

Physiology of Menopause



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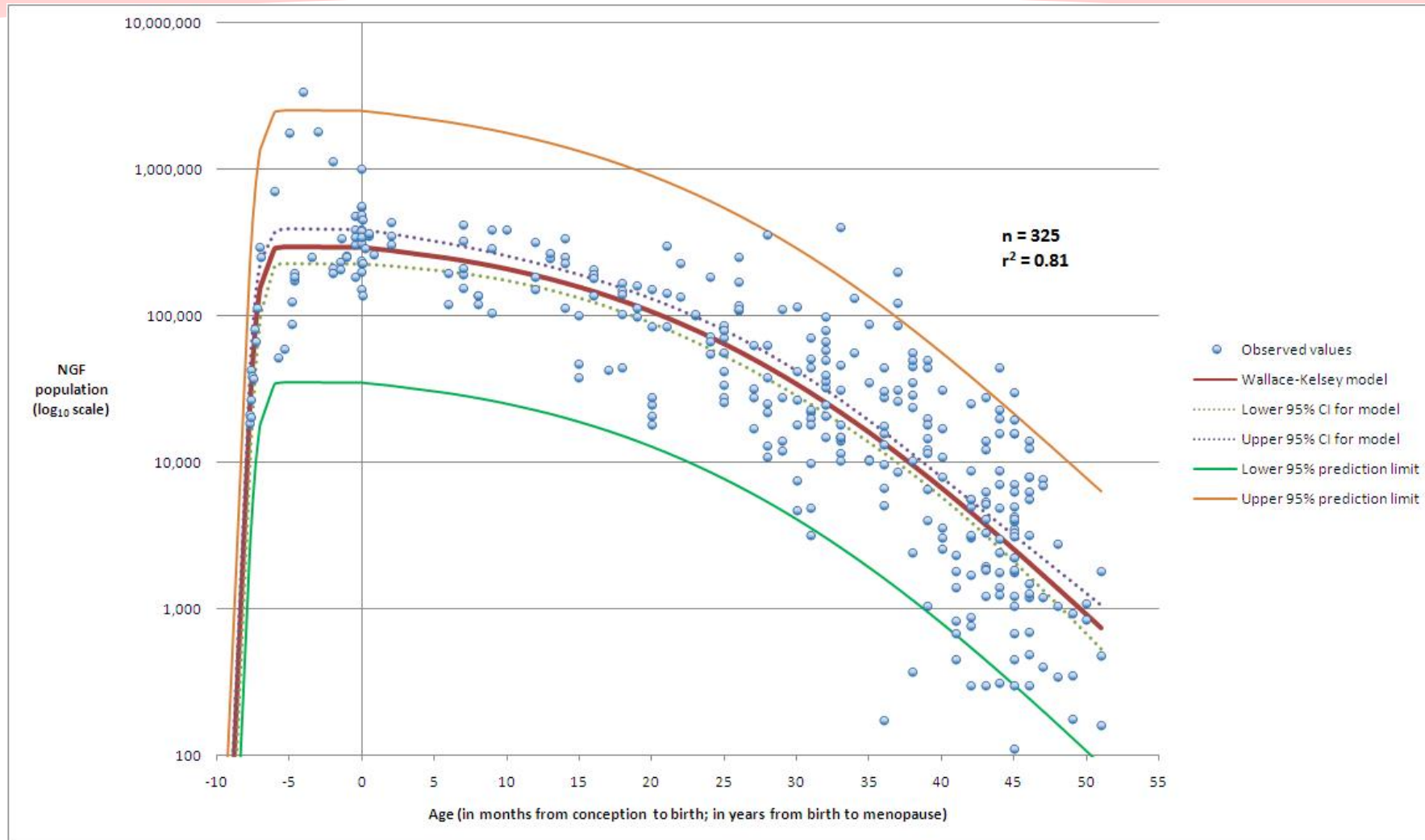
I have received consulting fees
and honoraria for speaking from
Pfizer Canada Inc.

I have no other competing or
potentially competing interests

What I want to talk about

- Apoptosis and the ovary
- Endocrine changes
- Neurological changes
- Bone and joint changes
- Urogenital changes
- Cardiovascular changes

Ovarian reserve from conception to menopause



Wallace WH, Kelsey TW. PLoS One 2010 Jan 27;5(1):e8772.

Apoptosis and ovarian reserve

- During fetal life, apoptosis primarily involves the oocyte
- After birth, and in adult life, it involves primarily follicular granulosa cells, although oocytes in primordial follicles may also be affected
- 99.9% of follicles present at birth never reach the stage of ovulation, but undergo atresia
- The reduction in oocyte complement < 38 years is due to both oocyte loss and accelerated follicular growth; in women > 38 years it is solely due to faster initiation of growth

STRAW + 10 Staging System for Reproductive Aging

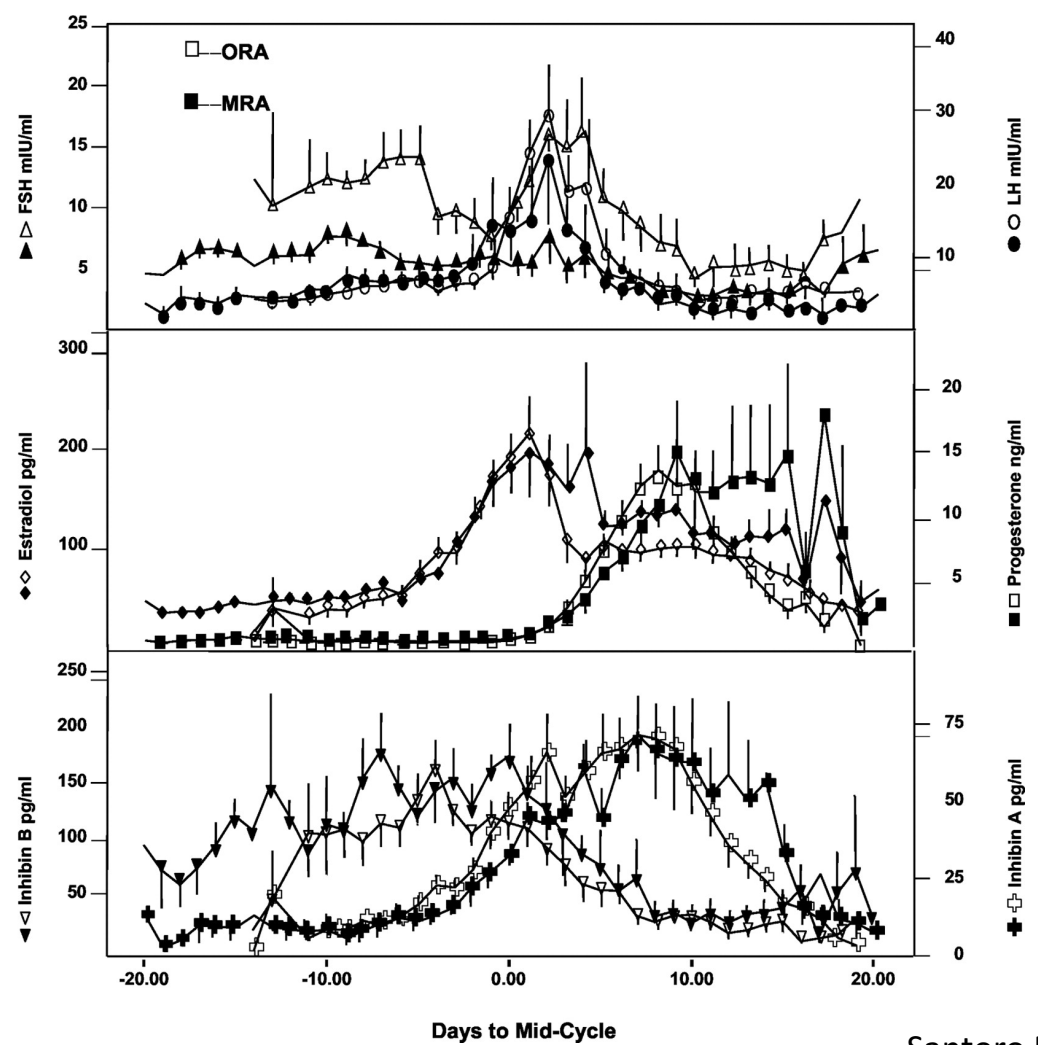
Menarche					FMP (0)					
Stage	-5	-4	-3b	-3a	-2	-1	+1 a	+1b	+1c	+2
Terminology	REPRODUCTIVE				MENOPAUSAL TRANSITION		POSTMENOPAUSE			
	Early	Peak	Late		Early	Late	Early		Late	
					Perimenopause					
Duration	variable				variable	1-3 years	2 years (1+1)	3-6 years	Remaining lifespan	
PRINCIPAL CRITERIA										
Menstrual Cycle	Variable to regular	Regular	Regular	Subtle changes in Flow/ Length	Variable Length Persistent ≥7- day difference in length of consecutive cycles	Interval of amenorrhea of ≥=60 days				
SUPPORTIVE CRITERIA										
Endocrine FSH AMH Inhibin B			Low Low	Variable* Low Low	↑ Variable* Low Low	↑ >25 IU/L** Low Low	↑ Variable Low Low	Stabilizes Very Low Very Low		
Antral Follicle Count			Low	Low	Low	Low	Very Low	Very Low		
DESCRIPTIVE CHARACTERISTICS										
Symptoms						Vasomotor symptoms Likely	Vasomotor symptoms Most Likely		Increasing symptoms of urogenital atrophy	

