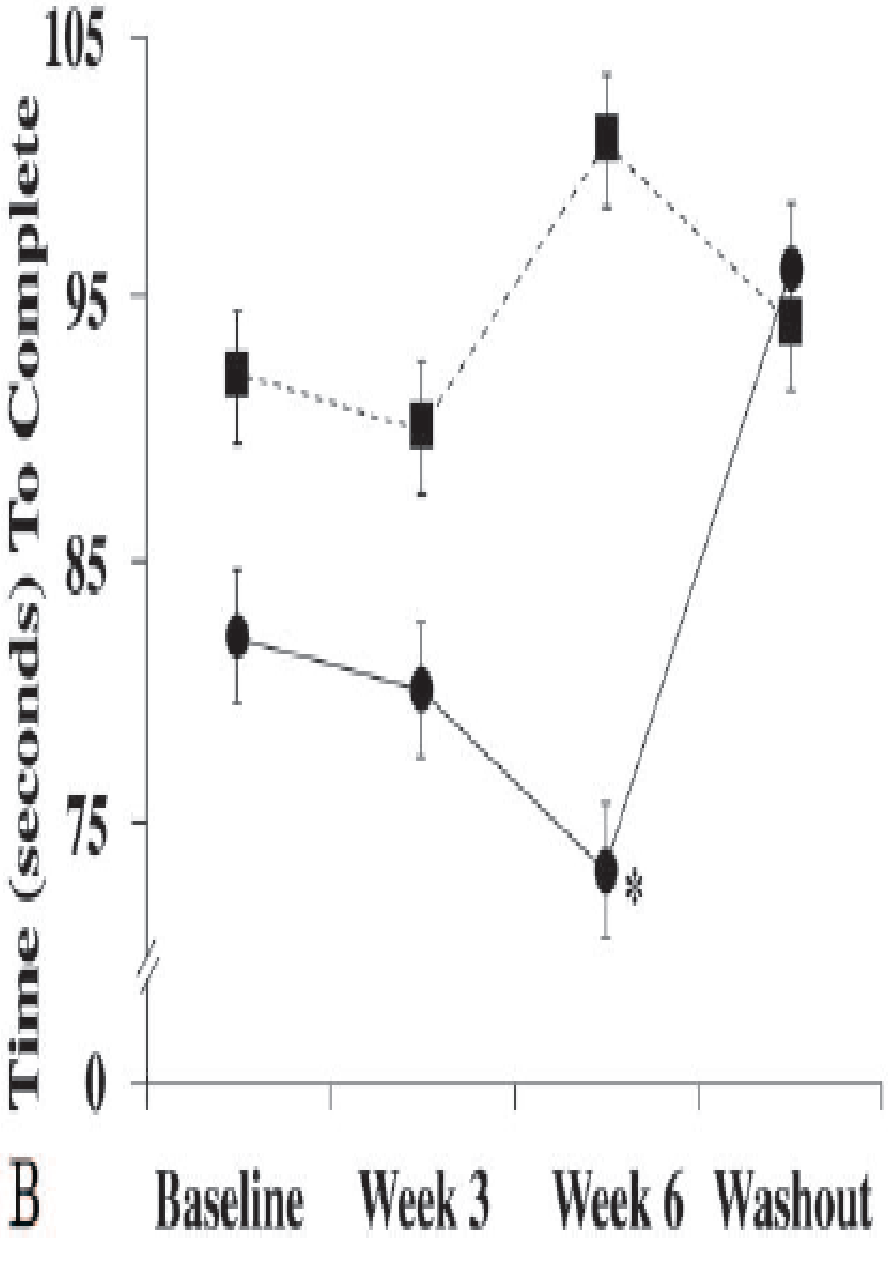
Testosterone improves spatial memory in men with Alzheimer disease and mild cognitive impairment

M.M. Cherrier, PhD; A.M. Matsumoto, MD; J.K. Amory, MD; S. Asthana; W. Bremner, MD; E.R. Peskind, MD; M.A. Raskind, MD; and S. Craft, PhD

