Myths and Mysteries of Menopause



The Economist Dec 14 2019

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Disclosures: Sarah L Berga MD
April 2026

CONSULTING:

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American Journal of Obstetrics and Gynecology, Advisory Board: 2003-2025

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Mayo Clinic Proceedings, *Editorial Board*: *2019-present*

Menopause, *Editorial Board*: 1999-present

Sumitomo Pharma, Consultant: Sept 14, 2026

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Amazing advances in knowledge and applications over the last 70 years

Over the last 70 years, we have seen a scientific explosion in our understanding of reproductive endocrinology and hormone action that continues to be translated into a vast array of diagnostics and treatments

- **Hormonal contraception**
- **Medication abortion**
- **Ever safer hormonal preparations for treating menopausal syndrome**
- **Increasing array of hormonal preparations for infertility, preterm labor, and neurotrauma**
- **In-vitro fertilization and other high tech infertility interventions**
- **Gender-affirming hormone therapies (GAHT)**
- **Genetic analysis for carrier screening, noninvasive prenatal screening (NIPS), fetal diagnostics**
- **Increased availability and better practices for oncofertility**
- **Hormonal treatments for postpartum depression and other hormone-related mood disorders**
- **Increasing array of formulations for endocrine-responsive conditions including endometriosis, breast cancer, and prostate cancer**
- **Treatments for stress-related conditions, including infertility and preterm labor**

3 Myths

- **All estrogens are the same, one dose for all**
  - Estrogen is a class of hormones and there are as many as 300 types
- **All progestins are the same, dose unimportant**
  - Progestin is a term for a class of hormones with similar cellular actions
  - There are many subclasses within the class and many types
- **Estrogens cause breast cancer**
  - Not all estrogens are the same
  - Not all breast cancers are the same
  - WHI found that use of conjugated equine estrogen (CEE) alone significantly reduced breast cancer incidence ($P = 0.005$)

3 Mysteries

- **Timing of initiation?**
- **Timing of discontinuation?**
- **Whether and how to individualize HRT?**

Myth Busters and Menopause Detectives



ON THE COVER

Women make up about half the population, but most of what we know about women's biology comes from extrapolation of studies in men. This has been changing in recent years, and this special issue highlights some of the progress in understanding the biological basis of sex differences in health and disease and medical issues relevant to women's health across different stages of life. See the section beginning on page 42. Illustration: Chiara Vercesi

SPECIAL ISSUE

Women's Health

INTRODUCTION

42 A lifelong focus on women's health
—Y. Nusinovich *et al.*

PERSPECTIVES

44 Does the postmenopausal ovary still matter?
Ovaries may influence health long after their reproductive function ends —M. B. Stout and F. E. Duncan

REVIEWS

46 Shaping maternal physiology: Immune control of reproductive adaptation
—D. Corral and Y. Belkaid

53 X and Y chromosomes as determinants of aging and disease
—D. B. Dubal *et al.*

60 Reframing menopause and menopause hormone therapy as opportunities for healthy aging
—L. L. Gravelsins *et al.*
PODCAST

69 Sex-specific mechanisms of chronic pain
—A. Venkataraman *et al.*

ACOG
American College of Obstetricians & Gynecologists

ACOG CLINICAL PRACTICE GUIDELINE

NUMBER 13

NOVEMBER 2026

(REPLACES PRACTICE BULLETIN NUMBER 141, JANUARY 2014).

Management of Menopause-Related Vasomotor, Sleep, and Mood Symptoms

Committee on Clinical Practice Guidelines–Gynecology. This Clinical Practice Guideline was developed by the American College of Obstetricians & Gynecologists' Committee on Clinical Practice Guidelines–Gynecology in collaboration with Bruce Pier, MD, Robert Kauffman, MD, MSCP, and Catherine Cansino, MD, MPH.

Clinical Perspective

Hormonal Options for Perimenopause

A Clinician Toolkit

Jaclyn Piasta, DNP, WHNPBC, and Amani Zewail, MD

Obstetrics and Gynecology (Green Journal)
November 2026

Myth Busters and Menopause Detectives

ACP puts hormone therapy first for menopause symptoms

Estrogen-based therapy is now recommended first for vasomotor symptoms, with SNRIs, SSRIs, gabapentin, and neurokinin receptor antagonists reserved for later lines.

Pharmacologic Treatments for Females with menopausal Vasomotor Symptoms: A Clinical Guideline from ACP
Annals of Internal Medicine https://doi.org/10.7326/ANNALS-26-01205



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Science 1 OCTOBER 2026 3

Hormonal Options for Perimenopause

A Clinician Toolkit

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Barriers to applications and implementation

Implementation and access constrained by:

- **Attitudes**
- **Cost**
- **Workforce**
- **Complexity**
- **Health literacy**

Myth Busters and Menopause Detectives

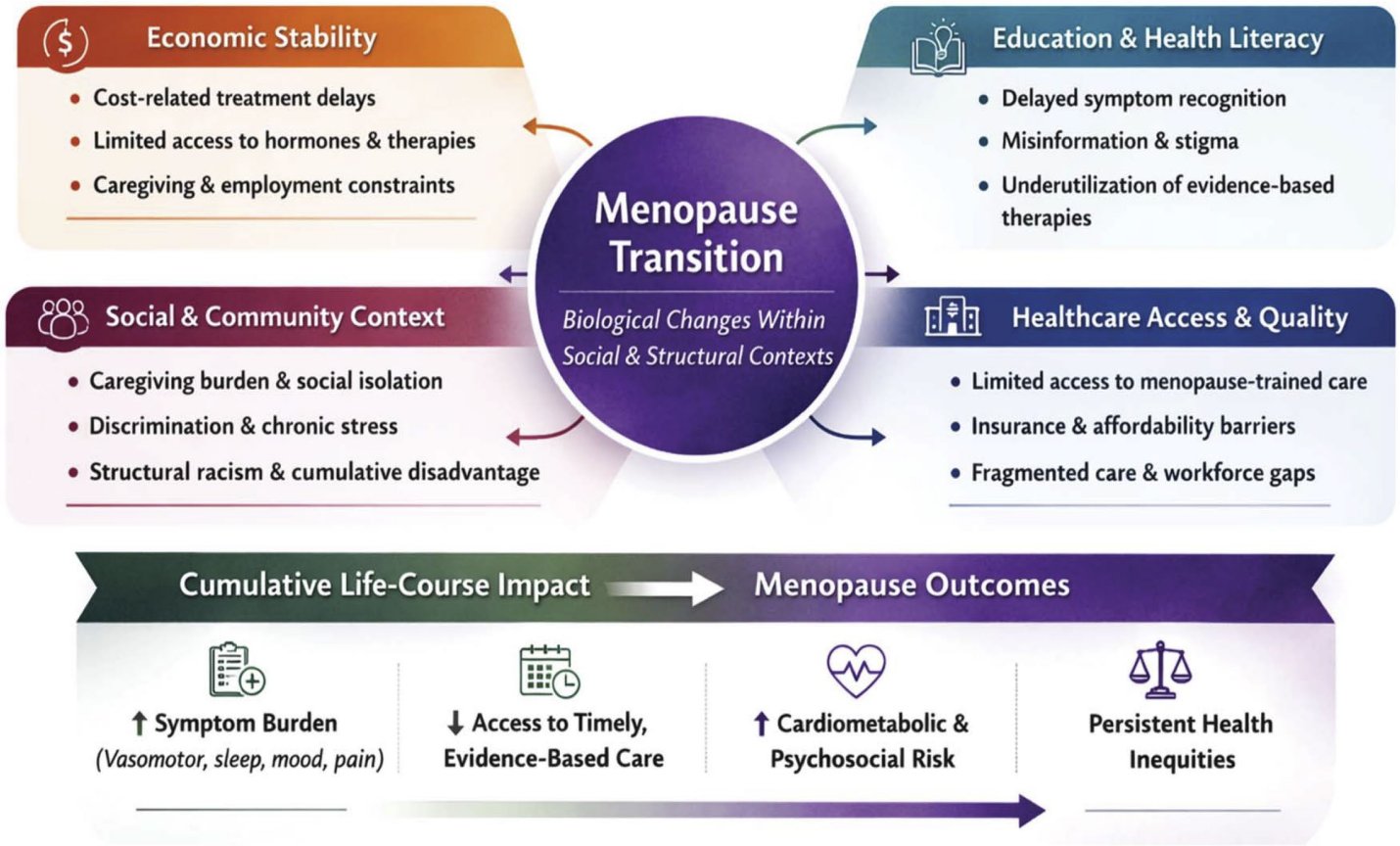


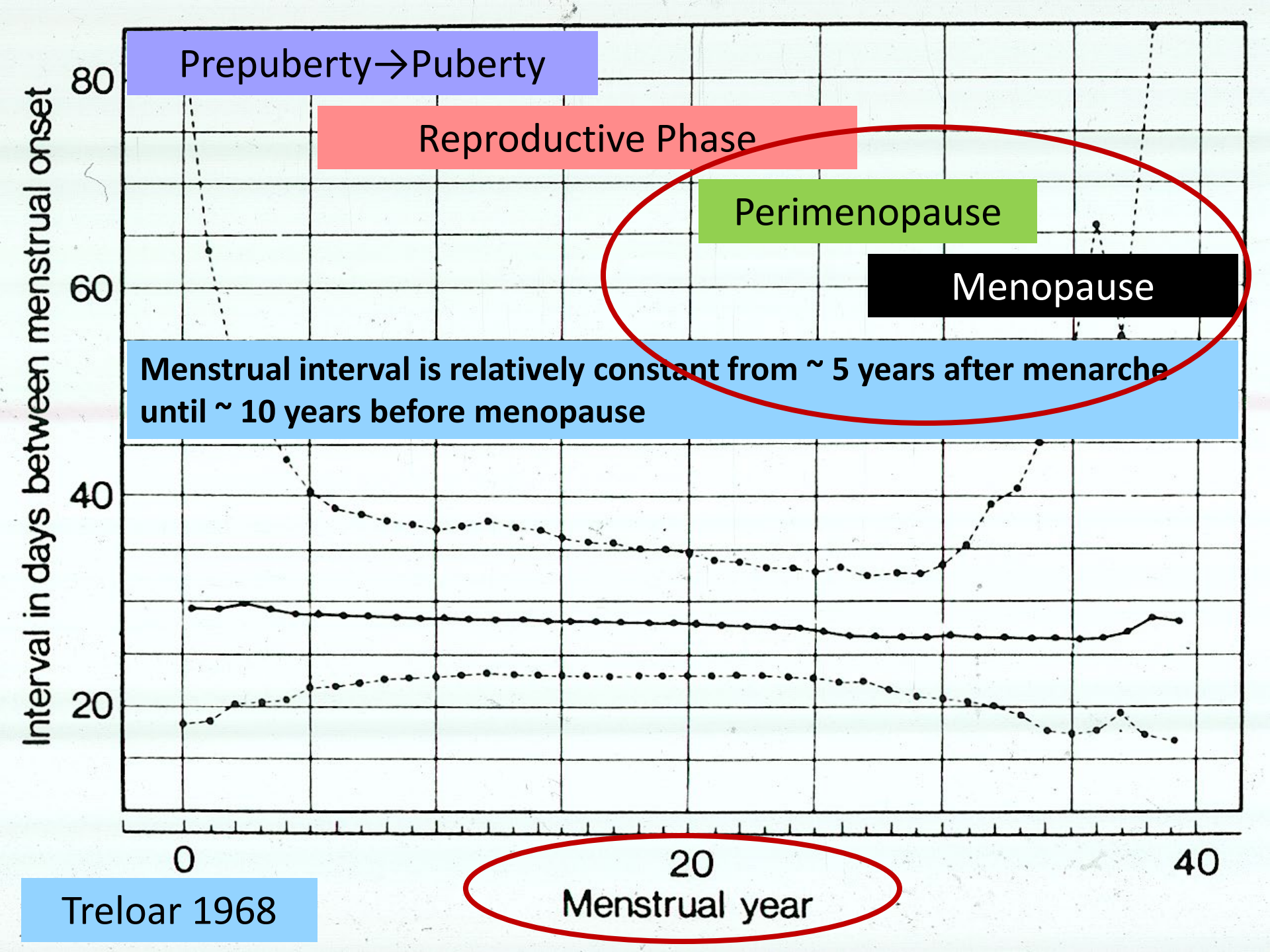
Fig. 1. Social determinants of health (SDoH) and the effect on midlife women. This conceptual framework illustrates how four key domains of SDoH converge on the menopause transition, depicted as a biological process occurring within, and inseparable from, social and structural contexts.

