Estrogen Exposures in Midlife, Memory and Dementia

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Midlife estrogen exposures

Two questions

- Do midlife estrogen exposures affect memory?
- Do midlife estrogen exposures affect risk of Alzheimer's disease?

Memory and natural menopause

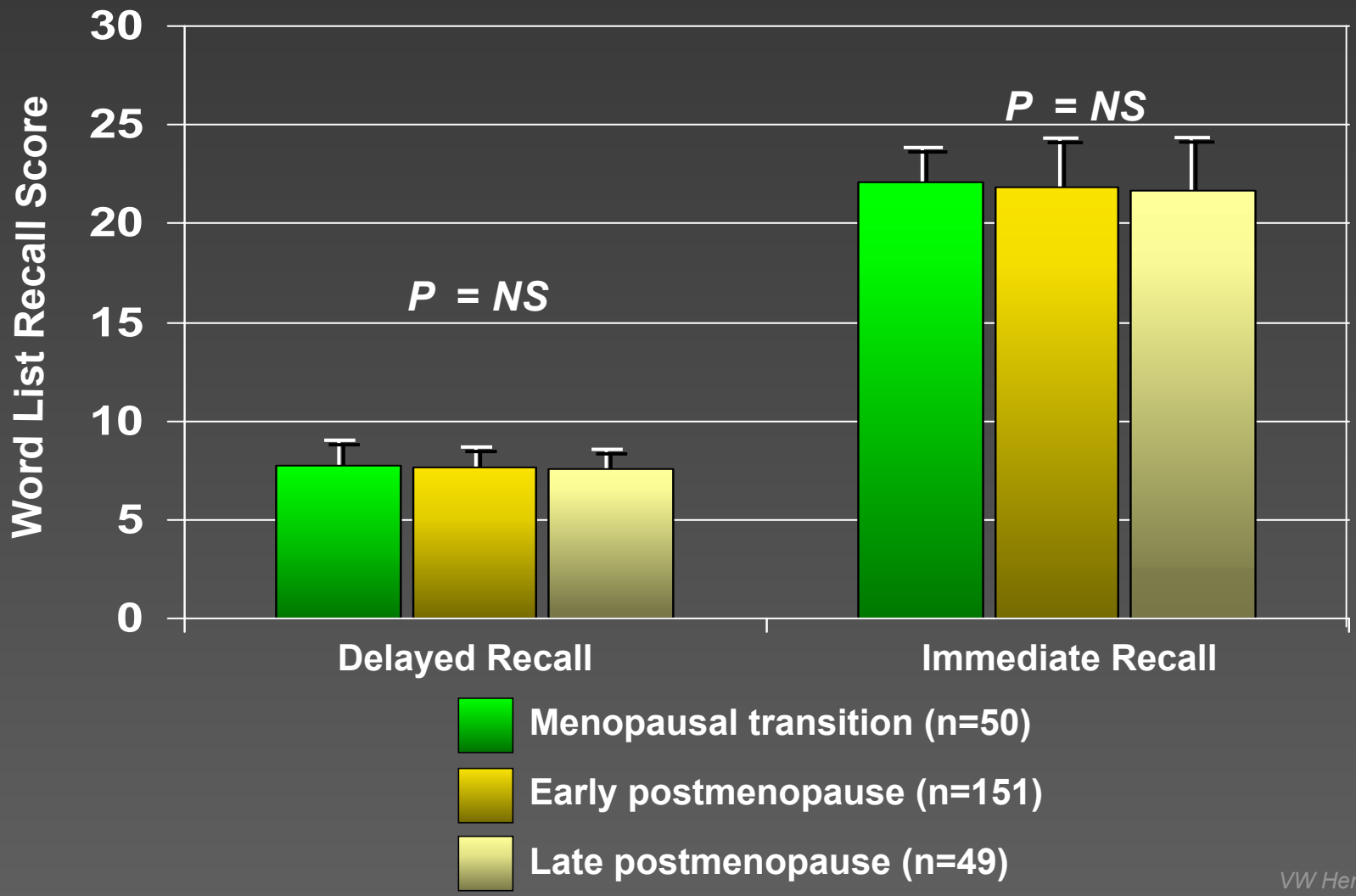
Melbourne Women's Midlife Health Project