Abstract—*Objective:* To determine the efficacy of testosterone (T) supplementation on cognition in a sample of men with Alzheimer disease (AD) or mild cognitive impairment (MCI). *Methods:* Fifteen patients with AD and 17 patients with MCI aged 63 to 85 years completed a randomized, double-blind, placebo-controlled study. Nineteen participants received weekly intramuscular (IM) injections of 100 mg T enanthate and 13 participants received weekly injections of placebo (saline) for 6 weeks. Cognitive evaluations using a battery of neuropsychological tests were conducted at baseline, week 3, and week 6 of treatment and again after 6 weeks of washout. *Results:* Peak serum total T levels were raised from baseline an average of 295% in the active treatment group. Improvements in spatial memory ($p < 0.05$) and constructional abilities ($p < 0.05$) and verbal memory were evident in the T group. No changes were noted for selective and divided attention or language. Prostate specific antigen did not significantly change during this brief treatment. *Conclusion:* Testosterone supplementation may benefit selective cognitive functions in men with Alzheimer disease and mild cognitive impairment.

NEUROLOGY 2005;64:2063–2068


Total Points Correct
19
18
17
16
15
14
0
*
A
Baseline
Week 3
Week 6
Washout


Time (seconds) To Complete
105
95
85
75
0
*
B
Baseline
Week 3
Week 6
Washout

Effects of Testosterone on Cognition and Mood in Male Patients With Mild Alzheimer Disease and Healthy Elderly Men

Po H. Lu, PsyD; Donna A. Masterman, MD; Ruth Mulnard, PhD; Carl Cotman, PhD; Bruce Miller, MD; Kristine Yaffe, MD; Erin Reback, BS; Verna Porter, MD; Ronald Swerdloff, MD; Jeffrey L. Cummings, MD

Background: There is a compelling need for therapies that prevent, defer the onset, slow the progression, or improve the symptoms of Alzheimer disease (AD).

Objective: To evaluate the effects of testosterone therapy on cognition, neuropsychiatric symptoms, and quality of life in male patients with mild AD and healthy elderly men.

Design: Twenty-four–week, randomized, double-blind, placebo-controlled, parallel-group study.

Setting: Memory disorders clinics as well as general neurology and medicine clinics from University of California medical centers at Los Angeles, San Francisco, and Irvine.

Patients or Other Participants: Sixteen male patients with AD and 22 healthy male control subjects. Healthy elderly control men were recruited from the community through advertisements as well as through the university-based clinics.

Intervention: Testosterone and placebo, in the form of hydroalcoholic gel (75 mg), were applied daily to the skin of the participants.

Main Outcome Measures: Instruments assessing cognitive functioning (Alzheimer's Disease Assessment Scale–Cognitive Subscale, California Verbal Learning Test, Block Design Subtest, Judgment of Line Orientation, Developmental Test of Visual-Motor Integration), neuropsychiatric symptoms (Neuropsychiatric Inventory), global functioning (Clinician's Interview-Based Impression of Change), and quality of life (Quality of Life–Alzheimer Disease Scale).

Results: For the patients with AD, the testosterone-treated group had significantly greater improvements in the scores on the caregiver version of the quality-of-life scale ($P=.01$). No significant treatment group differences were detected in the cognitive scores at end of study, although numerically greater improvement or less decline on measures of visuospatial functions was demonstrated with testosterone treatment compared with placebo. In the healthy control group, a nonsignificant trend toward greater improvement in self-rated quality of life was observed in the testosterone-treated group ($P=.09$) compared with placebo treatment. No difference between the treatment groups was detected in the remaining outcome measures. Testosterone treatment was well tolerated with few adverse effects relative to placebo.

Conclusions: Results suggest that testosterone replacement therapy improved overall quality of life in patients with AD. Testosterone had minimal effects on cognition.

