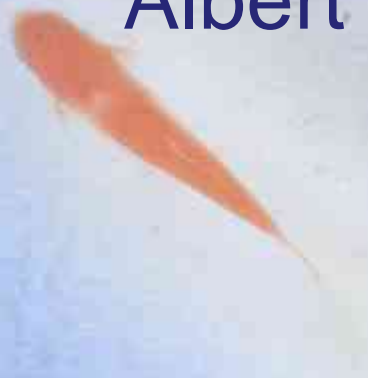# Women's Health at Mid-Life: Lessons Learned from SWAN, the Study of Women's Health Across the Nation

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Industry Support

- QuatRX: consultant
- Ferring: clinical research study

SWAN

- Cohort assembled in 1995-96

- Purpose: to study aspects of women's health through the menopausal transition

SWAN

Embedded concepts
- Changes in health status in mid-life will have significance for a woman's future health
- Changes related to menopause need to be disentangled from those due to aging

SWAN Cohort Assembly

- Population-based, cross-sectional screening survey administered to 16,065 women

- Eligibility for longitudinal cohort study:
  - At least one period within past 3 months
  - Age 42-52 at baseline visit
  - Uterus and at least one ovary
  - Not pregnant, nursing or taking hormones

SWAN Cohort Assembly

- From the screened population, a community based sample of 3,302 women was derived:

- 7 sites across the USA

- Each site recruited ate least 150 non-Hispanic Caucasians and one other ethnic minority (African-American, Hispanic, Chinese, Japanese)

Annual Assessments

- Physical measures
  - Anthropometrics, BP, BIA, physical function
- Survey instruments
  - Psychosocial, demographic, cognitive
- Blood sampling
  - FSH, E2, T, DHEAS, TSH (baseline only)
  - Cardiovascular markers

Cohort Assembly

Cross-sectional Survey
(Sampling frame) N=16,065

Longitudinal Cohort
N=3,302

Nested Substudies: SWAN
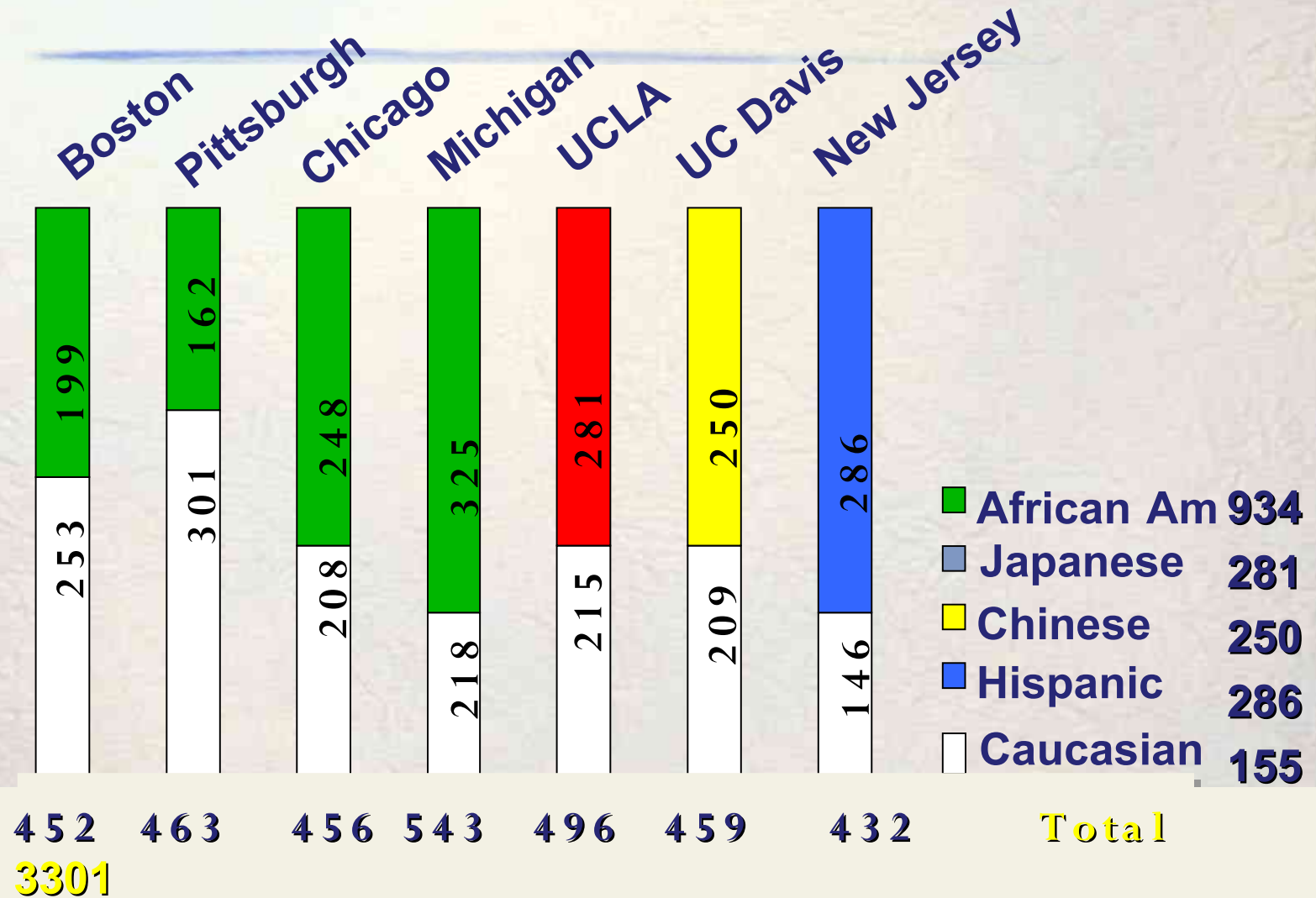Heart, Bone, Daily Hormone
Study, Sleep, Psych