- Population-based cohort, established 1991
  438 participants
- Ages 45-55 years, menstruating, no hormone therapy
- After 8 years, 387 (88%) women available
  326 participated in memory testing
- 10-item word list
  - 3 immediate recall trials
  - 1 delayed recall trial
- **Hypothesis: Estrogen exposures are associated with better memory**

Reproductive stage and memory

Melbourne Women's Midlife Health Project

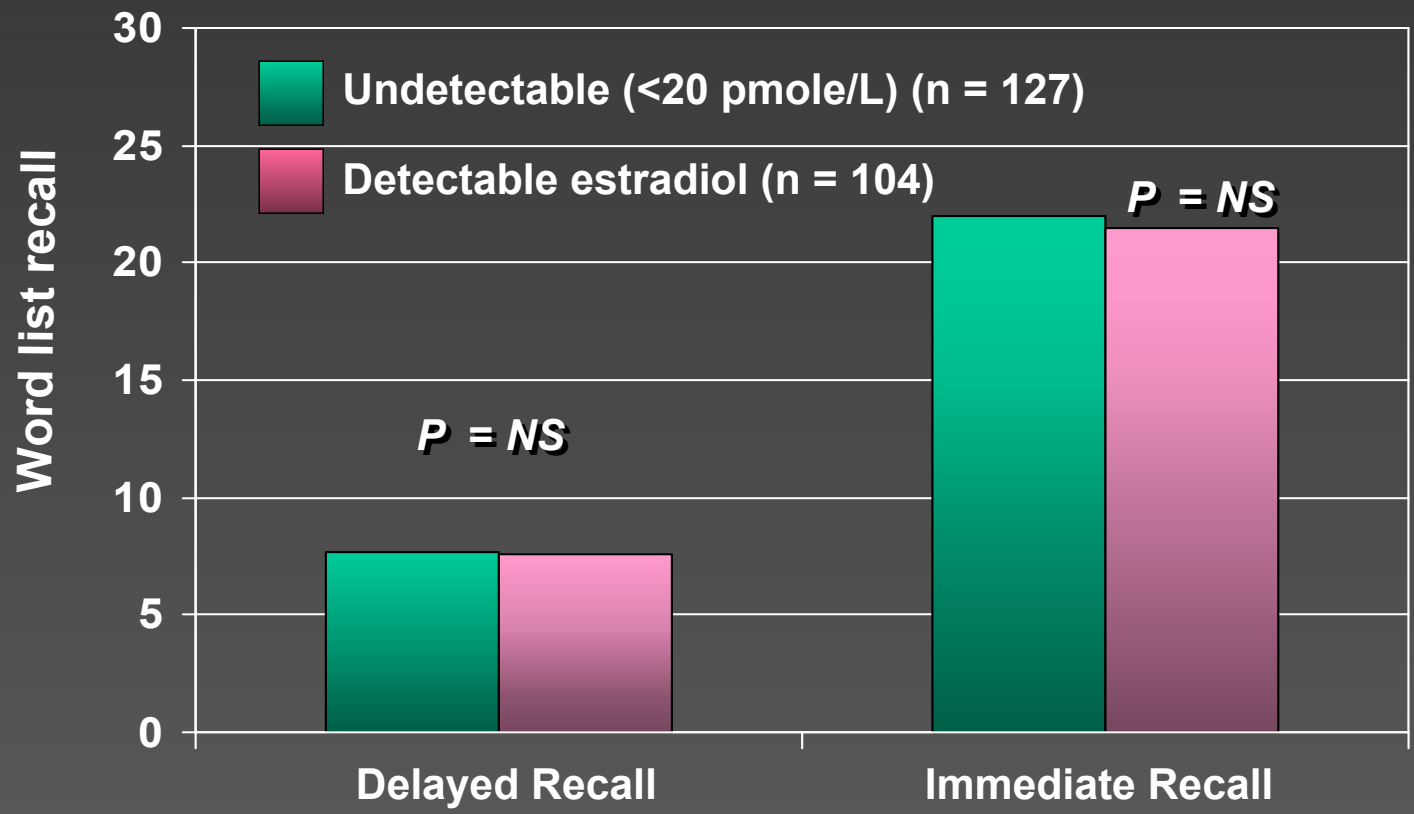
after: Henderson, Guthrie, Dudley, Burger, Dennerstein, *Neurology* 60:1369-1371, 2003.



