MENOPAUSE & PERIMENOPAUSE

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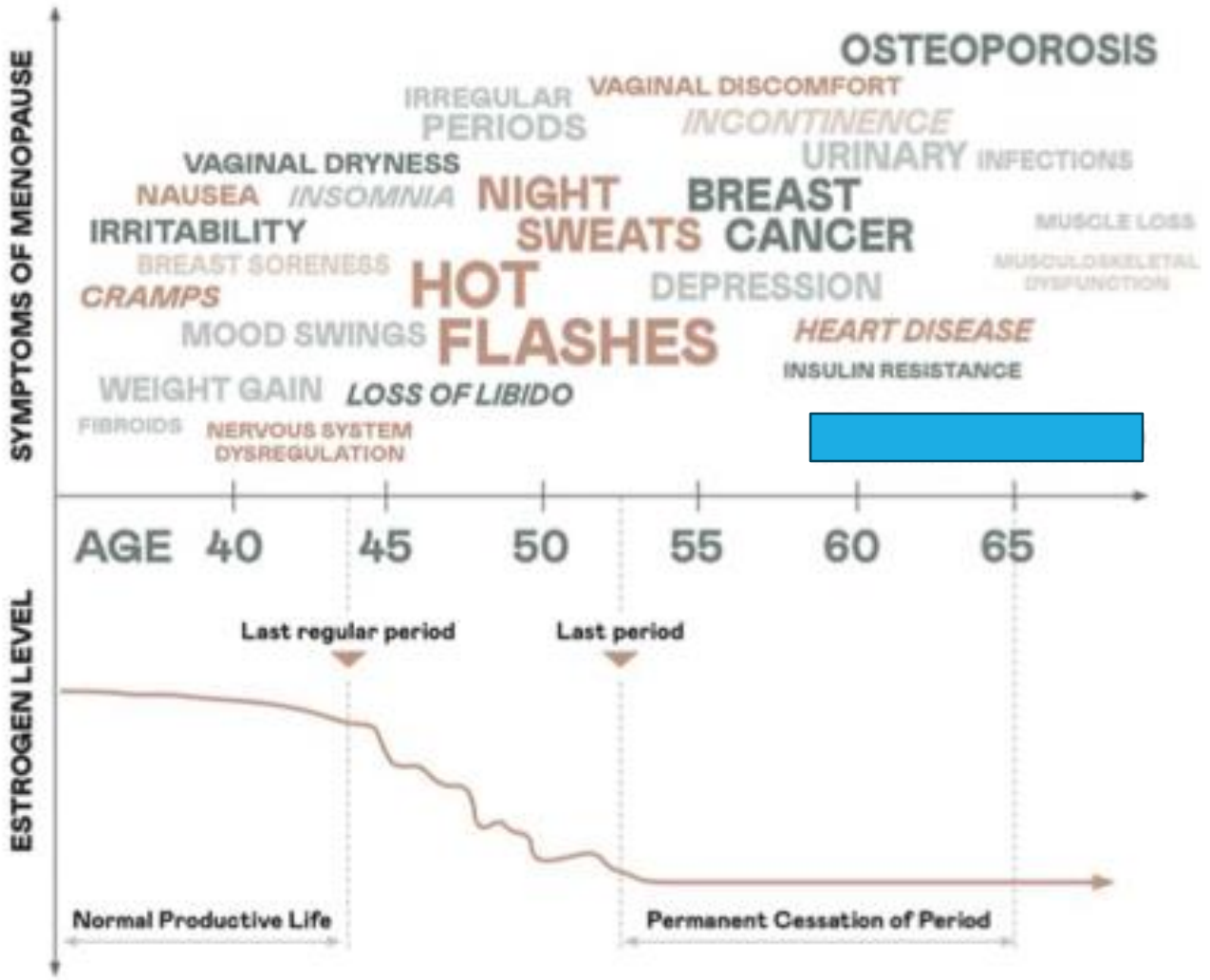
Learning Objectives

- Recognize key hormonal shifts in perimenopause and menopause
- Summarize age-related changes in brain metabolism and structure in women, with emphasis on declining estrogen and mitochondrial function
- Evaluate the role of hormone therapy in a personalized longevity strategy
- Apply updated framework to optimize women’s health after 40

