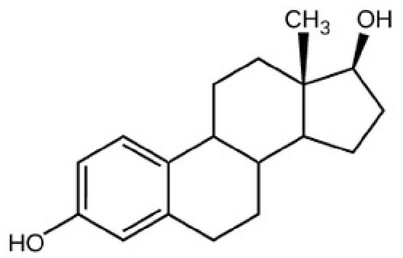
Circulating hormones, menopause related symptoms, and cognition

WHI Investigator Meeting, May 7-8, 2026

Jennifer W. Bea, Heather Ochs-Balcom, Kara Michels, Tracy Madsen, Laura Harrington

Beyond Estrogen



Estrogen association with menopausal symptoms has been well examined

Other hormone and hormone metabolite associations with menopause symptomatology and outcomes are not understood

Long-term hormone trajectories as post-menopausal women age and hormone metabolite effects on outcomes are nearly absent from the literature

WHI now has repeated measures of FSH, LH, and SHBG and copious hormone metabolite measures due to ancillary studies

Recent results of hormone and hormone metabolite effects on symptoms, adipose accretion, sleep, and cognition to be presented by our panel

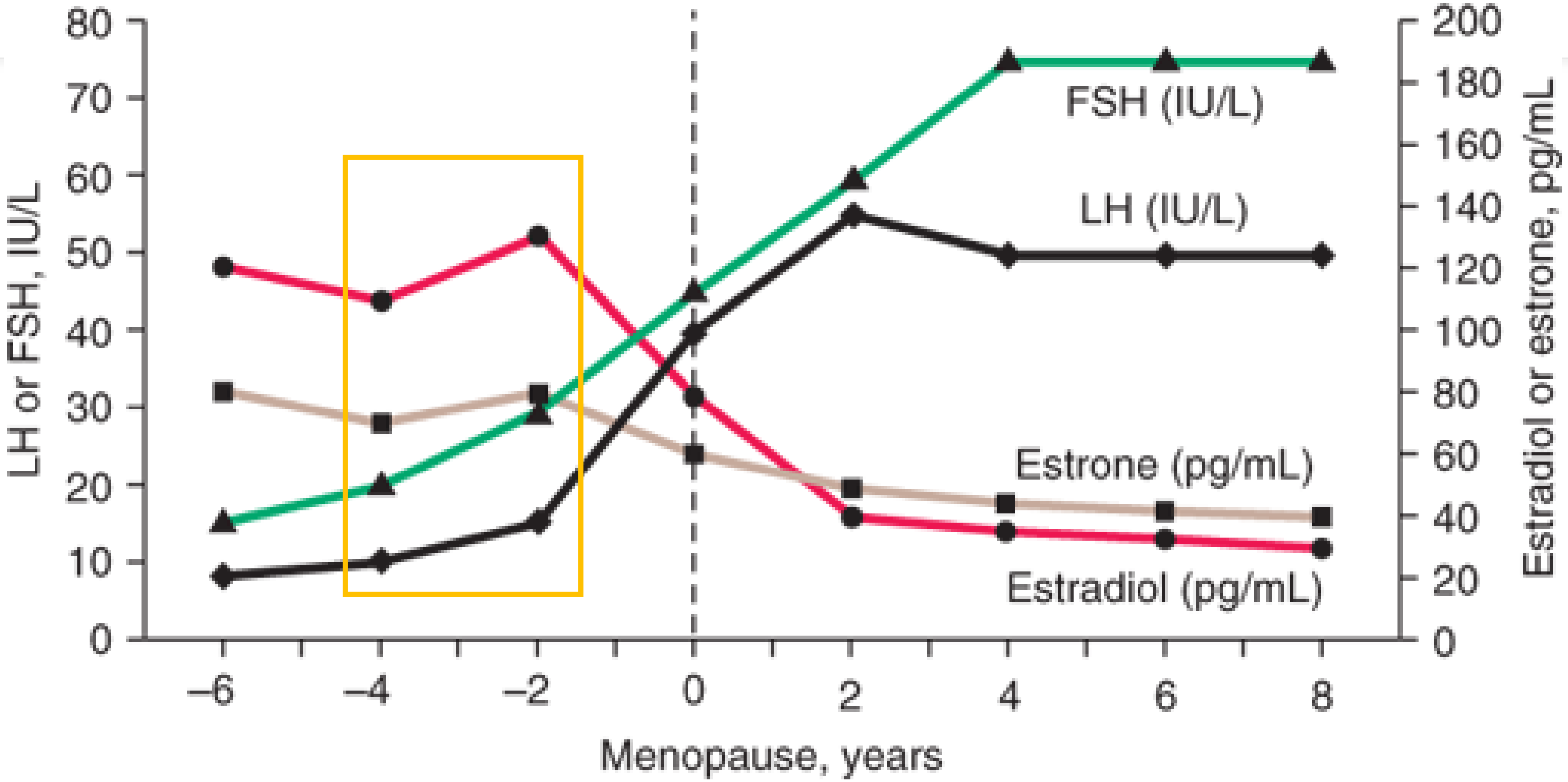
Item	Presenter/Facilitator	
Introduction	Jennifer W. Bea, PhD Department of Health Promotion Sciences, University of Arizona	
Characterizing natural gonadotropin variability after menopause and links with adipose tissue in the WHI	Heather Ochs-Balcom, PhD Department of Epidemiology & Environmental Health, University at Buffalo	
Circulating hormone metabolites associated with sleep and vasomotor symptoms in menopausal hormone therapy users and non-users	Kara Michels, MPH, PhD Department of Epidemiology & Population Health, Albert Einstein College of Medicine	
Endogenous hormones, cognition, and risk of dementia in the WHI	Tracy Madsen, MD, PhD, FACEP, FAHA Department of Emergency Medicine University of Vermont Laura Harrington, PhD, MPH Health Research Institute Kaiser Permanente Washington	 
Q/A	Panel	

Characterizing natural gonadotropin variability after menopause and links with adipose tissue in the WHI

Heather Ochs-Balcom, PhD
Professor, University at Buffalo

WHI Investigator Meeting, May 7-8, 2026

Endocrinology of menopause



JL Jameson, AS Fauci, DL Kasper, SL Hauser, DL Longo, J Loscalzo. Harrison's Principles of Internal Medicine, 20th Ed. McGraw-Hill; 2018.

Gonadotropin hypothesis; action beyond reproduction

- FSH and LH are not just reproductive hormones
- FSHR expressed in extra-gonadal tissues
  - Adipose tissue
  - Vascular endothelial cells
  - Tumors
  - Osteoclasts
  - Cerebral cortex, hippocampus

Lizneva et al *Front Endocrin* 2019; Palak et al *Mol Med* 2024; Li X et al *Theranostics* 2017

Preclinical work on FSH and adipose tissue

AR

Bloc
adi

Peng Liu[1]*,
Wahid Abu
Jianhua Li[1], Valeria Shnay
Ling-Ling Zhu[1], Douglas
Solomon Epstein[1], Jamee
Edward X. Guo[4], Christo

Article

FSH blockade improves cognition in mice with Alzheimer's disease

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Trends in
Molecular Medicine

CellPress

Review

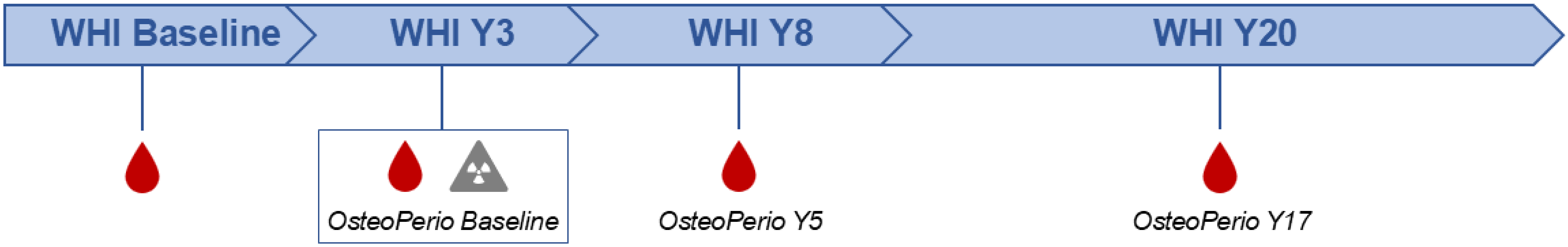
Targeting FSH for osteoporosis, obesity, and Alzheimer's disease

Funda Korkmaz[1], Judit Gimenez-Roig[1], Farhath Sultana[1], Victoria Laurencin[1], Fasilet Sen[1], Liam Cullen[1], Steven Sims[1], Anusha Pallapati[1], Satish Rojekar[1], Guzel Burganova[1], Georgii Pevnev[1], Uliana Cheliadinova[1], Darya Vasilyeva[1], Ofer Moldavski[1], Tal Frolinger[1], Anisa Gumerova[1], Orly Barak[1], Vitaly Ryu[1], Daria Lizneva[1], Keqiang Ye[2], Anne Schafer[3], Clifford J. Rosen[4], Tony Yuen[1], Se-Min Kim[1,*], and Mone Zaidi[1,*]

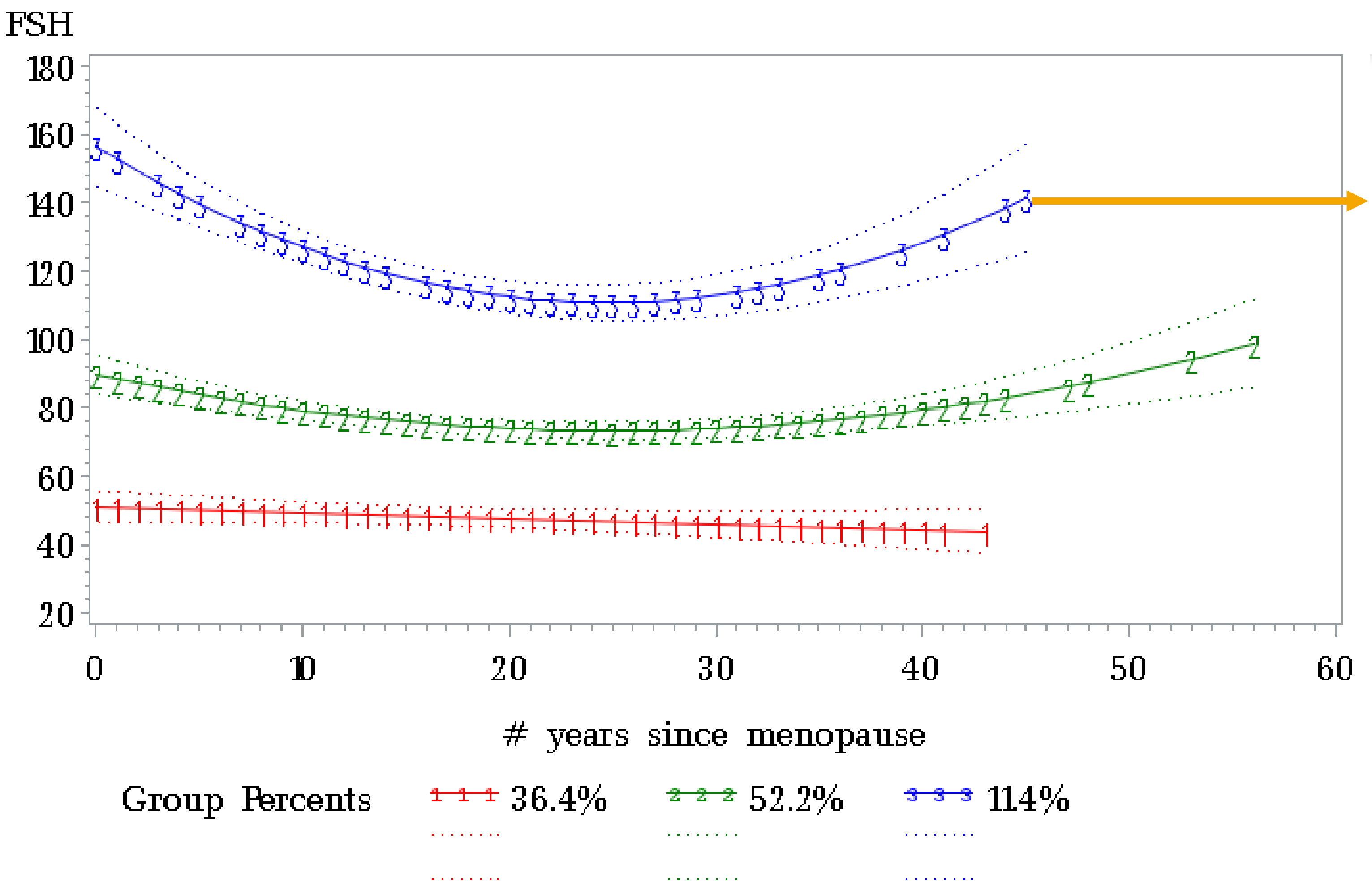
Liu et al *Nature* 2017

Characterizing gonadotropin variability postmenopause

- N=291 women OsteoPerio (OS; PI: Wactawski-Wende) not using HT*
- 20-year trajectories estimated using hormones measured at four timepoints:



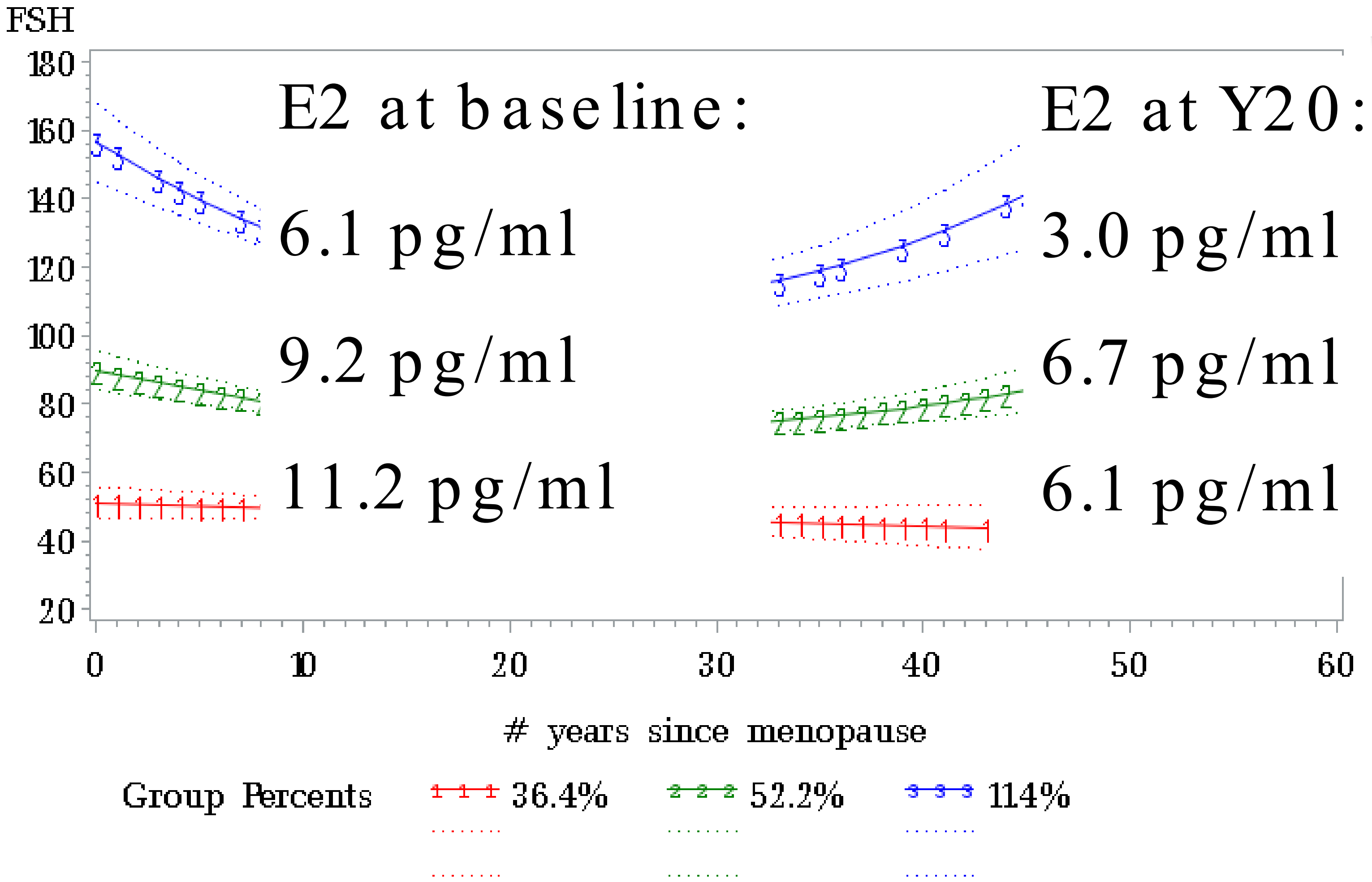
FSH trajectories



- Women in the high trajectory (11%):
  - More likely to be never smokers
  - Less kcal/day
  - Lower BMI, waist circ, % fat, fat mass, SAT, VAT

Lima S et al Menopause 2026; Nagin et al Annu Rev Clin Psychol 2010

FSH trajectories



E2 at baseline:

6.1 pg/ml

9.2 pg/ml

11.2 pg/ml

E2 at Y20:

3.0 pg/ml

6.7 pg/ml

6.1 pg/ml

- FSH difference between high and low trajectories = 77 mIU/ml

Lima S et al Menopause 2026

Baseline menopausal symptoms in past four weeks per trajectory group. N=291.

Mean (SD) or N (%)	FSH: Low 105 (36.1%)	FSH: Moderate 154 (52.9%)	FSH: High 32 (11.0%)	P-value
Menopausal symptoms scores				
Vasomotor score	0.76 (1.15)	0.71 (1.18)	1.09 (1.38)	0.247
Hot flashes score	0.40 (0.64)	0.36 (0.63)	0.69 (0.78)	0.037
Night sweats score	0.36 (0.59)	0.35 (0.64)	0.41 (0.76)	0.897
Sleep				
Sleep duration				0.377
≤6 hr.	34 (32.4%)	53 (34.6%)	13 (40.6%)	
7 hr.	41 (39.0%)	55 (35.9%)	15 (46.9%)	
≥8 hr.	30 (28.6%)	45 (29.4%)	4 (12.5%)	
WHI insomnia rating score				0.177
<9	70 (66.7%)	116 (75.3%)	20 (62.5%)	
≥9	35 (33.3%)	38 (24.7%)	12 (37.5%)	
Sleep quality				0.397
Restless	19 (18.1%)	25 (16.3%)	9 (28.1%)	
Average quality	43 (41.0%)	56 (36.6%)	13 (40.6%)	
Sound or restful	43 (41.0%)	72 (47.1%)	10 (31.3%)	

Menopausal symptom score is created by creating numeric value for each severity level: None = 0; Mild = 1; Moderate = 2; Severe = 3. Vasomotor sums hot flashes and night sweats scores. Vasomotor symptom score range: 0-6. Hot flashes and night sweats score ranges: 0-3.
Sleep quality: "Very restless" grouped with "Restless"; "Very sound or restful" grouped with "Sound or restful".
Statistical significance tested using one-way ANOVA, adjusted for years since menopause, for continuous variables; Chi-square for categorical variables.

Lima S et al Menopause 2026

EDITORIAL

Understanding the biology of dynamic changes in serum gonadotrophins during postmenopausal life

James K. Pru, PhD

A robust assessment of postmenopausal changes in FSH and LH synthesis and secretion beyond a few years from the menopausal transition, as well as their potential association with menopausal symptoms has not been completed.

JK Pru Menopause 2026 33(1): 1-2.

SWAN Study N=1316 non HT users	WHI OsteoPerio Study N=290 non HT users
Women in menopausal transition	Post-menopausal women followed for 20 years
Estimated 3 FSH trajectories that all rose around the final menstrual period then plateaued out to 8 years after FMP	Identified 3 FSH trajectories that remain relatively stable after menopause
<u>Ending serum FSH levels</u>: • 35 IU/L for low trajectory • 90 IU/L for middle trajectory • 120 IU/L for high trajectory	<u>Baseline serum FSH levels</u>: • 48.1 IU/L for low trajectory • 78.0 IU/L for middle trajectory • 124.8 IU/L for high trajectory
Race, ethnicity and BMI were related to trajectory: -Women in high FSH trajectory more likely to be normal weight <u>(inverse associations)</u> -Women in low FSH trajectory were more likely to be AA, Hispanic, overweight or obese; -Women in middle trajectory were more likely to be Japanese	Higher FSH and LH trajectories are associated with lower adiposity <u>(inverse associations)</u> We investigated FSH-adiposity* associations in a larger sample, with control for estradiol, SHBG, and HT use…

Tepper et al J Clin Endocrin Metab 2012

FSH and adiposity

CLIMACTERIC
https://doi.org/10.1080/13697137.2025.2595986

ORIGINAL ARTICLE

Follicle stimulating hormone, luteinizing hormone and adiposity trajectories in postmenopausal women

Yihua Yue[a], Sarah M. Lima[a], Kathleen M. Hovey[a], Jennifer W. Bea[b,c], Jean Wactawski-Wende[a], JoAnn E. Manson[d,e], Denise Roe[b], Janet L. Funk[b,f], Andrew O. Odegaard[g], Shelby G. Ziller[h], Robert Wallace[i], Su Yon Jung[j,k], Jane A. Cauley[l] and Heather M. Ochs-Balcom[a]

Yue Y et al Climacteric 2025

FSH and adiposity associations

From OsteoPerio Study:	B	Y3	Y8	Y20
N=675	serum	serum, DXA	serum, DXA	serum, DXA

DXA scan + VAT and SAT; serum; B, Baseline; Y, Year

- FSH and LH associations with longitudinal changes in BMI, whole body adiposity, and abdominal adiposity after menopause.
  - Group-based trajectory modeling of multiple measures of adiposity over three study visits over 17 years - Polytomous logistic regression
  - GEE models