Quaile. Menopause and Social Determinants. Obstet Gynecol 2026.

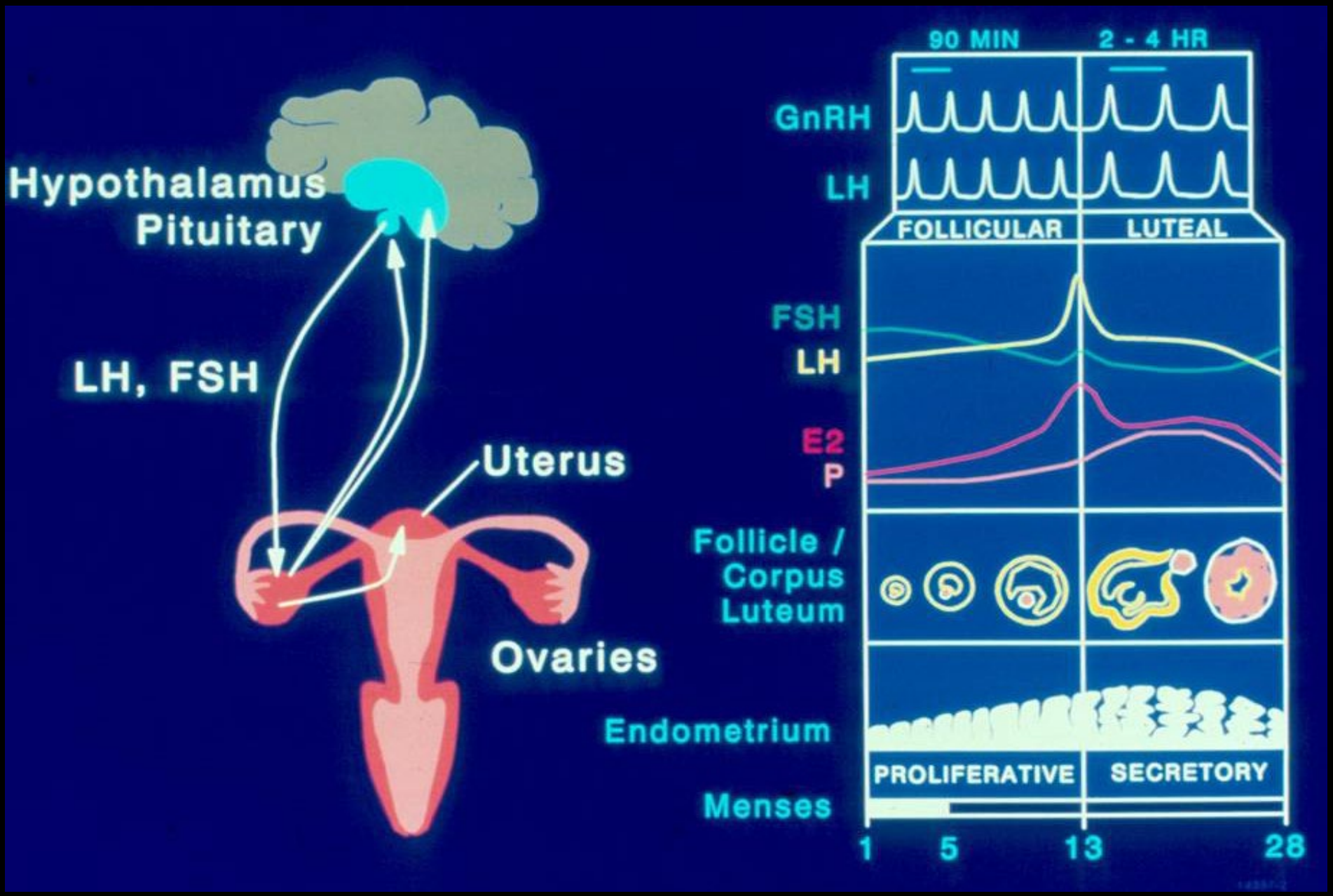
Lexicon

- **Perimenopause**: stage(s) of reproductive life cycle during which ovarian secretion of hormones changes because of a decline in oocyte (egg) quantity and quality
  - Generally occurs between ages 40-55 y
  - Commonly termed **climacteric** or **perimenopause** but increasingly termed **menopausal transition**
  - **Diminished ovarian reserve = perimenopause**

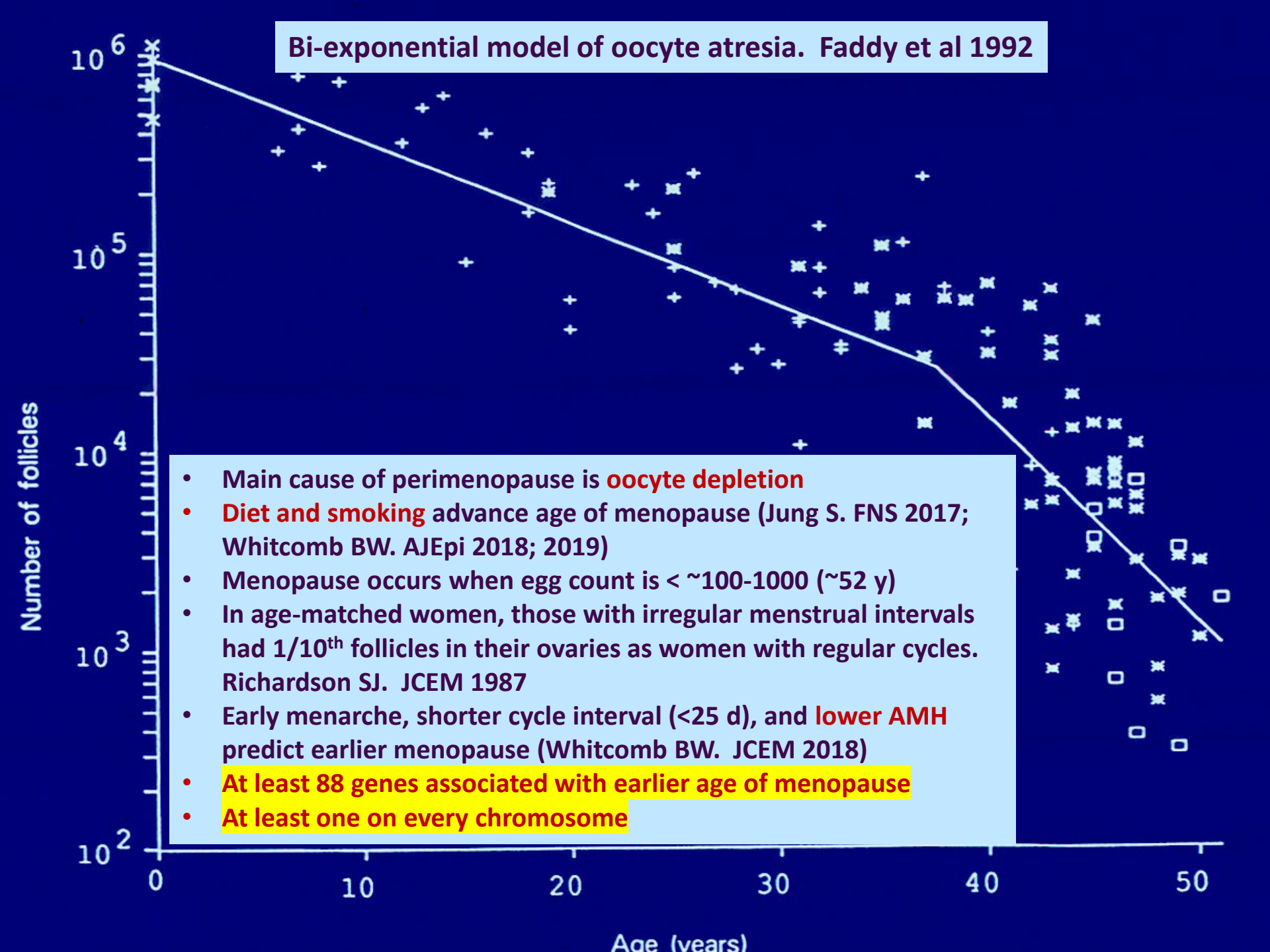
- **Menopause**: cessation of ovulatory ovarian function
  - Mean age around 51-52 years
  - No change in ovarian androgen secretion


Prepuberty→Puberty
Reproductive Phase
Perimenopause
Menopause
Menstrual interval is relatively constant from ~ 5 years after menarche until ~ 10 years before menopause
Interval in days between menstrual onset
80
60
40
20
0
20
40
Menstrual year
Treloar 1968

Idealized Menstrual Cycle



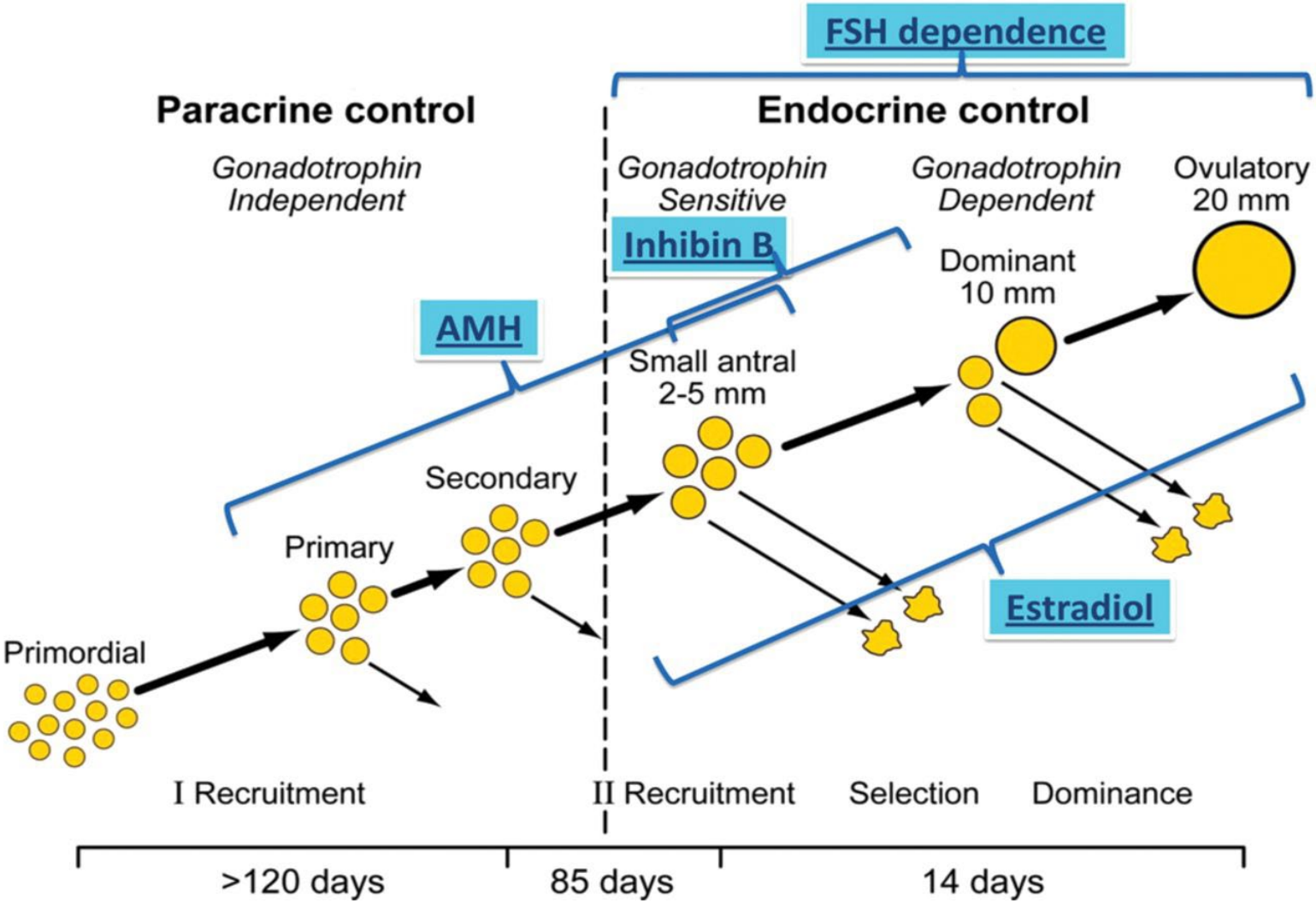
Bi-exponential model of oocyte atresia. Faddy et al 1992