Estradiol levels and memory

Melbourne Women's Midlife Health Project

after: Henderson et al., *Neurology* 60:1369-1371, 2003.



Based on 231 MWMHP participants in menopausal transition or postmenopause not using hormone therapy

Estradiol levels and memory

Melbourne Women's Midlife Health Project

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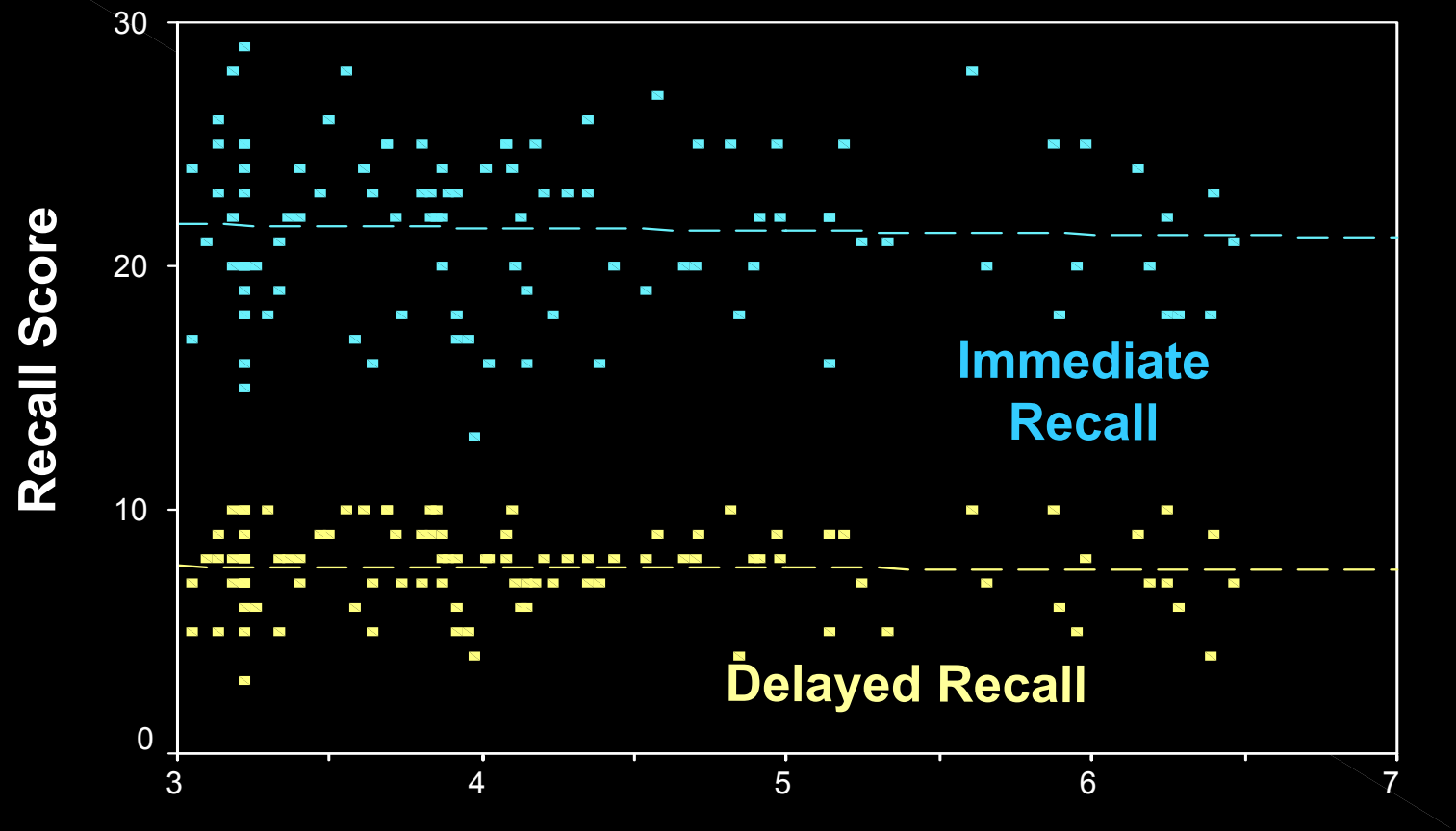