Harlow SD et al. *J Clin Endocrinol Metab* 2012;97:1159-68

What I want to talk about

- Endocrine changes

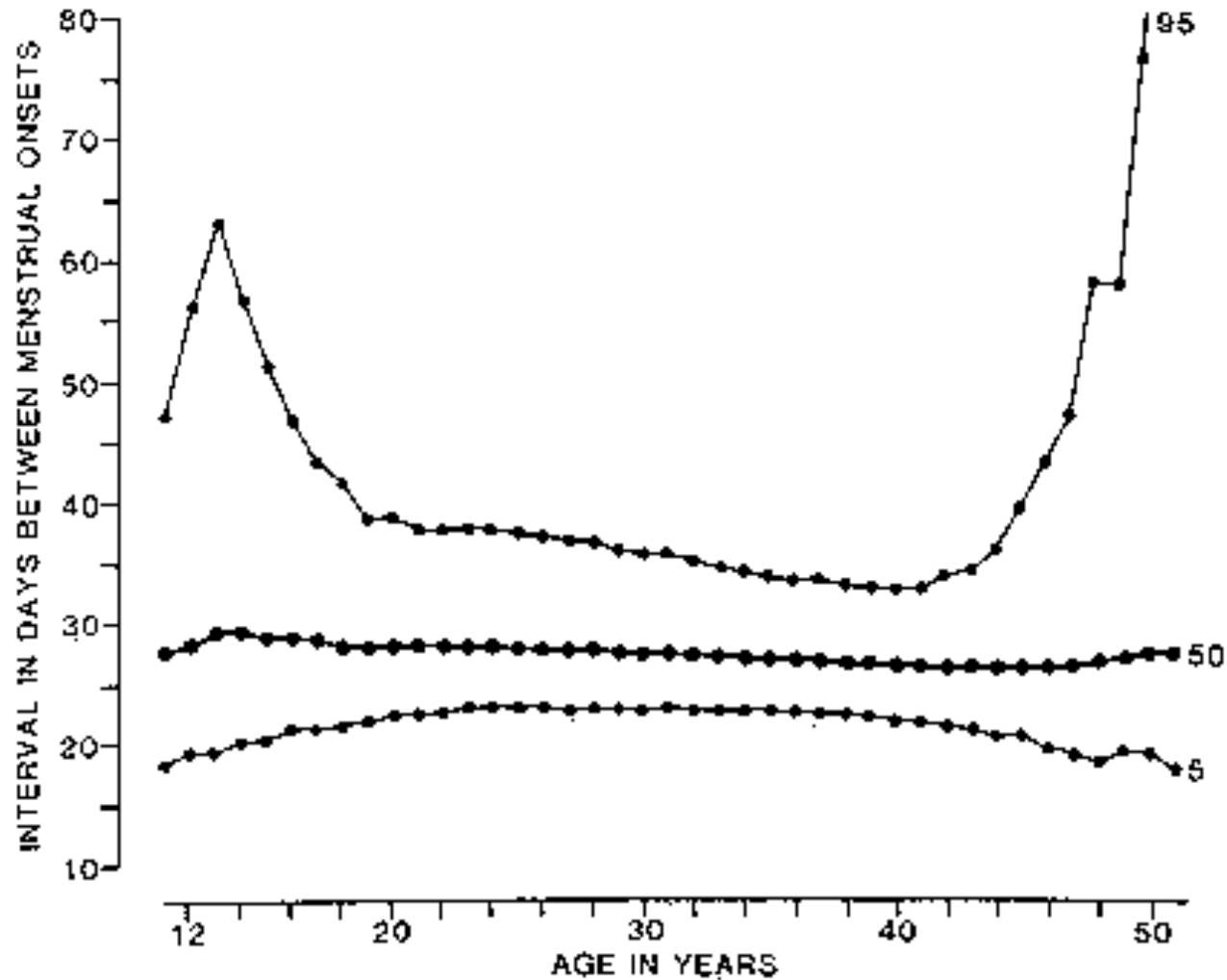
Daily hormone levels in women in mid-reproductive age and older reproductive age



22 women (either mid-reproductive age or older reproductive age) underwent daily pelvic ultrasound and blood sampling

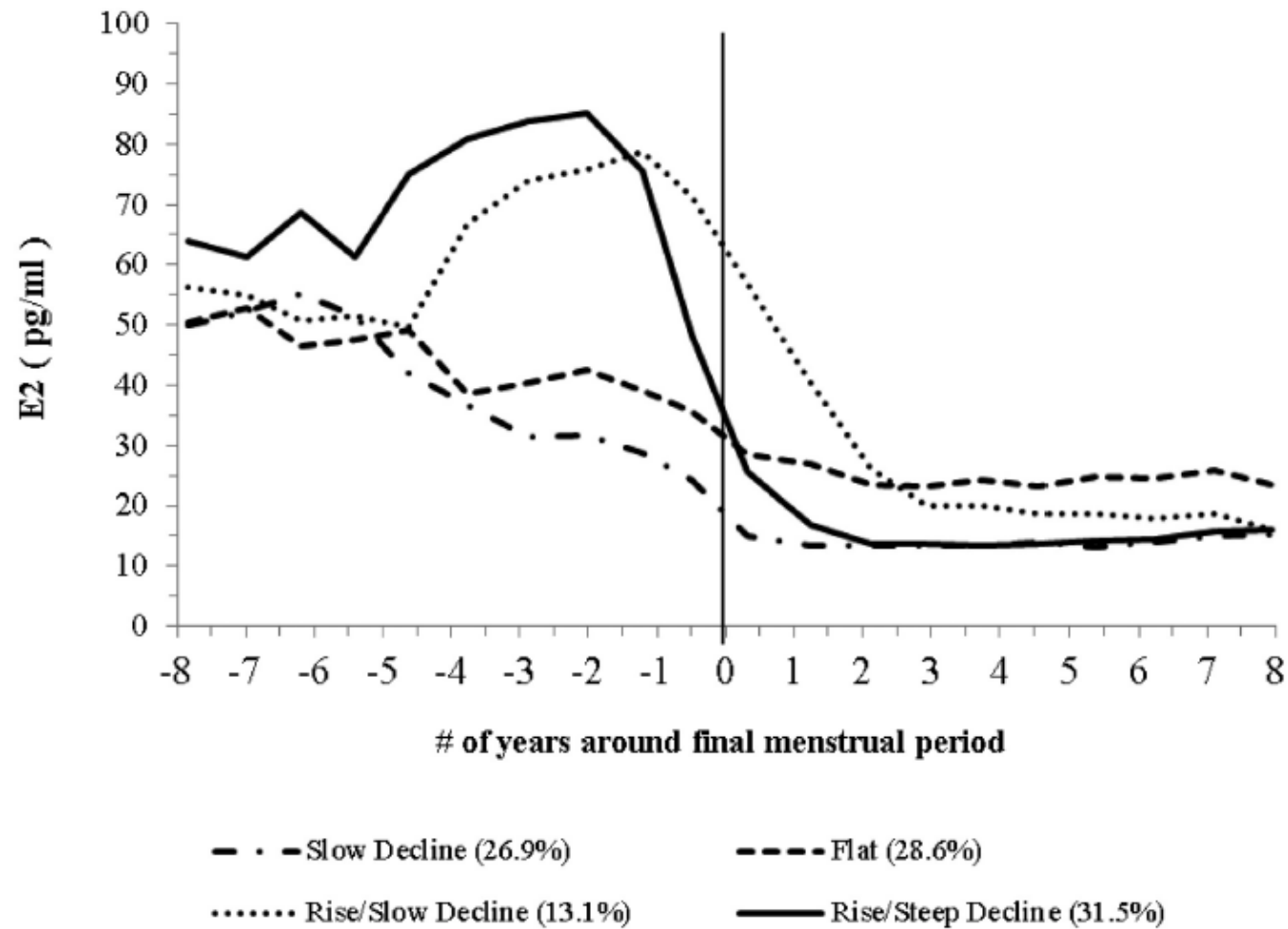
Santoro N et al. *J Clin Endocrinol Metab* 2003;88:5502-9

Age and menstrual cycle length



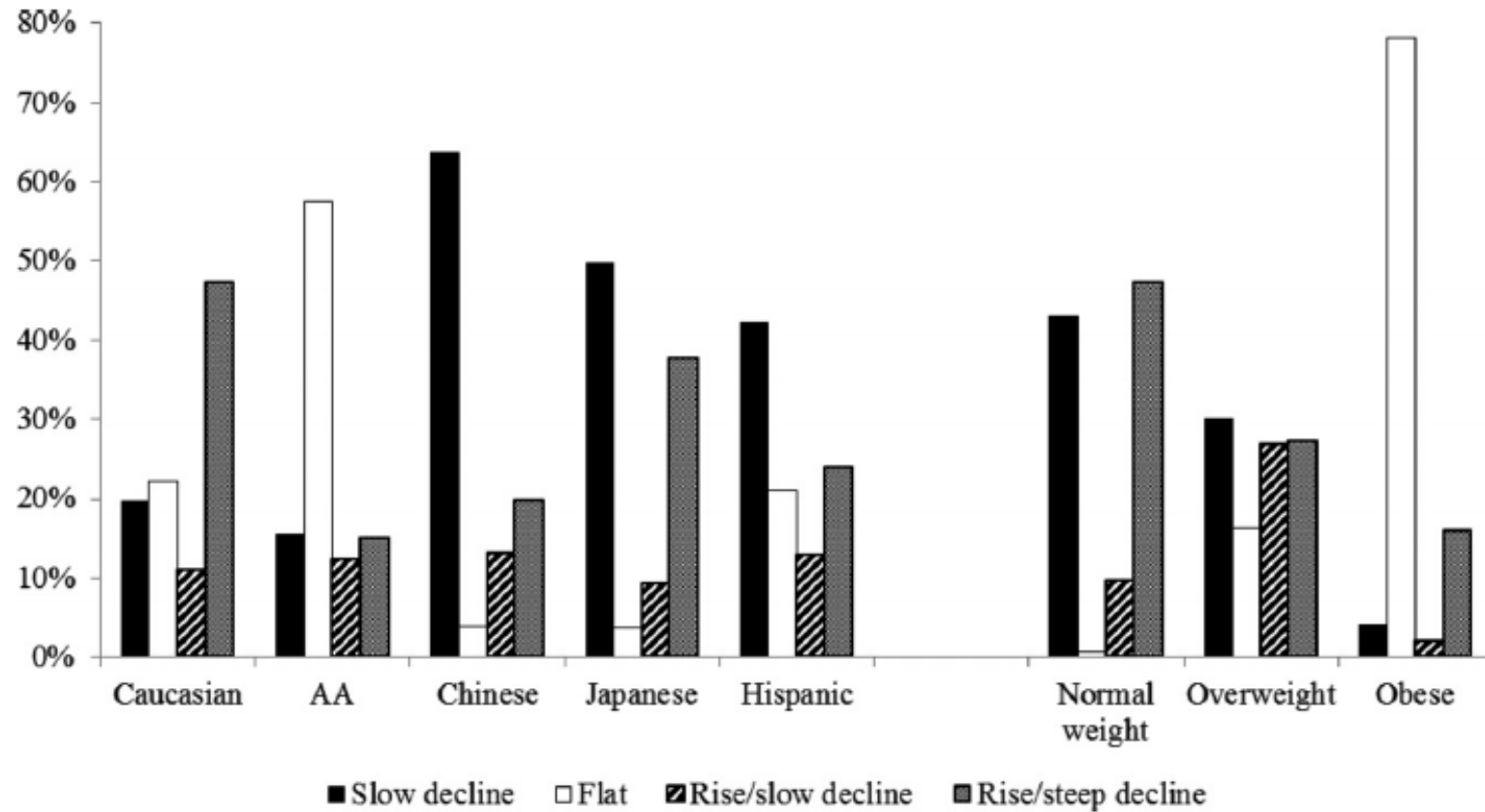
Treloar et al. *Int J Fertil* 1967;12:77-126

Trajectory of E₂ changes (SWAN)