- Main cause of perimenopause is **oocyte depletion**
- **Diet and smoking** advance age of menopause (Jung S. FNS 2017; Whitcomb BW. AJEpi 2018; 2019)
- Menopause occurs when egg count is < ~100-1000 (~52 y)
- In age-matched women, those with irregular menstrual intervals had 1/10th follicles in their ovaries as women with regular cycles. Richardson SJ. JCEM 1987
- Early menarche, shorter cycle interval (<25 d), and **lower AMH** predict earlier menopause (Whitcomb BW. JCEM 2018)
- **At least 88 genes associated with earlier age of menopause**
- **At least one on every chromosome**

AMH is produced in early stages of follicle development (characterized by gonadotrophin-independent growth)

Inhibin B and estradiol (E2) produced by follicles at later stages of development when growth is FSH-dependent

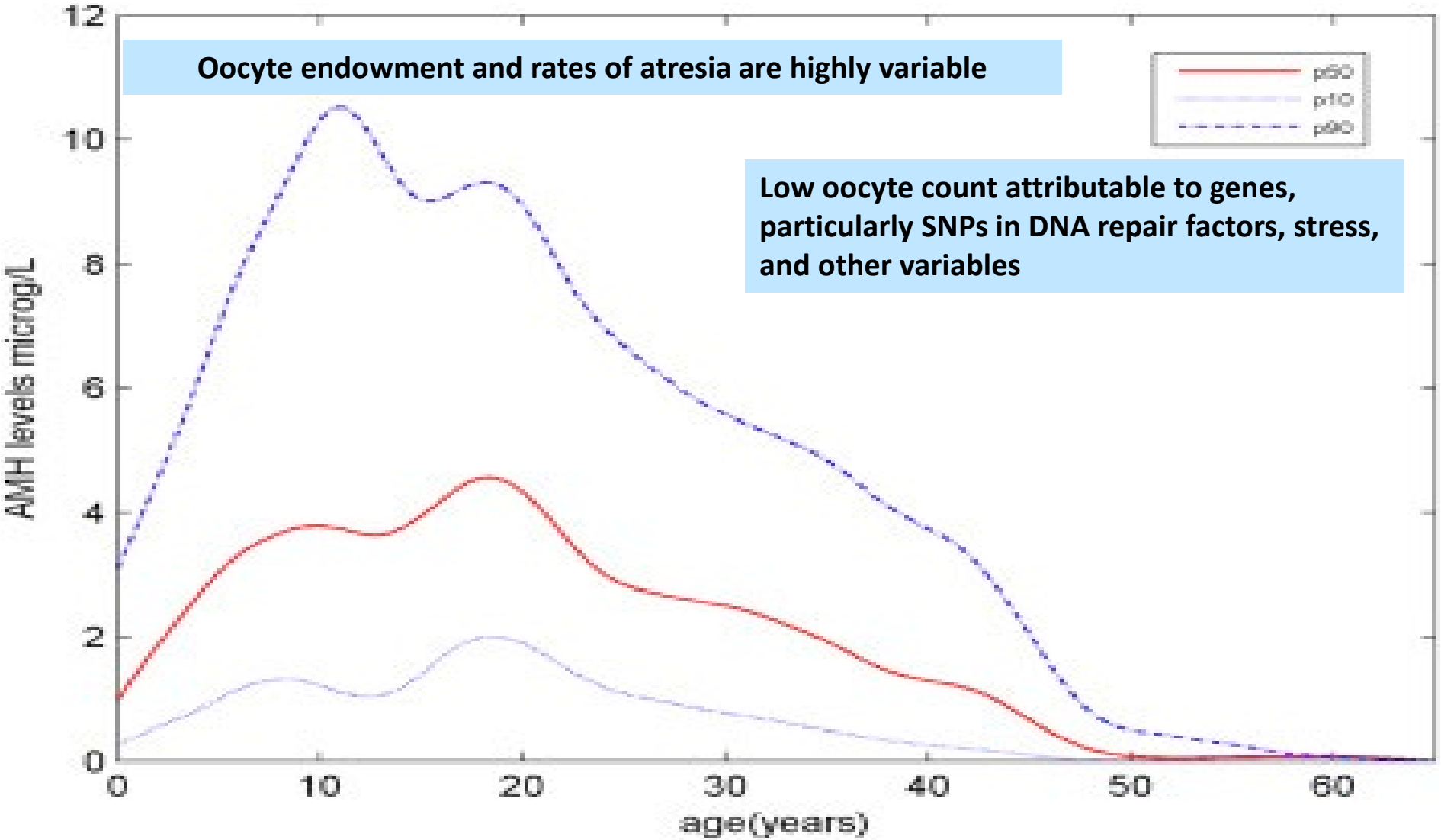


Simone L. Broer et al. Hum. Reprod. Update 2014;20:688-701

human reproduction update

Antimüllerian hormone (AMH) from neonatal to postmenopause

(10th, 50th, and 90th percentiles of serum AMH value)

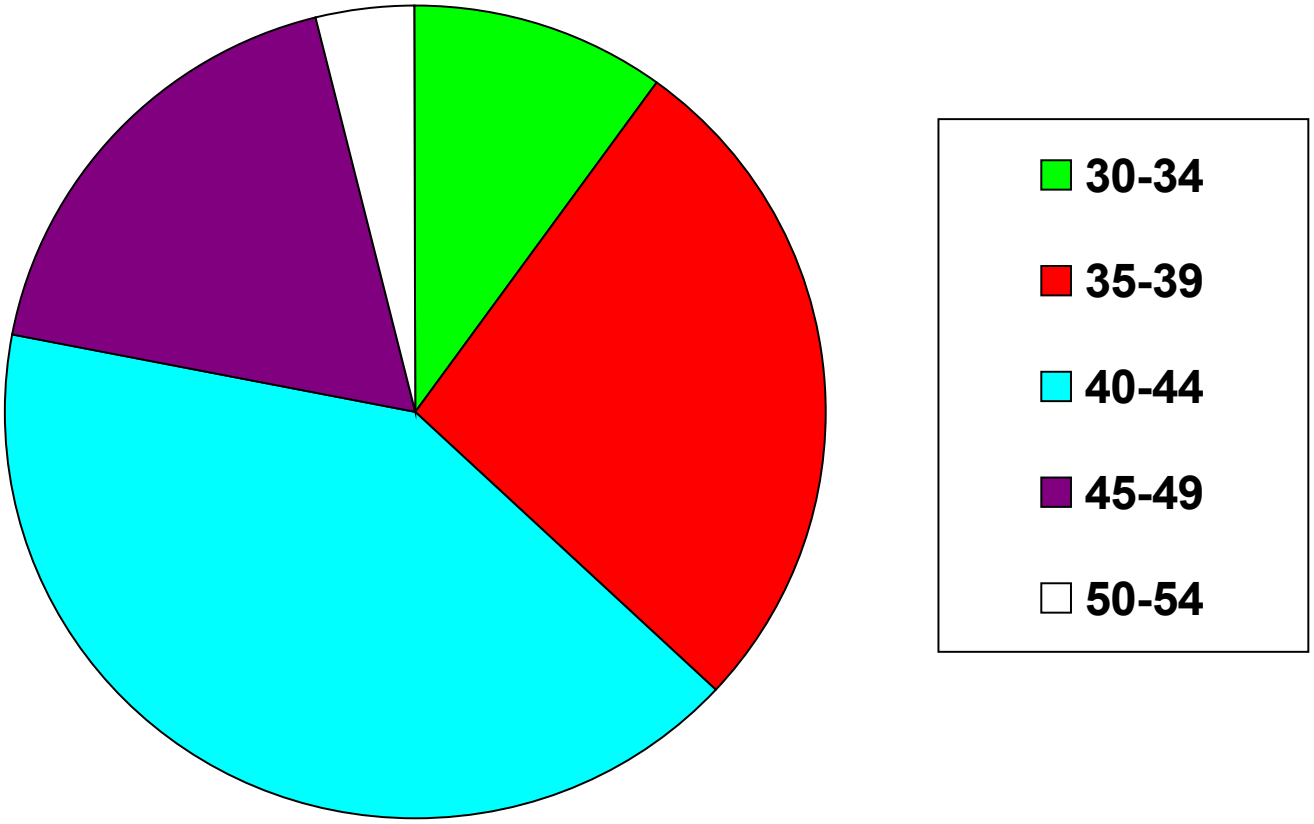


Fertil Steril 2016;105:481–485

Understanding the Perimenopause

When cycles become irregular, hormonal profiles are not predictable

Age at initial menstrual cycle change



Seattle Midlife Women's Health Study. Mitchell et al. Menopause 2000;7:334

You may want to know…..

- **What are the benefits and risks of hormone use at midlife and beyond for overall health?**
- **Does hormone use foster better brain health as women age?**
- **Do the options for hormone therapy during perimenopause and menopause differ?**
- **What are the pros and cons of different formulations, doses, routes of administration?**

Important Longitudinal Observational Studies

- **Tremin** – Treloar 1967
- **Melbourne** Women's Midlife Health Project
  - 2201 women, one site (Guthrie et al 2004)
- **Seattle** Midlife Women's Health Study
  - (Mitchell et al 2000)
- **SWAN** – Study of Women's Health Across the Nation
  - US, multiple sites, multiethnic, 3302 women
- **FREEDOM**
  - UK, one site, 112 women (Miro et al 2004)

Climacteric symptoms in a Swedish population

5990 women 46-62 y

- **depression/irritability 57%**
- **muscle/joint pain 57%**
- **hot flashes 53%**
- **sleep disturbance 52%**
- loss of libido 37%
- vaginal dryness 21%

nonHRT use 45%; effectiveness 31-63%

HRT use 21%; effectiveness 70-90%

Stadberg. Acta Ob Gyn Scand 1997;76:442

Cognitive impairment at midlife
Saving grandmother's brain

- **Several studies have identified an association between perimenopause and increased rates of depression, stress, and cognitive "fog"**

- **SWAN 4x increase in major depressive episodes**
  (Bromberger JT et al 2011)

Will hormone use at midlife and beyond foster better health?

- **During perimenopause and early menopause, women report reduced quality of life due to hot flashes, joint pain, insomnia, mental "fog", trouble concentrating, difficulty with word finding, irritability, and reduced libido**

- **Women are at increased risk for some neurodegenerative disorders, including dementia, as compared to men**