SWAN Substudies

Bone N=1902	Daily Hormone Study N=848	SWAN Heart N=559	Psych (SCID) N=589	Sleep N=365

Cross-Sectional Survey

- Answers questions in a population-based sample of over 16,000 women
  - Most representative data in SWAN
  - 15 minute screening survey
  - Determined eligibility for cohort
  - Self-reported responses to key questions about menopause

Who are the SWANs?

Boston	Pittsburgh	Chicago	Michigan	UCLA	UC Davis	New Jersey
199	162	248	325	281	250	286
253	301	208	218	215	209	146

African Am 934
Japanese 281
Chinese 250
Hispanic 286
Caucasian 155

452 463 456 543 496 459 432 Total

3301

Hysterectomy
SWAN Screener (n=15,160)

Ethnicity	Odds Ratio	95% CI
Caucasian	1.0	reference
African-American	1.66	1.46,1.88
Hispanic	1.64	1.29,2.07
Chinese/Japanese	0.44	0.34,0.56

Hot Flashes

- Affect most women at some point in the menopausal transition (75%)

- Prevalence peaks -2 to 1 yr before/after the FMP; returns to near-premenopausal levels 8 years later (Politi)

- 16% of women have persistent VMS long after menopause (Barnabei)

Race/Ethnicity and VMS—SWAN Baseline

Race/ethnicity	N*	% with HFs/night sweats	Adjusted OR (95% CI)
African Amer	750	46.5	1.38 (1.11, 1.74)
Caucasian	1418	36.6	Referent
Chinese	218	28.9	0.66 (0.42, 1.05)
Hispanic	239	49.4	1.56 (0.92, 2.65)
Japanese	198	34.3	0.94 (0.61, 1.46)

* SWAN Baseline, age 42–52 y, N = 2823; Gold EB, AJE. 2004;159:1189
† Adjusted for age, education, menopausal status, BMI, smoking, passive smoke, alcohol, fat, fiber,genistein, calories, physical activity, premenstrual symptoms, OTC pain meds,comorbidity,stress,site

Longitudinal VMS by Ethnicity: SWAN

- Baseline: Most VMS reported by African-Americans and Hispanics
  - Hispanic women reported *less* symptoms over time and with progress through the transition, but more negative associations (embarassment) with VMS

Gold EB, AJPH 2006; 96:1226

Longitudinal VMS by Ethnicity: SWAN

- Japanese and African-American women: sx sensitivity related to VMS

- Baseline anxiety related to VMS

- Baseline depressive symptoms related to VMS

- Chinese women: fewest VMS

BMI and Hot Flashes

- Increased BMI linked to increased VMS
- Body fat by BIA associated with increased VMS reporting (OR=1.27, 95% CI=1.14-1.42)
- Body fat alters thermoreglation and impairs heat dissipation
- Postmenopause increased E production by adipose tissue may mitigate VMS

Thurston RC, AJE 2008; 167:78

Other Possible Modifiers

Cultural/Genetic

- Different sex steroid enzyme synthesis
- Different dietary factors
- Different methods of coping
- Different 'tempo' of the transition by ethnicity

Social/Political

- SES
- Acculturation
- Discrimination

VMS Increase Across the Transition

Stage	OR	95% CI
Pre	---	---
Early Peri	1.86	1.47, 2.34
Late Peri	6.64	4.80, 9.20
Postmenopause	4.96	3.51, 7.01

Gold EB, AJPH 2006; 96:1226

Other Aspects of Menopause Vary By Ethnicity

Symptom	Most	Fewest	Reference	
Early/Premature Menopause	His-panic (3.7%)	Jap-anese (0.8%)	Luborsky, Hum Reprod 2003;118:199	

Vaginal Symptoms Vary by Ethnicity

Symptom	Most	Fewest	Reference
Vaginal Dryness	Hispanic (17.9-58.6%)	Caucasian (21.2%)	Green, SGI 2008

Depressive Symptoms Vary by Ethnicity

Symptom	Most	Fewest	Reference
CESD >16	Japanese OR 1.39 [0.93-2.17]	Chinese OR 0.51 [0.33-0.79]	Bromberger, J Affect Dis 2007;103:267

Self-Reported Sleep Problems Vary by Ethnicity

Symptom	Most	Fewest	Reference
Trouble Sleeping	Hispanic (14.4%)	Japanese (6.5%)	Kravitz, Sleep 2008; 31:979

Common Symptoms and Ethnicity: Summary

- Most symptoms from SWAN cross-sectional study, baseline and longitudinal study are concordant

- Hispanic and African-American women appear to report more symptoms overall

Common Menopausal Symptoms and Ethnicity

- Ethnicity is confounded by:
    - BMI: higher in African-Americans
    - SES, education: lowest in Hispanics
    - Geography: each SWAN site has unique features to its population sample

BMI: A Major SWAN Covariate

- Many aspects of menopause vary with BMI
  - Vasomotor symptoms
  - Hormones
  - Metabolic risk factors
  - Mood and psychosocial measures
- Age at menopause does NOT vary with BMI!