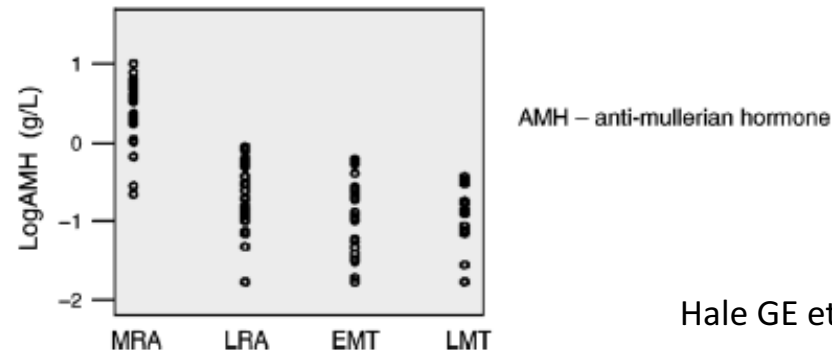
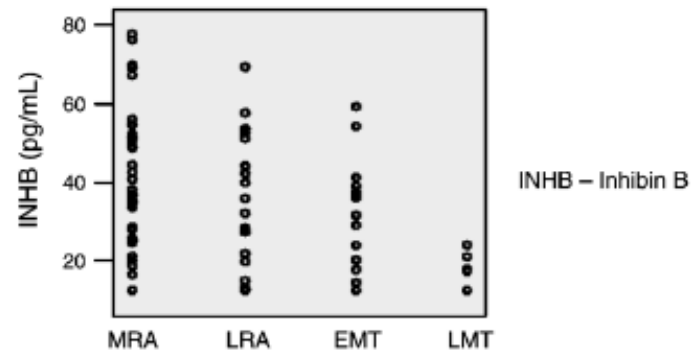
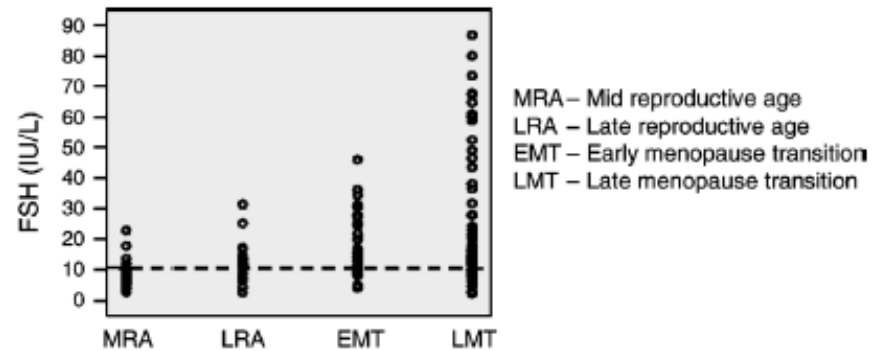
Tepper PG et al. *J Clin Endocrinol Metab* 2012;97:2872-80

Trajectory of E₂ changes (SWAN)



Tepper PG et al. *J Clin Endocrinol Metab* 2012;97:2872-80

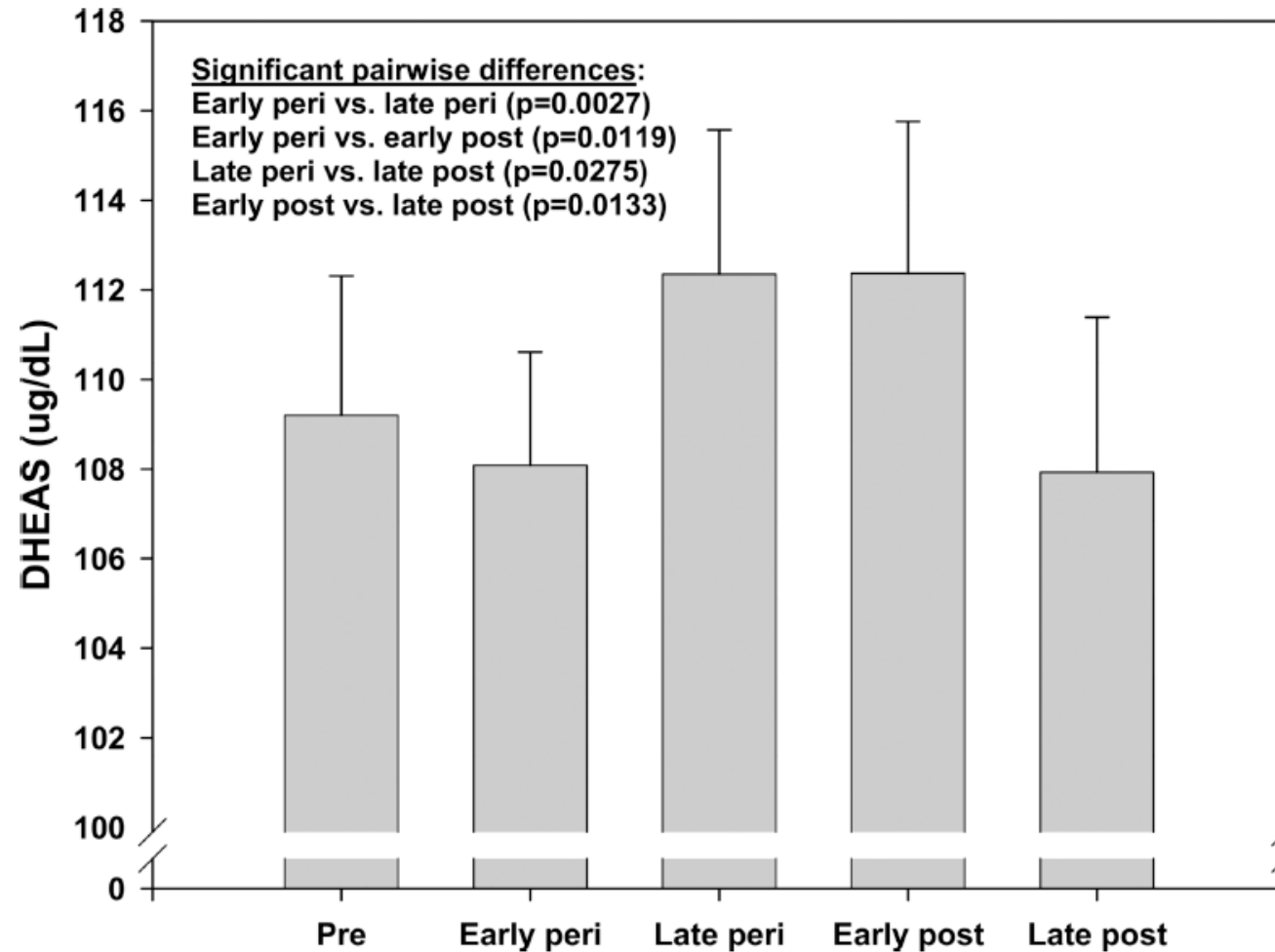
FSH, Inhibin-B, AMH levels



77 women aged 21-35 or 45-55 submitted three blood samples weekly over one menstrual cycle

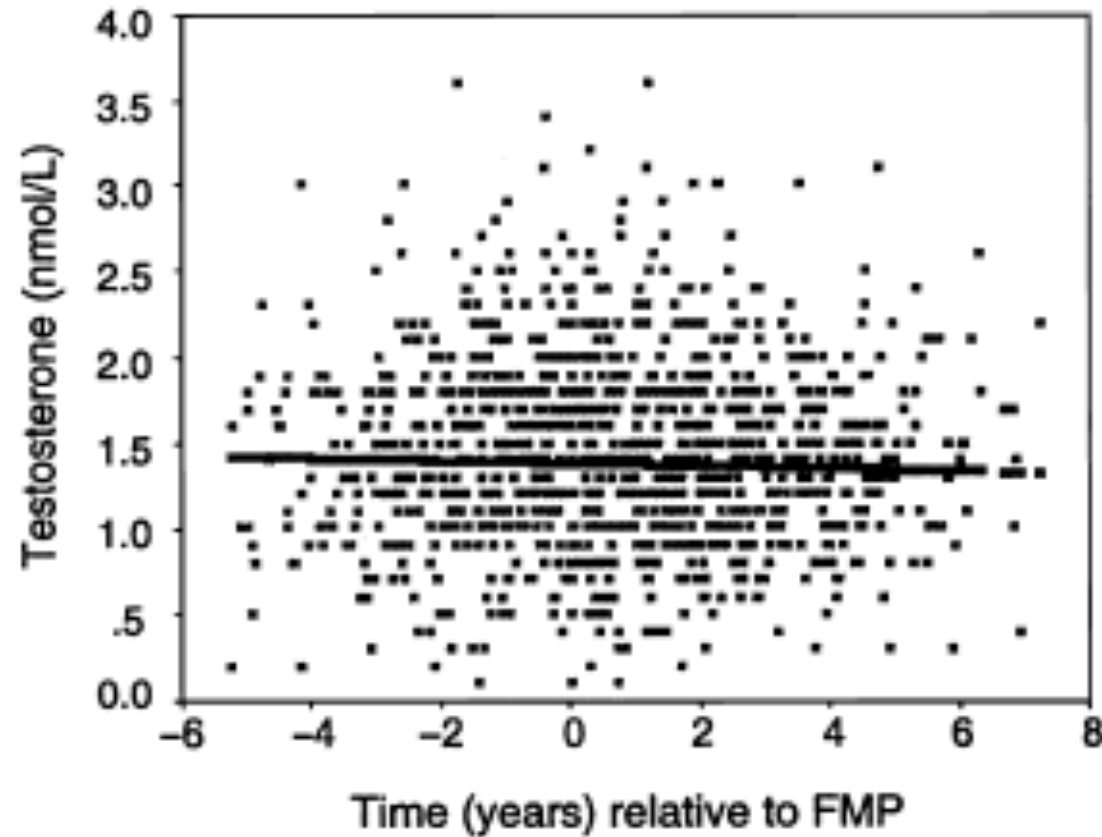
Hale GE et al. *J Clin Endocrinol Metab* 2007;92:3060-7

DHEA-S levels (SWAN)



Crawford S et al. *J Clin Endocrinol Metab* 2009;94:2945-51

Testosterone levels (MWMH)



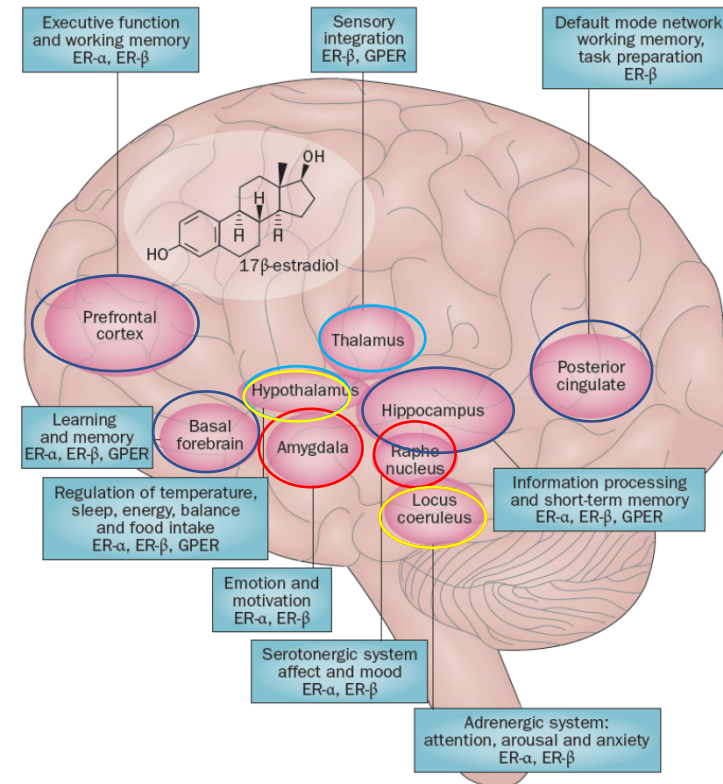
Burger HG et al. *Menopause* 2008;15:603-12