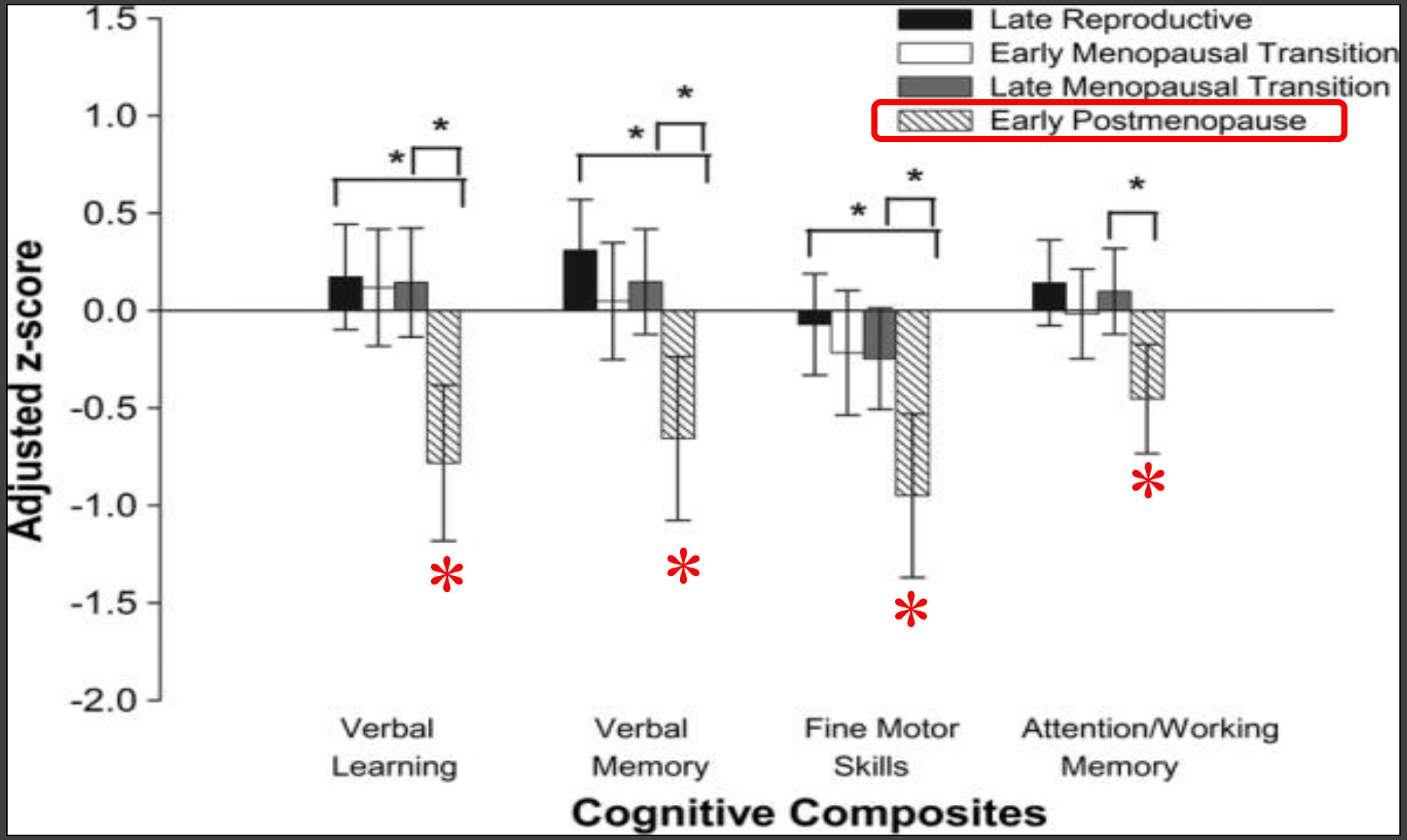
- **Early loss of ovarian function, including surgical menopause prior to the expected time of natural menopause, increases the risk of neurodegenerative disorders, and reduces QOL**

Saving grandmother's brain

- **The brain is a target tissue of sex hormones such as estradiol, progesterone, and androgens including testosterone**

- **Hypothesis: Hormonal management will slow - but will not fully prevent - brain and overall aging**
  - **Estrogens maintain brain metabolism, synapses, mood, and cognition**
  - **Progestins increase irritability and slow metabolism**
  - **Most androgens are aromatized to estrogens**

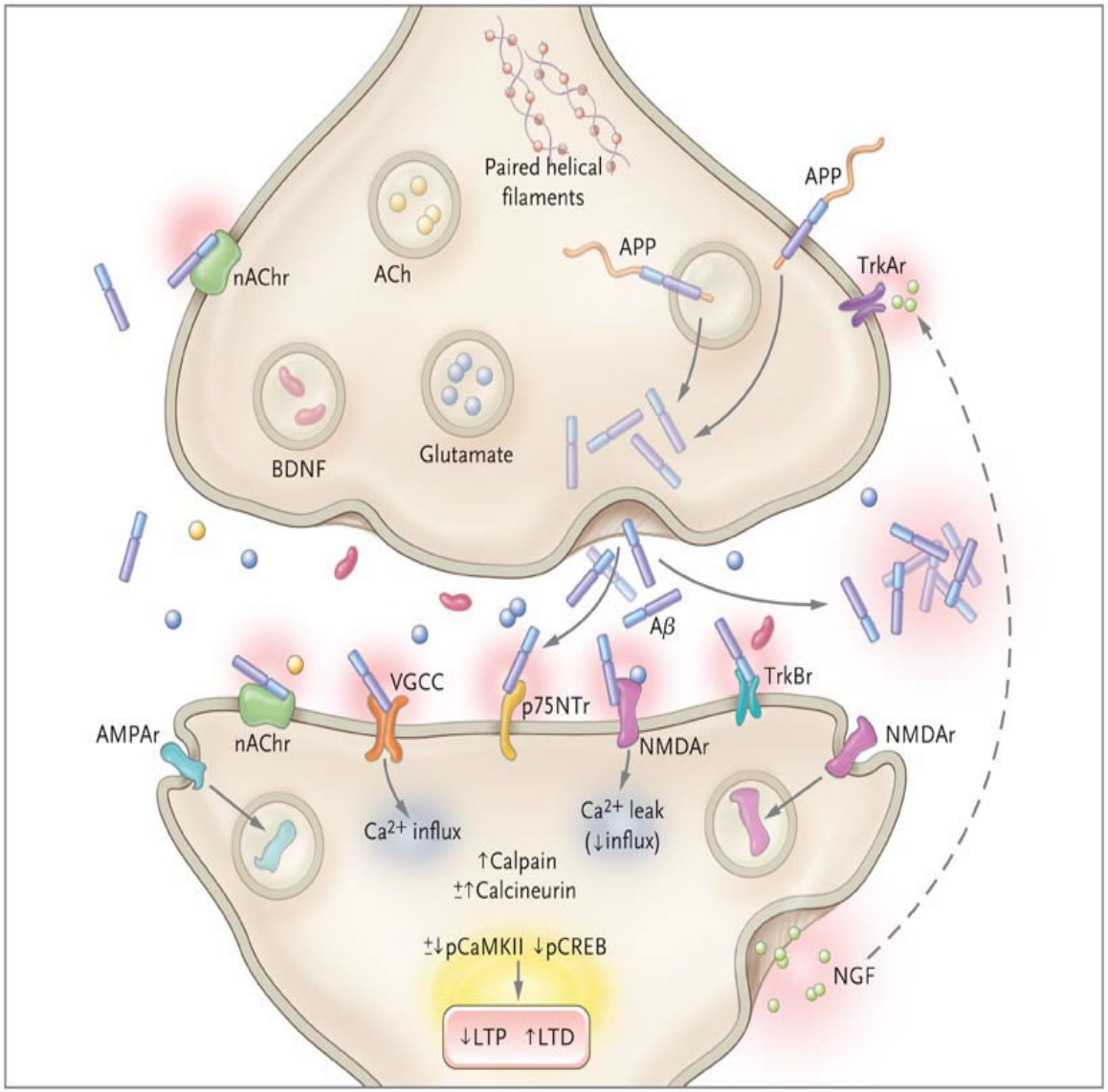
Cognition in perimenopause: the effect of transition stage



Adjusted z-scores and standard errors as a function of the menopausal transition stage for verbal learning, verbal memory, fine motor skills, and attention/working memory cognitive composites.

Weber M, Rubin L, Maki P. Menopause. 20(5):511-517, 2013. DOI: 10.1097/gme.0b013e31827655e5

Synaptic Dysfunction in Alzheimer's Disease



AD primarily a disorder of synaptic failure / loss.

Synaptic loss correlates best with cognitive decline in AD.

Hippocampal synapses begin to decline in patients who develop mild cognitive impairment (MCI).

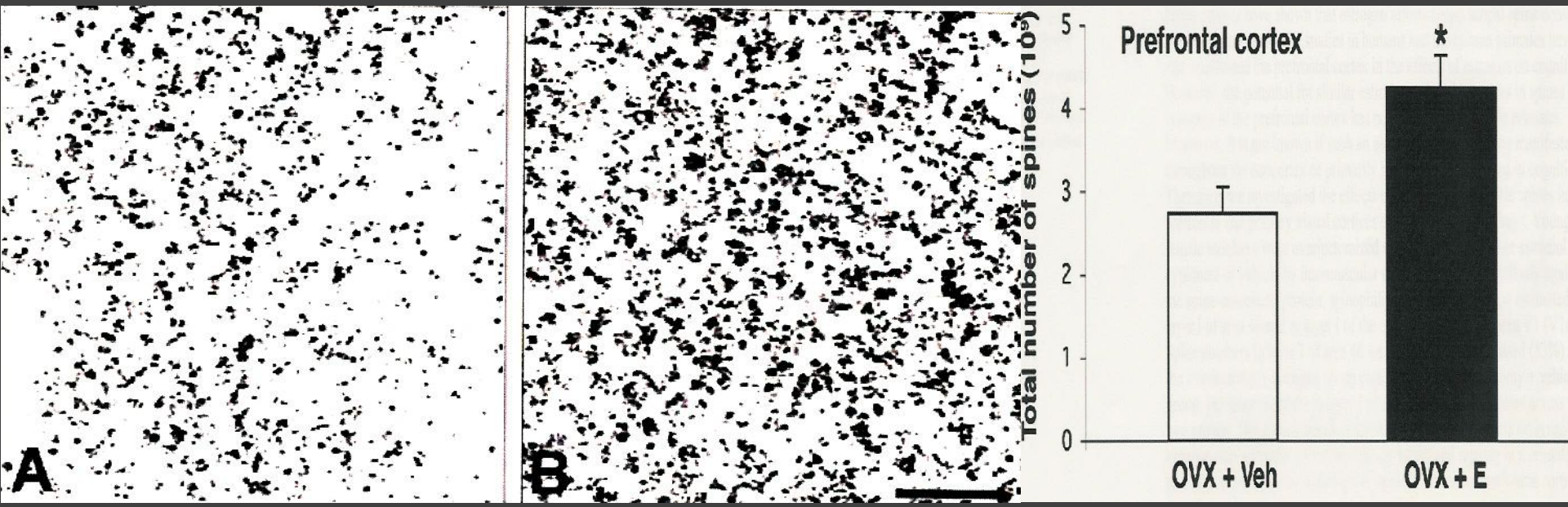
Aging itself causes synaptic loss, particularly in dentate gyrus of hippocampus.

In mild AD, about 25% are lost.

Querfurth H, LaFerla F. N Engl J Med 2010;362:329-344

The NEW ENGLAND JOURNAL of MEDICINE

E2 increases spine density in rhesus prefrontal cortex

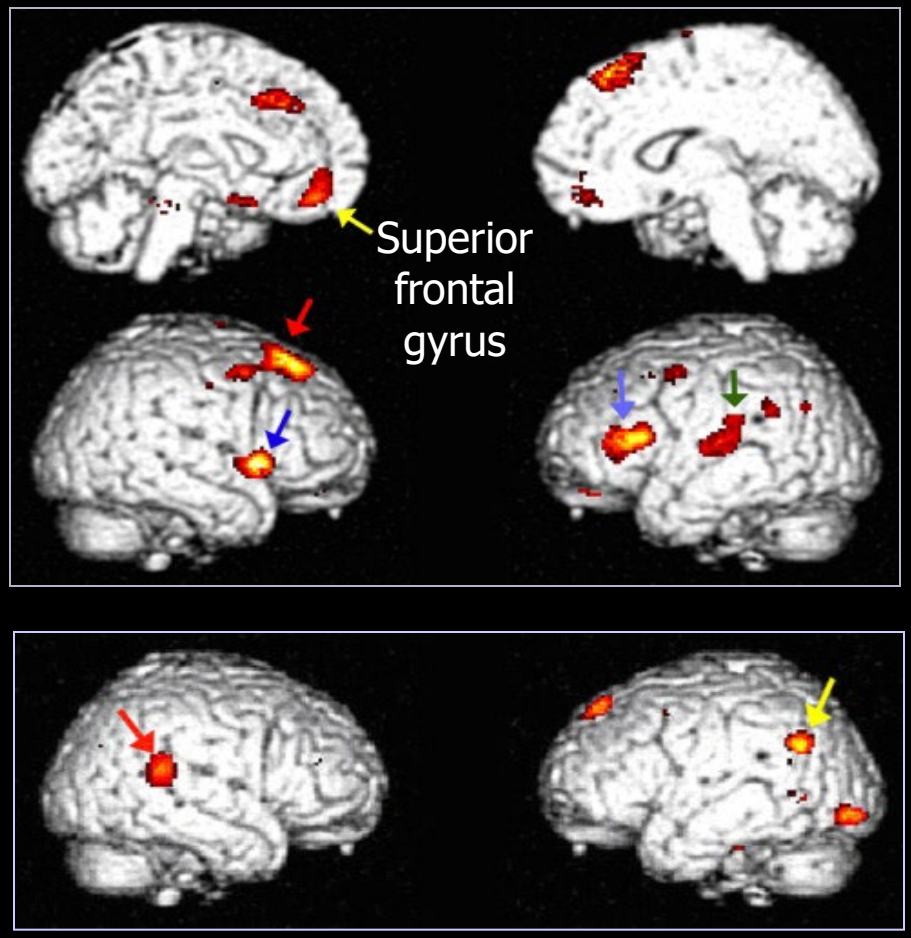


- There are more cells in the mammalian brain than stars in the Milky Way
- In the cortex, each neuron forms as many as 10,000 synapses with target cells