Serum Reproductive Hormones by BMI Tertiles n=2930, SWAN

Enter the Transition

- Change in reproductive hormones inevitable consequence of menopause and the transition

- How do reproductive hormones interact with key SWAN outcomes?

Menopause Stages

- Pre: no change in cycle regularity
- Early Transition: increased irregularity but at least one menses within past 3 months
- Late Transition: 3-11months amenorrhea
- Post: 12 months amenorrhea

SWAN Baseline

- Women aged 42-52

- Approximately 50/50 pre/early transition

- By 6th follow-up: 75% women postmenopausal

Ideal Cohort Problem: BMD

- When does bone loss begin in relation to the menopause?

- Do rates of bone loss vary among ethnic groups across the menopausal transition?

- What factors are associated with variation in rates of bone loss among women?

The Menopause Transition: SWAN baseline analyses
(Finkelstein et al., JCEM 87:3057-67, 2002)

The Menopause Transition: SWAN follow-up analyses

Annual unadjusted spine BMD (g/cm2)

BMD change in spine and total hip in pre (red bars), early peri (blue), late peri (yellow), and postmenopausal (green) women (n = 1902)

Finkelstein, J. S. et al. J Clin Endocrinol Metab 2008;93:861-868

Complex Cohort Problem: Daily Hormone Study

- Cuts across all SWAN sites

- Cuts across all SWAN research questions

- Can hormonal patterns and menstrual cycle dynamics provide useful data on the timing, tempo or comorbidities associated with the MT?