Arch Neurol. 2006;63:177-185

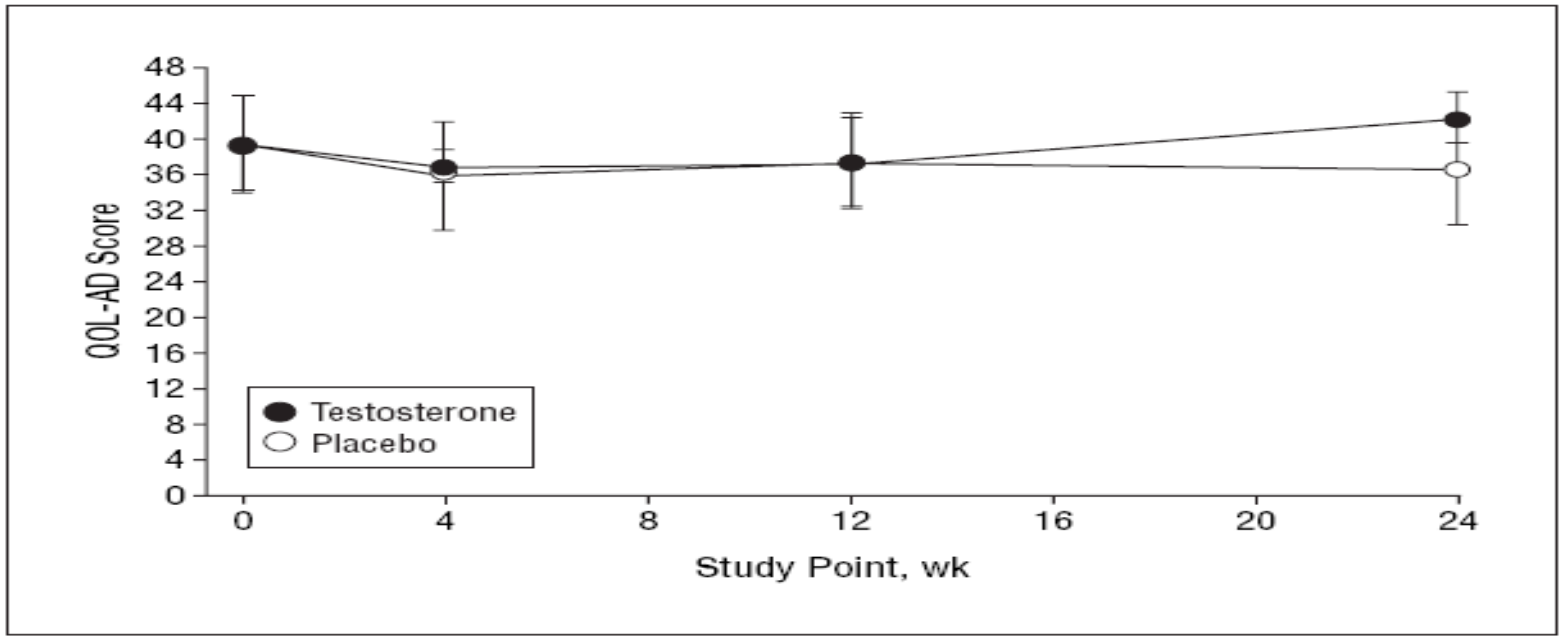


Figure 2. Change in Quality of Life–Alzheimer Disease (QOL-AD) scores (caregiver) across study points in male patients with AD receiving testosterone and placebo.

The role of aromatization in testosterone supplementation

Effects on cognition in older men

M.M. Cherrier, PhD; A.M. Matsumoto, MD; J.K. Amory, MD; S. Ahmed, MD; W. Bremner, MD; E.R. Peskind, MD; M.A. Raskind, MD; M. Johnson, BS; and S. Craft, PhD