Tang et al. Cereb Cortex 2004; 14: 215

Brain metabolism and HT

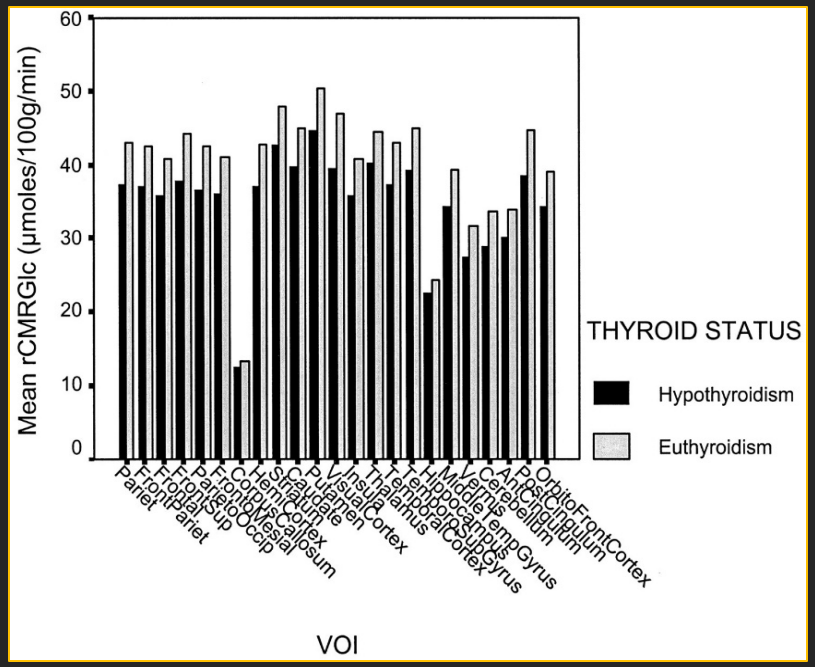
- PMW (mean age 58) at risk for AD taking HT for >1 y (mean 10 y) underwent **2 FDG-PET scans** at 1-y (#53) and 2-y (#45) intervals to evaluate brain metabolism
- **Half randomized to continue & half to stop HT**
- 18 PMW - 0.625 mg CEE (9 + progestin)
- 36 PMW - 0.1 mg E2 (24 + progestin)
- All Provera exc 2 Prometrium (1/grp)
- **HT users showed relative preservation of frontal and parietal cortical metabolism**
- Unopposed E2 users showed better metabolism in precuneus/posterior cingulate cortical (PCC), the area wh undergoes most significant decline in earliest stages of AD
- **E2 users 3SD better in verbal performance than CEE users**
- **E+P had lower metabolism than E alone**



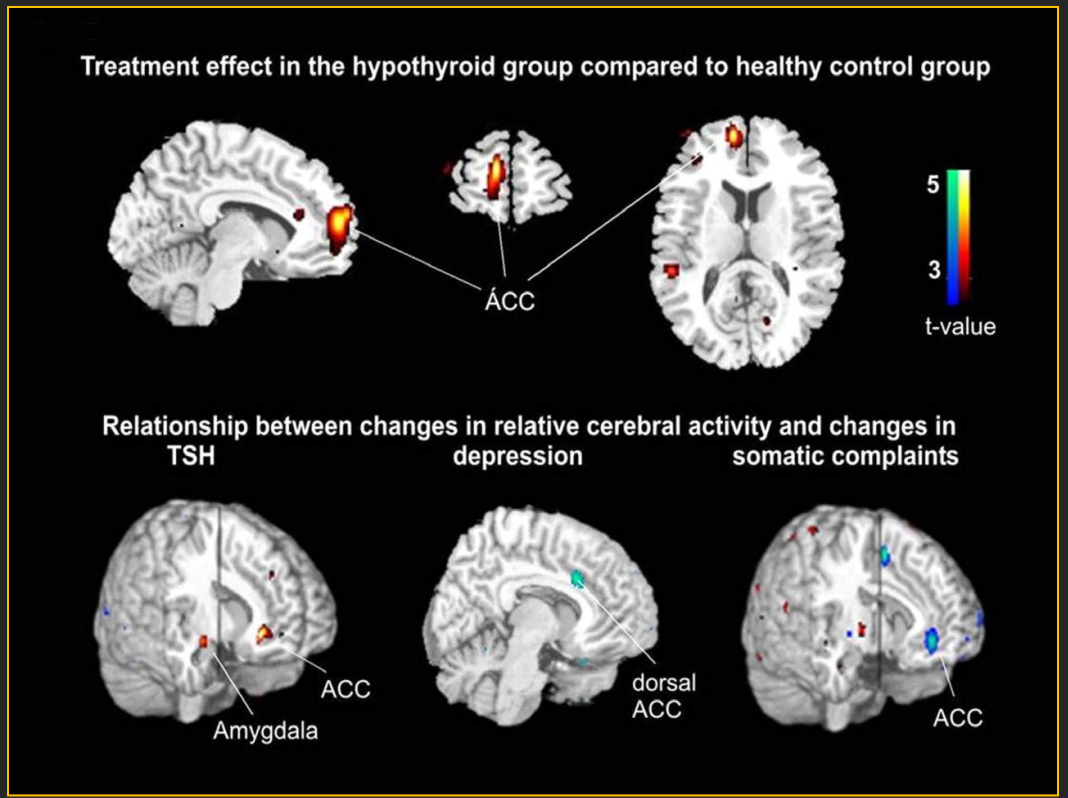
Areas of greater metabolism in E2 vs CEE users.
Yellow - Wernicke's area.
Red - superior temporal gyrus.

Silverman DHS. Psychoneuroendocrinol 2010
Rasgon NL. PLOS ONE 2014 Vol 9, e89095

Thyroid and brain: an analogy?



Decreased CBF (↓23%) and brain metabolism (↓12%) by PET with 15-O2 and F-2-deoxyglucose after total thyroidectomy before T4. Pts were depressed, anxious, and psychomotor slow when hypothyroid. Constant EL. JCEM 2001

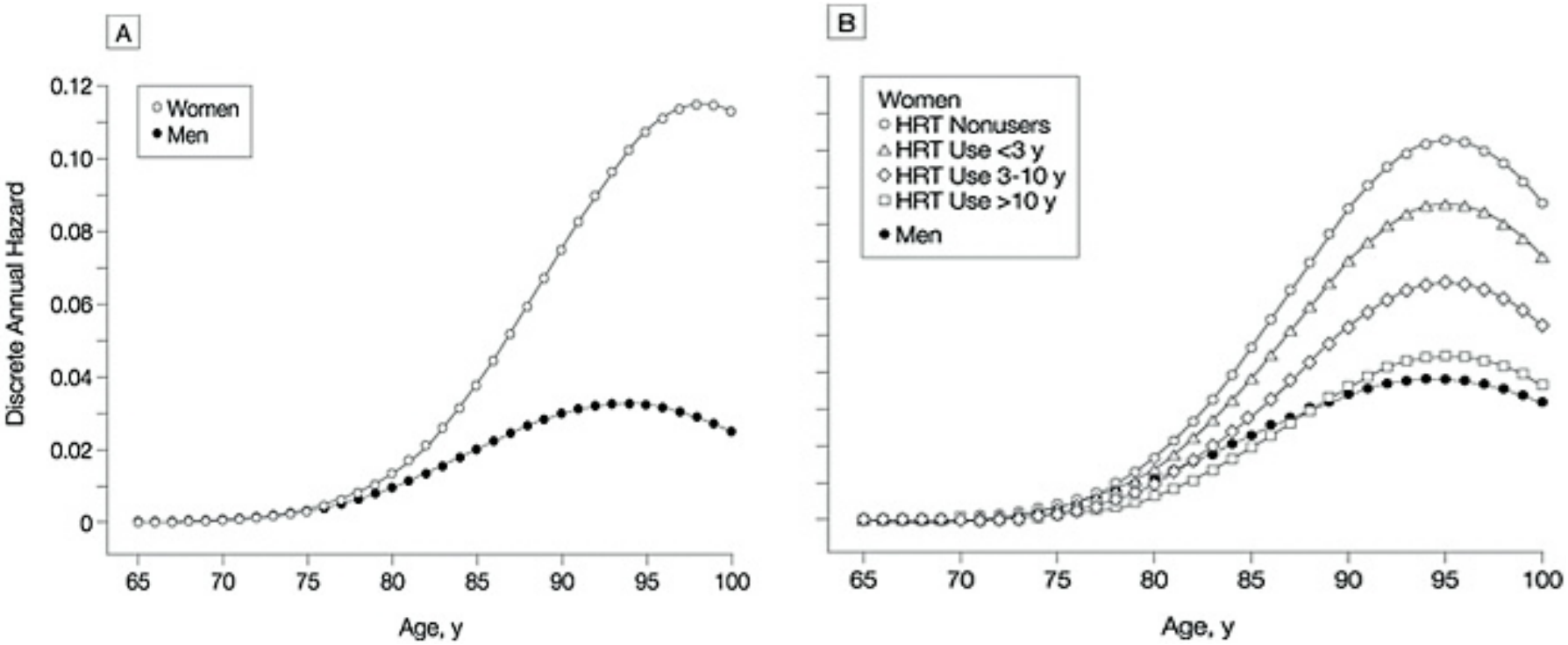


Brain glucose metabolism B/A T4 replacement. Reduction of behavioral complaints during thyroid HT assoc with restoration of metabolic activity. Bauer M et al. JCEM 2009

SEX DIFFERENCES IN ALL-CAUSE DEMENTIA:

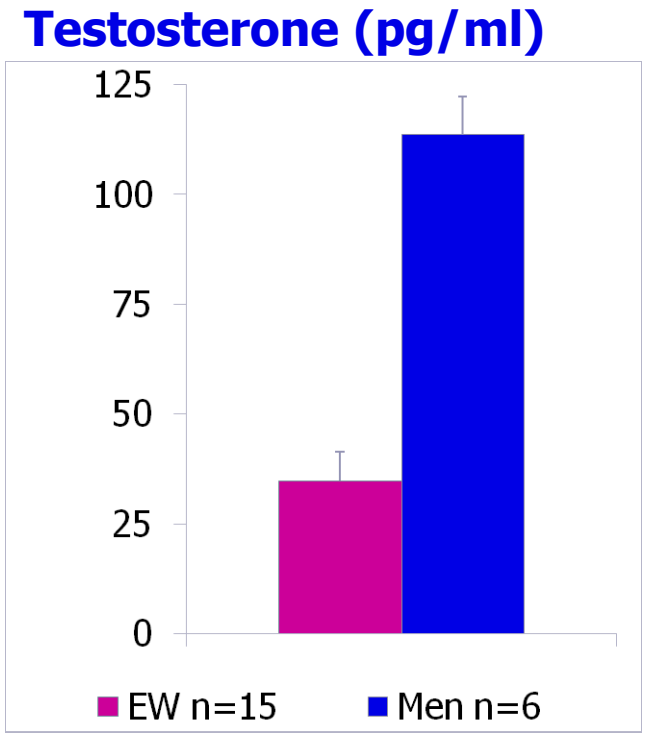
Cache county prospective observational cohort

