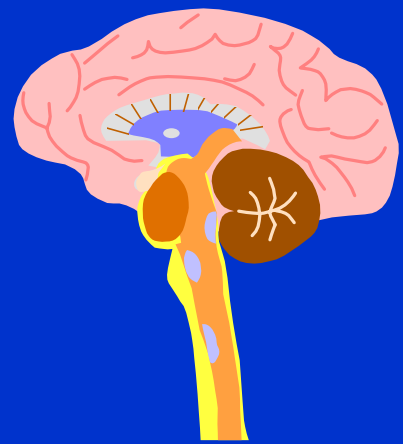
Observational Research on Hormones and Dementia

Problems of Bias and Confounding (and Preliminary Results)



Terminology

- E estrogen alone
- EP estrogen plus progestin

Hormones & Cognition/Dementia
Many Questions

- Does E prevent cognitive dysfunction following oophorectomy at a young age?
- Does E or EP prevent cognitive dysfunction that occurs during the perimenopause?
  - Is this due to an effect on symptoms and/or dysphoria?

Hormones & Cognition/Dementia
Many Questions

- Does E or EP improve cognition in women with dementia?
- Does E or EP prevent the decline in cognition that occurs with aging?
- Does E or EP alter progression of MCI to dementia?
- Does E or EP prevent the development of dementia?

Hormones & Cognition/Dementia
Many Questions

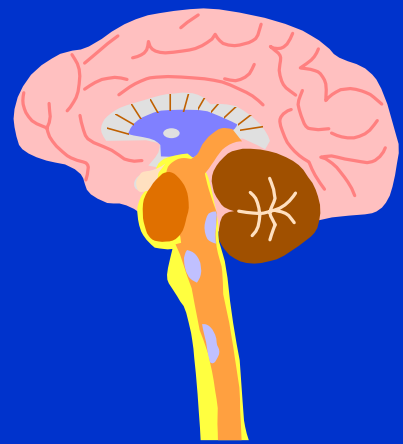
- Does E or EP use starting in the perimenopause and continued into older ages prevent cognitive decline and / or the development of dementia

- Does long-term E or EP use prevent cognitive decline and / or the development of dementia?

- Is an effect of E or EP on dementia different between different preparations or by mode of administration?

Hormones & Cognition/Dementia
Many Questions

- Does E or EP use prevent AD but cause vascular dementia?



Hormone & Cognition/Dementia
Many Biases

- Proxy bias : Women with dementia / CI cannot reliably report on their prior use of E / EP and so the study relies on proxies for information about E / EP use; but proxies are not able to provide this information (missing information) or under-report prior E / EP use

Hormone & Cognition/Dementia
Many Biases

- Proxy bias
  - Affects case-control and cross-sectional studies most
  - Can be overcome by enrolling only those who self-report and/or by study designs that rely on independent ascertainment of exposure (chart review/record linkage)

ERT and Cognition/Dementia
Many Biases

- Dementia bias : Women with CI / dementia are asked about their hormone use; but because of their memory problems they may under-report their prior use of E / EP

Women's Memory Study

Hormone Use by Prescription Compared with Self-reported Hormone Use

	User by Prescription		
	Unimpaired	CI	Dementia
Self-Report			
Ever User	93.8 %	85.8 %	80.9 %
Never User	6.2 %	13.4 %	17.7 %
Not sure	0.0 %	0.8 %	4.2 %