Abstract—*Objective:* To determine the contribution of conversion of testosterone (T) to estradiol on cognitive processing in a population of healthy older men who received T supplementation. *Methods:* Sixty healthy, community-dwelling volunteers aged 50 to 90 years completed a randomized, double-blind, placebo-controlled study. Participants were randomized to receive weekly IM injections of 100 mg T enanthate plus daily oral placebo pill (T group, n = 20), 100 mg testosterone enanthate plus 1 mg daily of anastrozole, an aromatase inhibitor (oral pill), to block the conversion of T to estradiol (AT group, n = 19), or saline injection and placebo pill (placebo group, n = 21) for 6 weeks. Cognitive evaluations using a battery of neuropsychological tests were conducted at baseline, week 3 and week 6 of treatment, and after 6 weeks of washout. *Results:* Circulating total T was increased from baseline an average of 238% in the T and AT treatment groups. Estradiol increased an average of 81% in the T group and decreased 50% in the AT group during treatment. Significant improvements in spatial memory were evident in the AT and T treatment groups. However, only the group with elevated estradiol levels (T group) demonstrated significant verbal memory improvement. *Conclusion:* In healthy older men, improvement in verbal memory induced by testosterone administration depends on aromatization of testosterone to estradiol, whereas improvement in spatial memory occurs in the absence of increases in estradiol.

NEUROLOGY 2005;64:290–296

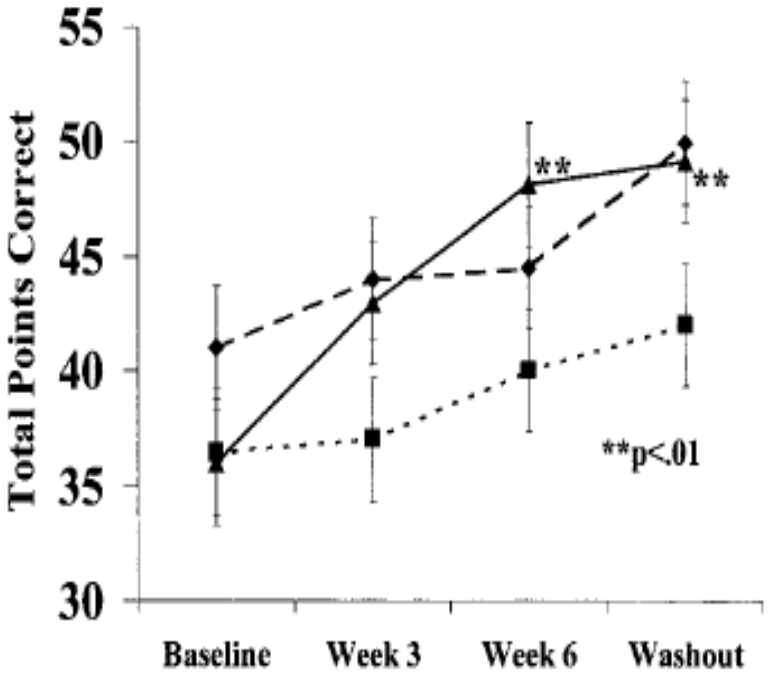
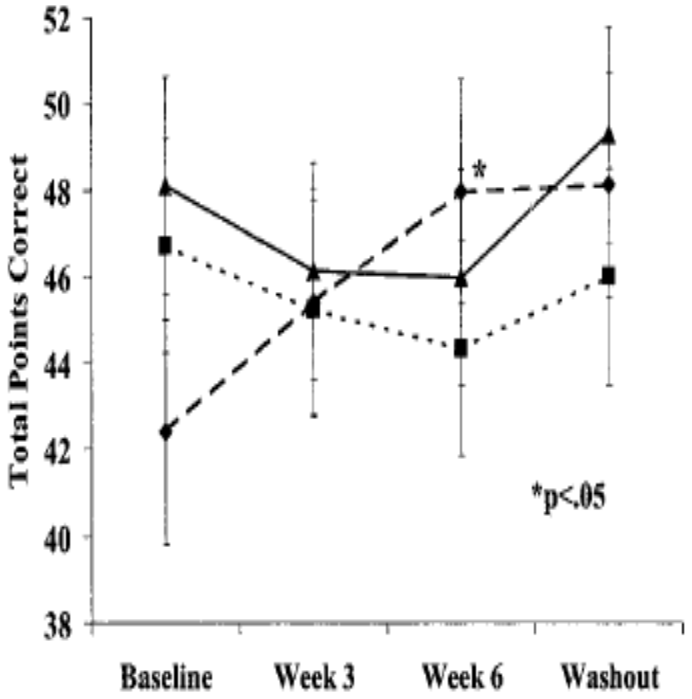


Figure 2. Mean total points correct on the route test, a

- Route test
  - Spatial memory
- AT group
  - Pure T?