Yue Y et al Climacteric 2025

VAT trajectory, 3 DXA scans

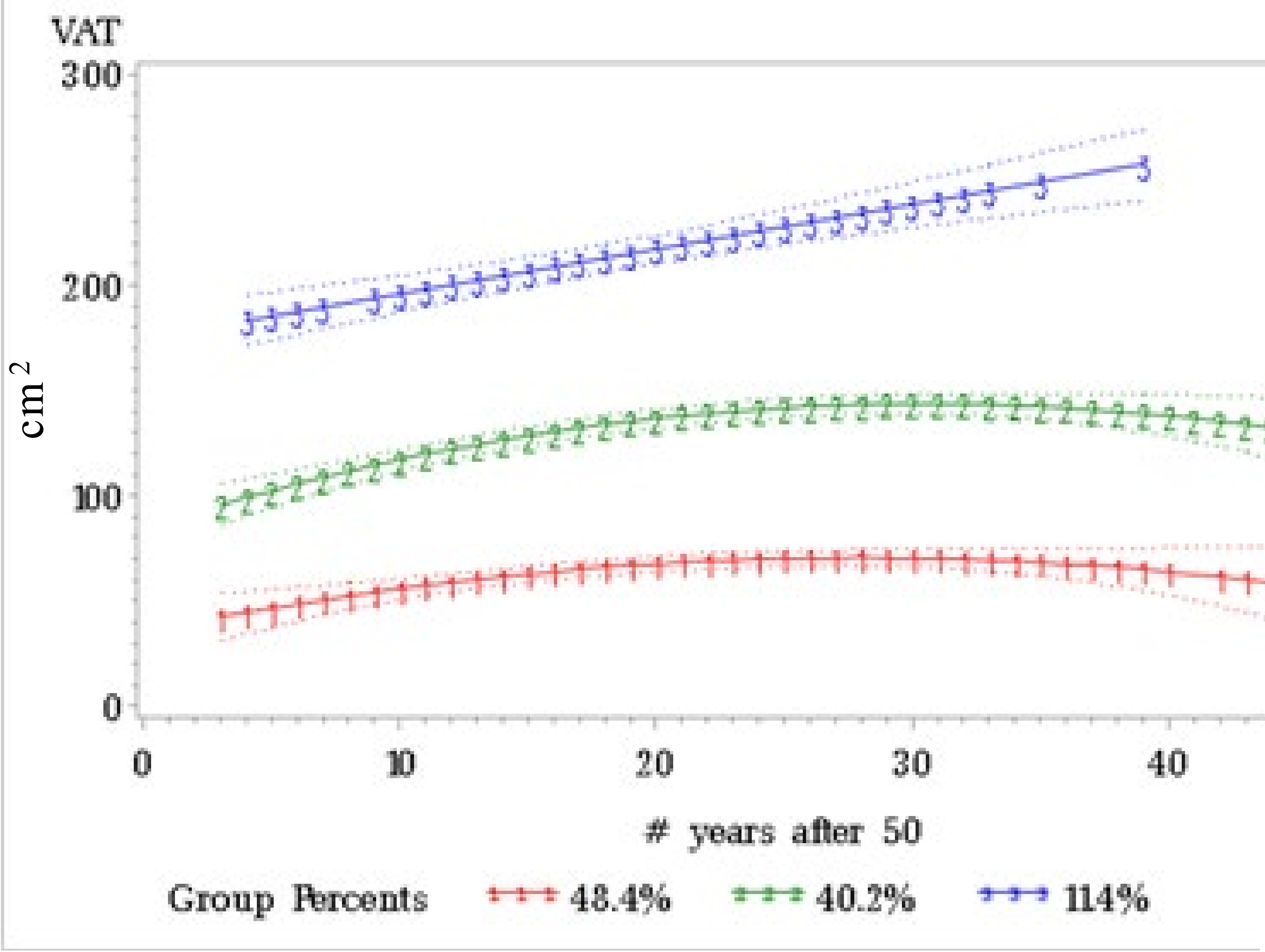


Figure Key

High Trajectory
Moderate Trajectory
Low Trajectory

Yue Y et al Climacteric 2025

FSH inversely associated with adiposity

Table 1. Baseline characteristics by adiposity trajectory group (N=675).

	Baseline Characteristic	Adiposity Trajectory Group: Low	Adiposity Trajectory Group: Moderate	Adiposity Trajectory Group: High	P-value
VAT	Overall, N (%)	328 (48.6%)	272 (40.3%)	75 (11.1%)	
	Age, y	66.0 (6.9)	65.4 (6.6)	63.7 (5.3)	0.022
	Never HT, N (%)	96 (29.3%)	84 (30.9%)	24 (32.0%)	0.490
	HEI, mean (SD)	68.5 (10.3)	65.8 (10.5)	64.5 (9.8)	0.001
	FSH (mIU/mL)	62.1 (30.6)	54.4 (27.4)	44.8 (21.5)	<0.001
	LH (mIU/mL)	34.2 (14.5)	31.6 (13.6)	26.4 (11.7)	<0.001
	E^2 (pg/mL)	32.1 (33.0)	30.6 (32.4)	26.6 (28.7)	0.398

Yue Y et al Climacteric 2025

FSH inversely associated with adiposity

GEE models showing associations between FSH, LH and continuous adiposity measures over time.

	VAT (cm^2) β (95% CI)	SAT (cm^2) β (95% CI)	BMI (kg/m^2) β (95% CI)	Percent Fat (%) β (95% CI)
FSH model[1,2]				
FSH, mIU/ml	-0.54 (-0.69, -0.40)	-1.11 (-1.42, -0.79)	-0.05 (-0.07, -0.04)	-0.04 (-0.05, -0.02)
5-year adiposity change	5.84 (4.06, 7.62)	1.47 (-2.60, 5.53)	0.08 (-0.06, 0.22)	0.28 (0.09, 0.47)
17-year adiposity change	20.45 (16.53, 24.37)	12.15 (4.28, 20.03)	0.75 (0.45, 1.05)	0.77 (0.40, 1.15)

1. Models adjusted for baseline age, physical activity in MET hrs/wk, HT use (never, former, current).
2. FSH model sample size: n=674 at baseline, n=670 at year 5, n=319 at year 17.
Bold = P<0.05.

Yue Y et al Climacteric 2025

What next?

- In our postmenopausal sample, inverse associations are robust to E2, HT use, time since menopause.
- These findings are counter to the preclinical work.
- Are we are missing that earlier window of FSH change?
  - SWAN; Sowers et al J Clin Endocrin Metab 2007

More FSH-related work to come…

- FSH adipose in the HT trials…under review
- FSH and breast cancer…ongoing
- FSH and hypertension – visit our poster!
- FSH and dementia in OsteoPerio…ongoing
- Gonadotropins and cognition/ADRD in WHIMS, R01 under review
- FSH-bone related work… grant in the works
  - Mattick et al Osteoporos Int 2023
- FSHR & other related genes…in planning stages

The FSH Team (so far)

- Jennifer Bea (UA), Heather Ochs-Balcom (Buffalo)
- <u>Collaborators</u>: Jean Wactawski-Wende, JoAnn Manson, Janet Funk, Denise Roe, Lesley Tinker, Andrew Odegaard
- <u>UB/UA graduate students</u>: Shelby Ziller, Yihua Yue, Sarah Lima, Lindsey Mattick, Michaela Stockwell, John Alexander, Kayla Brown, Michaela Stockwell







THE UNIVERSITY OF ARIZONA
Mel & Enid Zuckerman
College of Public Health

University at Buffalo

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- DOD #OS950077 (PI: Wactawski-Wende)
- R01 DE013505 (PI: Wactawski-Wende)
- Adipose and lean soft tissue depots, cancer risk and mortality (PI: Bea, NCI R01CA253302)
- Abdominal adipose tissue depots and CMD (PI: Odegaard, NIA R01AG055018)
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Circulating hormone metabolites associated with sleep and vasomotor symptoms in MHT users and non-users

Kara A. Michels, PhD, MPH

Assistant Professor
Department of Epidemiology and Population Health
Albert Einstein College of Medicine
Bronx, NY

7 May 2026

Women's Health Initiative Investigator Meeting
Bethesda, MD

EINSTEIN
Albert Einstein College of Medicine

Montefiore
Inspired Medicine

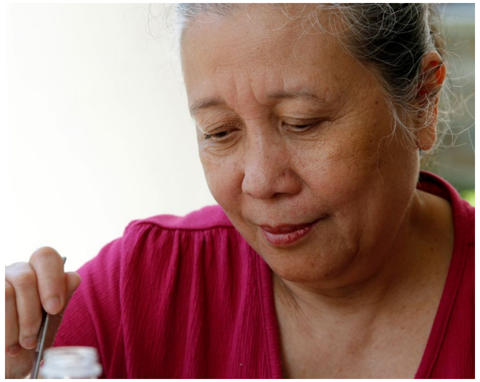
Menopause symptoms dramatically affect quality of life

Symptoms associated with the menopausal transition:

- Vaginal dryness
- Hot flashes/Night sweats
- Sleep disruption
- Depression/mood changes

Vasomotor symptoms associated with increased healthcare costs and work productivity loss

30-80% of women experience vasomotor symptoms across the menopausal transition, which may persist for years

Images from the National Cancer Institute (Public Domain)

Santoro et al. Endocrinol Metab Clin North Am, 2015. 26316239
Gold et al. Am J Pub Health, 2006. 16735636
Avis et al. JAMA Intern Med, 2015. 25686030
Sarrel et al. Menopause, 2015. 25714236

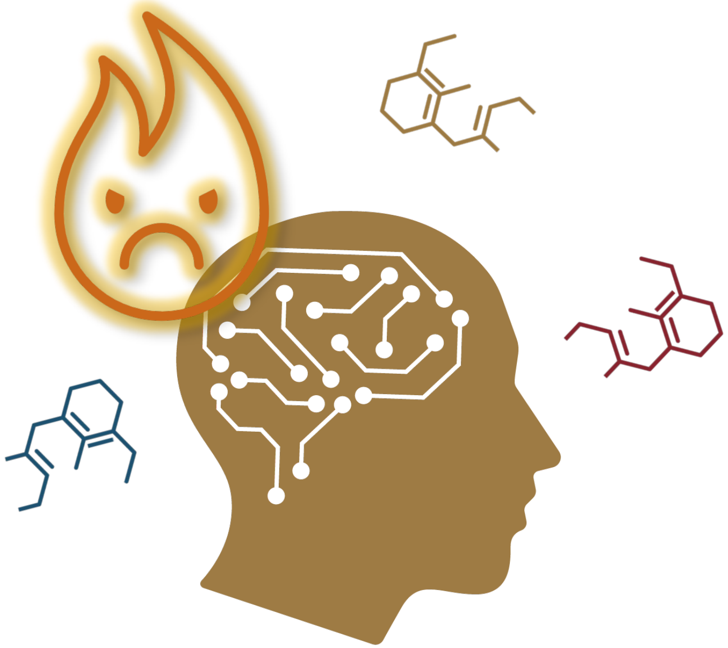
Is it more than just “estrogen?”