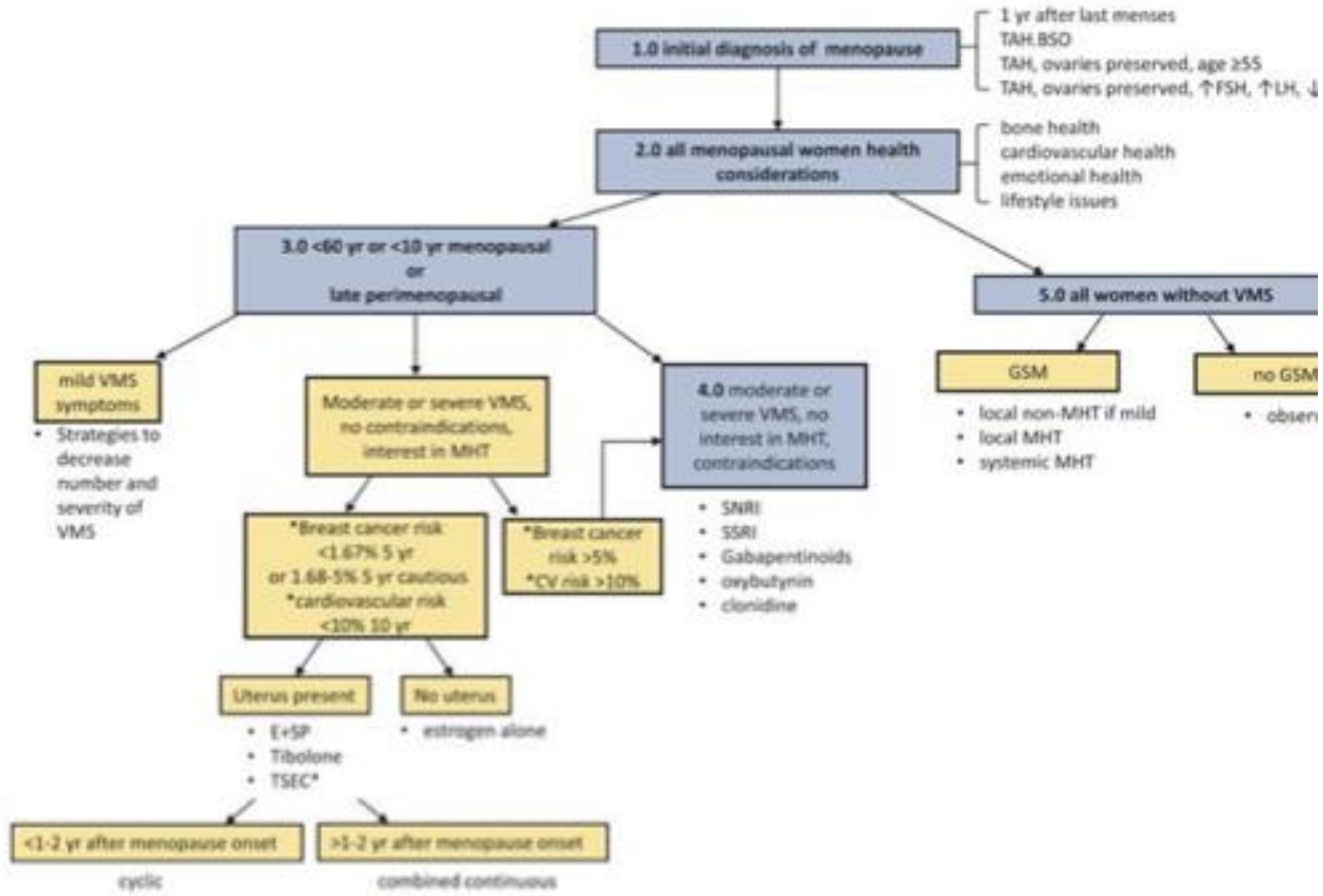
I Background:
Status Quo Menopause Care

- Biology of menopause is universal, but the personal experience varies dramatically
- Nature and severity of symptoms, psychological, social, and contextual considerations, most of which are modifiable
- Underfunded, lack of research, lack of knowledge
- Previous negative experience in accessing advice or treatment
- Discouraged women from pursuing help.
- Primary care lacks information and confidence in prescribing HT
- Up to 75% of women don’t get the treatment they need