12 compared with baseline. The AT group demonstrated a significant improvement at weeks 6 and 12 compared with baseline. An interaction effect was also evident ($p < 0.01$).



- Story Recall
  - Verbal memory
- T group
  - Estrogen effect?

Testosterone & Brain

- Neural aspects
  - Androgen receptors in hippocampus
  - Neuroprotective & Neurotrophic factor
  - ↑ CBF in hippocampus
- In young adults,
  - **spatial cognition** : most sensitive to T.
- In the elderly
  - Free T. was assiated. with higher scores visual & verbal memory and visuospatial functions and with a reduced rate of decline in visual memory.
  - Verbal memory improved by aromatization?

Only Short term, Small-sized Clinical Trials with T. in elderly men

Table 1. Examples of estrogen actions that directly or indirectly affect the brain[a]

Neuroprotection
Apoptosis
Oxidative stress
Excitatory neurotoxicity
Ischemic damage
Neurotrophic effects
Growth factors synthesis
Neurite growth
Synaptic plasticity
Neurotransmitter effects
Acetylcholine
Noradrenalin
Serotonin
Dopamine
Glutamate
Reduced β-amyloid formation in brain
Increased cerebral blood flow, glucose transport, and glucose metabolism
Variable effects on inflammatory markers
Variable effects on thrombosis and thrombolysis

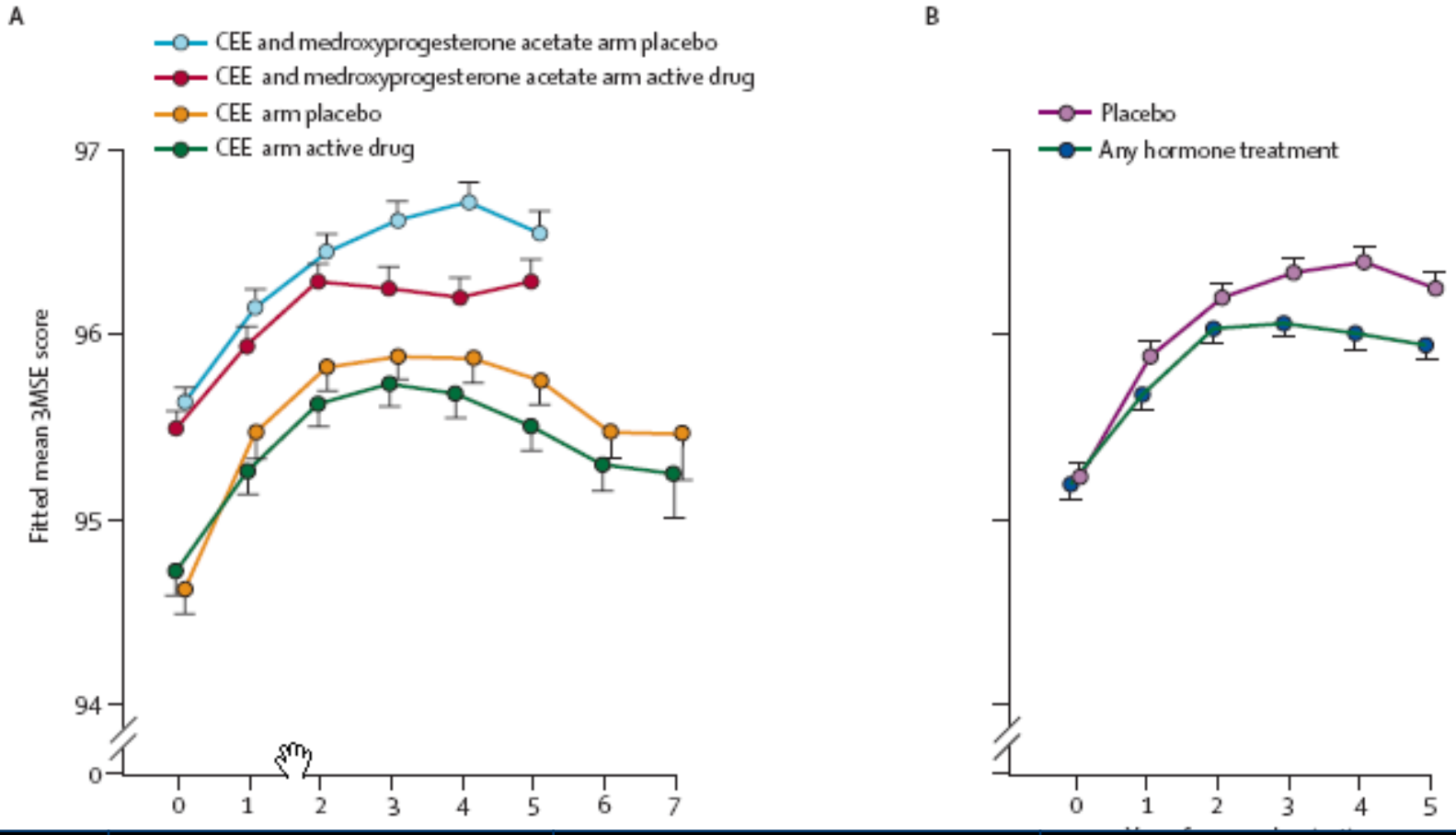
[a] Modified from (Henderson, 2000).