Colloquially we blame menopause symptoms on loss of ovarian “estrogen” or lower DHEA

Decreasing estradiol and increasing FSH associated with vasomotor symptoms

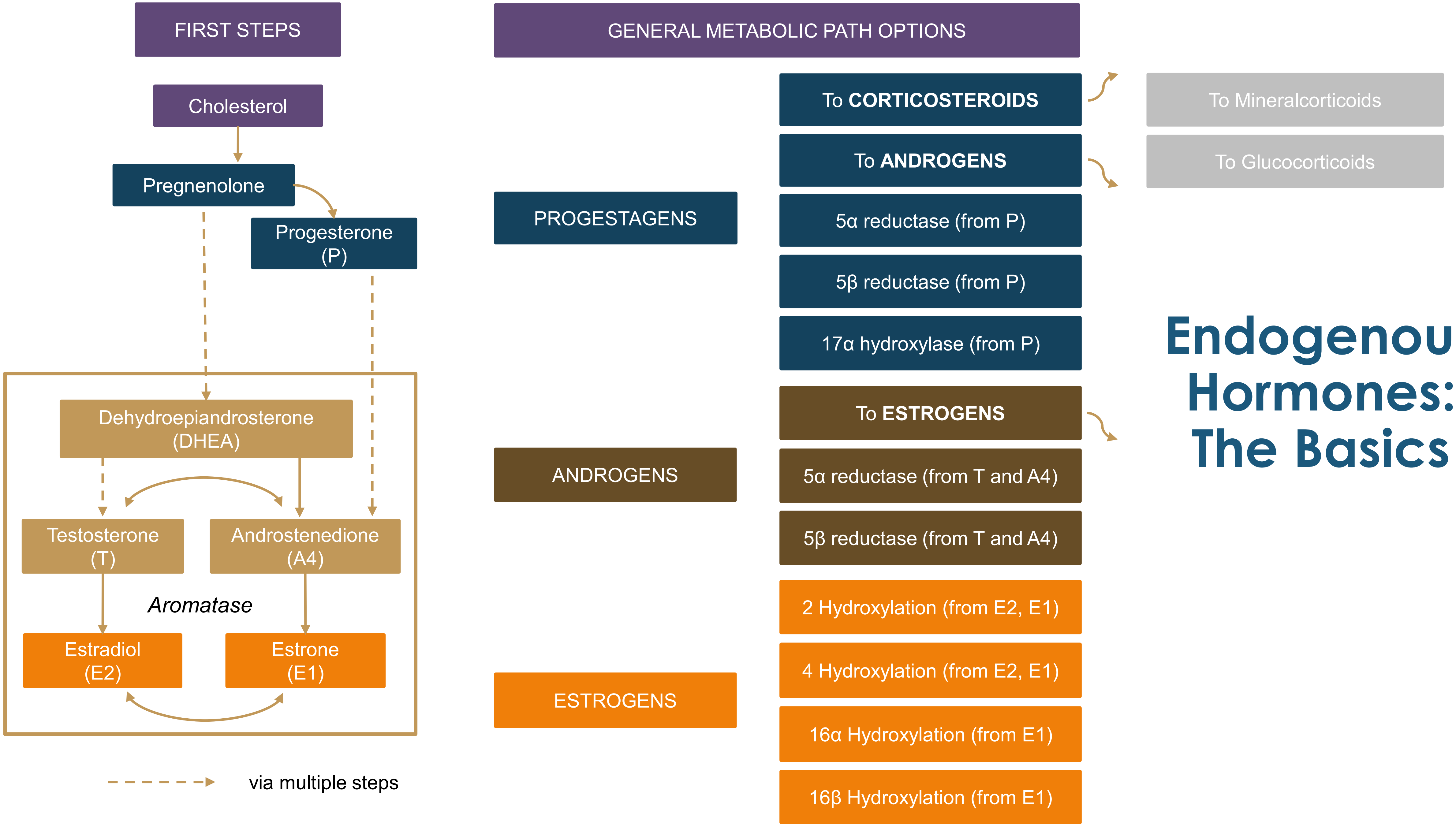
Androgen loss is a recognized contributor to sleep problems

There are many sex hormone metabolites, but historically they have been difficult to measure

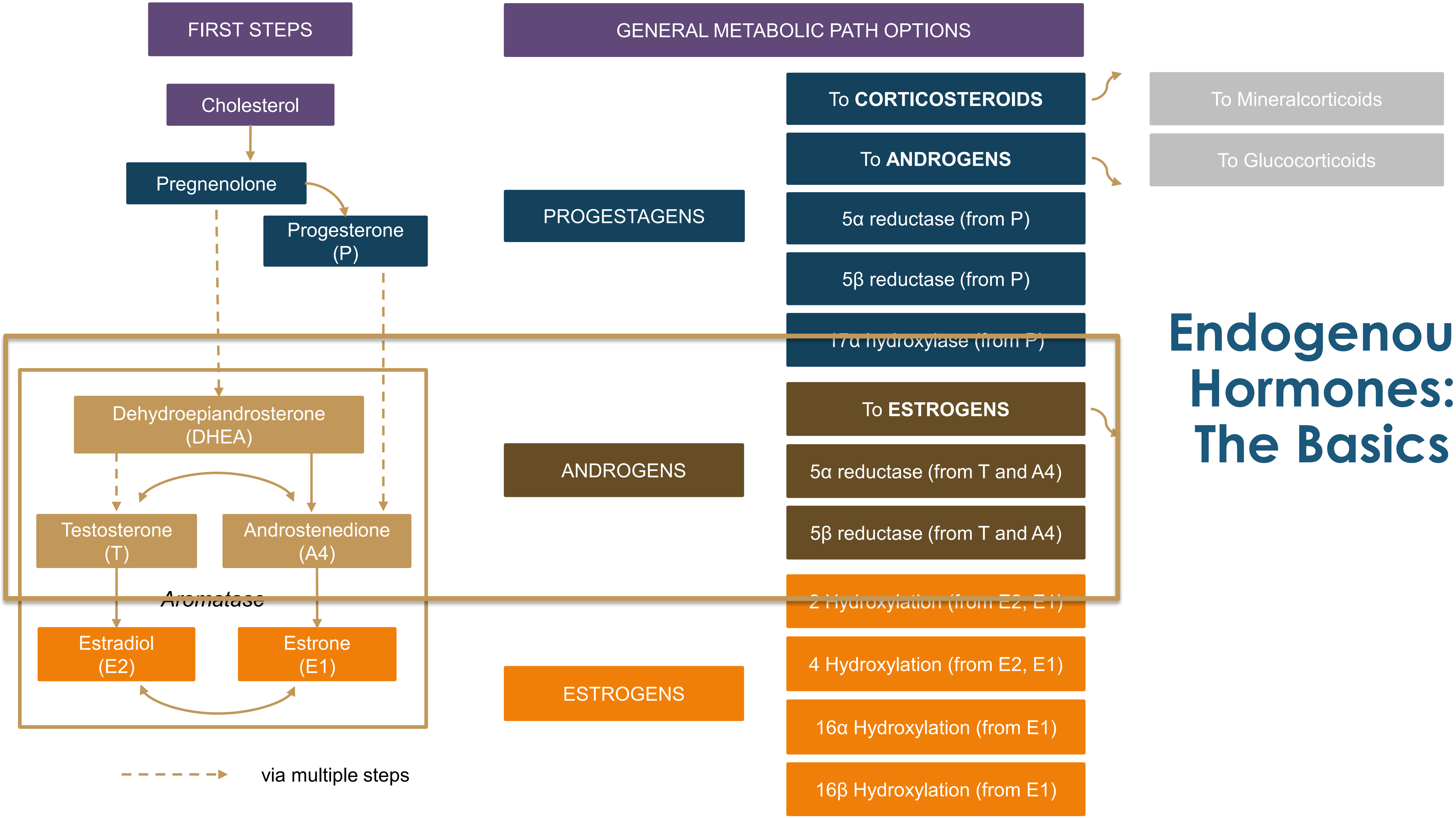


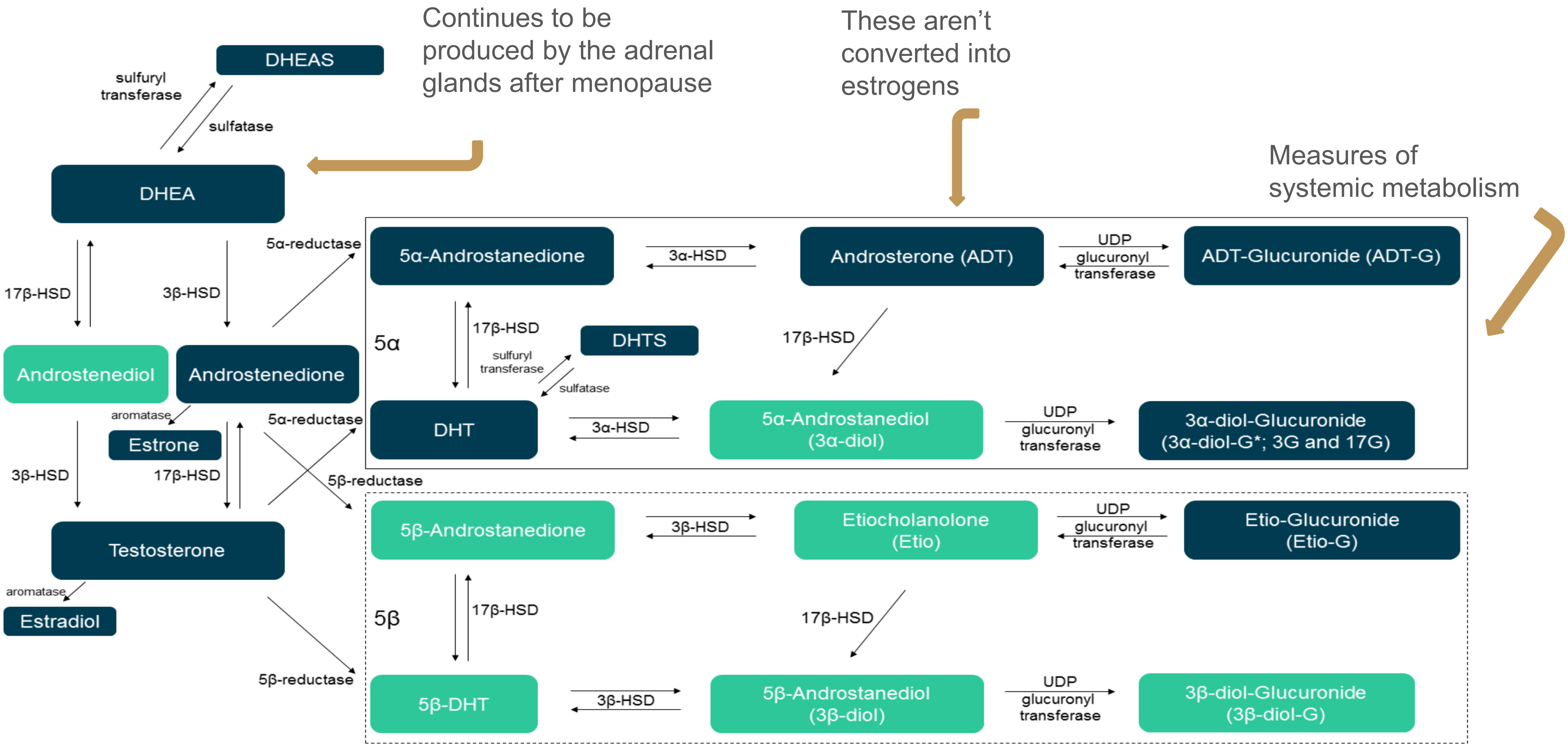
Randolph. JCEM, 2005. 16144949
Woods. Menopause, 2014. 24781854

Endogenous Hormones: The Basics



Endogenous Hormones: The Basics





Michels. JNCI Cancer Spectrum, 2019. 31321379.
Labrie. J Steroid Biochem, 2015. 24923731
Schiffer. Mol Cell Endocrinol, 2018. 28865807

Menopause symptoms → Circulating concentrations of other sex hormones

WHI-OS AS297

Nested case control study in the Women's Health Initiative Observational Study

- 1,864 women with ovarian (n=399) or endometrial cancer (n=585), plus women selected as controls
- Matched on age, race, blood draw year, menopausal hormone therapy (MHT) use, and time since MHT use

MHT users (n=881) and non-users (n=901)

25+ androgen and estrogen metabolites

- Pre-diagnosis serum (mean=6.9 years before)
- Stable isotope dilution high performance LC-MS/MS assays

Brinton. CEBP, 2016. 27197275
Trabert CEBP, 2016. 26908437.
Trabert. Cancer Causes and Control, 2019. 31542834.
Michels. JNCI Cancer Spectrum, 2019. 31321379.
Trabert. Int J Can, 2019. 30684389.