Based on 104 nonusers of hormone therapy; *P's = NS*

Endogenous estrogen exposures

Melbourne Women's Midlife Health Project

after: Henderson et al., *Neurology* 60:1369-1371, 2003.

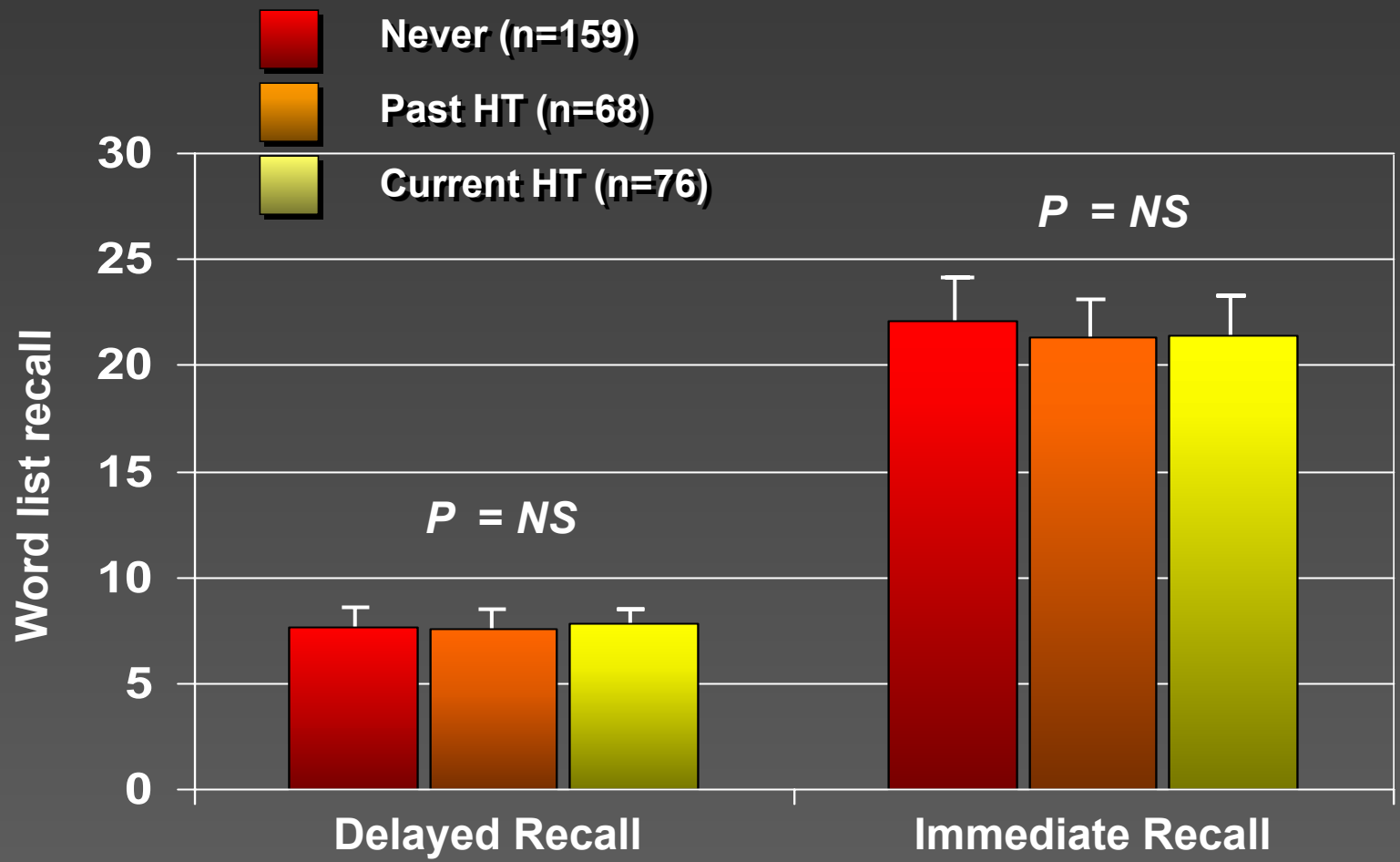
There was no relation between delayed recall or immediate recall and