**Percentage of Cycles with Evidence of Luteal Activity
By Chronologic Age**

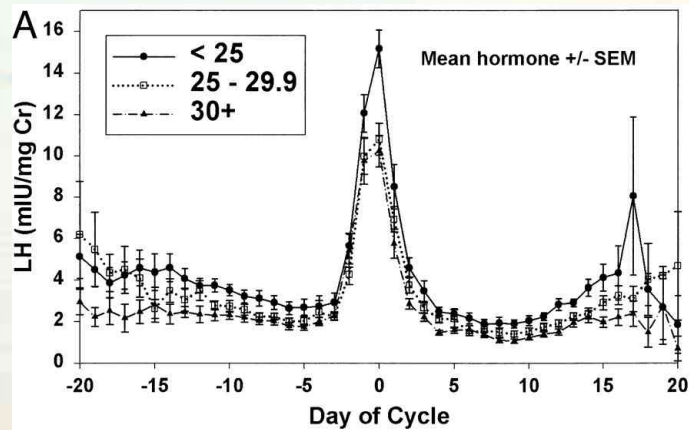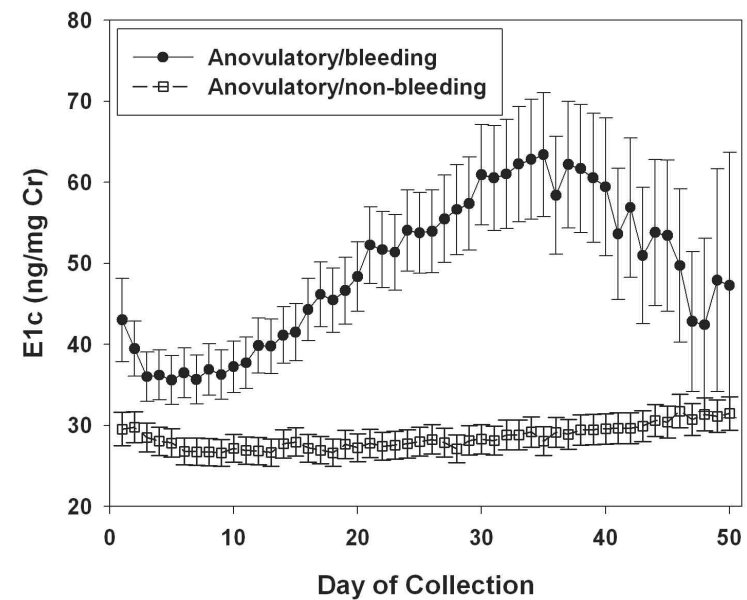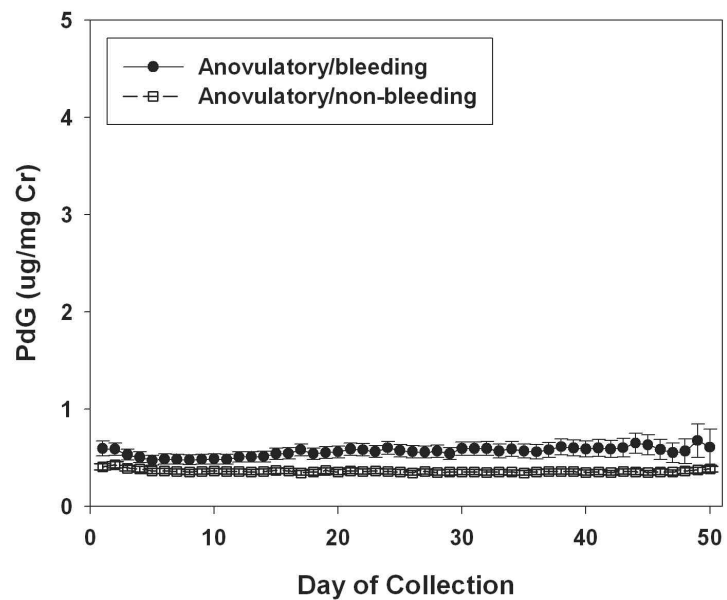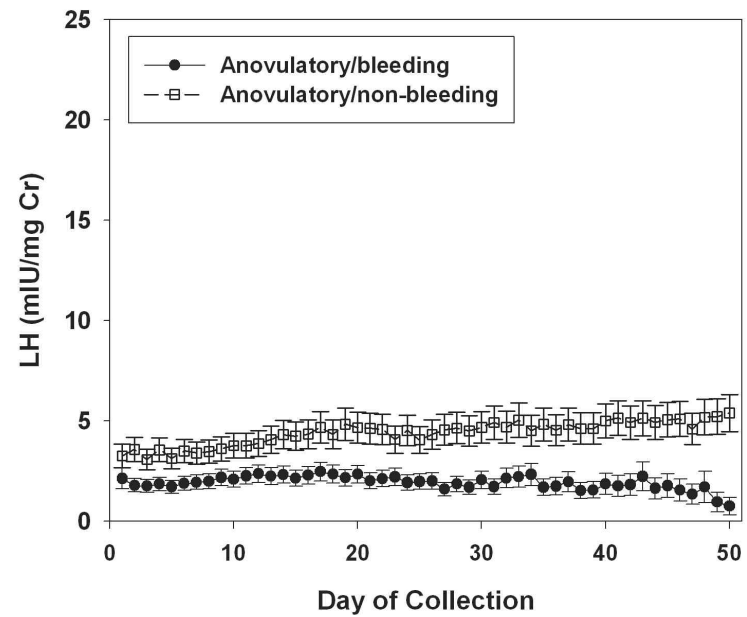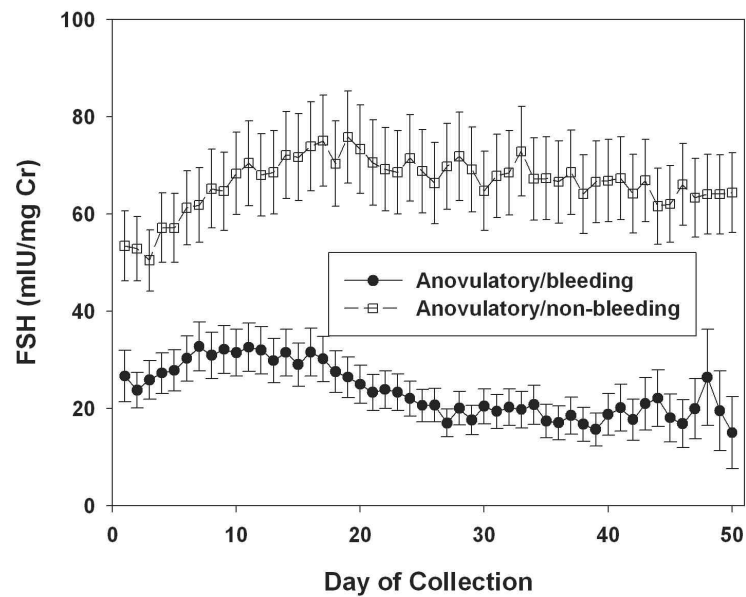# Daily urinary hormones in 848 ovulatory cycles in SWAN compared to 29 midreproductive-aged women