What I want to talk about

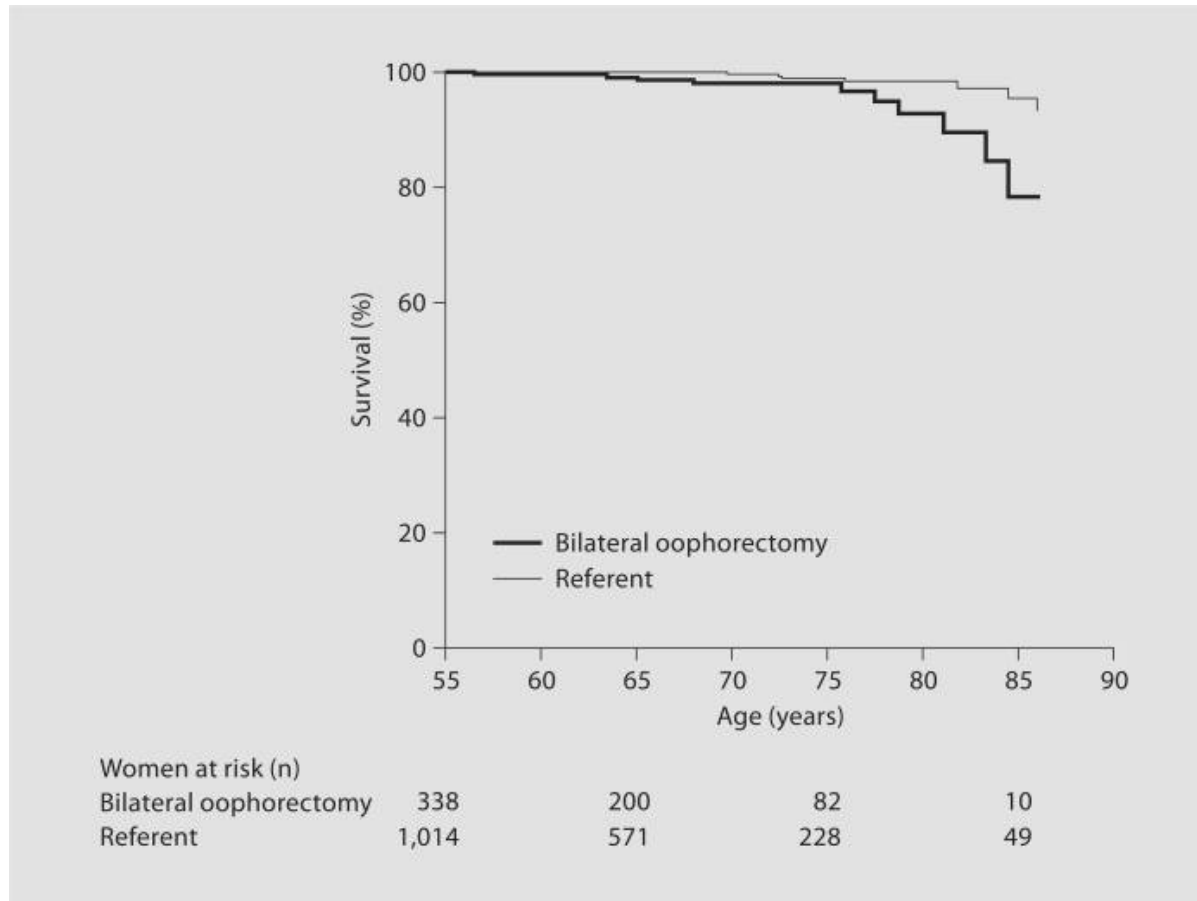
- Endocrine changes
- Neurological changes

Changes in neurological function associated with menopause

- Change in cognitive function
- Mood change (chiefly depression)
- Sleep disturbance
- Vasomotor symptoms



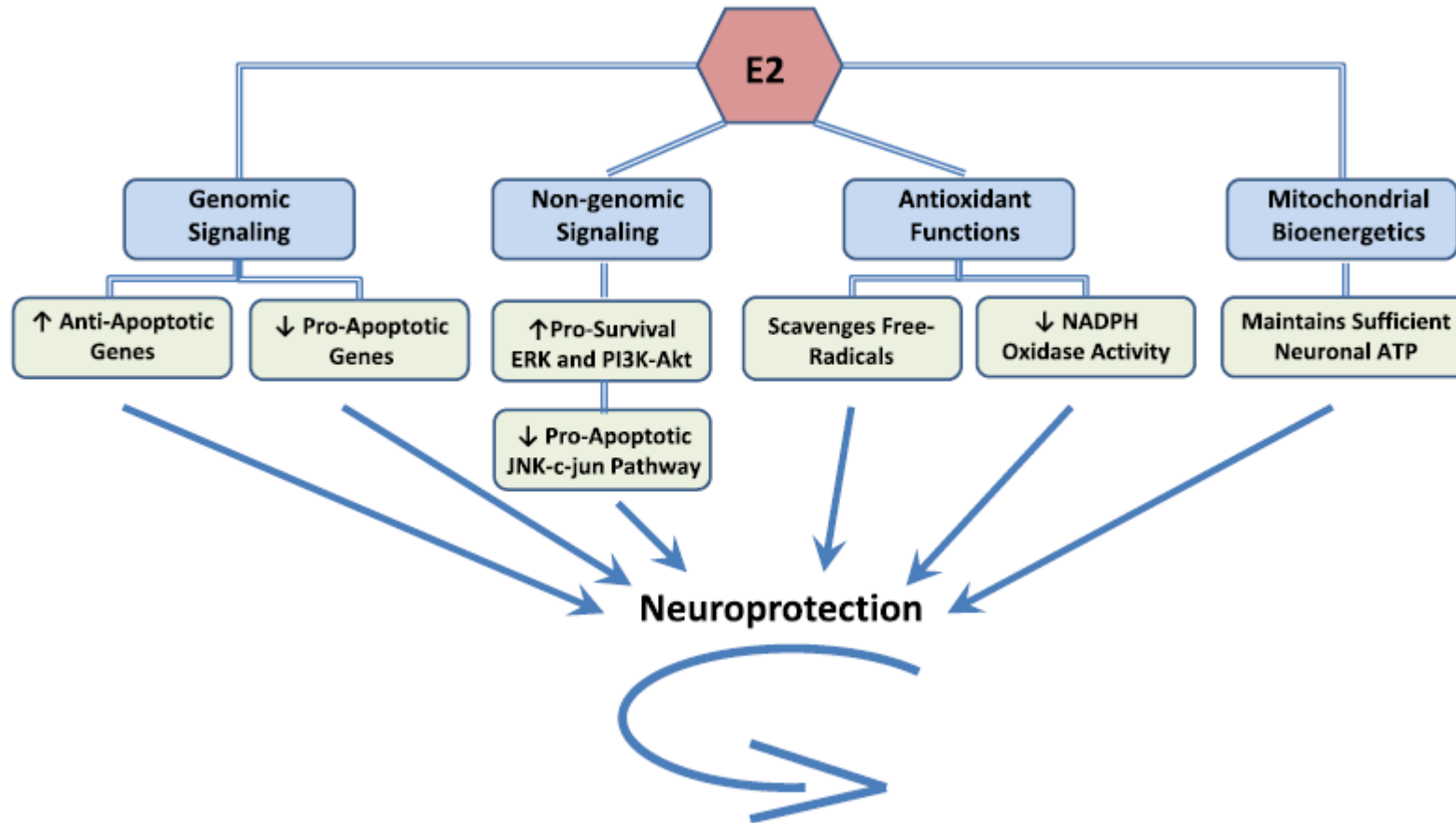
Death from neurological or mental disease in women with surgical menopause < 45



Hazard ratio 5.24
95% CI 2.02-13.6
 $P < 0.001$

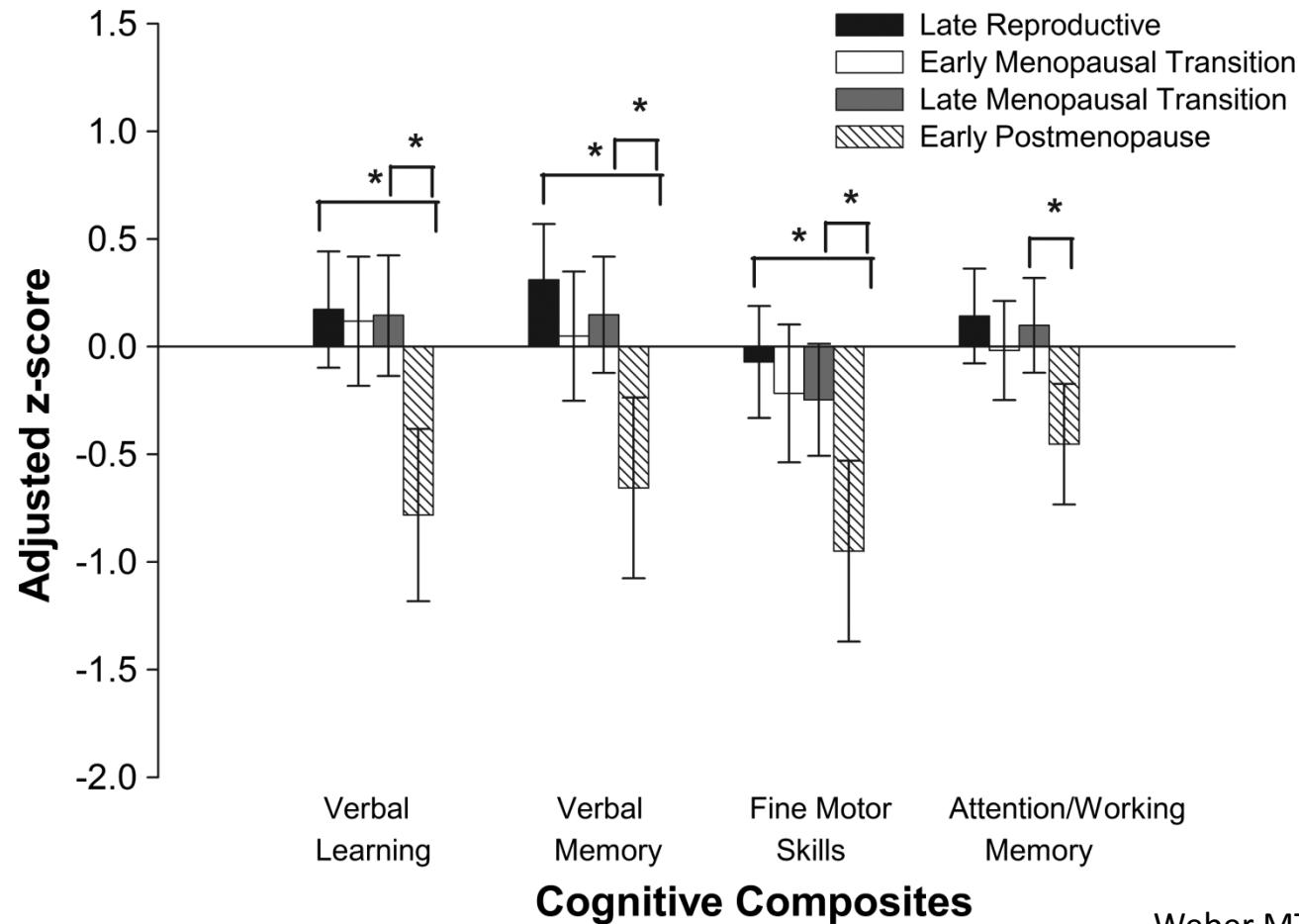
Rivera CM et al. *Neuroepidemiol* 2009;33:32-40