Hormone metabolites measured in this study

Parent Androgens
Dehydroepiandrosterone (DHEA)
Dehydroepiandrosterone sulfate (DHEAS)
Androstenedione
Testosterone
5α reductase Path
5a-androstanedione
Dihydrotestosterone (DHT)
Dihydrotestosterone sulfate (DHTS)
Androsterone (ADT)
Androsterone glucuronide (ADTG)
5a-androstane 3a,17B diol-3-glucuronide (3a-diol-3G)
5a-androstane 3a,17B diol-17-glucuronide (3a-diol-17G)
5β reductase Path
Etiocholanolone glucuronide

Parent Estrogens
Total Estrone
Unconjugated Estrone
Conjugated Estrone
Total Estradiol
Unconjugated Estradiol
Conjugated Estradiol
2-Hydroxylation Path
2-Hydroxyestrone
2-Hydroxyestradiol
2-Methoxyestrone
Unconjugated 2-Methoxyestrone
Conjugated 2-Methoxyestrone
2-Methoxyestradiol
Unconjugated 2-Methoxyestradiol
Conjugated 2-Methoxyestradiol
2-Hydroxyestrone-3-methyl ether

4-Hydroxylation Path
4-Hydroxyestrone
4-Methoxyestrone
4-Methoxyestradiol
16α-Hydroxylation Path
Estriol
Unconjugated Estriol
Conjugated Estriol
16a-Hydroxyestrone
16-Ketoestradiol
16-Epiestriol
17-Epiestriol

Trabert. J Steroid Biochem Mol Biol, 2016. 26416142
Xu. Anal Chem, 2007. 17848096

Symptoms

At baseline, women were asked about the frequency of symptoms each week, during the last 4 weeks:

- Trouble falling asleep
- Waking several times at night
- Waking early than planned
- Difficulty going back to sleep
- Overall quality of sleep

- Hours of sleep in a typical night
- Hot Flashes
- Night Sweats

Levine. Psychol Assess. 2003. 1287774
Cauley. J Bone Miner Res. 2019. 30461066

Symptoms

At baseline, women were asked about the frequency of symptoms each week, during the last 4 weeks:

- Trouble falling asleep
- Waking several times at night
- Waking early than planned
- Difficulty going back to sleep
- Overall quality of sleep

Sleep disturbance construct
Mild (0-4)
Moderate (5-8)
Severe (9-20)

- Hours of sleep in a typical night — ≤6, 7, ≥8
- Hot Flashes
- Night Sweats

Yes versus no

Levine. Psychol Assess. 2003. 1287774
Cauley. J Bone Miner Res. 2019. 30461066

A cross-sectional snapshot

Linear regression

- Inverse probability weighted to control for oversampling of women who developed cancer
- Adjusted for matching factors, BMI, smoking, time since menopause, type of MHT
- Stratified by MHT use
- Geometric mean hormone levels (dependent variables)
- Percent differences in means

	Geometric mean concentration		
	Symptom not present	**Symptom present**	**% difference in means**
Hormone 1	Mean (95% CI)	Mean (95% CI)	% diff (95% CI)

Prevalence of sleep and vasomotor symptoms

	Never/former MHT users			Current MHT users		
	N	Unweighted %	Weighted %	N	Unweighted %	Weighted %
Sleep disturbance (severe)	275	31.4	33.1	244	27.9	25.9
Hours of sleep (<6 hours)	311	34.7	34.5	258	29.3	31.1
Hours of sleep (≥8 hours)	246	27.5	28.5	251	28.5	28.4
Hot Flashes	234	26.1	25.6	145	16.5	19.6
Night Sweats	226	25.3	27.4	176	20.0	23.4

Sleep duration in non-MHT users

Parent Androgens	Hours of sleep (≤6 hours)	Hours of sleep (≥8 hours)
Dehydroepiandrosterone (DHEA)	1.8 (-11.6, 17.1)	**18.1 (0.9, 38.2)**
Dehydroepiandrosterone sulfate (DHEAS)	3.3 (-13.7, 23.7)	16.2 (-3.2, 39.5)
Androstenedione	-1.2 (-11.2, 10.9)	7.6 (-4.0, 20.5)
Testosterone	-12.5 (-23.6, 0.2)	2.5 (-12.8, 20.4)
5α reductase Path		
5a-androstanedione	-7.8 (-18.1, 3.8)	2.0 (-9.8, 15.2)
Dihydrotestosterone (DHT)	-2.9 (-12.8, 8.2)	10.6 (-3.3, 26.5)
Dihydrotestosterone sulfate (DHTS)	7.8 (-6.6, 24.4)	5.2 (-11.5, 24.9)
Androsterone (ADT)	-8.1 (-15.7, 0.2)	6.4 (-2.7, 16.3)
Androsterone glucuronide (ADTG)	-2.0 (-17.9, 16.9)	16.4 (-5.6, 43.4)
3a-diol-3G	-3.8 (-19.0, 14.2)	**22.5 (0.8, 49.0)**
3a-diol-17G	-12.2 (-24.4, 2.0)	**20.8 (1.4, 43.8)**
Parent Estrogens		
Total Estrone	-7.4 (-20.5, 7.9)	0.5 (-12.8, 15.9)
Unconjugated Estrone	-5.2 (-15.8, 6.7)	6.0 (-5.4, 18.9)
Total Estradiol	**-14.2 (-25.7, -0.8)**	1.9 (-12.7, 18.9)
Unconjugated Estradiol	**-20.8 (-33.9, -5.1)**	3.0 (-13.5, 22.7)
2-Hydroxylation Path		
Sum: 2-Hydroxylation path	-6.75 (-16.79, 4.49)	-2.62 (-12.99,)
4-Hydroxylation Path		
Sum: 4-Hydroxylation path	-3.68 (-14.43, 8.42)	-5.28 (-15.92, 6.71)
16α-Hydroxylation Path		
Sum: 16a-Hydroxylation path	-5.81 (-18.28, 8.56)	-6.05 (-18.14, 7.83)

Sleep duration in MHT users

Parent Androgens	Hours of sleep (≤6 hours)	Hours of sleep (≥8 hours)
Dehydroepiandrosterone (DHEA)	-2.1 (-16.9, 15.3)	8.3 (-8.0, 27.4)
Dehydroepiandrosterone sulfate (DHEAS)	-7.4 (-23.7, 12.3)	-1.88 (-20.4, 21.0)
Androstenedione	-1.9 (-14.4, 12.4)	7.7 (-5.0, 22.1)
Testosterone	-2.7 (-16.5, 13.4)	7.0 (-7.6, 23.8)
5α reductase Path		
5a-androstanedione	9.5 (-4.6, 25.8)	9.5 (-4.5, 25.6)
Dihydrotestosterone (DHT)	0.1 (-10.8, 12.3)	2.4 (-8.3, 14.4)
Dihydrotestosterone sulfate (DHTS)	0.8 (-14.2, 18.4)	-7.0 (-20.5, 8.9)
Androsterone (ADT)	-0.2 (-8.3, 8.8)	-0.6 (-8.5, 8.0)
Androsterone glucuronide (ADTG)	-0.7 (-19.6, 22.6)	10.3 (-12.4, 39.0)
3a-diol-3G	2.2 (-15.5, 23.6)	12.7 (-7.3, 36.9)
3a-diol-17G	**19.2 (0.2, 41.9)**	**22.0 (1.6, 46.6)**
Parent Estrogens		
Total Estrone	-11.2 (-31.0, 14.4)	**-29.9 (-45.5, -9.9)**
Unconjugated Estrone	-8.9 (-25.6, 11.6)	-16.4 (-31.6, 2.2)
Total Estradiol	-20.7 (-37.7, 1.0)	**-29.3 (-44.1, -10.5)**
Unconjugated Estradiol	-6.0 (-24.9, 17.7)	-8.3 (-25.6, 13.2)
2-Hydroxylation Path		
Sum: 2-Hydroxylation path	-9.2 (-24.7, 9.4)	**-17.9 (-31.1, -2.3)**
4-Hydroxylation Path		
Sum: 4-Hydroxylation path	-6.2 (-22.4, 13.4)	**-16.6 (-30.4, -0.1)**
16α-Hydroxylation Path		
Sum: 16a-Hydroxylation path	-5.4 (-23.7, 17.5)	-15.1 (-31.8, 5.7)

Sleep disturbance construct

No clear relationship between sleep disturbance construct and hormone levels, regardless of MHT use

Trouble falling asleep 5+ nights/week

- MHT users **and** non-users: lower concentrations of androgens and estrogens (-20 to -70%)

Vasomotor symptoms

Parent Androgens	Never/Former MHT Users		Current MHT Users	
	Hot flashes	Night sweats	Hot flashes	Night sweats
DHEA	-1.8 (-15.8, 14.6)	-2.0 (-15.7, 14.0)	18.7 (-0.6, 41.6)	11.9 (-3.3, 29.5)
Androstenedione	0.6 (-9.9, 12.4)	-2.2 (-12.5, 9.4)	5.8 (-8.4, 22.2)	5.5 (-6.3, 18.8)
Testosterone	4.9 (-9.2, 21.2)	-1.2 (-14.9, 14.7)	3.2 (-10.5, 19.1)	3.8 (-9.2, 18.6)
5α reductase Path				
DHT	4.5 (-7.9, 18.5)	5.9 (-6.2, 19.7)	6.0 (-6.2, 19.8)	-2.9 (-13.5, 9.1)
DHTS	-9.6 (-22.4, 5.2)	-9.4 (-23.1, 6.7)	-2.7 (-19.2, 17.2)	5.5 (-9.6, 23.1)
ADT	0.1 (-7.8, 8.8)	2.3 (-5.9, 11.3)	5.1 (-4.3, 15.4)	-4.0 (-11.4, 4.1)
ADTG	2.6 (-16.3, 25.7)	**21.7 (0.2, 47.9)**	**33.6 (6.1, 68.3)**	**33.1 (10.7, 60.1)**
3a-diol-3G	-0.4 (-17.4, 20.2)	16.9 (-3.7, 42.0)	21.9 (-0.6, 49.4)	**22.9 (3.0, 46.7)**
3a-diol-17G	3.9 (-12.8, 23.8)	16.5 (-2.2, 38.7)	**26.5 (2.4, 56.2)**	**32.1 (10.9, 57.3)**
Parent Estrogens				
Total Estrone	-7.5 (-19.9, 6.9)	-8.2 (-20.8, 6.5)	**-29.8 (-48.9, -3.7)**	-1.2 (-25.1, 30.2)
Unconjugated Estrone	-5.0 (-15.3, 6.4)	-8.3 (-18.8, 3.5)	**-23.2 (-40.3, -1.3)**	-8.2 (-25.6, 13.3)
Total Estradiol	-3.0 (-16.4, 12.6)	-9.1 (-21.3, 4.9)	**-28.8 (-47.9, -2.6)**	0.5 (-23.6, 32.2)
Unconjugated Estradiol	-5.6 (-20.7, 12.4)	-6.9 (-21.9, 11.1)	-19.5 (-38.3, 4.9)	-4.7 (-24.2, 19.7)
2-Hydroxylation Path				
Sum: 2-Hydroxylation metabolites	-6.8 (-16.3, 3.8)	-9.5 (-18.4, 0.3)	**-20.9 (-36.4, -1.5)**	-5.7 (-22.1, 14.1)
4-Hydroxylation Path				
Sum: 4-Hydroxylation	-8.5 (-18.1, 2.3)	-8.9 (-18.0, 1.1)	-19.0 (-35.1, 0.9)	-3.19 (-20.5, [illegible]

It’s more than just “estrogen”

Higher glucuronidated androgens and lower methoxy-E1 and E2 metabolites were the most consistent hormone differences across symptoms

MHT users reporting symptoms often had lower levels of estrogens

- Not getting enough from MHT for symptom relief?
- Over producing some glucuronidated androgens?