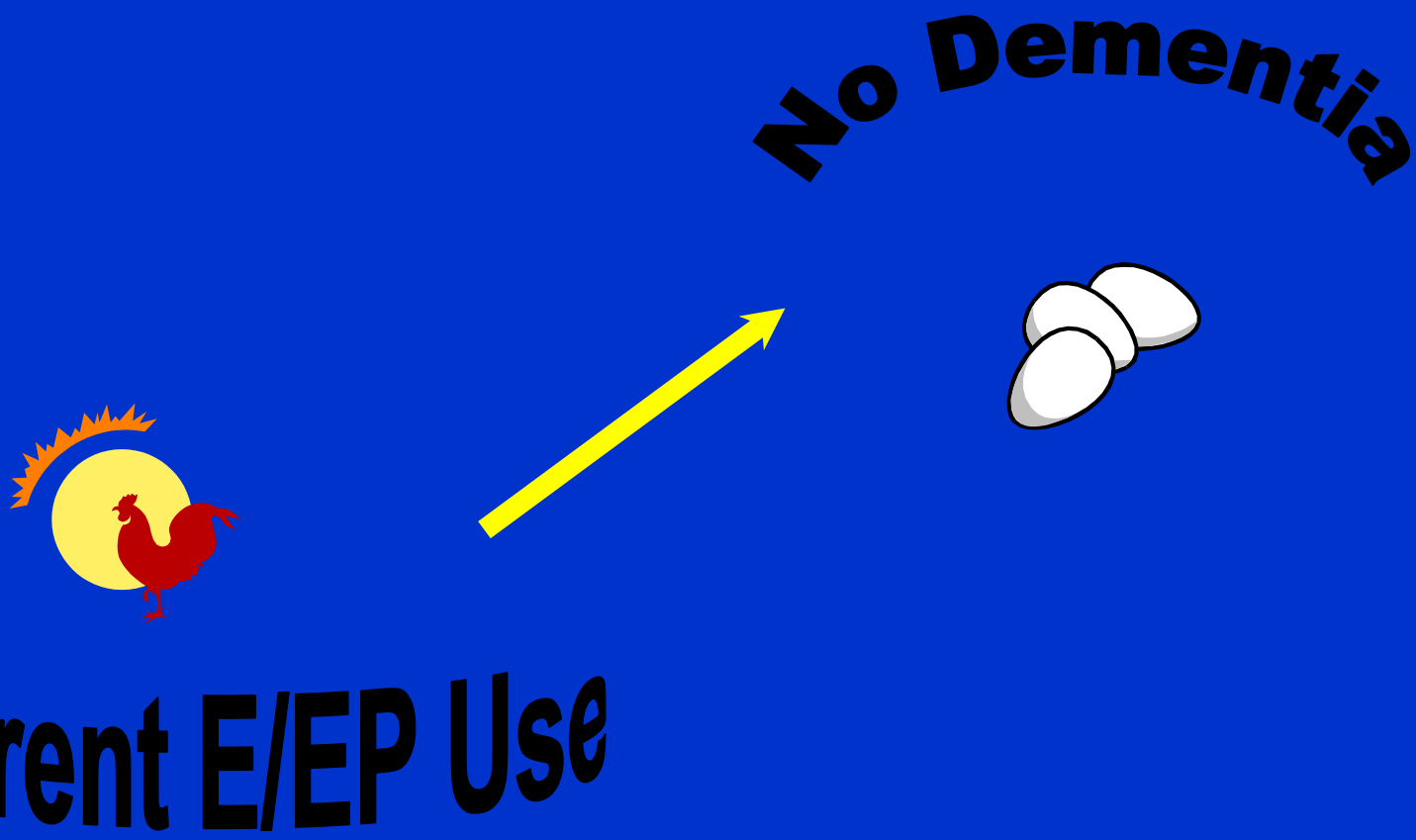
ERT and Cognition/Dementia
Many Biases

- Dementia bias :
  - Can be overcome by study designs that rely on independent ascertainment of exposure (chart review/record linkage)
  - Means that cohort studies must enroll for follow-up only women who are unimpaired at baseline

Hormones & Cognition/Dementia
Many Biases

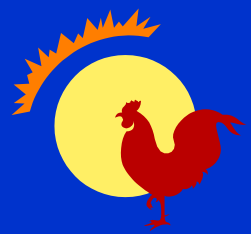
- Chicken Egg bias

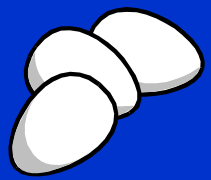
- Chicken / Egg bias



- Chicken / Egg bias

Current E/EP Use





No Dementia

Hormones & Cognition/Dementia
Many Biases

- Chicken Egg bias
  - Cannot be overcome in conventional case-control or cross-sectional studies

Hormones & Cognition/Dementia
Confounders

- SES
- Education

- Antioxidant use
- Statin use
- Aspirin use
- NSAID use

Hormones & Dementia/Cognition Confounders

- Uncontrolled and uncontrollable confounding: Differences between E / EP users that are unmeasured (and unmeasurable)

e.g., “Lifestyle”

KP Case-Control Study of E / EP and Vascular Disease

Adjusted Odds Ratio for MI (N=565 cases)

	OR (95% C.I.)
Use sunblock or sunscreen	0.54 (0.43-0.68)

Petitti and Sidney, unpublished

E / EP and CHD
Bias or Confounding

- Compliance : Women who use E / EP are compliant with the taking of medication; compliance is a marker for other differences in behavior that put women (and men) at lower risk of CHD

Coronary Drug Project

Adjusted RR of Incident CHD in Men According to Compliance with Clofibrate Treatment

Clofibrate

Compliance	% Mortality	RR
<80%	22.5	
>80%	15.7	0.7

N Engl J Med 1980;303:1038-1041

Coronary Drug Project

Adjusted RR of Incident CHD in Men According to Compliance with Clofibrate Treatment