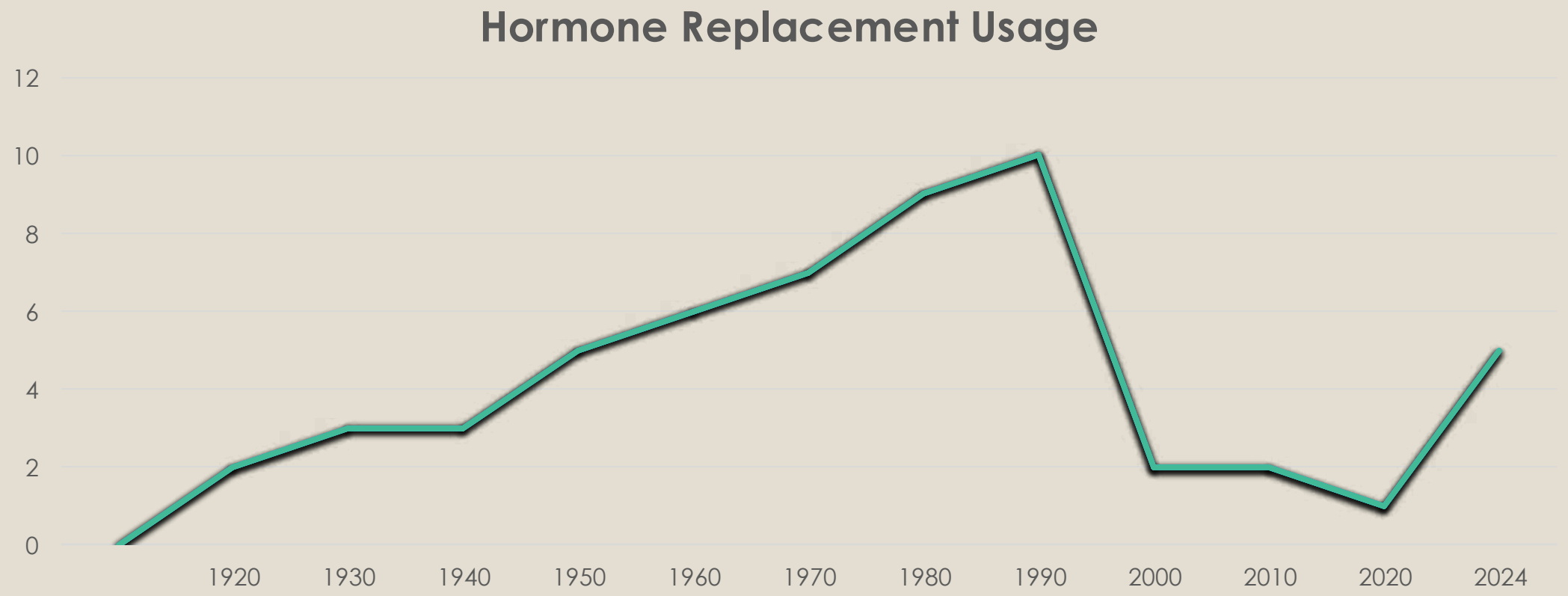
Clayton, *JAMA 2025 333(10):891-7*

Mgt of Menopause According to Endocrine Society Guidlines



Santen, ***The Journal of Clinical Endocrinology & Metabolism***, 2020, Vol. 105, No. 12, 3792–3806

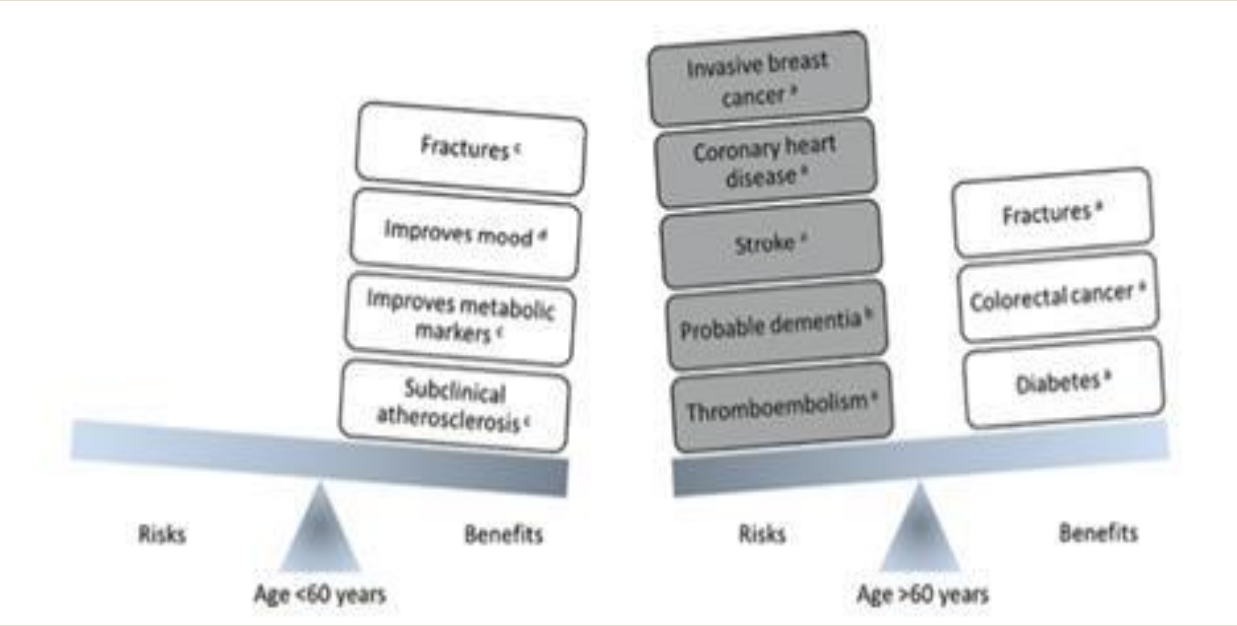
Rethinking Hormone Therapy



FDA lifts black box warning on HRT Nov 11, 2025

- Historic shift in how women's health treated
- Only One Black Box warning remains:
  - Highlights risk of endometrial cancer in women on estrogen without progesterone balance
- Signaling end of decades of fear-based messaging that discourages millions from accessing safe effective relief for menopause symptoms
- All estrogen containing therapies carried black box warning introduced after WHI (Women's Health Initiative) Study 2002 saying it increased risk of breast cancer, heart attacks, strokes and dementia—deeply flawed
  - WHI data reflected outcomes in women over 63(past the age where hormone therapy is typically initiated) taking conjugated equine estrogens and medroxyprogesterone (two forms no longer in use today)
- Over past 23 years, 50 million women denied or never offered HRT
- Re-evaluating the data:
  - Hormone therapy (when appropriately prescribed at appropriate age and dose improves short and longterm health outcomes (lower risk of Alzheimers, heart attack, hip fracture)