Mechanisms of estrogen neuroprotection



Scott E et al. *Front Neuroendocrinol* 2012;33:85-104

Change in cognitive function across menopausal transition

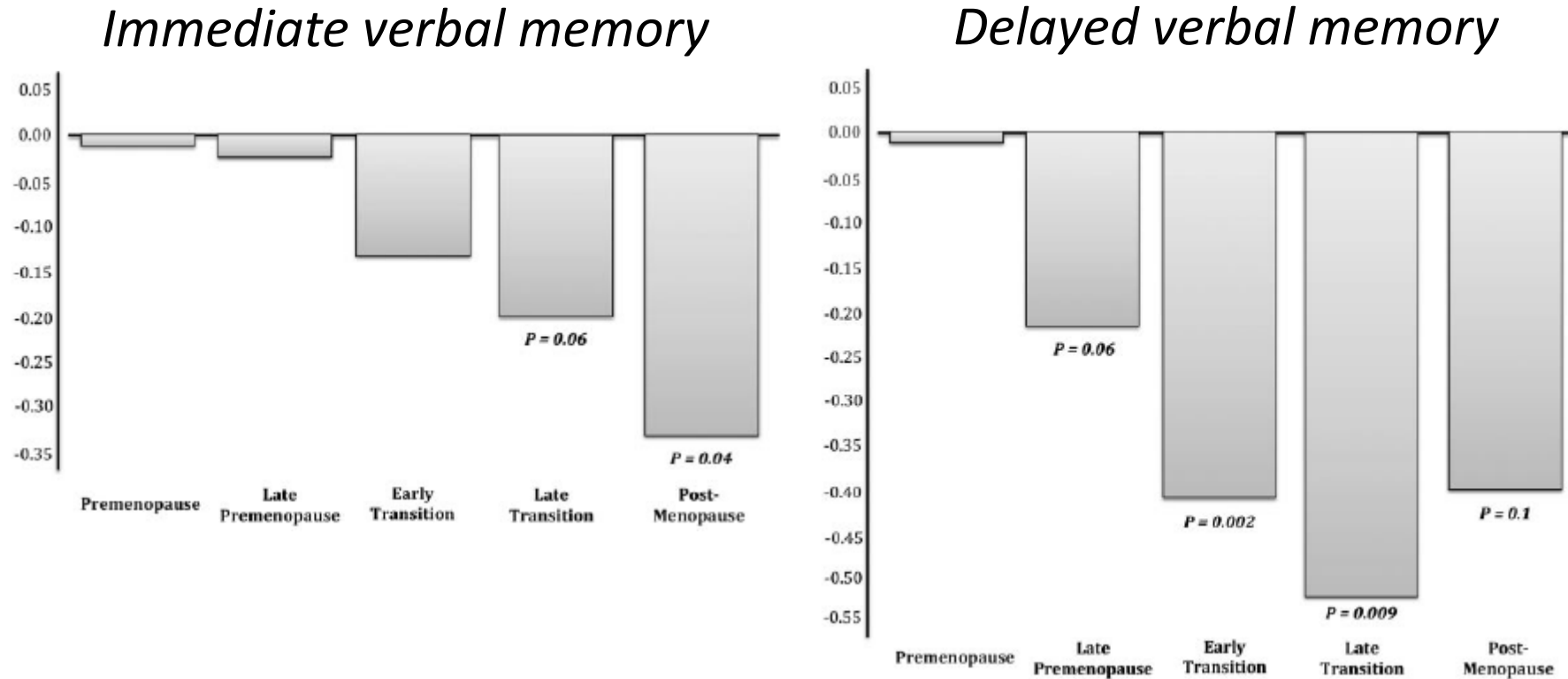


**117 mid-life women
assessed according to
reproductive stage**

Weber MT et al. *Menopause* 2013;20:511-17

Change in verbal memory across menopause

403 women monitored over 14 years



Epperson CN et al. *J Clin Endocrinol Metab* 2013;98:3829-38

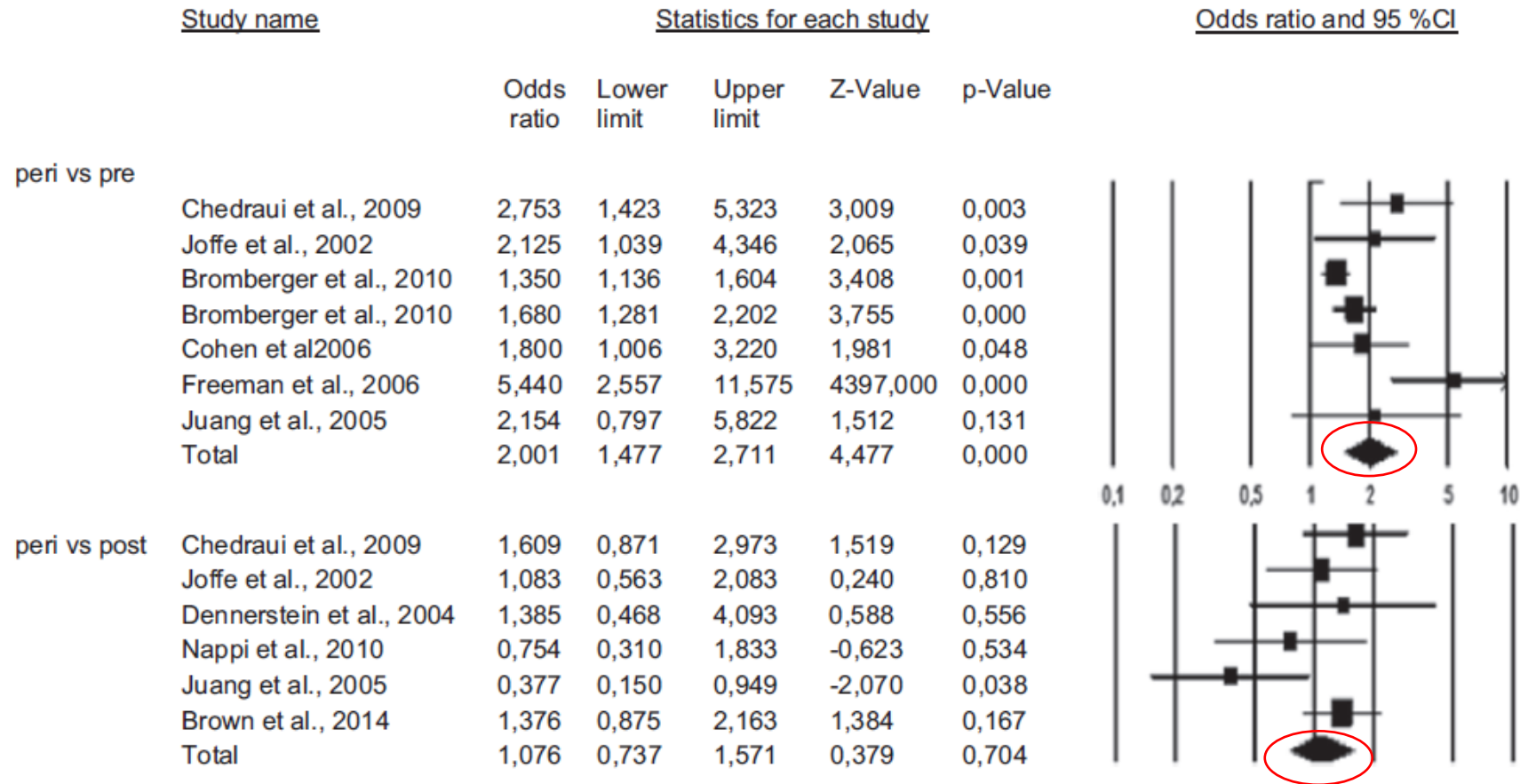
Cognitive aging in mid-life women (SWAN)

2124 participants, average age 54, followed for a median 6.5 years

- Cognitive speed declined by a mean of 4.9% over 10 years
- Verbal episodic memory (delayed testing) declined by a mean of 2% in 10 years
- Working memory and verbal episodic memory (immediate testing) did not decline significantly
- *Possible interventions to slow cognitive aging in these domains were not identified in this study*

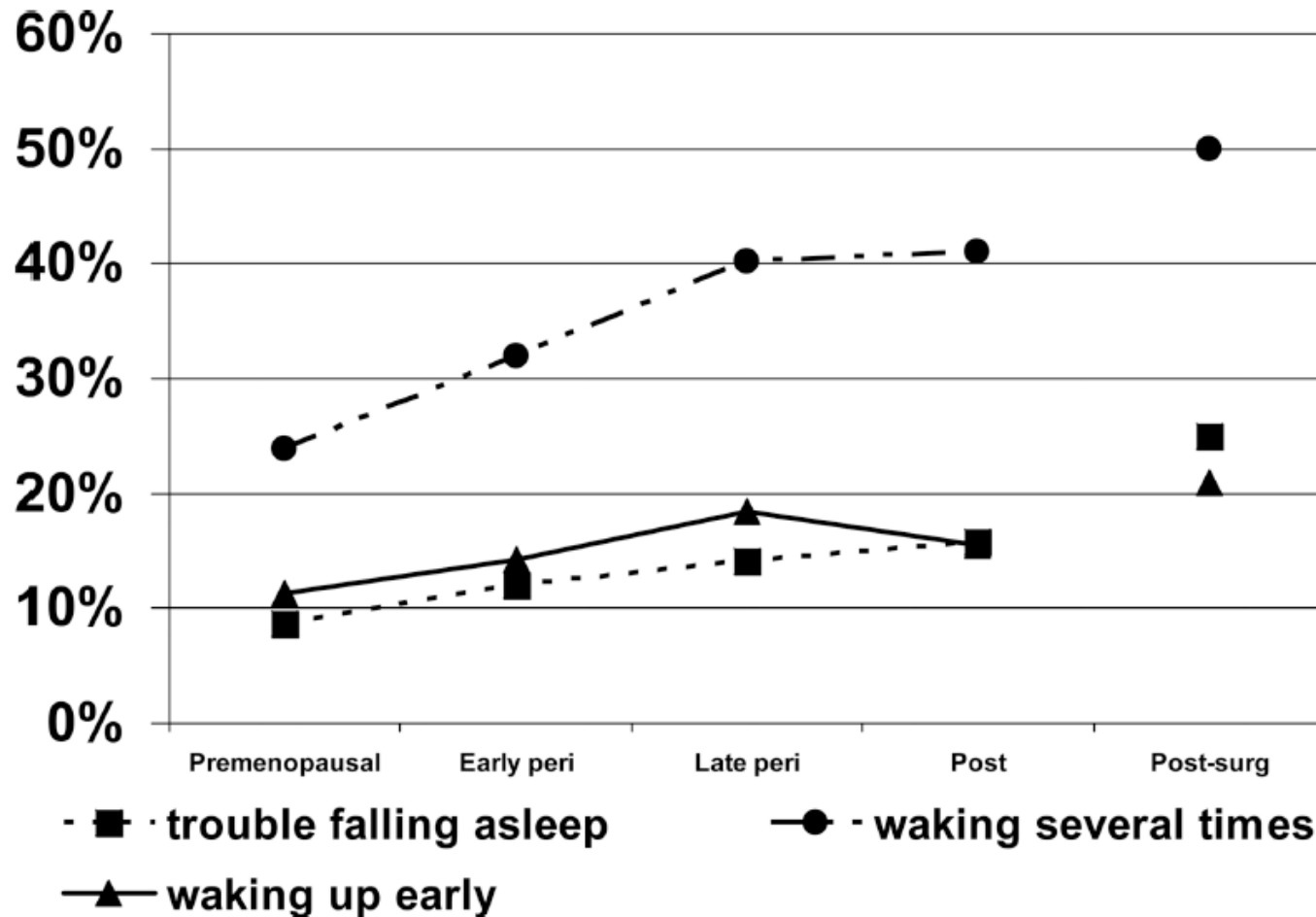
Karlamangla AS et al. PLoS One doi:10.1371/journal/pone.0169008