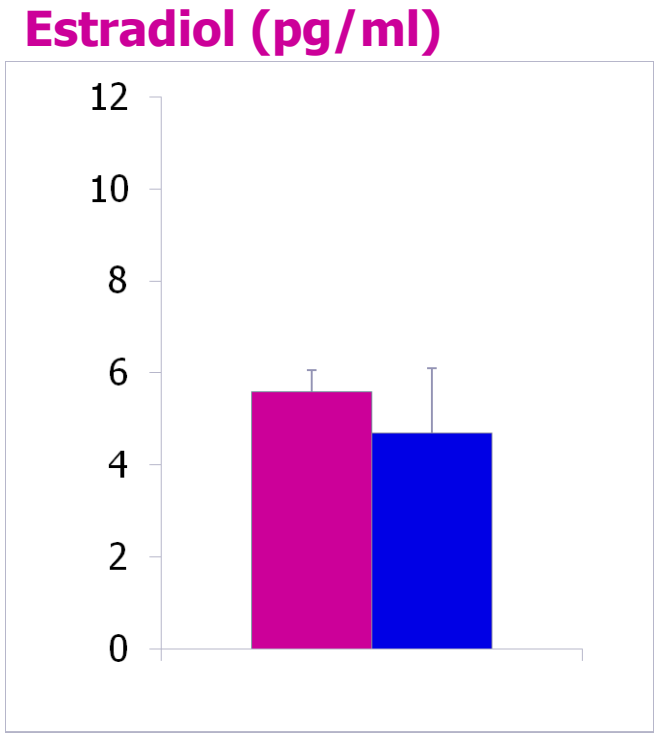
Dementia higher in women than men and at least partly hormonally mediated



Zandi PP et al. JAMA 2002;288:2123

CSF levels of testosterone and estradiol in women and men





Timing of hormone exposure matters–Olmsted County MN

Prophylactic oophorectomy before age 45 y

- **Death** **HR 1.67 (1.16-2.40)**
- **Depression** **HR 1.54 (1.04-2.26)**
- **Parkinson** **HR 1.68 (1.06-2.67)**
- **Dementia/CI** **HR 1.46 (1.13-1.90)**

Rocca WA et al. Neurology 2007; Lancet Oncology 2006; Menopause 2008

Estradiol (E2) use reduced death from both vascular dementia and AD

- 489,105 Finnish women using systemic HT from 1994-2009
- 581 died of vascular dementia
  - E2 oral and transdermal
  - P mostly norethindrone or MPA
  - Risk ↓↓ ~38% by E2 or E2-P use
- 1057 died of Alzheimer dementia
  - Risk ↓ ~15% after 5 years of use
  - Risk reduction similar regardless of age at initiation (<60 vs ≥ 60 years)

Mikkola TS et al. JCEM 2017;102:870-877

Association between ERT use and AD

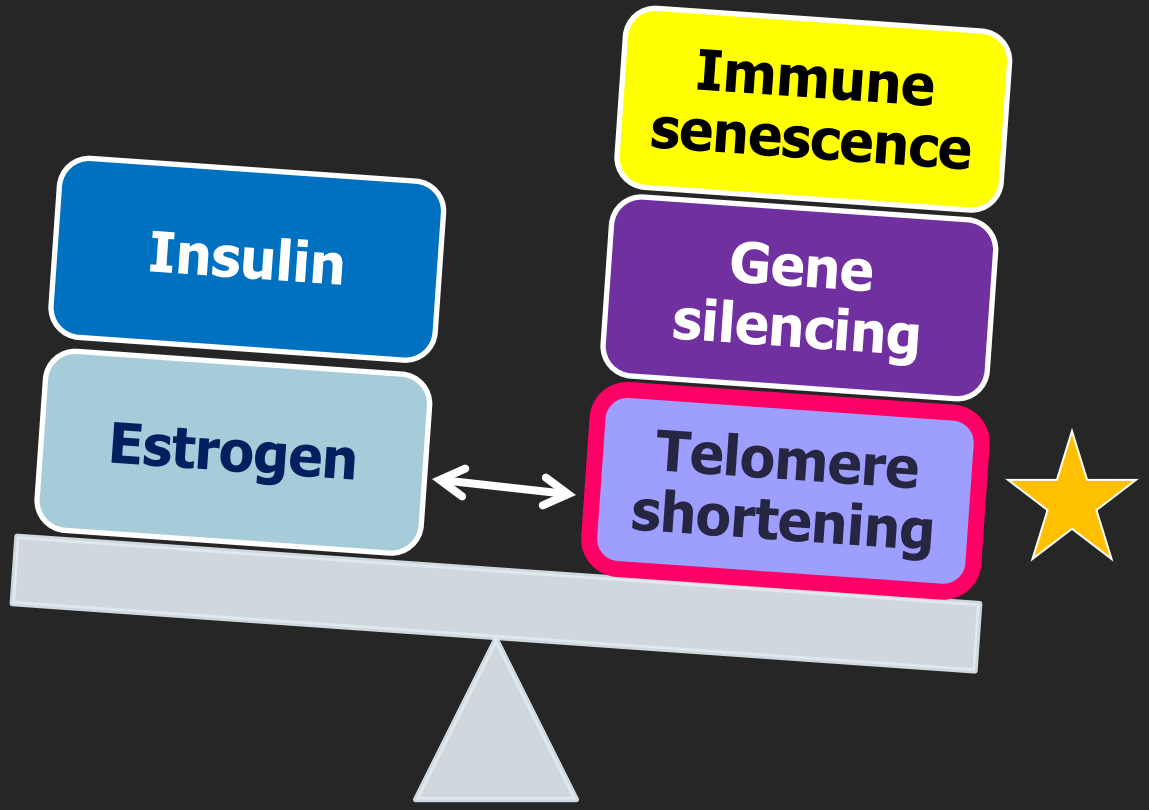
- **Cohort study of estrogen only users and dementia outcomes in women in 2 independent large-scale data sets – National AD Coordinating Center (NACC) and AD Neuroimaging Initiative (ADNI)**
- **NACC - 258 ERT users and 2701 nonusers**
- **ADNI - 110 ERT users and 1948 nonusers**

- **OR of AD path on autopsy in ERT users = 0.65 (0.48-0.88), p=0.005**
- **OR of clinical AD autopsy in ERT users = 0.61 (0.55-0.67), p<0.0001**
- **OR of memory symptoms/functional decline in ERT users = 0.67 (0.61-0.72), p<0.0001**
- **ERT assoc with decreased serum and CSF amyloid levels**

Bruno et al Neurology 2026;107:e218413

Growth, mitosis, cellular repair, & **oncogenesis**

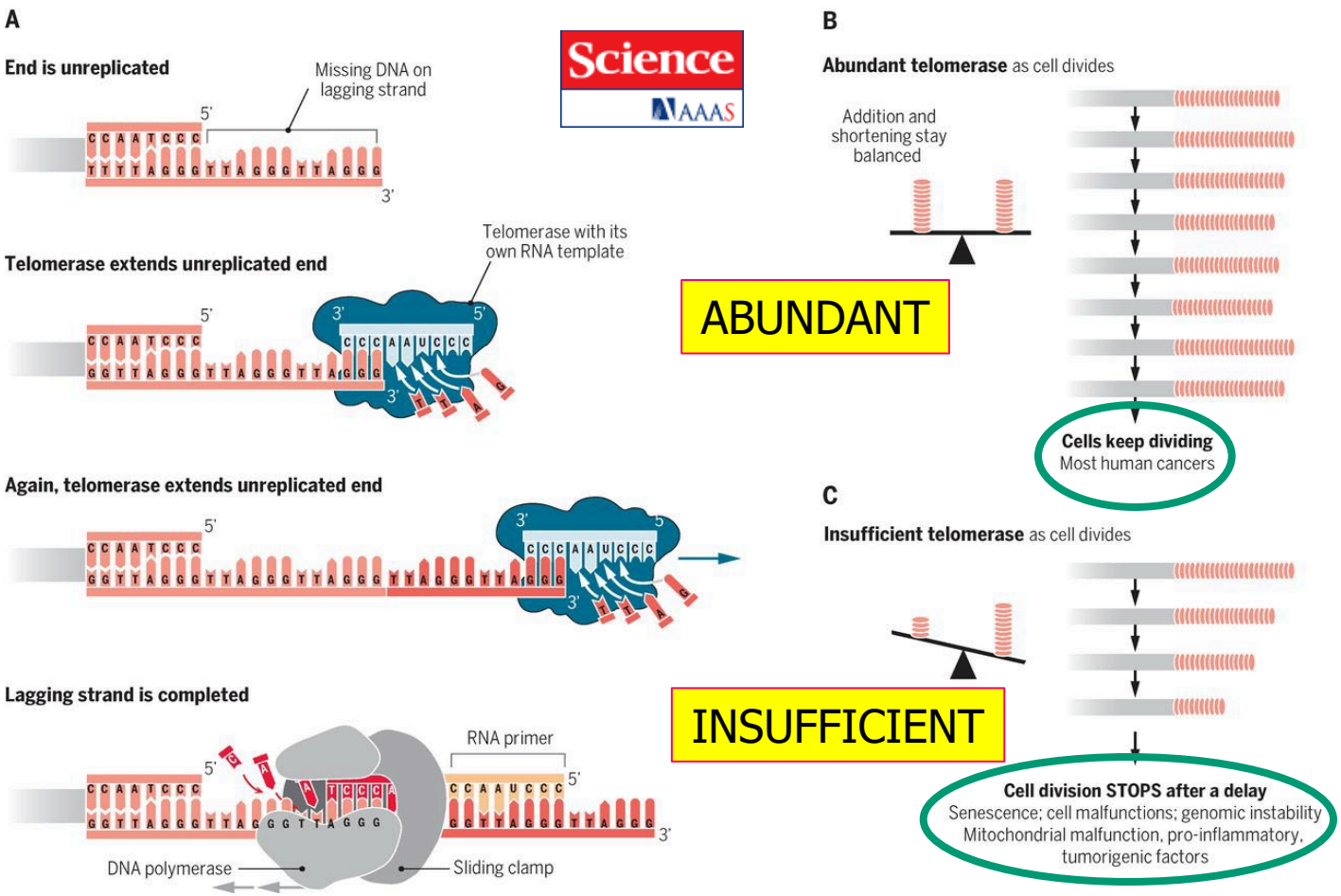
Cellular senescence, apoptosis & **aging phenotypes**



HORMONE ACTION DEPENDS ON CELL SEX AND AGE

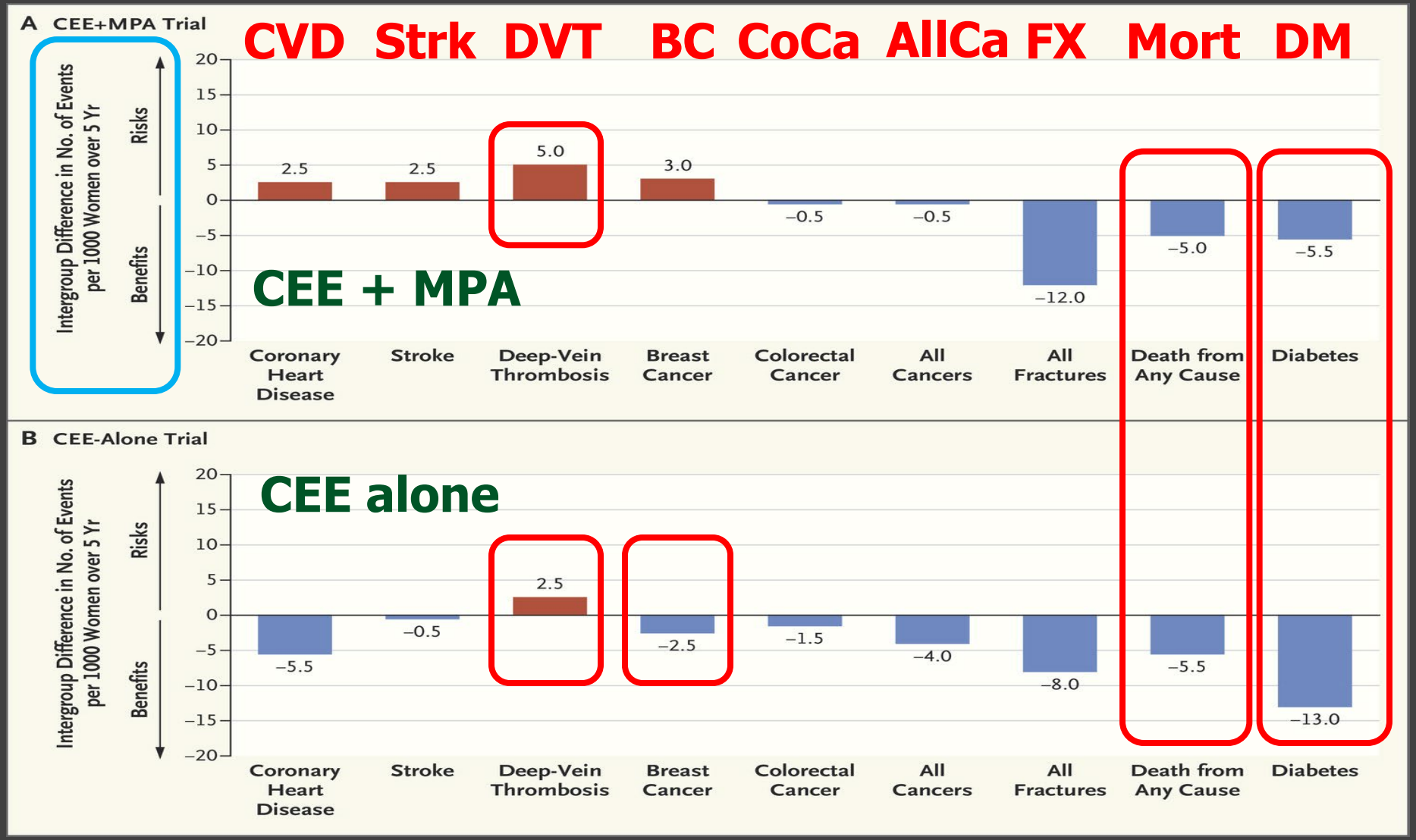
Accurate vs inaccurate cell division vs cell death