RISK/BENEFIT FROM WHI



"Findings from that trial, which treated a population of older, asymptomatic patients, have been extrapolated over the past 21 years to all estrogen products, all menopausal women, and all delivery mechanisms. Our patients deserve a more nuanced, individualized approach." B Levy

Levy B, Simon JA. *Obstet Gynecol* 2024 Jul 1;144(1):12-23

Menopause 3.0

- Women outlive men across all populations, eras, and under extreme stressors
- Advantage spans nearly all major causes of death—except Alzheimer's
- Survival gap begins in infancy, pointing to biology not social or behavioral factors [1,2]

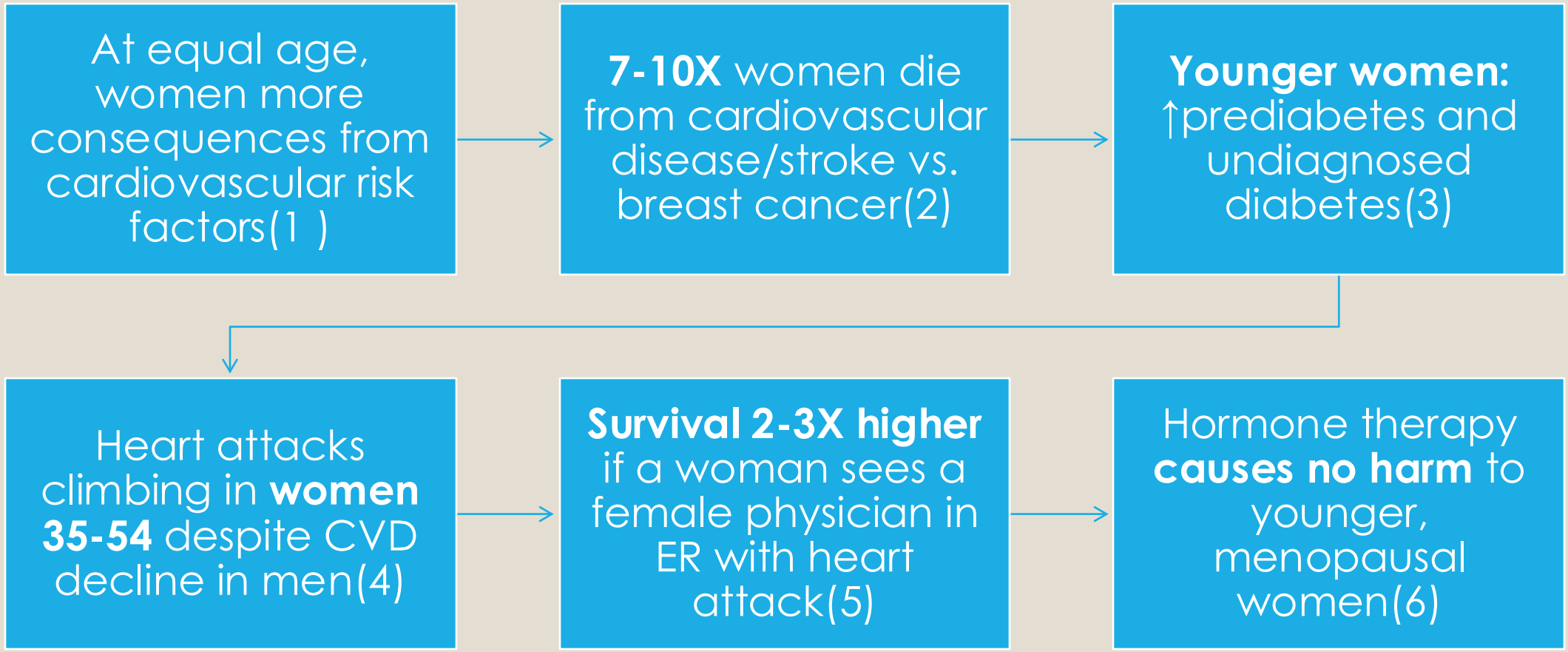
Step Aside Longevity Bros. It's Time for the Longevity Ladies.

A growing number of female scientists, entrepreneurs and influencers are edging into a space long dominated by men. Their study of hormones and ovaries could unlock the key to a longer life for everyone.