Santoro, N. et al. J Clin Endocrinol Metab 2004;89:2622-2631

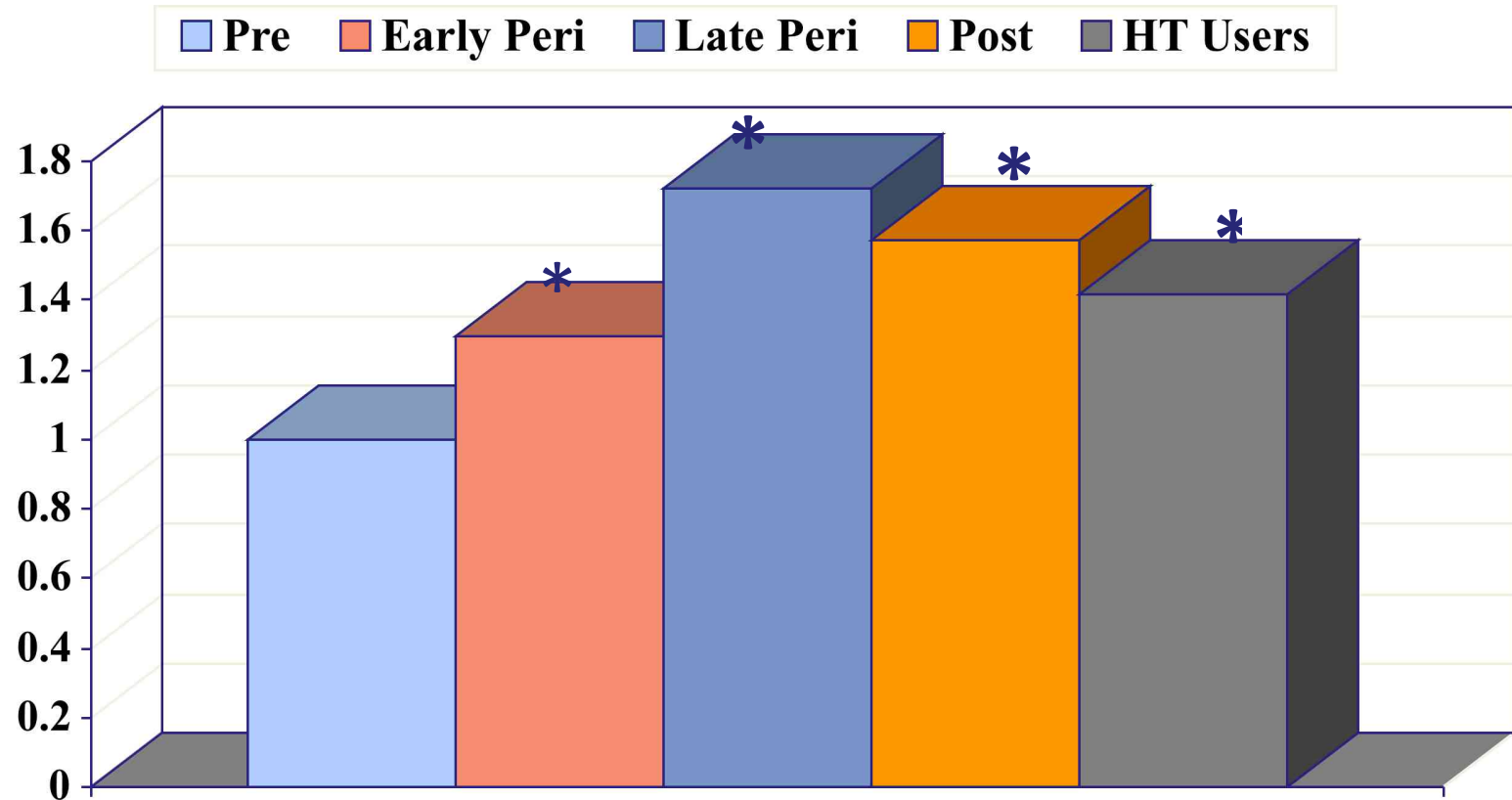Santoro, N. et al. J Clin Endocrinol Metab 2004;89:2622-2631

Putting it Together

- Interrelationships of hormones, menopausal stages and their change over time with key SWAN outcomes

How Does Mood Vary Across the Transition?