JAMA. 2001;285:1489-1499

Hormone Replacement Therapy and
Cognition Systematic Review and Meta-analysis

OR = 0.66

(0.53-0.82)



WHIMS	E+P trial (4.1yr, n=4532)	E alone trial (5.2yr, n=2947)	Combined
MCI	1.1 (0.7-1.6)	1.3 (0.95-1.9)	1.25 (0.97-1.6)
Dementia	2.1 (1.2-3.8)	1.5 (0.8-2.7)	1.8 (1.2-2.6)

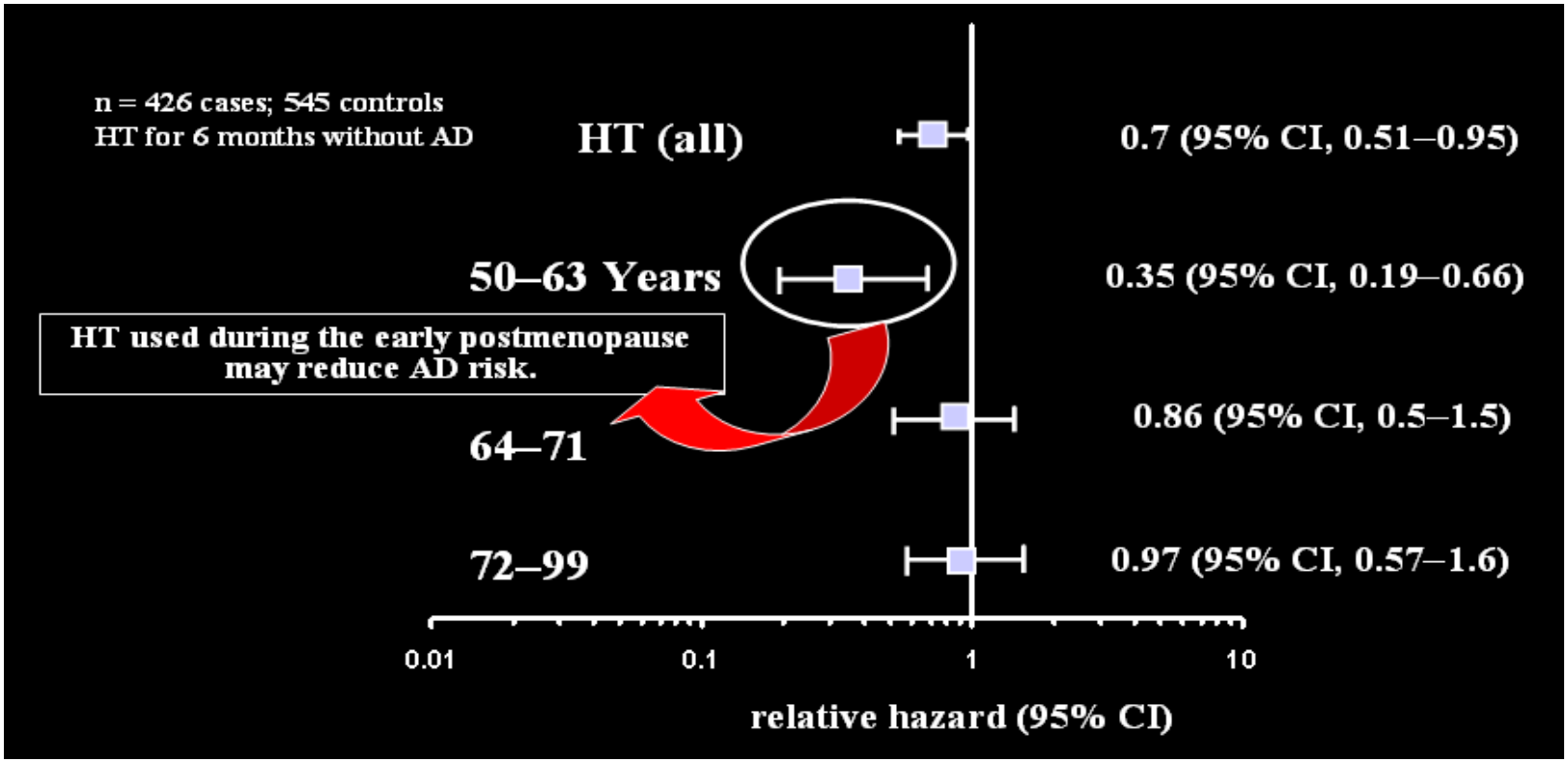
Observational St. vs WHIMS

Factor	Observational studies	WHIMS trials
Susceptibility to bias or confounding	Large (healthy-user bias)	Small
Primary outcome	AD	All-cause dementia
HT formulation	Often CEE; sequential progestin	Only CEE; continuous progestin
Menopausal symptoms	Common	Uncommon
Age at time of study	Variable; usually older	Older (65+ years)
Age at HT exposure	Usually younger	Older (65+ years)
Timing of HT initiation	Usually close to menopause	Remote from menopause

Cache County Study: Prospective Observational St. risk of AD : effect of timing & duration of HT use

Zandi PP. JAMA 2002;288:2123-9

Postmenopausal hormone therapy and Alzheimer's disease risk: interaction with age



Henderson. J Neurol Neurosurg Psychiatry. 2005