Long-term maintenance of telomeric DNA length requires telomerase



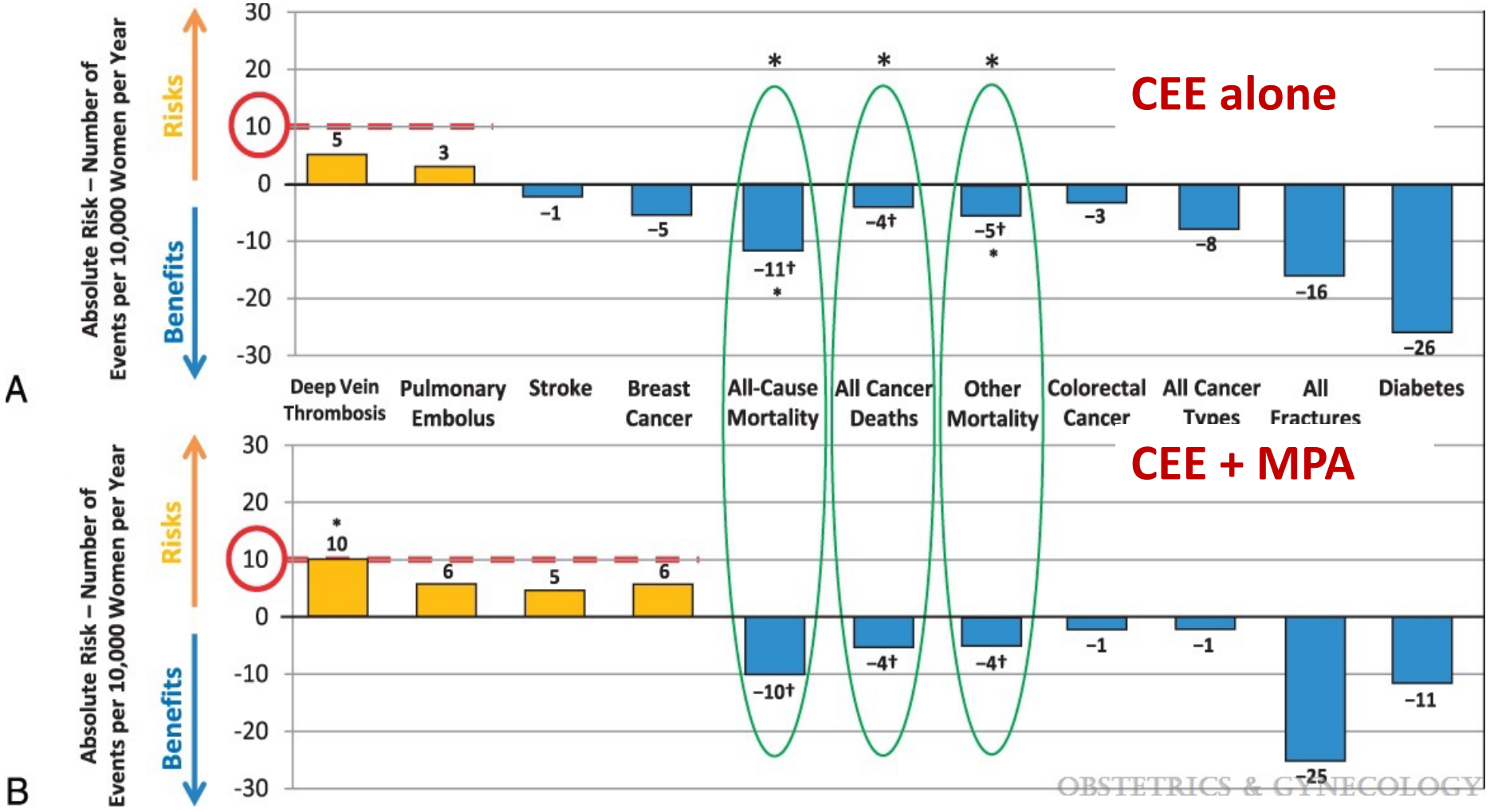
Blackburn et al. Science 2015;350:1193-1198

Benefits and Risks in the Women's Health Initiative (for women 50-59 y)



Manson JE, Kaunitz AM. N Engl J Med 2016;374:803-806.

Absolute benefits and risks associated with initiation of hormone therapy in women aged 50–59 years

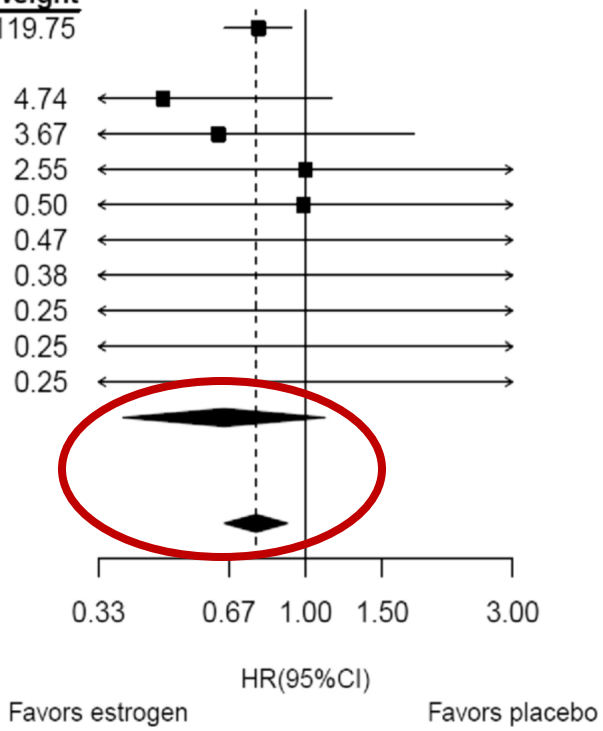


Elimination of the Black Box Warning on Menopausal Hormone Therapy.

Obstet Gynecol 147:642-646, May 2026.

Postmenopausal estrogen use and breast cancer

Trial name	Estrogen therapy (# cases) N	placebo (# cases) N	RR (95%CI)	Weight
Women's Health Initiative	(238) 5310	(296) 5429	0.78 (0.65, 0.93)	119.75
Smaller clinical trials				
ESPRIT	(7) 513	(15) 504	0.47 (0.19, 1.15)	4.74
DOPS	(6) 95	(9) 97	0.63 (0.23, 1.78)	3.67
WEST	(5) 337	(5) 327	1.00 (0.30, 3.50)	2.55
PEPI	(1) 175	(1) 174	0.99 (0.06, 15.96)	0.50
CHART†	(3) 562	(0) 137	3.48 (0.20, 60.47)	0.47
Genant†	(1) 116	(1) 40	0.28 (0.01, 6.68)	0.38
EPAT†	(0) 111	(1) 111	0.14 (0.00, 6.82)	0.25
ERA	(1) 100	(0) 105	7.77 (0.15, 391.96)	0.25
Gallagher†	(0) 20	(1) 19	0.13 (0.00, 6.48)	0.25
Total of smaller clinical trials	**(24) 2029**	**(33) 1514**	**0.65 (0.38, 1.11)**	
Total of smaller clinical trials plus Women's Health Initiative	**(262) 7339**	**(329) 6943**	**0.77 (0.65, 0.91)**	



Chlebowski RT et al. Randomized trials of estrogen-alone and breast cancer incidence: a meta-analysis. Breast Cancer Res Treat 2024 206:177-184

Hormone therapy after oophorectomy and breast cancer risk in women with BRCA pathogenic variant (PV)

- Retrospective multicenter cohort study conducted in Israel
  - largest study ever done

- 919 women who took HRT after risk reducing bilateral oophorectomy
  - BRCA1 PV (496) and BRCA2 PV (423)
  - 9 years FU
  - 16% developed invasive breast cancer
  - 42% used and 58% never used HRT

- Estrogen-only HRT not associated with increased BC risk
  - In BRCA1 lower risk

- Estrogen-progestin HRT did not change BC risk

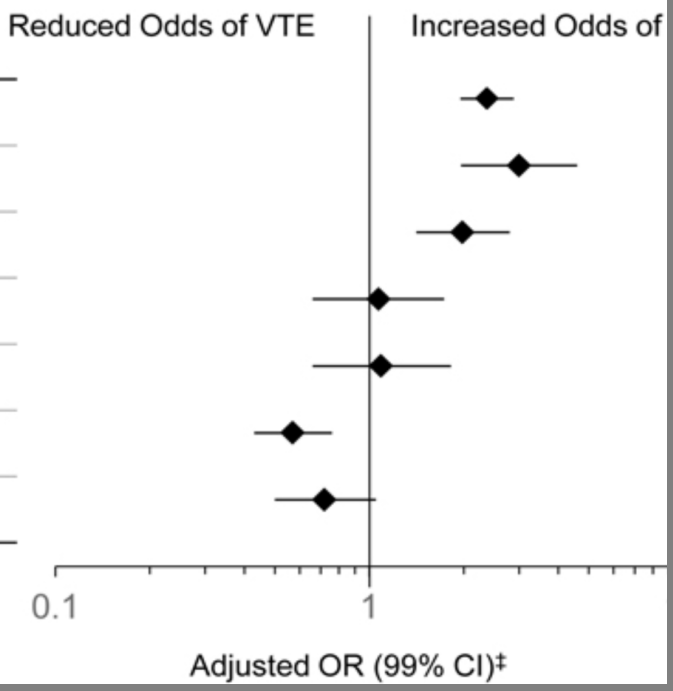
Regev-Sadeh et al. JAMA Network Open 2026;9(4):e265648

Perimenopause: Which Progestin is Best?