- **Time since final menstrual period (*P*'s = *NS*)**
- **Body mass index at cohort entry and at time of memory assessment (year 8) (*P*'s = *NS*)**
- **Duration of reproductive life among never-users of hormone therapy (age at menopause minus age at menarche) (*P's = NS*)**

Hormone therapy and memory

Melbourne Women's Midlife Health Project

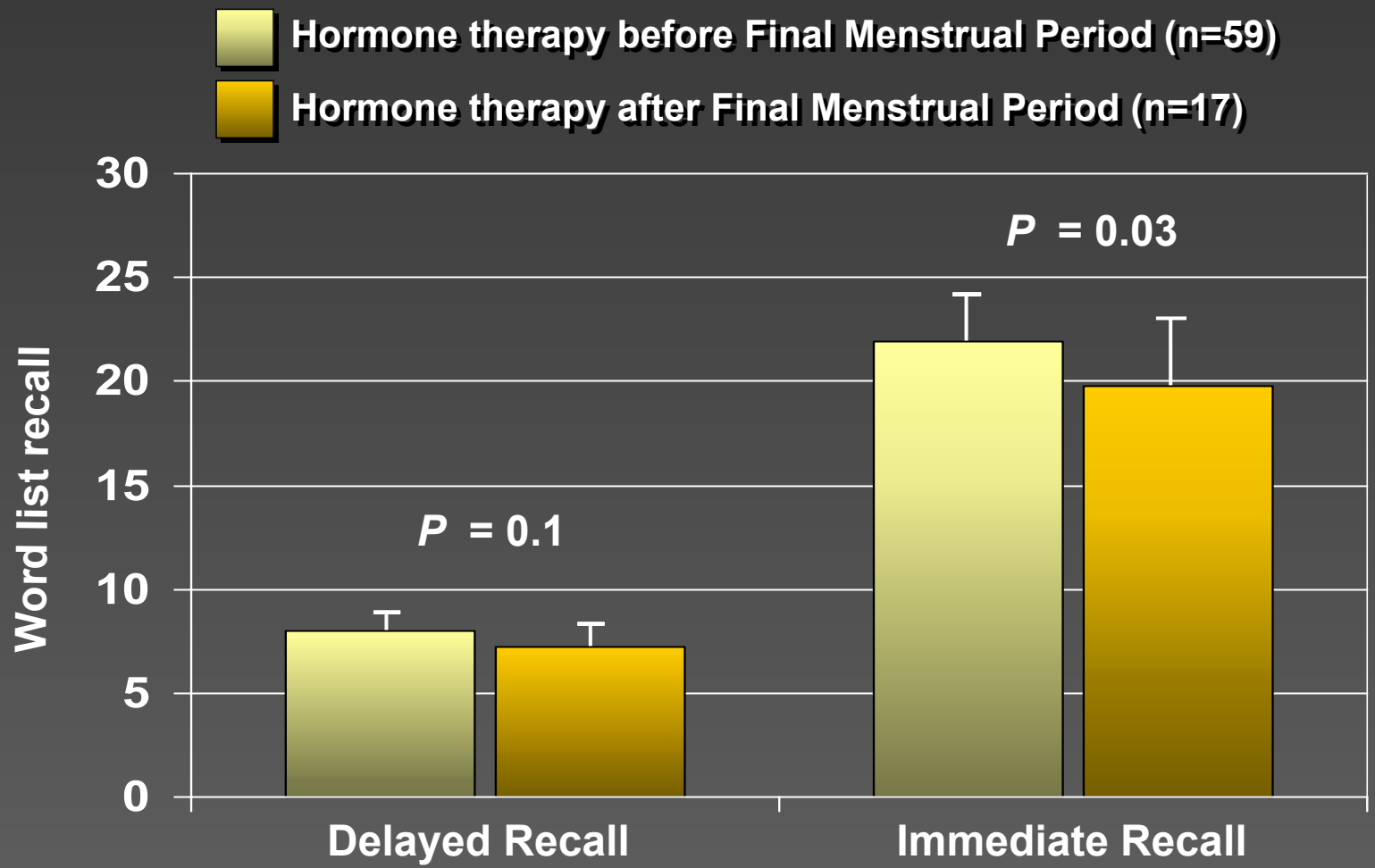
after: Henderson et al., *Neurology* 60:1369-1371, 2003.



Timing of hormone therapy

Melbourne Women's Midlife Health Project

after: Henderson et al., *Neurology* 60:1369-1371, 2003.



Estrogen and memory in midlife

Conclusion

- Estrogen loss associated with natural menopause and estrogen exposures in midlife do not substantially affect memory

  (Limited observational evidence)

- Timing of hormone therapy could be relevant to memory

  (Hypothesis)

Midlife estrogen exposures

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HT and Alzheimer risk

Multi-Institutional Research in Alzheimer Genetic Epidemiology (MIRAGE)

after: Henderson, Benke, Green, Cupples, Farrer. *J. Neurol. Neurosurg. Psychiatry*, in press

- MIRAGE probands met criteria for probable AD
- MIRAGE controls are first degree relatives or spouses, with age censored at year of proband symptom onset
- Female, postmenopausal
- Exposure: HT used for more than six months initiated at least one year prior to dementia onset / censored age
- Other variables included age, education, race, alcohol use, smoking, NSAIDs, hysterectomy/oophorectomy, *APOE*

HT and Alzheimer risk

Multi-Institutional Research in Alzheimer Genetic Epidemiology (MIRAGE)