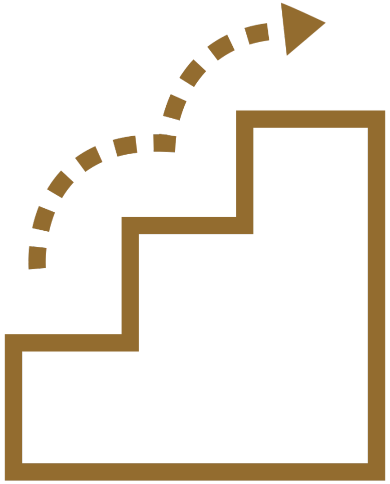
Relationship between hormones and each sleep symptom likely unique

Peripheral androgen metabolism merits investigation

Where from here?

Urogenital symptoms

Do some women have unique hormone metabolism before menopause? Is that predictive of subsequent symptoms?



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Questions? Ideas? Collaborations?

Kara’s Website/Email

SCAN ME

Endogenous Hormones, Cognition, and Risk of Dementia in the WHI

WHI Investigator Meeting

May 7, 2026

Tracy E. Madsen, MD, PhD

University of Vermont Larner College of Medicine

Laura B. Harrington, PhD, MPH

Kaiser Permanente Washington Health Research Institute

2/3 of persons with diagnosed dementia are women

Exogenous Hormone Therapy and Cognition

- Evidence of adverse associations between exogenous E+P HT use and cognitive outcomes in WHIMS

- Previously…
  - Box warning on all E HT and E+P HT reporting increased risk of “endometrial cancer, cardiovascular disorders, breast cancer, and, **in women older than 65 years, probable dementia”**

- Generally, an increased interest in whether HT impacts long-term dementia risk

Espeland MA et al. *JAMA Intern Med*. 2013;173(15):1429-1436; Wittes J et al., *JAMA 2026*; 335;(14):1201-1202.

Endogenous sex hormones and brain health?

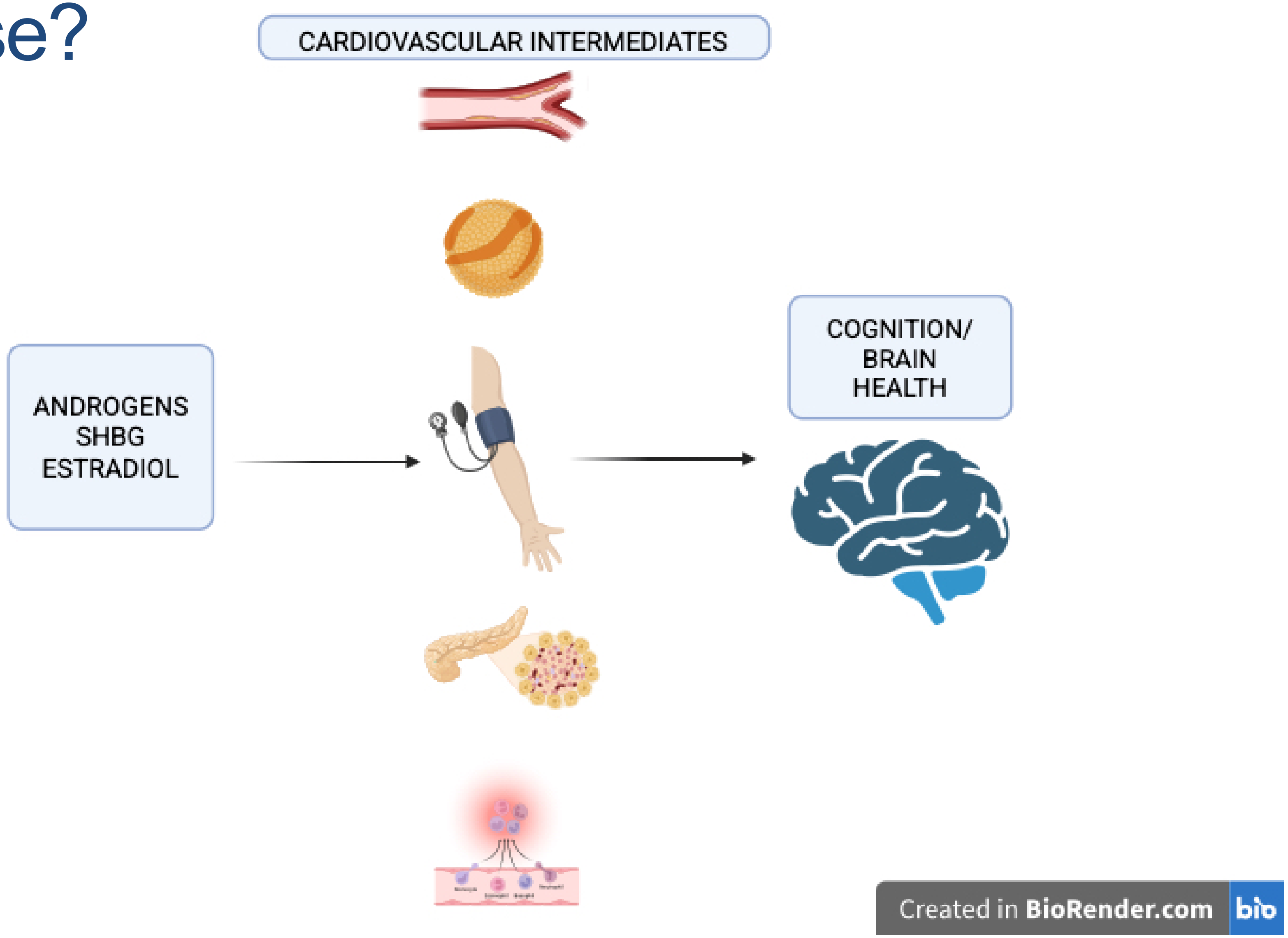
- Associations between endogenous sex hormones and brain health are poorly understood

- In postmenopause:
  - Estrogen concentrations drop
  - Adrenal androgen production remains relatively intact
  - SHBG (which binds to both estrogen and testosterone) increases in the later postmenopausal years

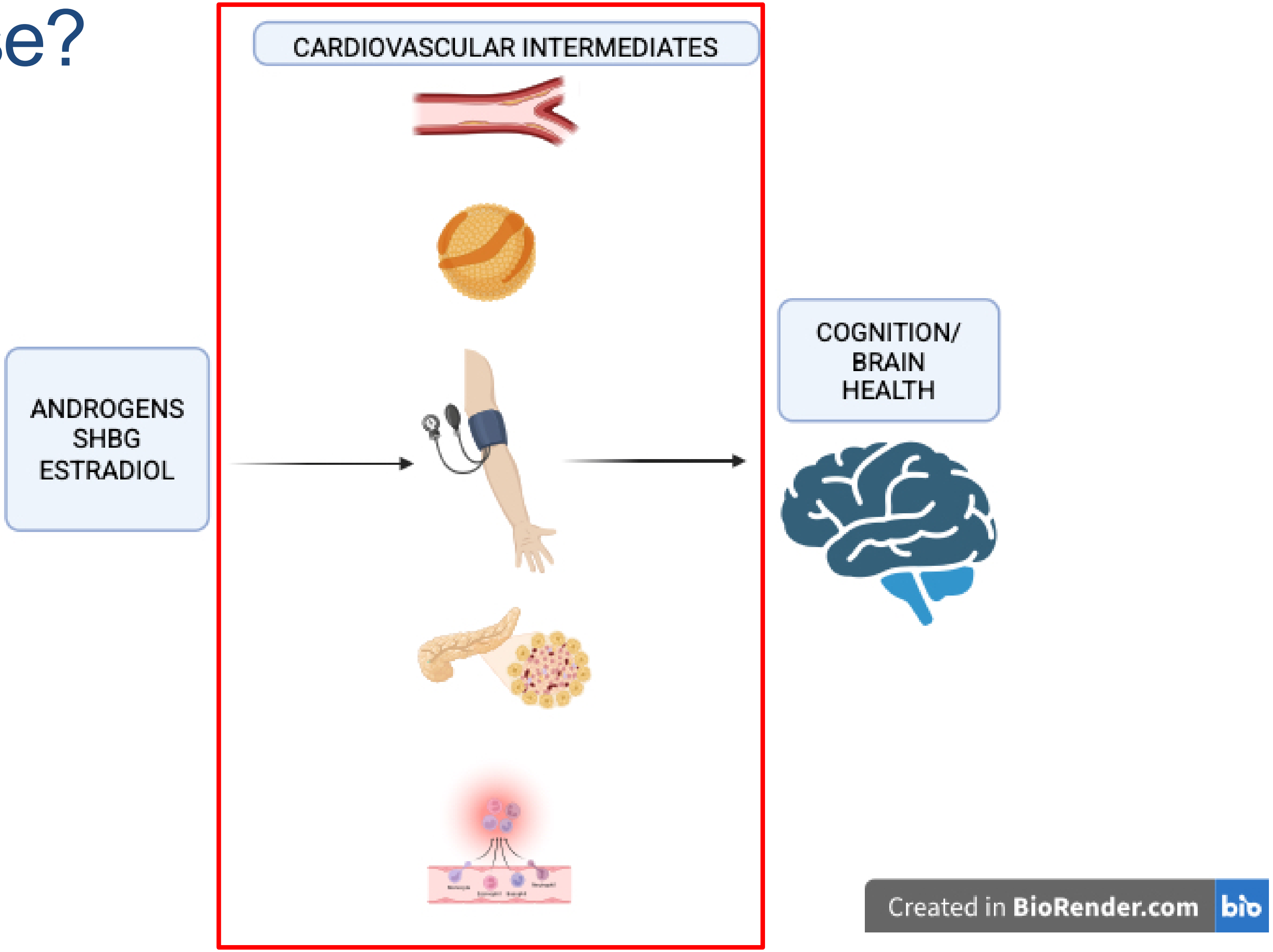
- Evidence suggests:
  - Estrogen and androgen receptors are present in the brain
  - Associations between endogenous estrogens and brain health are inconsistent
    - Some suggest an inverse association and others report no association

Xu Q et al., *Front Aging Neurosci.* 2024;16:1356791; Yaffe K. et al., *Neurobiology of Aging.* 2007; 28(2):171-178; Sultana F et al., *Climacteric.* 2003; 26(2):121-128; Koyama AK et al., *Alzheimer's & Dementia.* 2016;12(7):758-765.; Henderson et al., *Proc Natl Acad Sci USA*. 2013; 110(50):20290-20295.