Zarulli, V. *Proceedings of the National Academy of Sciences of the USA* 118, no. 20 (2021): e2010588118.

https://www.wsj.com/health/wellness/step-aside-longevity-bros-its-time-for-the-longevity-ladies

Statistics for Women



1.https://www.cdc.gov/heartdisease/women.htm (accessed 9/9/25), Mehta, L. S., et al. *Circulation* 147, no. 19 (2023): 1471–87
2.Tsao, C. W., et al. *Circulation* 145, no. 8 (2022): e153– e639; Tsao, C. W., et al. *Circulation* 147, no. 8 (2023): e93–e621;
3.Fan, J., M. Yao, and Y. Ma. *Endocrine Practice* 30, no. 12 (2024): 1126–1133.
4.Mehta, et al. *Circulation* 147, no. 19 (2023): 1471–1487.;Yoshida, Y., et al. *American Journal of Preventive Medicine* 64, no. 3 (2023): 423–427.
5.Greenwood, et al. *Proceedings of the National Academy of Sciences of the United States of America*115, no. 34 (2018): 8569– 8574.
6.GershF,etal.*ProgressinCardiovascularDiseases*84(May–June2024):60–67.

Aging Isn't Linear:

- Nonlinear "waves" of biomolecular change age 44 and 60
- **80% of women experience psychological or physical symptoms**
- **Mood: Women > 2X to be afflicted, observed in U.S. and globally**
- **Sleep disorders**
  - 2X reflecting bidirectional relationship between sleep/wake cycle and sex hormones/gonadotropins
  - Menopause-related sleep disturbance may influence eating behaviors/timing, directly affect immunometabolism, particularly abdominal adiposity
  - Menopause is associated with increased risk of sleep apnea.
- **VMS associated with indicators of cardiovascular disease (CVD) risk, e.g., adverse CVD risk factor profile, greater subclinical CVD and events**
  - Untreated vasomotor instability impairs endothelial function->increased risk of peripheral vascular and cerebrovascular function, HTN, osteoporotic fracture, CVD, depression, and cognitive impairment

Xiaotao Shen et al., "Nonlinear Dynamics of Multi-Omics Profiles During Human Aging," Nature Aging 4, no. 11 (November 2024): 1619–1634 https://doi.org/10.1038/s43587-024-00692-2. PubMed

"With aging there can be a decline in the brain's ability to generate the fuel it needs. The key is maintaining the body's system of glucose metabolism, and that entire process in women is regulated by estrogen."

ROBERTA DIAZ BRINTON, PH.D.
DIRECTOR, CENTER FOR INNOVATION IN BRAIN SCIENCE, UNIVERSITY OF ARIZONA

II Age Related Changes in Brain Metabolism

N=2,231 dementia-free Framingham Heart Study (gen 3) participants, mean 48.5y, 53% women

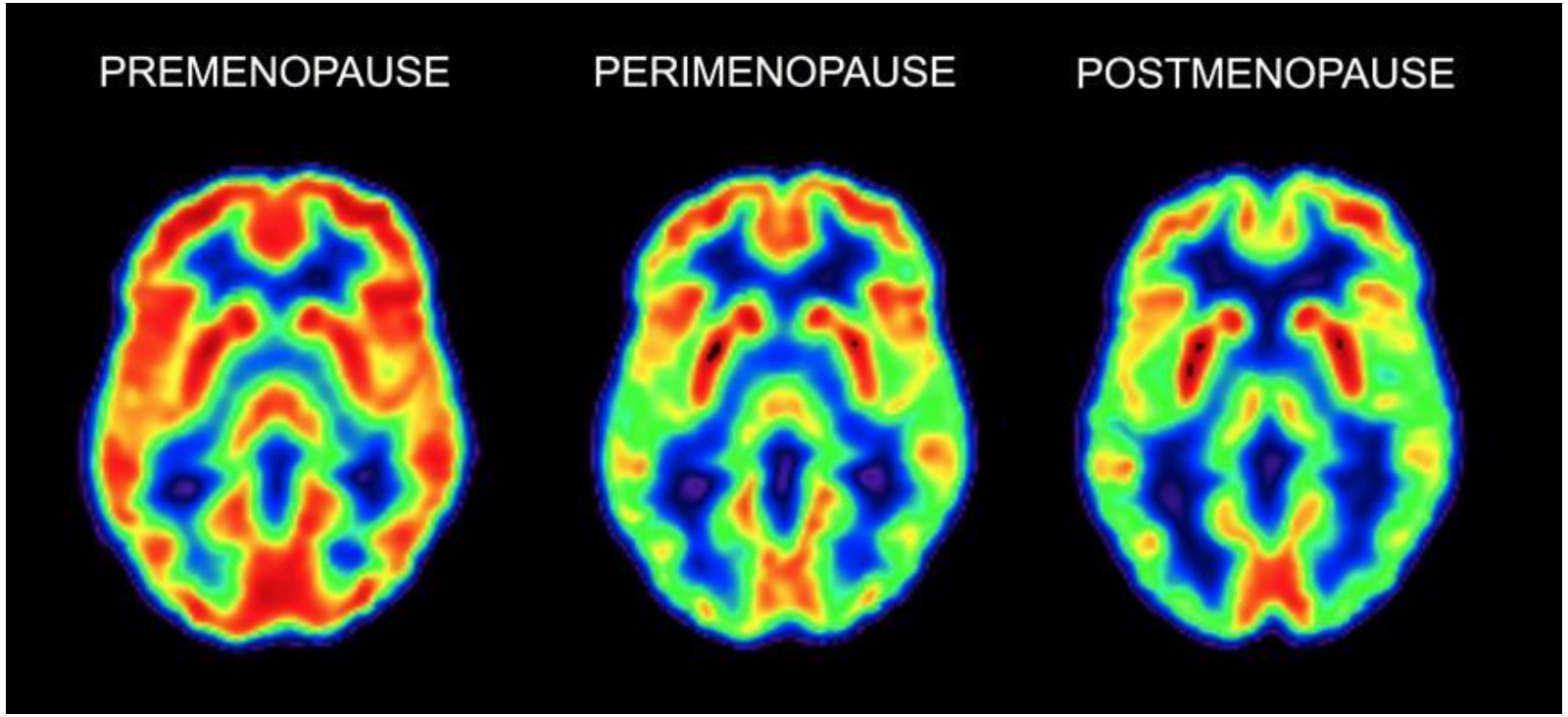
Higher morning salivary cortisol associated with…