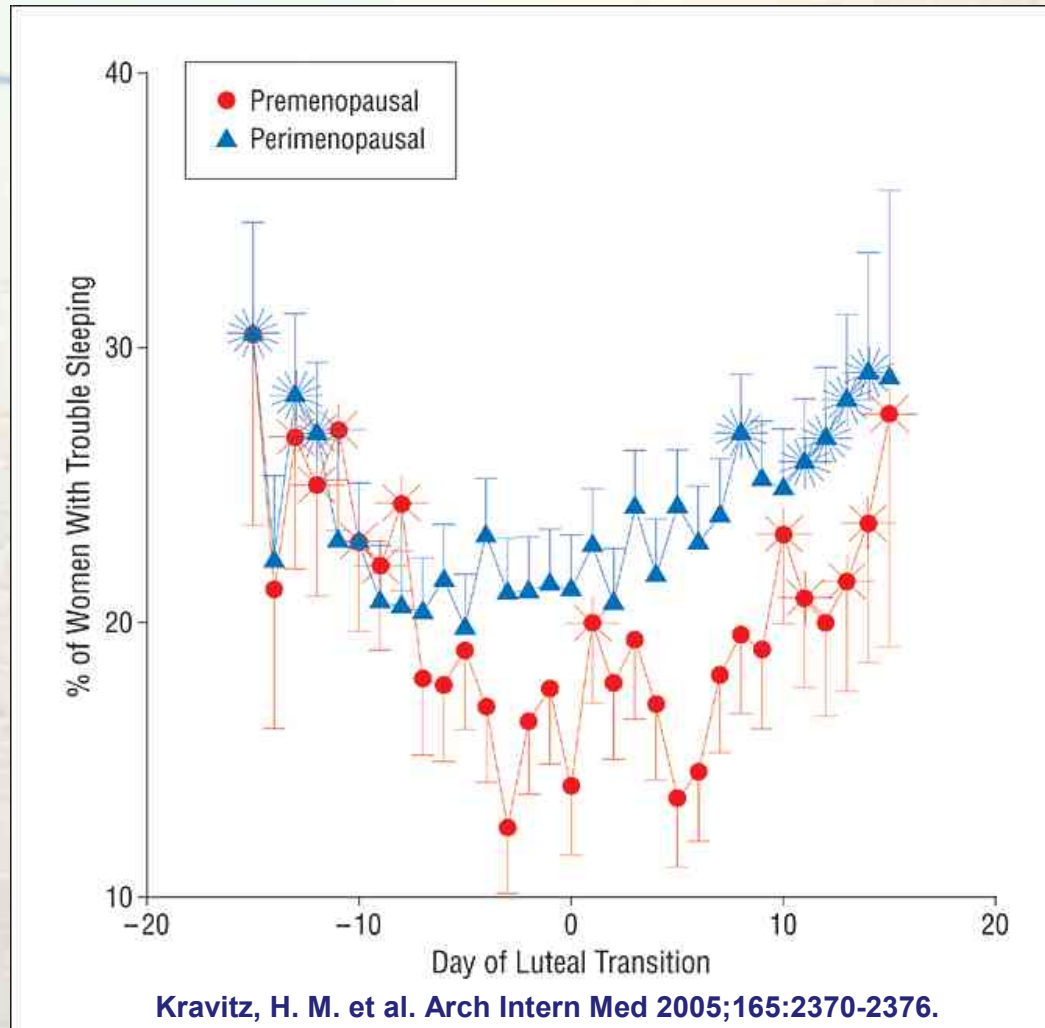# Adjusted <u>OR for CES-D > 16</u> Across Visits 00-05 by Menopausal Status (p=.005)

Premenopause=reference group. *95% CI does not include 1 (Bromberger, J Affect Disord 2007)
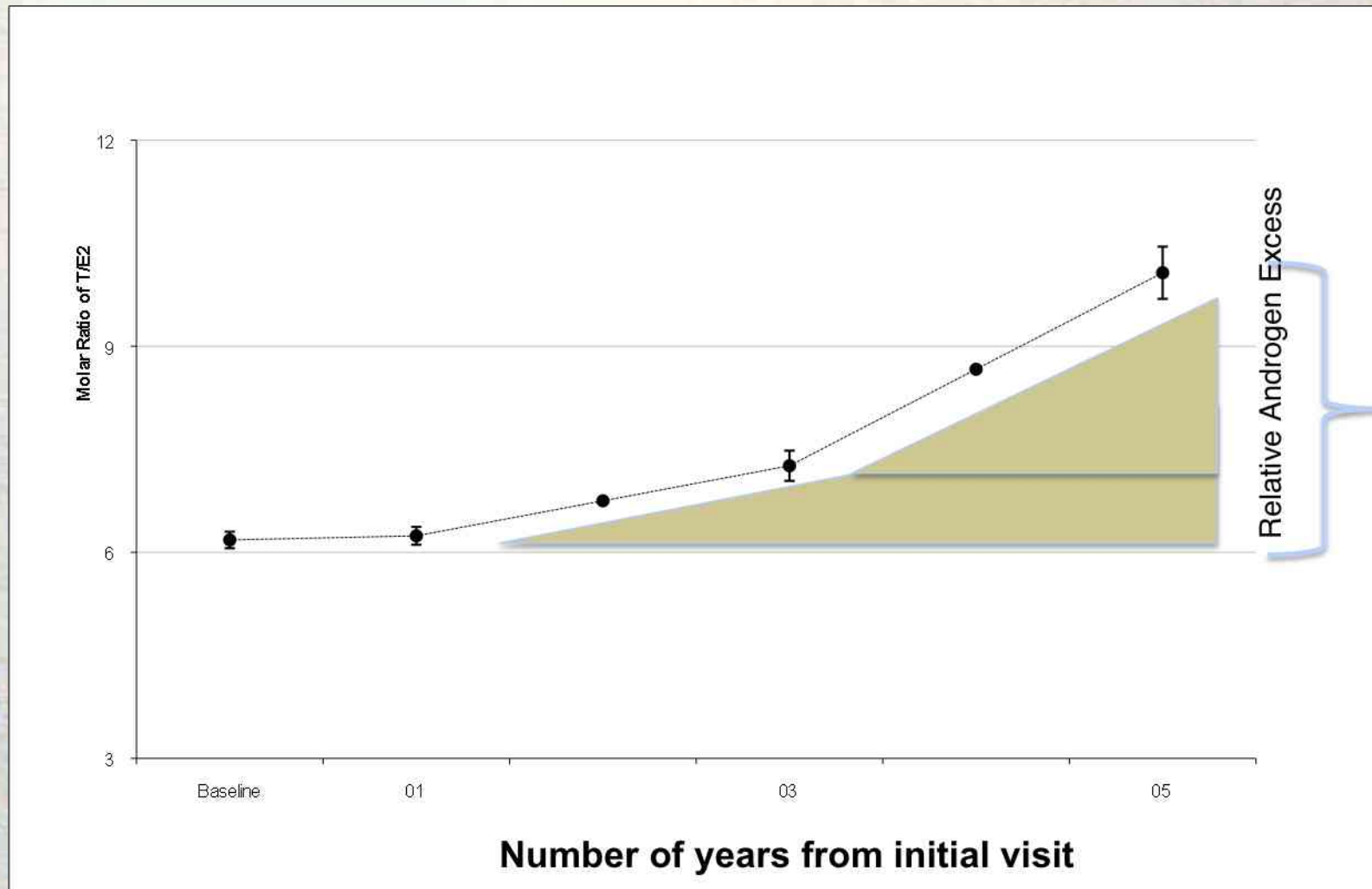
Do Day-to-Day Hormones Relate to Sleep?