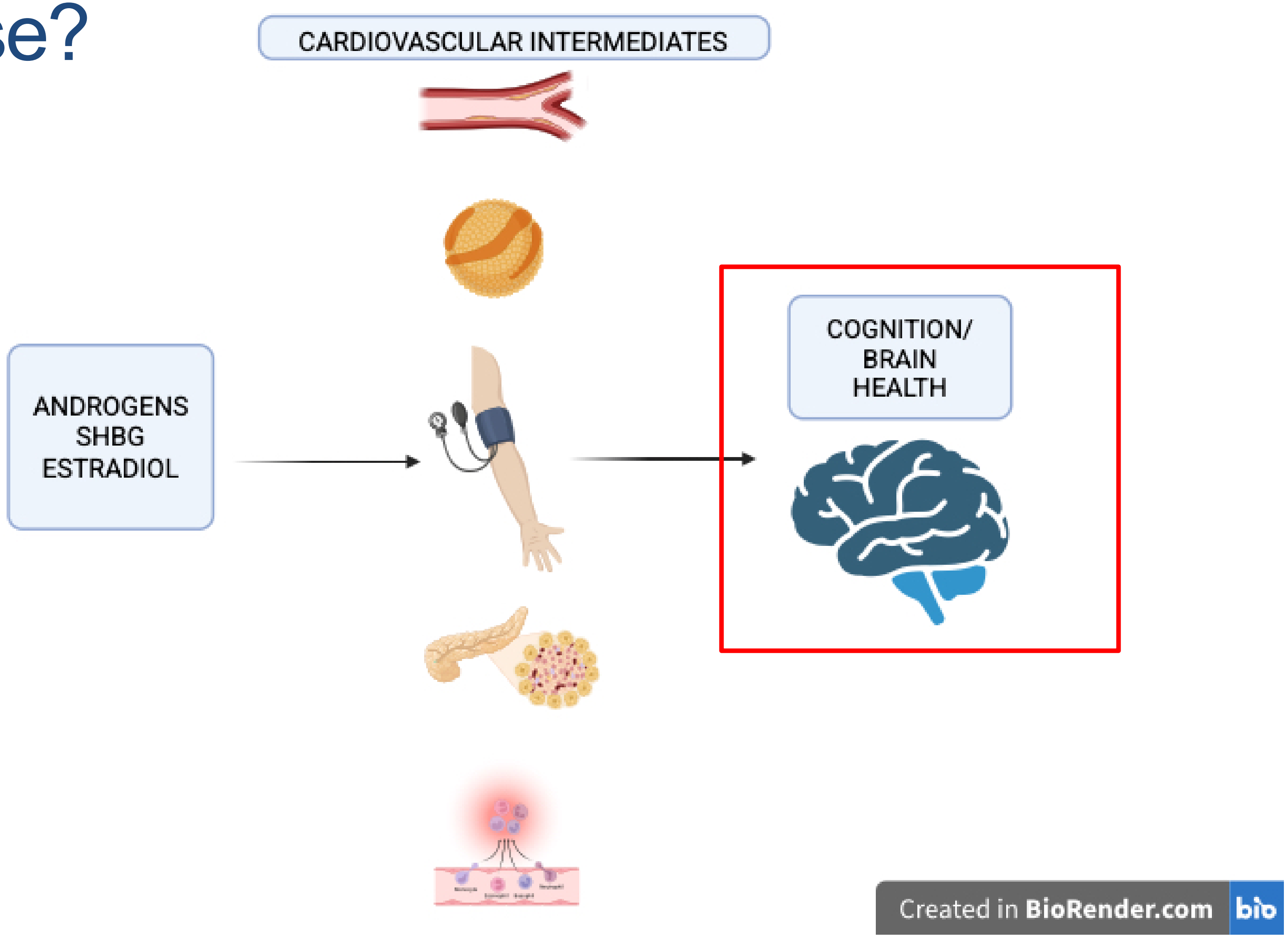
Mechanism through cardiometabolic disease?



Mechanism through cardiometabolic disease?



Mechanism through cardiometabolic disease?



Study Objectives

- **Primary Objective:** Among postmenopausal women, to evaluate associations between sex hormone binding globulin (SHBG) and endogenous estradiol (E2) and:
  (a) cognition over time;
  (b) risk of mild cognitive impairment (MCI) and probable dementia (PD).

  Hypothesis: Among postmenopausal women, lower levels of E2 and SHBG will be associated with: (a) greater change in cognition over time; and (b) greater risk of incident MCI or PD.

- **Secondary Objective**: To evaluate the association between total testosterone (T) and: (a) cognition over time and (b) risk of MCI/ PD.

Study Design and Population

Setting: Women's Health Initiative Memory Study (WHIMS) (n=7479)

SAMPLE FOR PRIMARY ANALYSIS

N=2081 Unique participants with both estradiol and SHBG measured via immunoassay* at the Hormone laboratory

SAMPLE FOR SECONDARY ANALYSIS

Subsample of N=442 with Total T, Estradiol, and SHBG

Exposure and Outcome

- **Exposure**
  - Baseline (pre-hormone therapy randomization) endogenous levels of SHBG, E2, and total T
  - Measured by immunoassay at the Reproductive Endocrine Research Laboratory (University of Southern California, Los Angeles, CA, USA)

- **Outcome**
  - Cognition measured by the Modified Mini Mental State Exam (3MSE)
    - Annually between WHI baseline in 1995-1998 and 2007
  - Adjudicated MCI and PD diagnoses

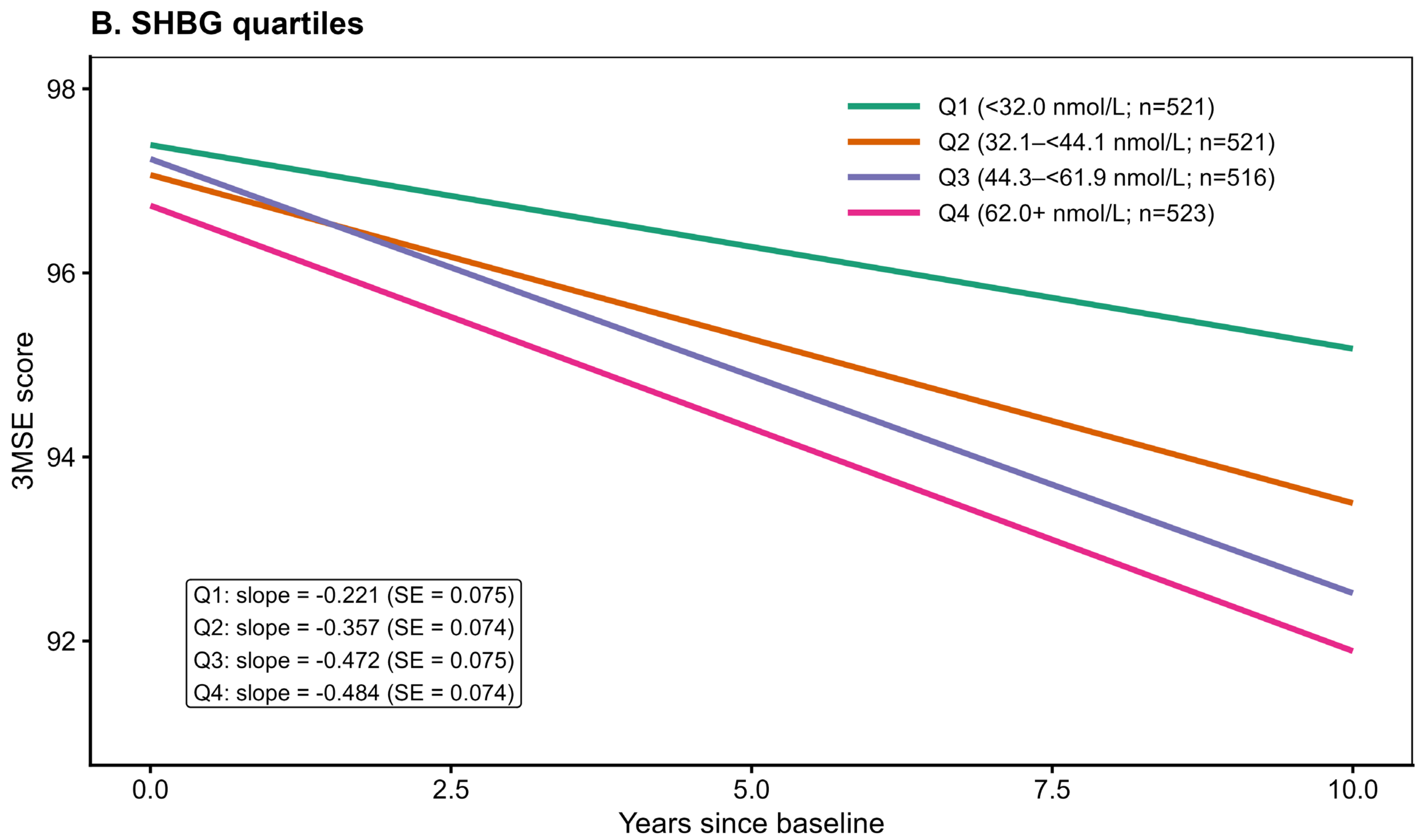
Statistical Analyses

- Linear mixed effects models
  - Evaluate the association between baseline E2, SHBG, and T levels (by quartile) and change in 3MSE over time, adjusted for confounders
- Cox proportional hazards models
  - Evaluate the association between log-transformed E2, SHBG, and T levels at baseline and risk of MCI or PD, censoring at death and loss to follow-up

Results:
Baseline Characteristics by Baseline SHBG

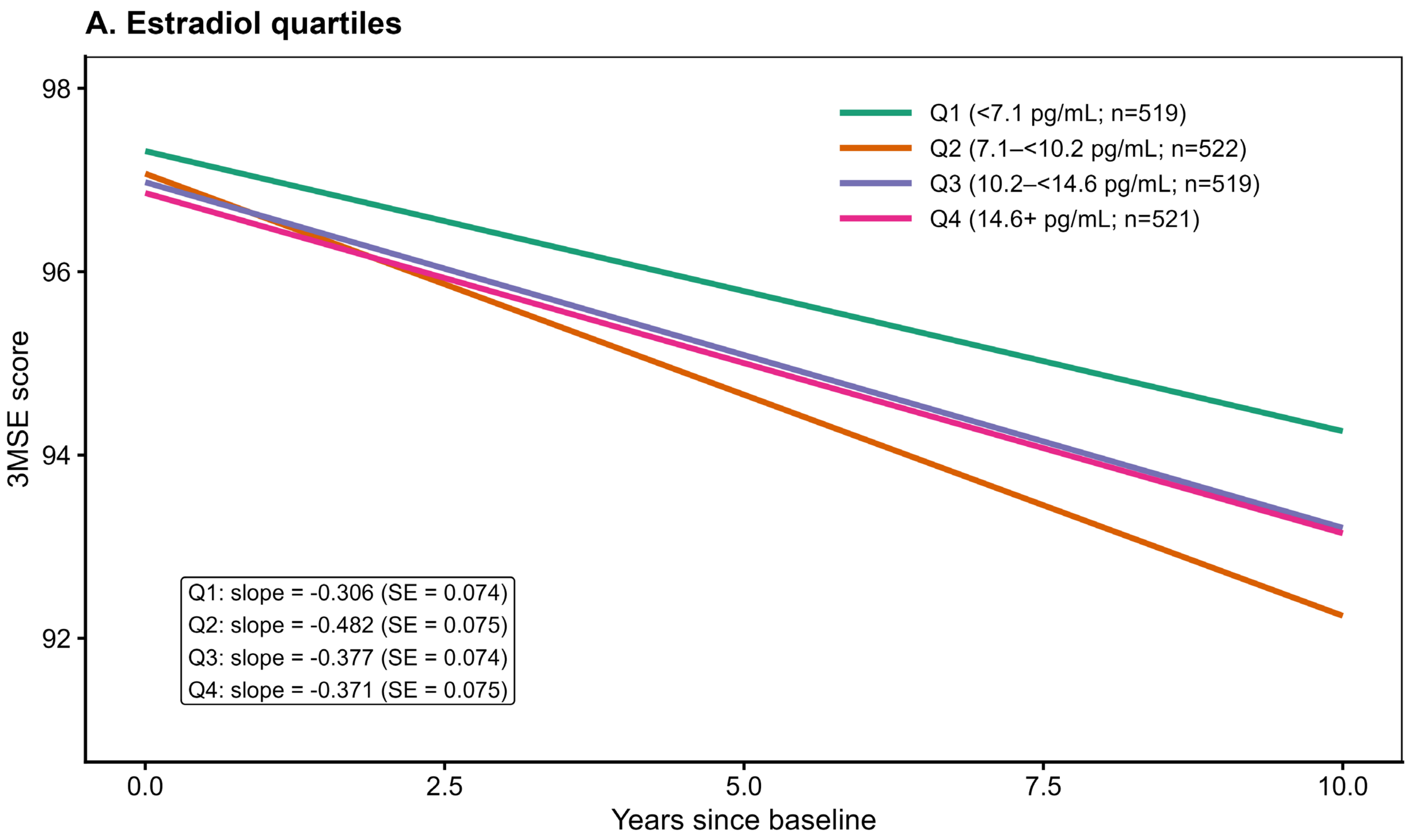
Characteristic	Overall	Quartiles of SHBG (nmol/L)			
		<32	32.0≤44.1	44.1≤62	62+
N	**2,081**	**521**	**520**	**520**	**520**
Age, (mean ± SD)	71 ± 4	70 ± 4	71 ± 4	72 ± 4	71 ± 4
Black Race, N(%)	139 (7%)	38 (7%)	28 (5%)	42 (8%)	31 (6%)
White Race, N(%)	1,869 (90%)	461 (89%)	477 (92%)	460 (89%)	471 (91%)
BMI, (mean ± SD)	29 ± 6	31 ± 6	30 ± 5	28 ± 5	26 ± 6
Age at menopause, (mean ± SD)	48 ± 7	48 ± 7	48 ± 7	49 ± 7	49 ± 6