Early postmenopausal hormone therapy may prevent cognitive impairment later in life

N=343 women
f/u at 5,11,15 yr
Age at f/u =65

Treatment	Cognition		Odds ratio (95% CI)	
	Score <6	Score ≥6	Unadjusted	Multivariate adjusted[a]
Never user (n = 107)	93	14[b]	1.00	1.00
Short-term HT (n = 154)	146	8	0.36 (0.15-0.90) *P* = 0.029	0.33 (0.13-0.84) *P* = 0.021
Long-term/current HT (n = 82)	78	4	0.34 (0.11-1.08) *P* = 0.067	0.36 (0.11-1.15) *P* = 0.083
Ever HT user (n = 236)[c]	224	12	0.36 (0.16-0.80) *P* = 0.012	0.34 (0.15-0.78) *P* = 0.011

Bagger. Menopause 2005;12(1):12-17

428 PMW >60yrs

REMEMBER pilot study

MacLennan Menopause 2006

(Research into Memory Brain function & Estrogen Replacement)

Hormone Therapy & Cognitive Function: Is there a Critical Period for Benefit?

- Critical Period Hypothesis
- early initiation ; may be beneficial
  - commenced within 4-6yrs of menopause
  - cardio- & neuro- protection
  - Verbal memory & other hippocampally mediated functions
- late initiation ; detrimental
  - commenced within many yrs after menopause
  - cardiac events & dementia ↑

Maki PM. Neuroscience 2006