Percentage of women with trouble sleeping by cycle day (n = 630)

Kravitz, H. M. et al. Arch Intern Med 2005;165:2370-2376.

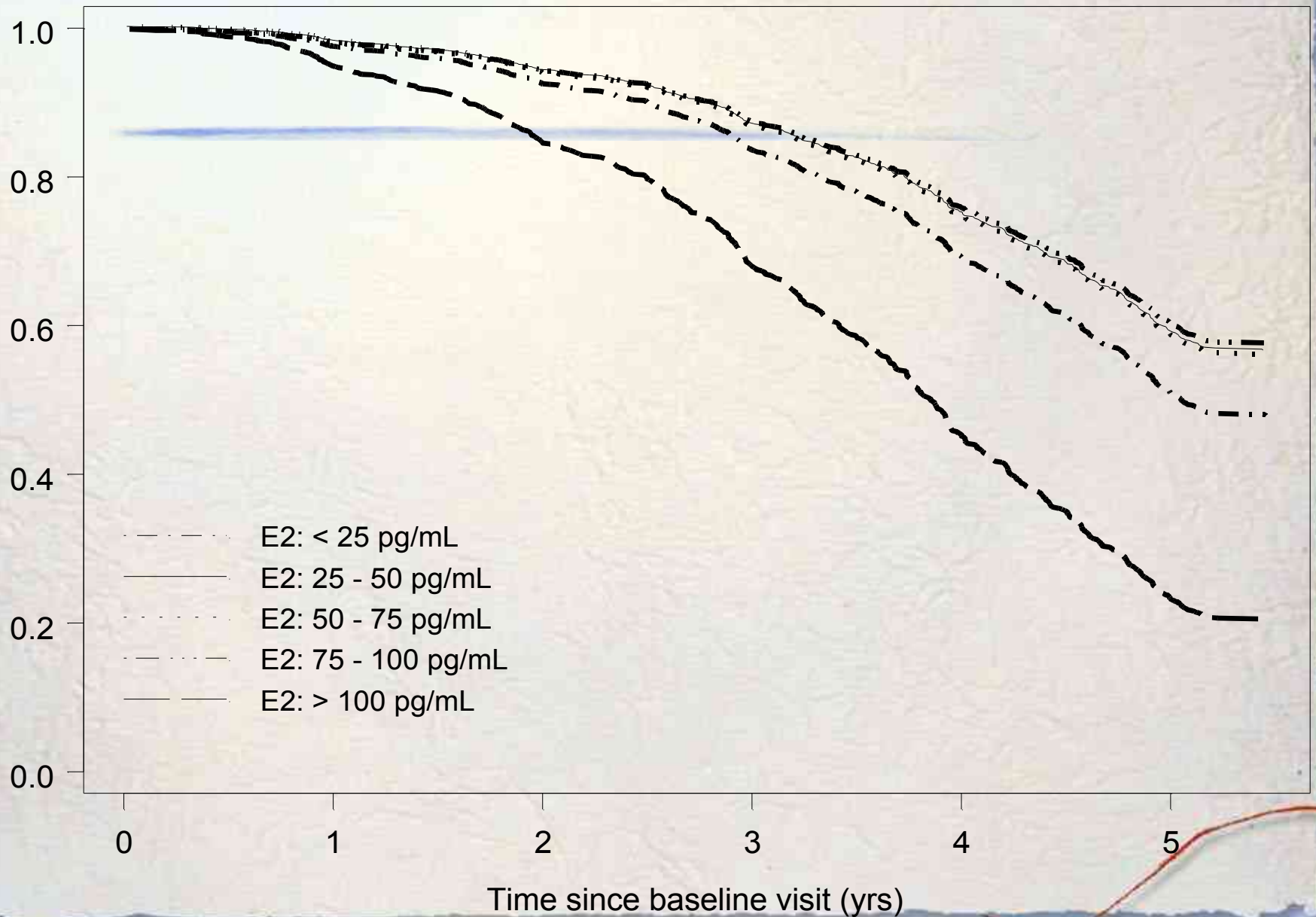# Molar Ratio of T to E is Related to Incident Metabolic Syndrome