Depressive symptoms in perimenopause vs premenopause and postmenopause: a meta-analysis



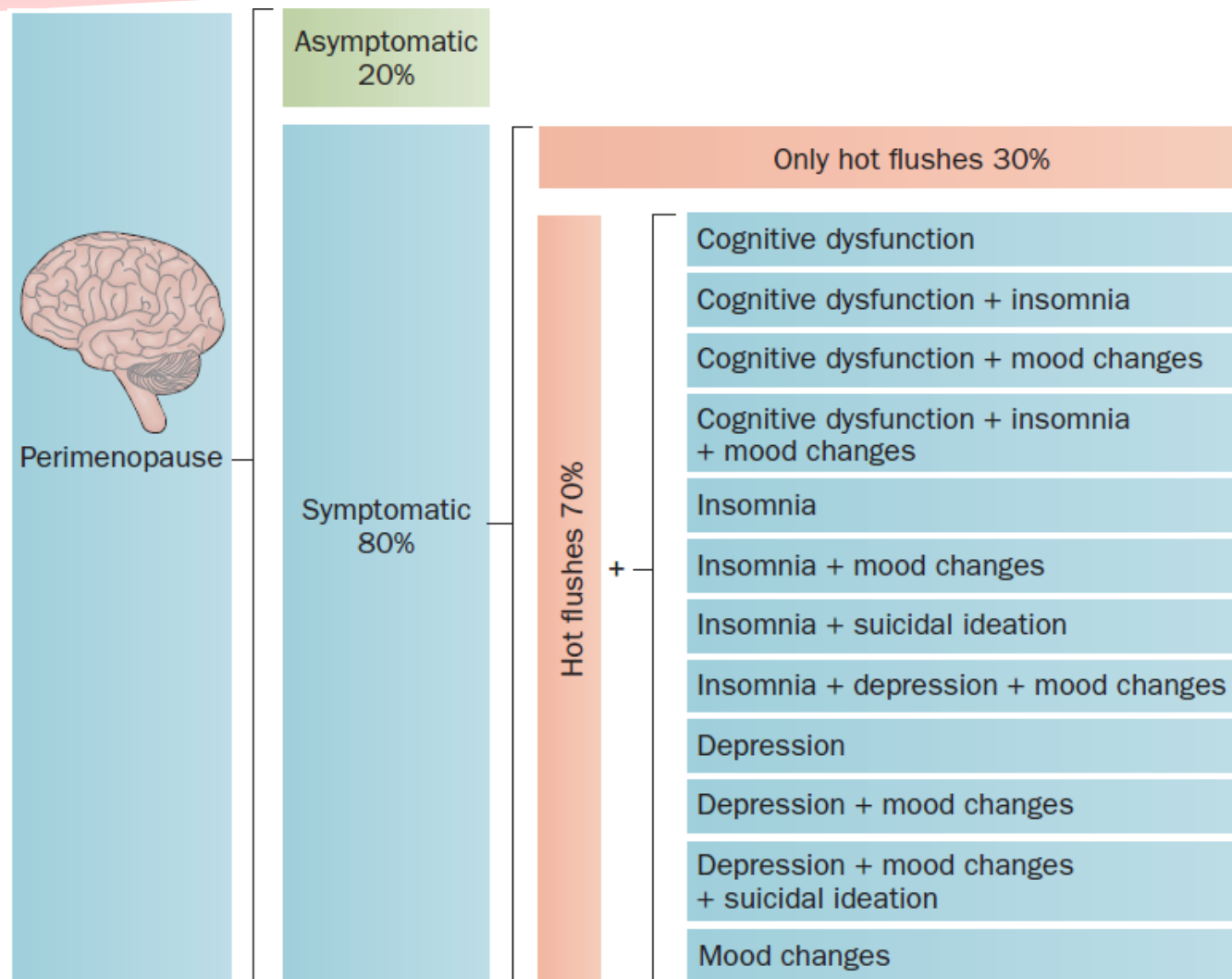
De Kruif M et al. *J Affect Disord* 2016;206:174-80

Prevalence of sleep difficulty across the menopausal transition (SWAN)



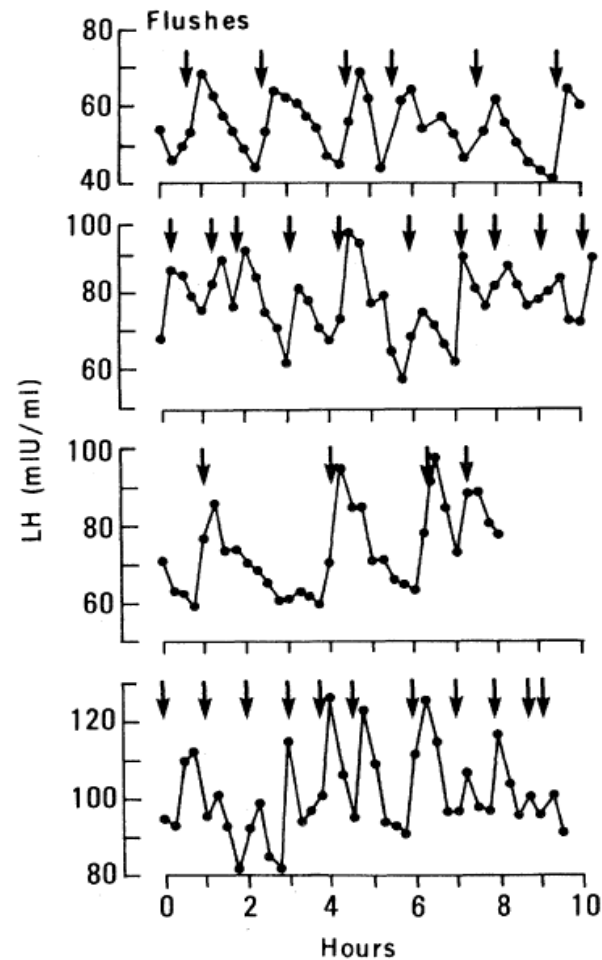
Kravitz HM, Joffe H. *Obstet Gynecol Clin North Am* 2011;38:567-86

Neurological symptoms in the menopausal transition



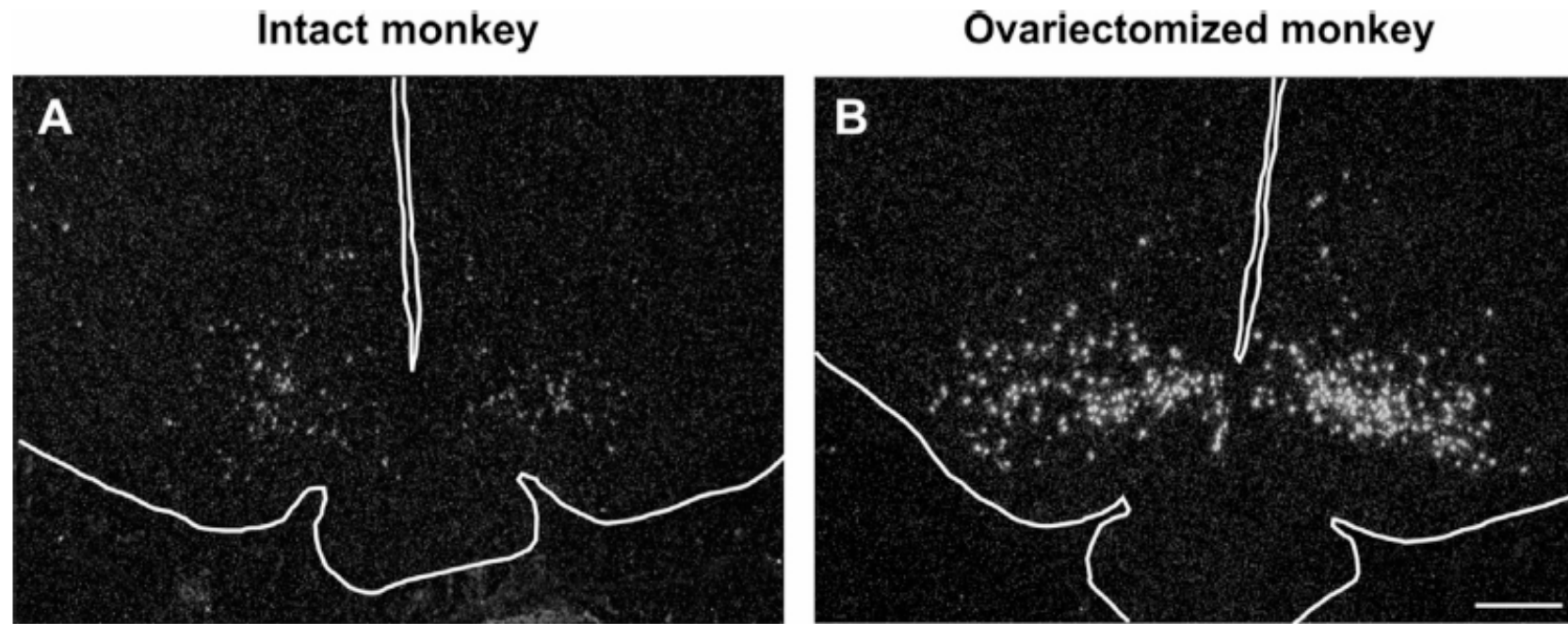
Brinton RD et al. *Nat Rev Endocrinol* 2015;11:393-405

Vasomotor symptoms and LH levels



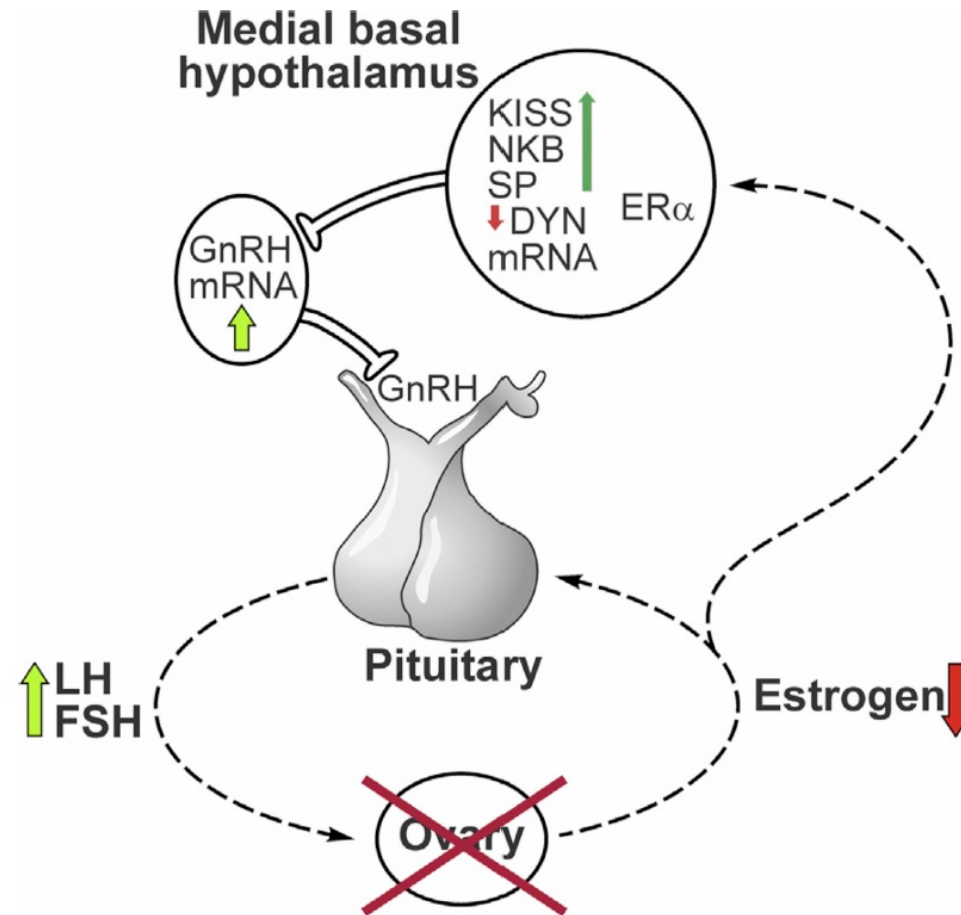
Casper & Yen. *J Clin Endocrinol Metab* 1981;53:1056-8