- worse memory and visual perception
- lower total occipital and frontal lobar gray matter volumes
- lower total cerebral brain volume in women but not men
- no effect modification by the APOE4 genotype in cortisol, cognition, or imaging traits

Echouffo-Tcheugui et al. J of *Neurology* (2018) 91(21):e1961-e1970 Brinton RD et al. Nat Rev Endocrinol. 2015;1(7):393-405

PET IMAGING

Red and yellow glc metab **20% decrease in metab** **25% decease**



Cerebral hypometabolism: glucose metabolism, decrease in brain energy (affects 80% of women)

Mosconi L et al. *PLoS One*. 2017 Oct 10;12(10)

Memory Loss, Brain Shrinkage, and Higher Beta Amyloid Load in Healthy Women with High Cortisol

- Chronic psychological stress = risk factor for Alzheimer's disease (AD)
- N=277 cognitively normal midlife individuals(men and women)
- Higher cortisol was associated with
  - lower total brain volume
  - lower glucose metabolism (CMRglc) in frontal cortex
  - higher β-amyloid (Aβ) load in AD-vulnerable regions
- Women: cortisol stronger associations with β-amyloid load + lower glucose metab frontal cortex seen more postmenopause
- Men: cortisol exhibited stronger associations with gray matter volume and PCr/ATP measures
- Higher cortisol associated with poorer delayed memory in men but not in women.
- Results]adjusted for age, APOE4 status, midlife health factors, and hormone therapy use.
- Sex-specific neurophysiological responses to stress, support stress reduction in AD prevention.

Mosconi, et al.2024 UT, San Antonio

Mental Health in Women 45-55

- Elevated risks of **suicide, sleep disturbances, and adverse effects from divorce,** often interacting
- Suicide: risk factors including psychiatric disorders, financial stress, alcohol misuse, and physical health problems.
  - Being divorced or separated is associated with a more than 200% increased risk of suicide mortality in this age group, and the risk is particularly pronounced in the year following divorce and among women with shorter marriages.
  - Women 3X more likely to attempt suicide than men
  - Perimenopause = GREATEST RISK
- Nearly half of perimenopausal women report insomnia, with sleep efficiency below 85% being common. Sleep disturbances are strongly linked to psychological symptoms such as depression, anxiety, and irritability
- Biological and psychological factors at work, precipitated further by environmental stressors

Weiss SJ, et al. J Psychiatr Res. 2022 Nov;155:493-500; Clements, C., et al. *The British Journal of Psychiatry: The Journal of Mental Science*, 2025: 1–7; Cranney, S., and S. T. Wilkinson. *Journal of Affective Disorders*, 2025: 119862; Hou, S. Y., et al. *Sleep Medicine* 113 (2024): 172–179; Hou, F., et al. *The British Journal of Psychiatry: The Journal of Mental Science*, 2025: 1–7; Na, Pil Jung, et al. 2025. *JAMA Psychiatry* 82 (4): 337–346.