after: Henderson et al., *J. Neurol. Neurosurg. Psychiatry*, in press

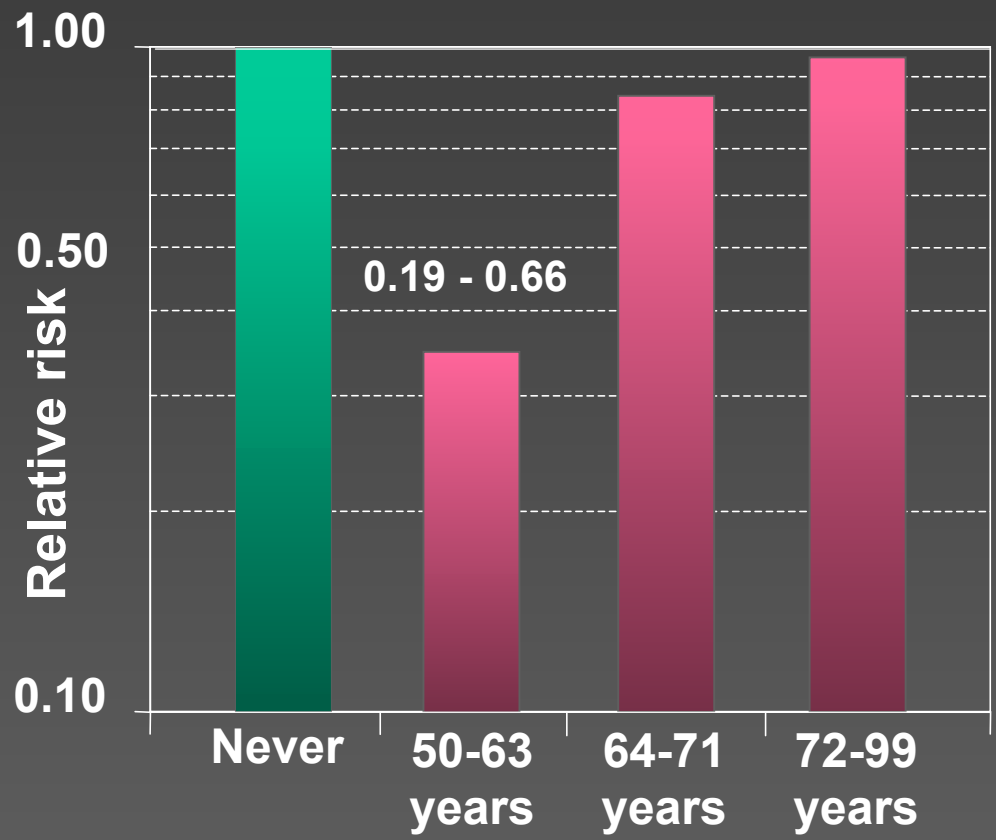
- 426 cases; 545 controls
- 35% HT exposure in control group; most common HT was CEE (80%)
- HT associated with 30% AD risk reduction (OR = 0.70, 95% CI 0.51 - 0.95; adjusted for age, education, race)
- There was a significant interaction with age ($p = 0.03$)
- HT associated with reduced risk only in youngest age tertile
- Risk estimates essentially unchanged in analyses adjusting for other potential confounders; no other interactions between HT and covariates

HT and Alzheimer risk

Multi-Institutional Research in Alzheimer Genetic Epidemiology (MIRAGE)

after: Henderson et al., *J. Neurol. Neurosurg. Psychiatry*, in press

- 426 cases
  545 controls
- Effect modification by age



Interaction between age and HT use in MIRAGE

Possible interpretations

after: Henderson et al., *J. Neurol. Neurosurg. Psychiatry*, in press

- Spurious finding (chance, bias, confounding)
- HT is protective for early-onset forms of Alzheimer's disease but not late-onset forms
- HT is protective when used close to appearance of overt dementia
- Protective association of HT declines with advancing age
- HT is protective only when initiated or used within an early critical window

HT and Alzheimer's disease

Conclusion

- HT initiated in the late postmenopause significantly increases dementia risk during the first five years of use

  (Clinical trial evidence from WHIMS)

- HT may reduce risk of early-onset Alzheimer's disease, or may reduce Alzheimer risk when initiated at a younger age or used by women during an early critical window

  (Limited observational evidence)

Collaborators

- **Melbourne Women's Midlife Health Project**

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  J. Guthrie
  H. Burger
  M. Clark
  E. Dudley
  S. Elkaydi
  G. Trytell

Alzheimer's Association IIRG-01-2684

- **MIRAGE**

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