Neurokinin B m-RNA expressing neurons before and after oophorectomy



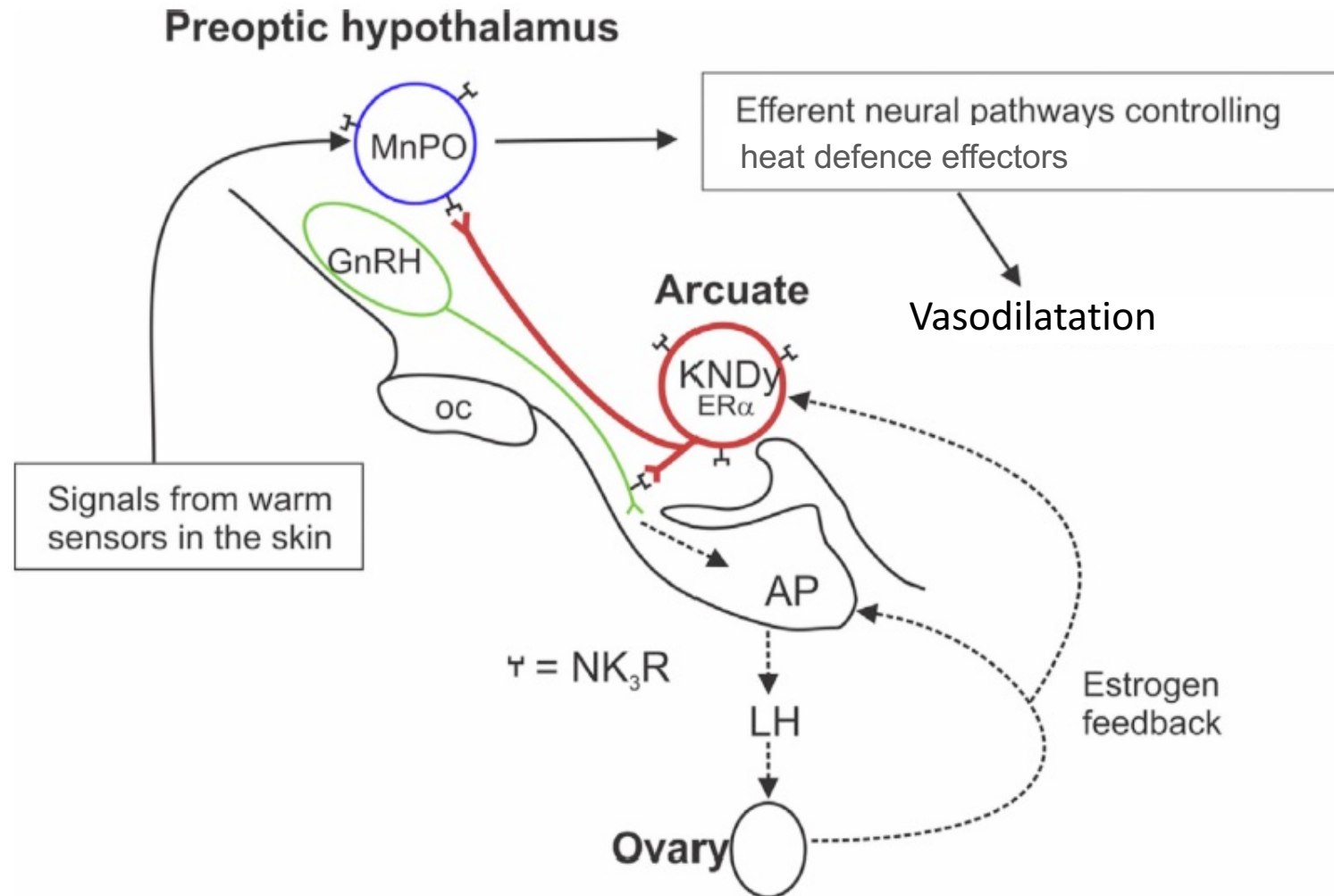
Rance NE et al. *Front Neuroendocrinol* 2013;34:211-27

Postmenopausal changes in neuronal activity



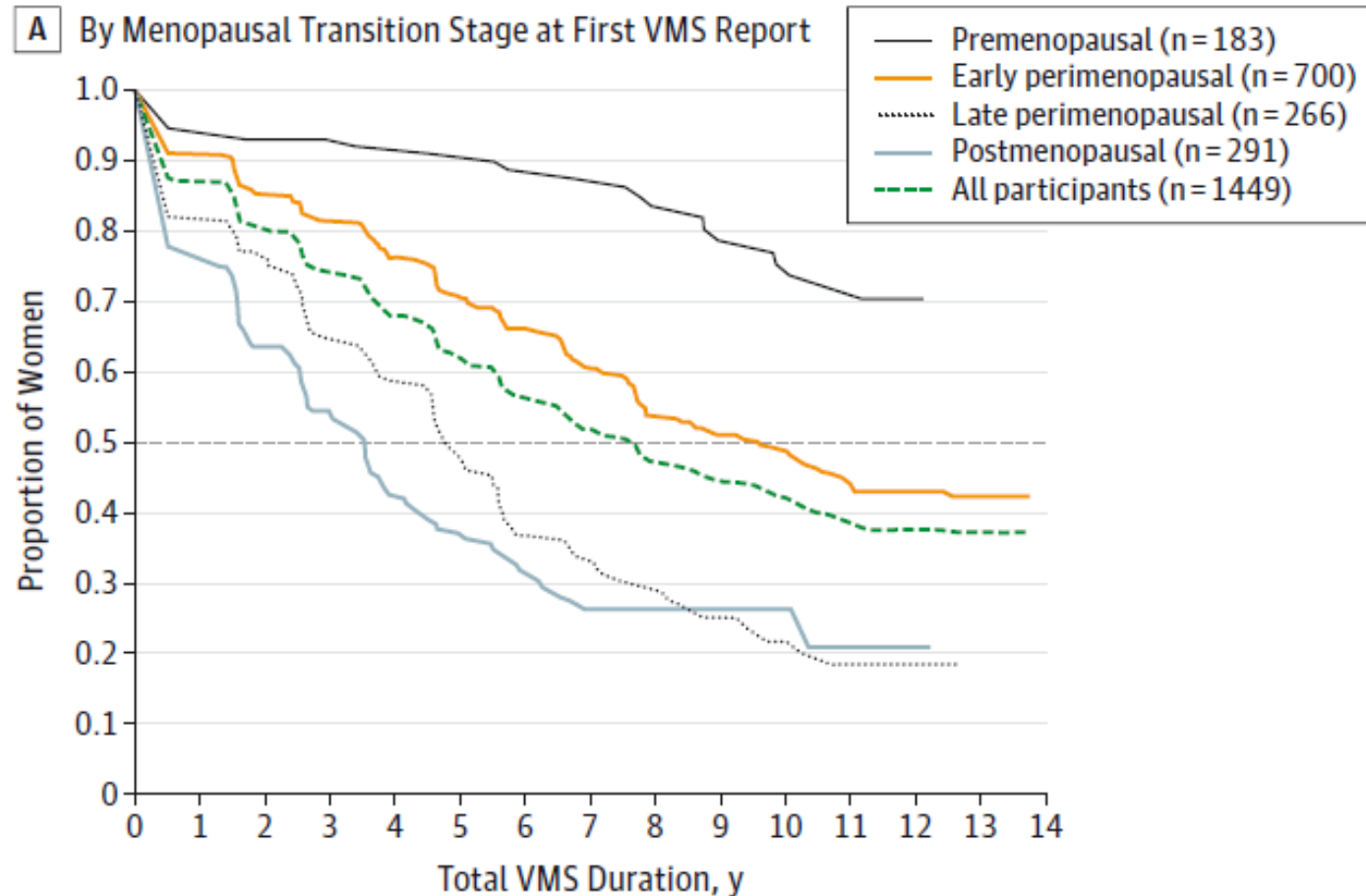
Rance NE et al. *Front Neuroendocrinol* 2013;34:211-27

KNDy neurons, GnRH neurons, and the heat-defence mechanism



Rance NE et al. *Front Neuroendocrinol* 2013;34:211-27

Total duration of vasomotor symptoms (SWAN)