Source	Circulating level
Slynd (drospirenone 4 mg)	40+ ng/mL
Depo-Provera (medroxyprogesterone acetate)	7 ng/mL
NETA (norethindrone acetate (5 mg))	4 ng/mL
Medroxyprogesterone acetate (MPA (10 mg))	3-4 ng/mL
Oral contraceptives	1-2 ng/mL
Nexplanon (68 mg etonogestrel)	0.14 ng/mL (range 0.05–0.7)
Mirena IUD (52 mg levonorgestrel (LNG))	0.1 ng/mL

Progestins and VTE

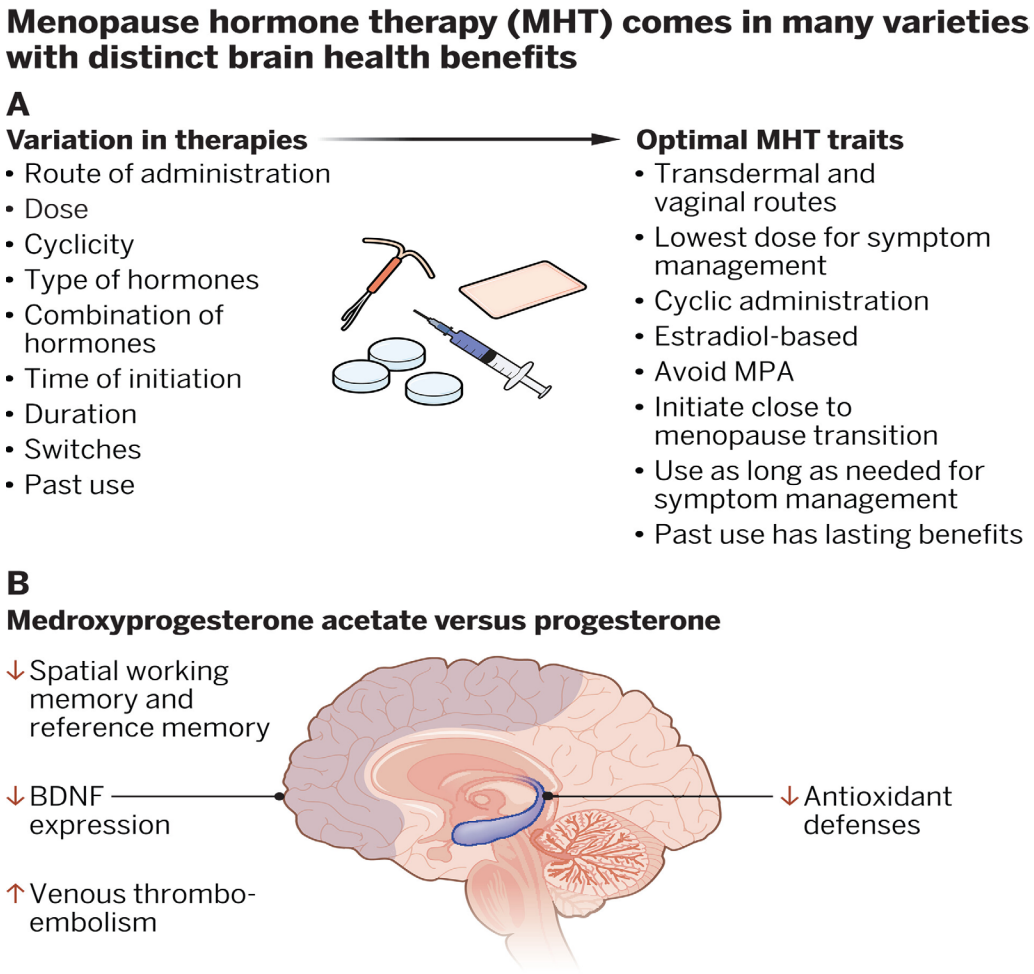
Progestogen*	No. (%) Cases with VTE	Controls	Crude OR (99% CI)†	Adjusted OR (99% CI)†
DMPA	355 (1.66)	657 (0.61)	2.76 (2.42-3.14)§	2.37 (2.04-2.75)§
NETA	87 (0.41)	114 (0.11)	3.88 (2.93-5.12)§	3.00 (2.17-4.15)§
MPA	111 (0.52)	232 (0.22)	2.43 (1.94-3.05)§	1.98 (1.53-2.58)§
Prog	51 (0.24)	202 (0.19)	1.28 (0.94-1.75)	1.07 (0.75-1.54)
Implant	39 (0.18)	177 (0.17)	1.14 (0.80-1.61)	1.09 (0.74-1.61)
NET	131 (0.61)	724 (0.68)	0.92 (0.76-1.11)	0.57 (0.46-0.71)§
LNG-IUD	77 (0.36)	446 (0.42)	0.88 (0.69-1.13)	0.72 (0.54-0.96)



Current use of progestogens and odds of venous thromboembolism (VTE).
*Exposures are listed using a progestogen dose hierarchy by Bergendal et al, modified to incorporate noncontraceptive progestogens (lowest to highest: levonorgestrel intrauterine device [LNG-IUD], oral norethindrone [NET], etonogestrel implant [implant], oral progesterone [prog], oral medroxyprogesterone acetate [MPA], oral norethindrone acetate [NETA], DMPA, depot medroxyprogesterone acetate [DMPA]).
†Referent group for each conditional logistic regression model is noncurrent users of any progestogen (ie, no progestogen use within 28 days before index date), n=125,027 (cases: n=20,554; controls: n=104,473).

Cockrum RH, Soo J, Ham SA, Cohen KS, Snow SG. Association of Progestogens and Venous Thromboembolism Among Women of Reproductive Age. Obstet Gynecol. 2022 Sep 1;140(3):477-487.

Reframing menopause and menopause hormone therapy (MHT) as opportunities for healthy aging



Gravelsins et al Science Oct 1, 2026

Hormones and mental health at midlife
Saving grandmother's brain

- **Mood and cognition are impacted by unpredictable and erratic hormone fluctuations**

- **Although fluctuations are "physiologic", they nonetheless challenge brain function**

- **Patients with pre-existing mental health compromise / conditions are most impacted by hormonal fluctuations and the associated lack of hormonal predictability**

Dental health

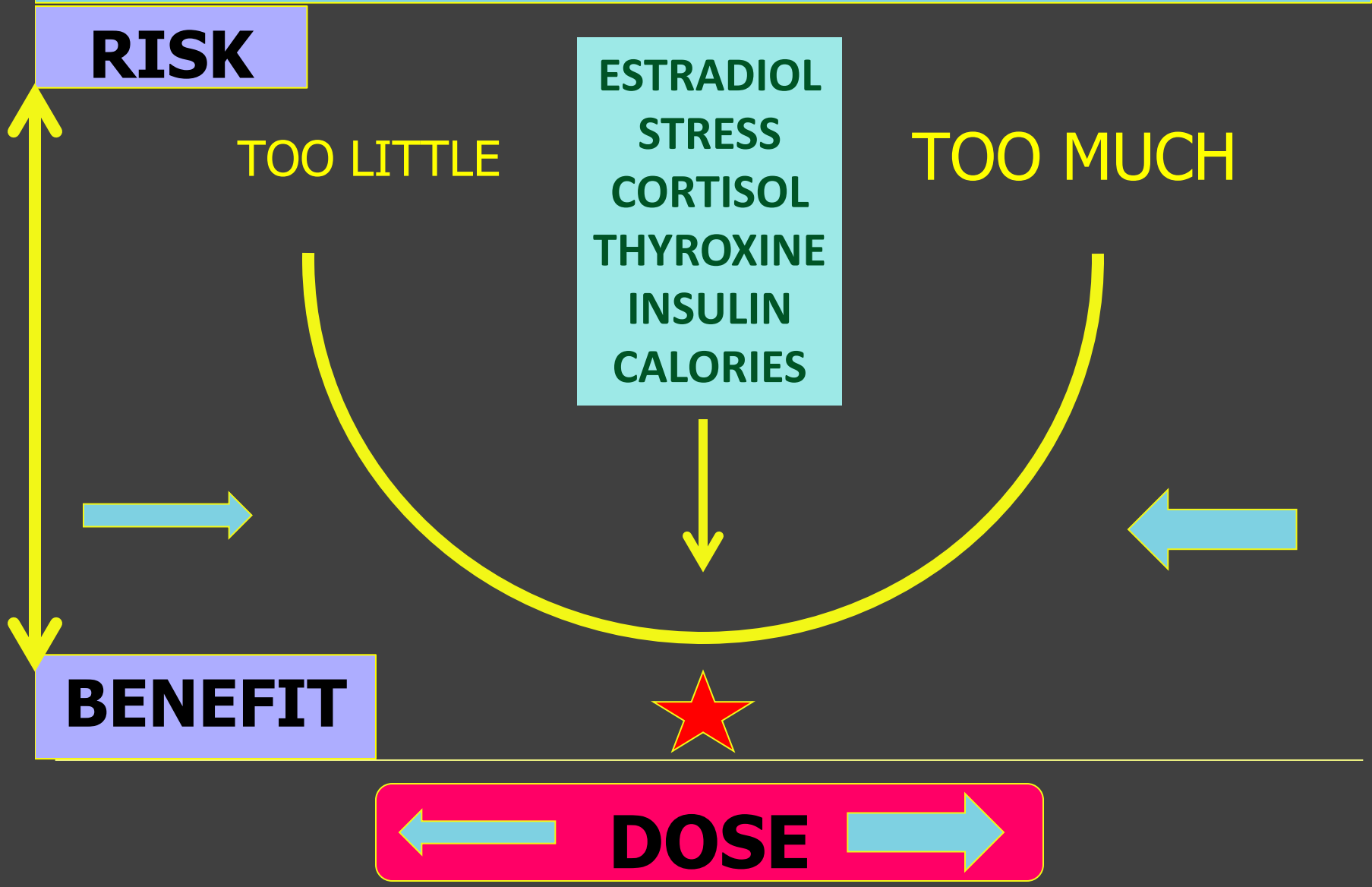
- **Teeth are bones -** bone loss increases the likelihood of tooth loss
- **Gum disease -** reduced estradiol and collagen predispose to gingivostomatitis and increase susceptibility to plaque and periodontal disease
- **Tooth sensitivity -** thinning gums expose tooth roots
- **Dry mouth** – reduced estradiol reduces saliva causing dry mouth which then increases the likelihood of tooth decay, bad breath, and difficulty swallowing
- **Burning mouth syndrome** – painful burning sensation linked to menopause

Skin health

- **Low estradiol / menopause linked to**
  - **epidermal thinning and wrinkles**
  - **hair loss**
  - **genitourinary syndrome of menopause**

FINDING THE SWEET SPOT

Dose-response is tightly regulated - both too much and too little has consequences



News you can use: MHT after 65

- Prescription drug / encounter records > 10 million Medicare women 2007-2020
- Examined the effects of different preparations of menopausal hormone therapy (MHT) on all-cause mortality, 5 cancers, 6 CVD conditions, and dementia
- Any E + any progestin better than any E + progesterone
- Both worse than E monotherapy
- **Any estrogen monotherapy** assoc with **REDUCED**

Mortality	**↓ 19% (0.81, 0.79-0.82)**
Breast cancer	**↓ 16%**
Lung ca	**↓ 13%**
Colorectal ca	**↓ 12%**
Anterior MI	**↓ 11%**
Congestive heart failure	**↓ 5%**
Atrial fibrillation	**↓ 4%**
VTE	**↓ 3%**
Dementia	**↓ 2%**

Baik et al Menopause 2024:31: 363-371.

News you can use: MHT after 65

- **Transdermal estradiol < 0.05 mg/d patch - without progestin / progesterone**

Mortality	**↓ 20%**
Breast cancer	**↓ 14%**
Lung cancer	**↓ 14%**
Colorectal cancer	**↓ 13%**
Endometrial cancer (without progestin or progesterone)	**↓ 22%**
Ovarian cancer	**↓ 13%**
Anterior MI	**↓ 13%**
Congestive heart failure	**↓ 10%**
Dementia	**↓ 8%**
Atrial fibrillation	**↓ 7%**
VTE	**↓ 6%**
Stroke	**↓ 5%**

Baik et al Menopause 2024:31: 363-371.

STEP 1: Differential Diagnosis and Concurrent Conditions

- Depression, anxiety, other psychiatric diagnoses
- Mild cognitive impairment and dementia
- Sexual dysfunction not due to hormonal changes
- Fibromyalgia and arthritis
- Hypothyroidism
- Diabetes mellitus
- Intra-articular glucocorticosteroid injections may lead to iatrogenic adrenal suppression and glucocorticoid excess and may mimic menopausal symptoms including hot flashes
- Other causes of ovarian compromise
- Uterine and endometrial pathology

STEP 2: Determine stage of perimenopause / menopause

- If not fully menopausal, review need for contraception

- Clarify expectations
  - Health maintenance
  - Improved overall well-being
  - Symptom management
  - Reversing aging
  - Remediation of specific issue

STEP 3: Select an estrogen

- **NOT ONE SIZE FITS ALL**
- **Not all estrogens are the same**
- **The safest estrogen is transdermal estradiol**
- **Transdermal estradiol is available as a patch, daily gel, or vaginal ring or gel**
- **Twice weekly patches give less constant estradiol levels**
- **The therapeutic goal is a circulating estradiol of 40-80 pg/ml midpatch or 12 hours after gel application**

STEP 4: Need for progestin?

- **Is a progestin needed?**
  - **Only indication is an “intact uterus”**
- **Progestins are depressogenic and more so in those with brain compromise**
- **Least progestin exposure (for the brain) with the least user burden and the best bleeding pattern is a progestin IUD**

Summary
Precision in Menopause Hormone Therapy

- **The clinical presentation of the climacteric / perimenopause / menopausal transition is pleiotrophic and symptoms are tissue-specific responses**
- **Initiate MHT in steps to improve patient engagement**
- **Careful follow-up thereafter**

Questions?
Comments?
Actions?