III. INDICATIONS FOR HORMONE THERAPY

- VASOMOTOR SYMPTOMS
- MOOD
- ANXIETY
- SEXUAL DYSFUNCTION
- CONGNITIVE DECLINE
- PREVENTION OF OSTEOPOROSIS
- HEALTHSPAN

Hormonal Assessment

- HCM (exam, Pap, mammogram, colonoscopy, etc.)
- Serum: Cardiometabolic risk profile + hormones (estradiol, progesterone and FSH (days 2–4 if cycle present), anti-Mullerian hormone, testosterone; advanced lipids with ApoB; A1c/fasting glucose; TSH and free T4 if symptomatic; ferritin with CBC)
- Coronary Artery Calcium age 45
- Dried urine testing for HPA, metabolomics
- Salivary cortisol for Cortisol Awakening Response, Diurnal pattern
- Optional // Use discretion
    - Genomics
    - Nutrition/micronutrients, gut function, heavy metals, other functional testing
    - Cognitive testing, sleep/mood
    - Biological age
    - Whole body imaging
    - Exercise performance (VO2 max, lactate threshold, grip strength, one-mile run, etc.)
    - Wearables: sleep, activity, HRV, daytime stress, resilience, continuous glucose monitoring
    - As needed: intestinal permeability, organic acids, DEXA, CIMT, bone turnover markers

Derby et al,Lipid Changes During the Menopause Transition in Relation to Age and Weight: The Study of Women's Health Across the Nation ,*American Journal of Epidemiology* 169, no. 11 (2009): 1352–61,. Nappi and Nappi, Menopause: A Cardiometabolic Transition, *The Lancet* Diabetes & Endocrinology Sep 2022 10(7)): 632–44

Benefits of Bioidentical Hormones

- Vasomotor symptoms
- Cardiovascular health/subclinical atherosclerosis
- Endothelial stabilization
- Bone density
- Genitourinary syndrome of menopause
- Brain health
- Sexual interest, desire, and function
- Decreased breast cancer and mortality
- Diabetes
- Skin

Levy B, Simon JA. A Contemporary View of Menopausal Hormone Therapy. Obstet Gynecol. 2024 Jul 1;144(1):12-23

Hormone Therapy and BC Risk

- Relationship between menopausal hormone therapy (HT) and breast cancer risk is complex created in part by the data as well as by confusion surrounding interpretation of the findings themselves. If you have breast cancer, hormone therapy could make it grow.
- Data aggregated from 2 trials: WHI (CEE, CEE + MPA). All other data are observational.
  - WHI showed in 2017 reanalysis that for a woman s/p hysterectomy, decreased breast cancer mortality for CEE (0.625mg) alone x 7.1 years with 18 yr follow up
  - When MPA added to the regimen, the decreased risk of CEE only was neutralized(1)
- Meta-analysis of 108,647 women followed prospectively, 5 years of HT starting at age 50 increases incident breast cancer by 1 in 50 users of estrogen plus daily progestin, 1 in 70 users of estrogen with cyclic progestin, and 1 in 200 users of estrogen-only therapy. 10 years of HT about double these rates.
- “The current state of science indicates that HT may or may not cause breast cancer but the totality of data neither establish nor refute this possibility. Further, any association that may exist between HT and breast cancer appears to be rare and no greater than other medications commonly used in clinical medicine.”
- Oral MP added to transdermal E2 is not associated with greater breast cancer risk even > 10 years

•1 Mikkola TS, et al. Menopause. 2016; 23(11): 1199-1203; 2 Hodis HN, et al. Climacteric. 2018; 21(6): 521-528. 3 Manson JE et al. JAMA. 2017;318(10):927-938;
•2 Collaborative Group on Hormonal Factors in Breast Cancer, The Lancet 2019 394(10204):1159-1168, 5 Stute P, et al. Climacteric. 2018 Apr;21(2):111-12

IV. Menopause: Intervention Blueprint

- **Circadian & sleep:** stabilize sleep/wake time; morning outdoor light(women need 30-60 min, men only 10-20); evening light minimization; last meal ≥3 h before bed(check cortisol and melatonin levels)
- **Exercise:** 2–3 days/w progressive resistance + 150–300 min/wk cardio + brief post-meal walks; aim to preserve muscle/mitochondria and improve insulin sensitivity (1)
- **Nutrition:**
  - Omega-3s, lycopene, polyphenols support mitochondrial structure & redox balance in menopausal women(2)
  - Protein distribution across meals; fiber and color first; alcohol guardrails(age 40n lose 5lbs muscle gain 5 lbs fat), so need to look at ideal body mass and amount of protein for you.
  - More benefits insulin sensitivity, adiposity reduction; upregulates mitochondrial-related SIRT1, IRS2 (3)

Hormone therapy: shared decision-making on bioidentical hormone therapy; anchor to CVD/breast cancer risk profiles while monitoring risk
Autonomic load: breath training; hot-flash-behavioral strategies; track dysregulation with measurement

1.Lundby C et al. (2017) *J Physiol* 595(24):6993–7011; Pileggi CA et al. (2022) *eBioMedicine* 83:104215.
2.Casas R et al. (2022) *Nutrients* 14(15):3112; D'Introno A et al. (2023) *Pathophysiology* 30(3):244–261; Rocha-Rodrigues S et al.
3.(2024) *AIMS Public Health* 11(1):110–12
4.Hofer, et al. *Cell Metabolism* 35, no. 7: 1091–1093; Purnomo, et al. 2025. *Nutrients* 17, no. 10: 1695; Rius-Bonet, et al. 2025. *Nutrition Reviews* 83, no. 2: e635–e648.