Using Longitudinal Data to Predict the FMP

- Baseline status: pre- or early peri
  - Baseline FSH and E2
  - Other baseline characteristics: BMI, smoking hx, education, activity
- Data through 6th FU visit to assess who experienced 12 months' amenorrhea
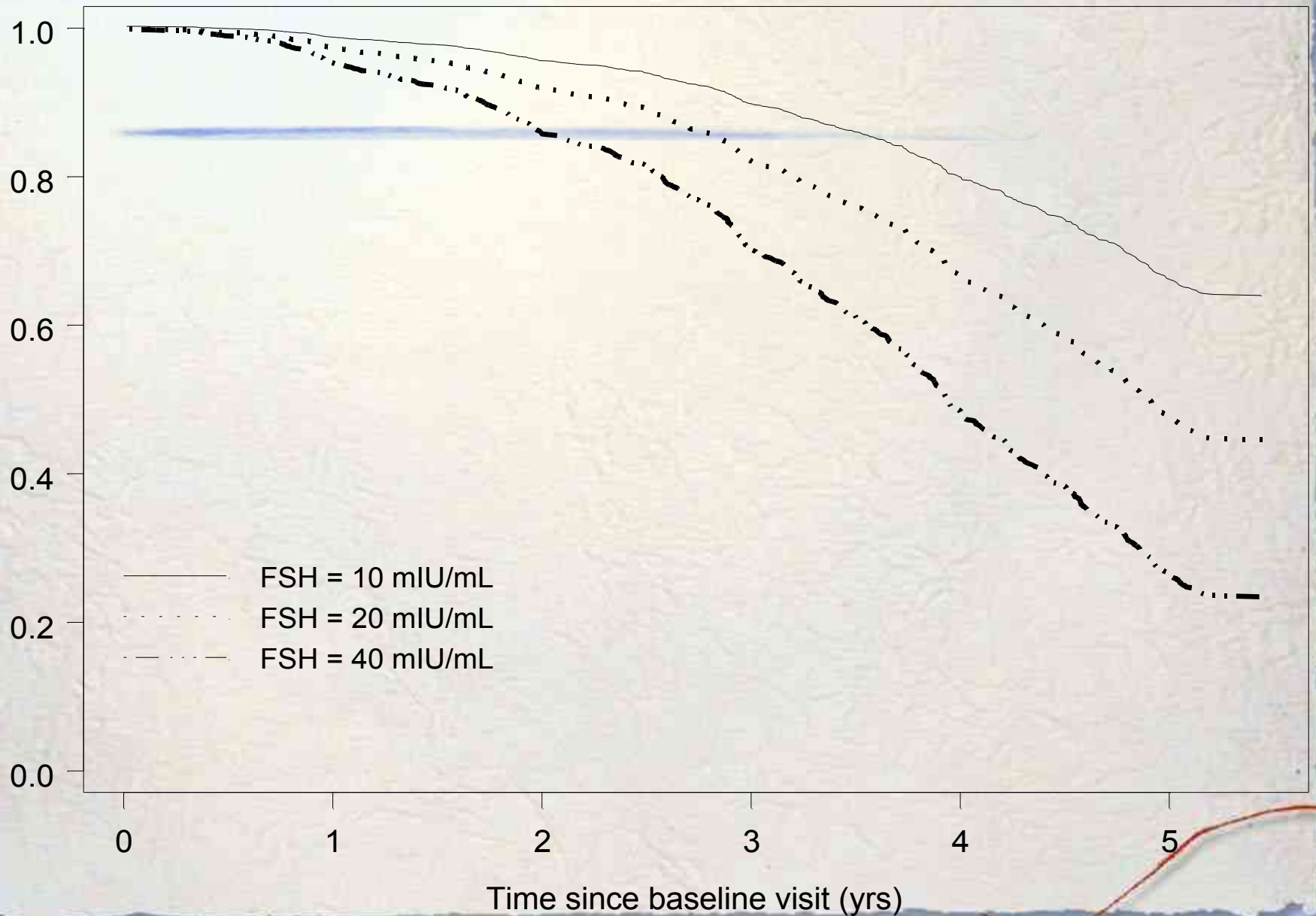
Key Predictors

- Age at baseline: each 1 yr increase in age associated with 42% RR of earlier FMP

- Menses that are farther apart or more variable

- Smoking

- Hot flashes, when present

- High FSH

- Both _**low**_ and _**high**_ E2

Predicting Using E2 levels, African American

Legend:
- E2: < 25 pg/mL
- E2: 25 - 50 pg/mL
- E2: 50 - 75 pg/mL
- E2: 75 - 100 pg/mL
- E2: > 100 pg/mL

Time since baseline visit (yrs)

Predicting Using FSH, Caucasian

FSH = 10 mIU/mL
FSH = 20 mIU/mL
FSH = 40 mIU/mL

Time since baseline visit (yrs)

Summary

- The menopausal transition transects the aging process

- Disentangling age from menopause is a key analytic issue

- Longitudinal cohort studies have much to offer in clarifying this process

Summary

- Ethnicity, BMI and psychosocial factors all have a profound bearing on the menopausal experience of women
- Ultimately, prediction of the timing and quality of the menopause transition will enable clinicians to provide individualized care to their midlife patients