	Clofibrate		Placebo	
Compliance	% Mortality	RR	% Mortality	RR
<80%	22.5		28.2	
>80%	15.7	0.7	15.1	0.6

N Engl J Med 1980;303:1038-1041

Beta-Blocker Heart Attack Trial
Adjusted RR of Incident CHD in Women According to Compliance with Treatment

	Beta-Blocker		Placebo	
Compliance	% Mortality	RR	% Mortality	RR
<75%	8.7		19.0	
≥75%	4.5	0.5	6.8	0.4

JAMA 1993;270:742-744

Women's Memory Study
Prospective Study of Dementia in Long-Term Hormone Users

Explicit attempt to overcome proxy bias, dementia bias, and to study long-term hormone use started at an early age

Women's Memory Study
Prospective Study of Dementia in Long-Term Hormone Users

- Hormone use for primary analysis (per protocol) based on information from computer-stored outpatient prescriptions filled in KPSC pharmacies

Women's Memory Study
Prospective Study of Dementia in Long-Term HRT Users

- Women defined as hormone user if they had 1 or more prescriptions for oral estrogen recorded in the prescription database in every year from 1992-1998

  - 1,944 E / EP users

Women's Memory Study
Prospective Study of Dementia in Long-Term Hormone Users

- Women defined as hormone non-user if they had no prescriptions for oral estrogen recorded in the prescription data in any year from 1992-1998

  - 1,980 non-users at baseline

Women's Memory Study
Prospective Study of Dementia in Long-Term Hormone Users

- Classification with dementia, CI, or as unimpaired based on telephone assessment (Telephone Interview of Cognitive Status modified and Telephone Dementia Questionnaire) supplemented with chart review

Women's Memory Study

Comparison of classification using TICSm and TDQ with "gold standard" dementia work-up at USC ADRC

	Dementia/Not	Dementia/CI/Normal
Sensitivity for dementia	0.83	0.83
Sensitivity for CI	---	0.50
Specificity	1.00	0.93
KAPPA	0.88	0.67

Women's Memory Study

Type and duration of hormone use at entry to the follow-up among hormone users by prescription

	Mean (yrs)	SD
E	29.0	± 11.6
EP	21.6	± 10.9

Women's Memory Study

Age at start of hormone use among hormone users by prescription, % distribution

	E	EP
<46	42	19
46-55	40	40
56-60	8	13
61+	10	27

Percents may not sum to 100 because of rounding

Preliminary Results

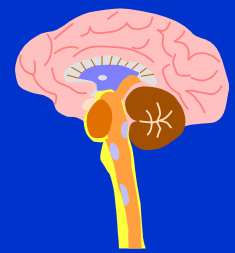
Follow-up year four of women without dementia at baseline

Age at Entry	Total N	Incident Dementia	Rate
75-79	1999	160	8.0
80-84	732	86	11.7
85+	175	27	15.4

Preliminary Results

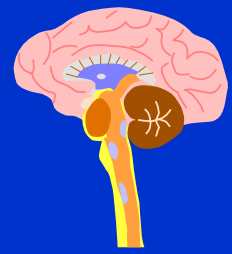
Follow-up year four of women without dementia at baseline

Education	Total N	Incident Dementia	Rate
< High School	331	44	13.3
HS+	2575	229	8.9



Preliminary Results

Follow-up year four of women without dementia at baseline



Hormone Use	Incident Dementia
Non-user	117
E	108
EP	48

Women's Memory Study
Limitations

- Some women classified as non-users may have used hormones in the past
- Dementia classification did not involve "gold standard" assessment
- EP users may used E only in the distant past

Women's Memory Study
Strengths

- Many very long-term users who began use at an early age
- Free of proxy bias and dementia bias
- Loss to follow-up minimized using dementia assessment

Observational Research Hormones and Dementia: Future

- Study of long-term, early exposure will require observational research; experimental studies will become observational as women select in and our of hormone use outside the protocol

Observational Research Hormones and Dementia: Recommendations

- Case-control designs may not be capable of yielding valid results for the question of hormone use and the development of dementia

Observational Research Hormones and Dementia: Recommendations

- Cohort studies should enroll subjects who are dementia free at baseline
- Independent confirmation of hormone use is highly desirable
- Loss to follow-up must be minimized

Observational Research Hormones and Dementia: Observation

- It is important to decide whether it is important to know the effect of hormones in AD separate from an effect on all dementia if hormones (some formulations and some modes of administration) increase the risk of stroke (subclinical and clinical) and dementia due to it

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Co-investigators are Valerie Crooks, Helena Chui, and Galen Buckwalter

Vicki Chiu did the programming