Reversing Biological Age: 8-Week Methylation Lifestyle Study in Women

- **Key Findings**
  - Lower biological age by 4.6 years (max 11 years)
  - Adherence 82 %, yet all but one showed measurable improvement
  - Improvements independent of disease status, effects on core aging mechanisms, not symptom relief
- **Lifestyle Framework**
  - Diet: Nutrient-dense, methylation-supportive: leafy greens, crucifers, beets, eggs, liver, turmeric, green tea
  - Exercise: ≥ 30 min/day × 5 days weekly @ 60-80 % intensity
  - Sleep: ≥ 7 hours nightly
  - Stress: Two × 10-min breathing sessions daily to elicit relaxation response
  - Supplements: polyphenol-rich greens powder + probiotics
- *Targeting DNA-methylation pathways through lifestyle change can reverse biological aging markers, offering a non-pharmacologic path to improved*

Summary:
Women 40+: Hormonal Support and Treatment


The Washington Post

Breaking News

Health Alert May 1, 11:13 a.m. EDT

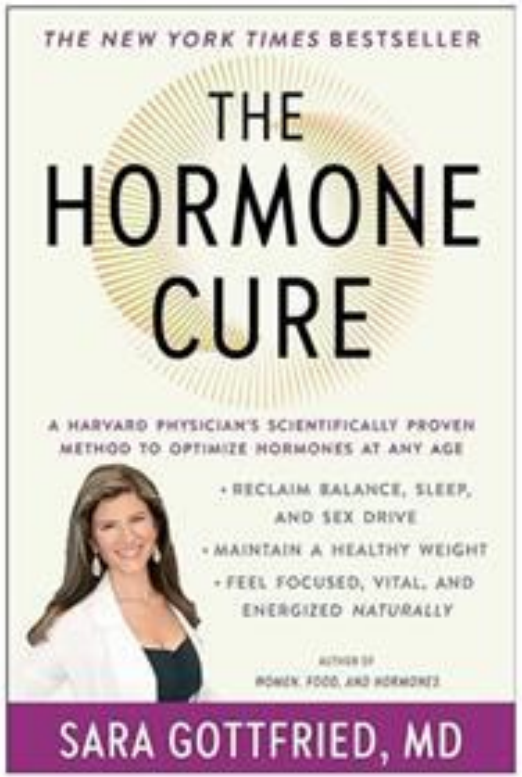
A landmark study scared women away from menopause hormone treatments. A 20-year follow-up has found fears were largely overblown.

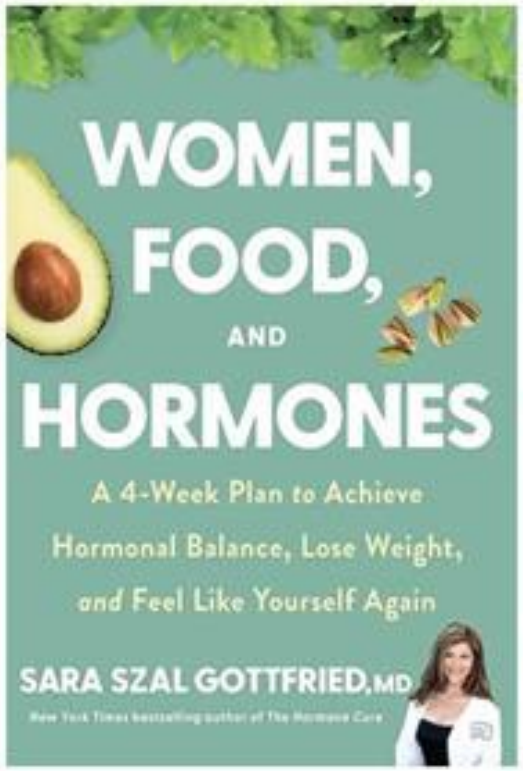
- Perimenopause is most volatile and symptomatic periods in female lifecycle, marked by **aging acceleration**
  - Even though physiology is universal ,individual experience is highly variable
  - Decreased cerebral metabolism as measured with PET modulated by mitochondria and estrogen
  - Massive knowledge, treatment and gender gap amplifies the dysregulation of perimenopause and menopause
  - Address with early testing. Lifestyle medicine (lifestyle levers, supplementation and bioidentical hormone therapy)
- We need **Menopause 3.0**
  - Every woman deserves consideration, counseling ,and treatment
  - Opportunity to re-imagine, re-shape, and re-vision our second half of life in a state of self-regulation and co-regulation

Manson JE, et al. *JAMA*. 2024;331(20):1748–1760.

Islam, R.M. 2025. *The Lancet Diabetes & Endocrinology*

Books to Read





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