Results: SHBG and 3MSE



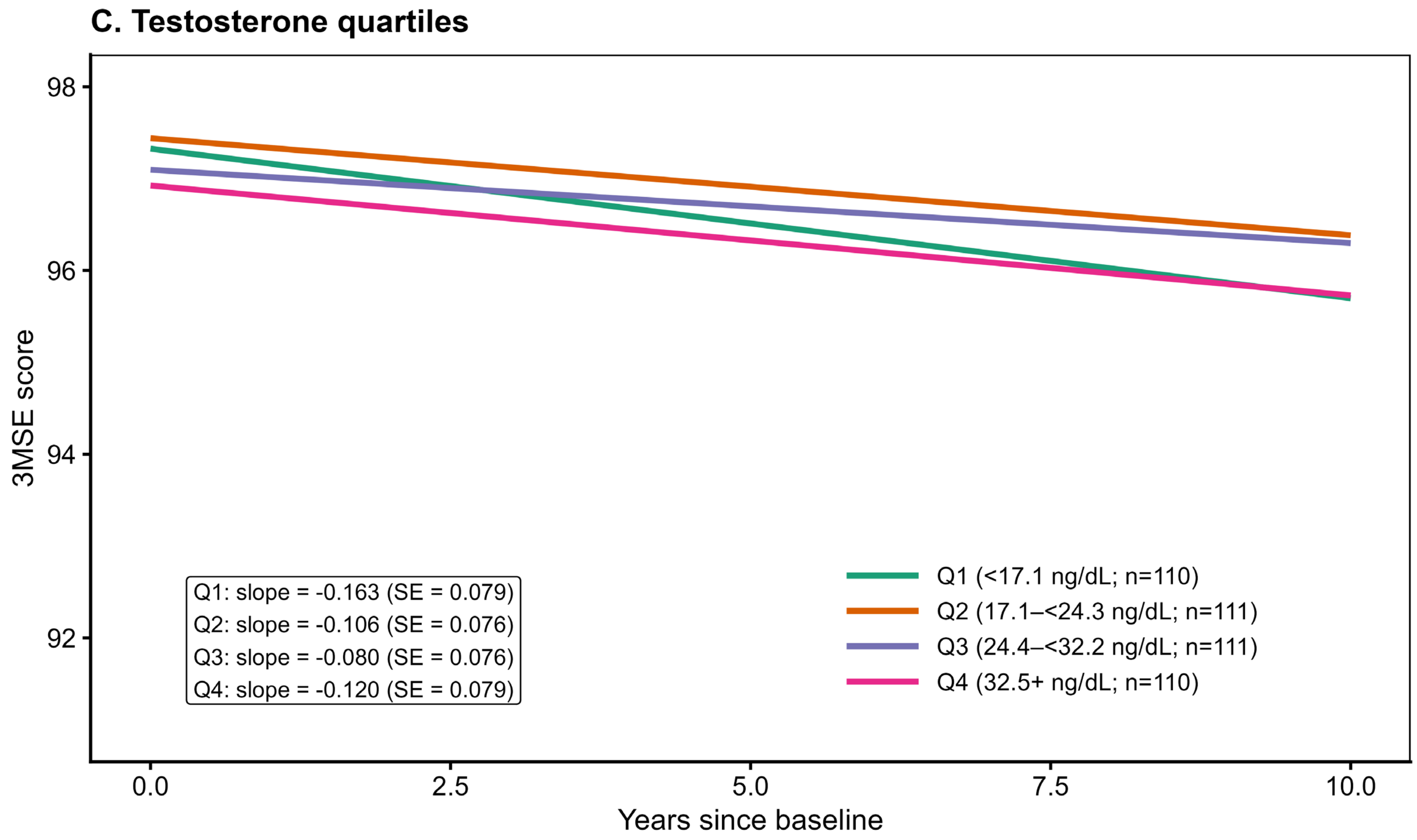
*Models adjusted for hormone therapy (HT) trial arm, age, age at menopause, BMI, ancillary study, physical activity, alcohol, education, smoking, cardiovascular comorbidities; p-value from log-transformed SHBG*time = 0.004

Results: E2 and 3MSE



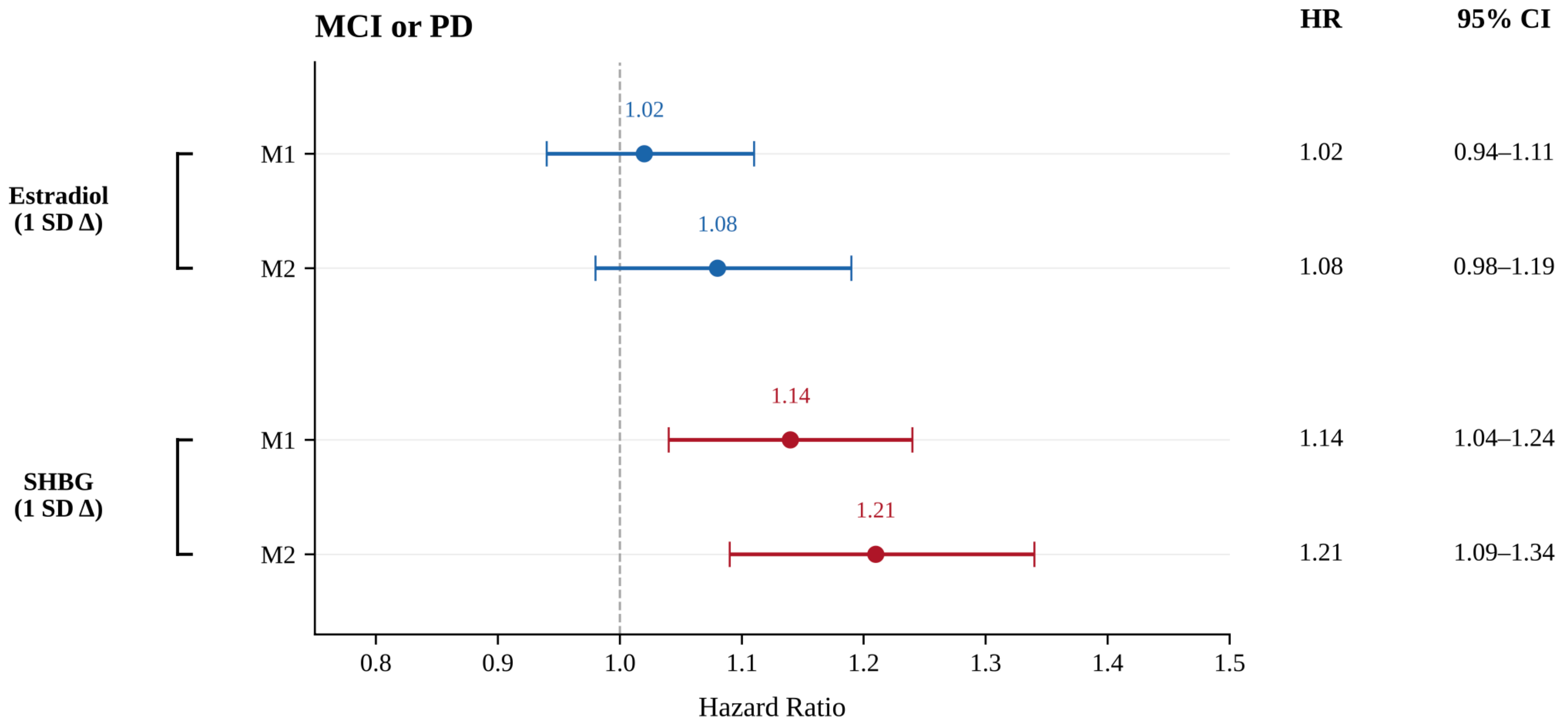
*Models adjusted for hormone therapy (HT) trial arm, age, age at menopause, BMI, ancillary study, physical activity, alcohol, education, smoking, cardiovascular comorbidities; p-value from log-transformed E2*time = 0.880

Results: T and 3MSE



*Models adjusted for hormone therapy (HT) trial arm, age, age at menopause, BMI, ancillary study, physical activity, alcohol, education, smoking, cardiovascular comorbidities; p-value from log-transformed T*time = 0.737

Results: Incident MCI / PD Risk



*M1: Age adjusted, stratified by HT trial arm (Cox Strata procedure); M2: M1 + adjusted for age at menopause, BMI, ancillary study, physical activity, alcohol, education, smoking, cardiovascular comorbidities

Results: Total T and MCI/PD Risk

Per 1 SD Δ

M1

M2

*M1: Age adjusted, stratified by HT trial arm (Cox Strata procedure); M2: M1 + adjusted for age at menopause, BMI, ancillary study, physical activity, alcohol, education, smoking, cardiovascular comorbidities

Strengths and Limitations

Strengths

- Large cohort of older women with adjudicated MCI and PD as well as repeated 3MSE measures
- Prospective study design

Limitations

- Hormones were measured by immunoassay, and at one time only (baseline)
- Not generalizable to pre/peri-menopausal women
- Total testosterone measured in smaller sample

Conclusions

- Important relationship between higher SHBG, worse cognition, and greater MCI/PD risk among postmenopausal women suggested
- Potential pathways through which SHBG may impact cognition include regulation of bioavailable sex steroids or through impact on other metabolic factors

Future Directions

- Ongoing sensitivity analyses include models adjusted for multiple hormones, APOE4 status, and stratified by HT arm / history of exogenous hormone use
- Future directions include evaluation of androgens and SHBG over time in relation to cognition and MCI/PD risk in larger sample (related ancillary study in progress)
- Analyses investigating endogenous sex hormones and CVD (existing ancillary study 758)

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Questions?

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