Avis NE et al. *JAMA Intern Med* 2015;175:4:531-9

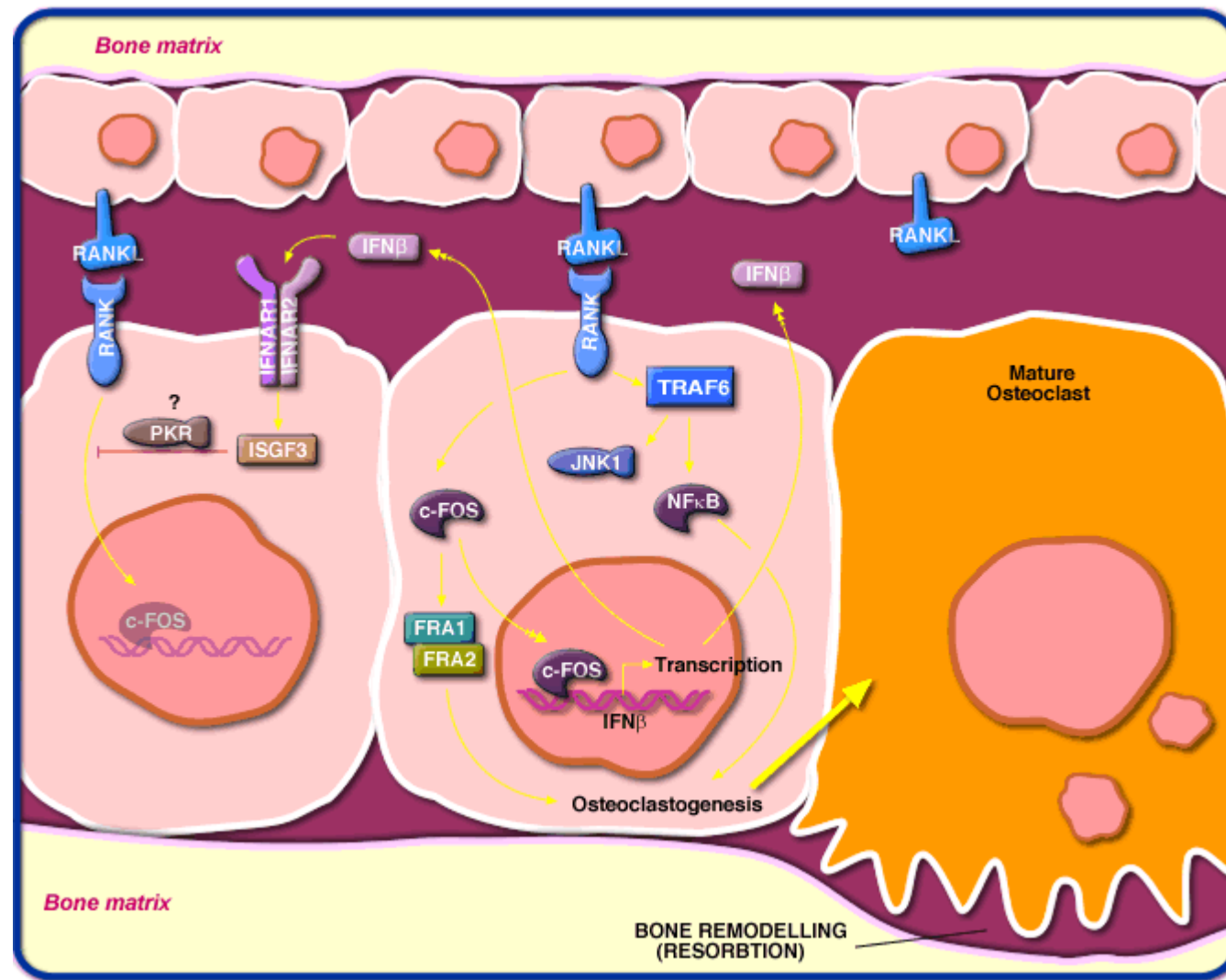
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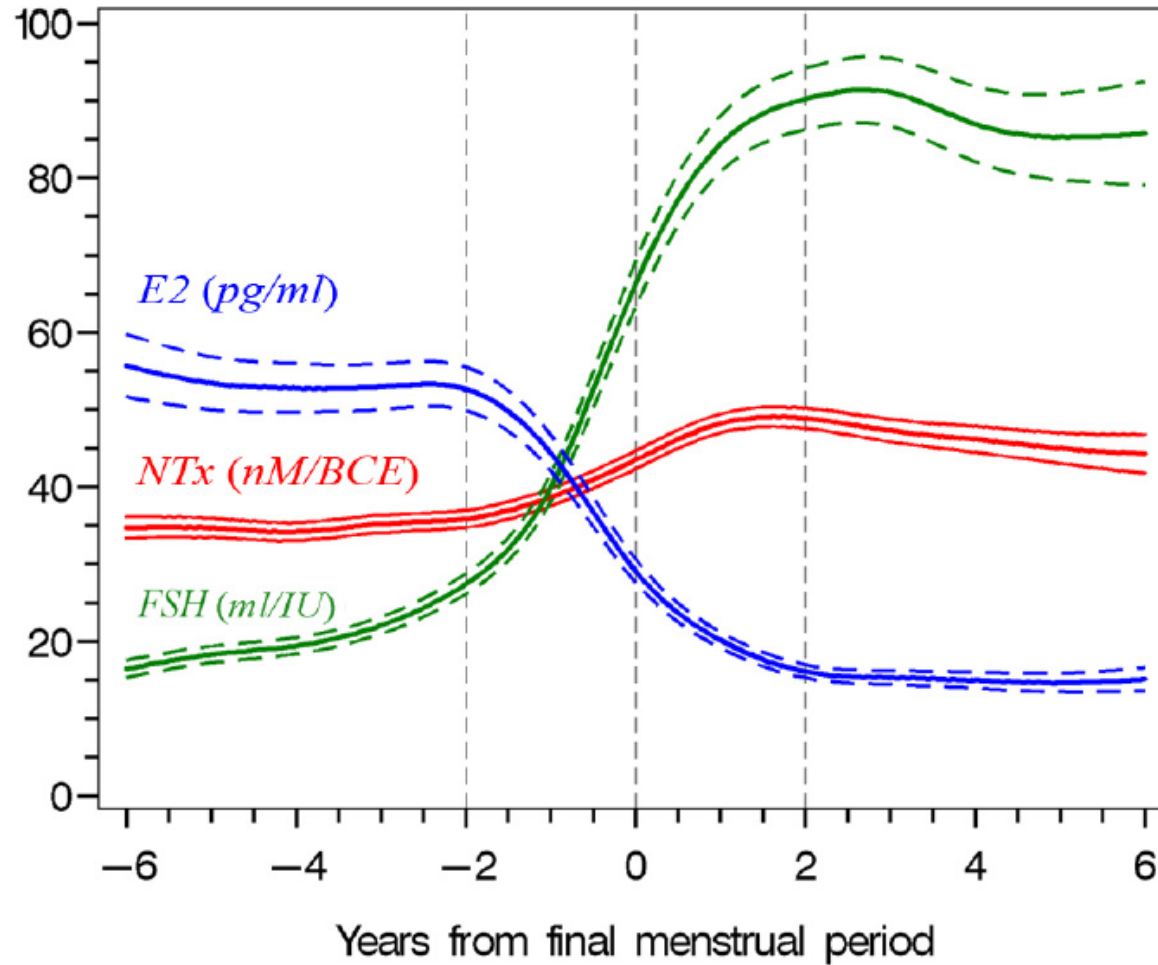
Vertebral osteoporosis



Osteoclastogenesis and the RANK/RANKL interaction



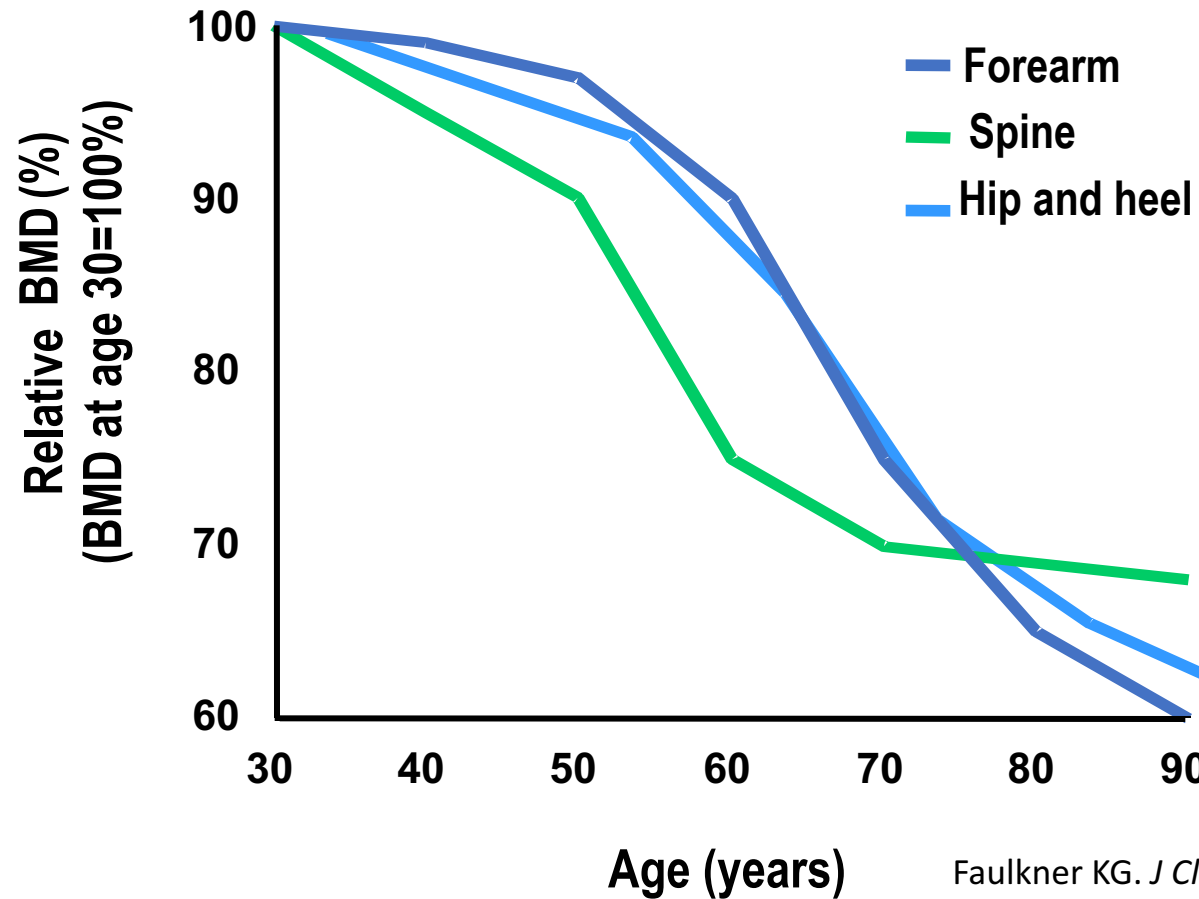
Change in bone resorption (SWAN)



NTx = urinary type 1 collagen N-telopeptide

Sowers MR et al. *J Clin Endocrinol Metab* 2013;98:2854-63

Bone loss rates for women



Faulkner KG. *J Clin Densitom* 1998;1:279-85

Risk factors for osteoporosis

Risk for low bone mass

Advanced age

Female sex

White or Asian race

Thin body build
(body weight < 57 kg)

Early menopause

Estrogen deficiency

Positive family history

Chronic use of corticosteroids

Lifestyle: inadequate calcium intake, cigarette smoking, excess alcohol intake, or lack of physical activity

Risk for fracture

Existing fracture

Reduced BMD

Positive family history of osteoporotic fracture

Advanced age

Smoking

Propensity to falls

Postural instability

Osteoporosis Society of Canada. *Osteoporosis Update* 1999

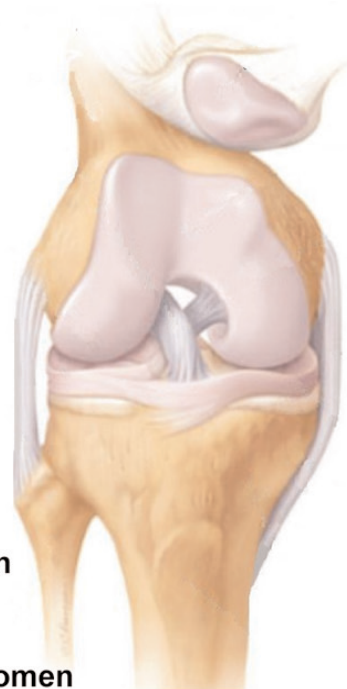
Estrogen effects on articular tissues

Cartilage

- Increases PG production in chondrocytes
- Decreases NF- κ B, iNOS, COX-2, ROS in chondrocytes
- Regulates [Ca²⁺]_i in chondrocytes
- Decreases cartilage damage in several animal models

Subchondral bone

- Regulates bone growth and remodeling
- Regulates OB development and function
- Regulates matrix production and mineralization
- Reduces bone formation and prevalence of total marginal osteophytes in OVX monkeys
- Decreases MRI-likelihood of bone attrition in women



Muscle

- Promotes myoblasts proliferation and differentiation
- Decreases muscle cell apoptosis
- Reverses muscle contractile dysfunction in rats
- Decreases muscle atrophy and calpain levels in rats
- Enhances muscle performance and structure in women

Synovium

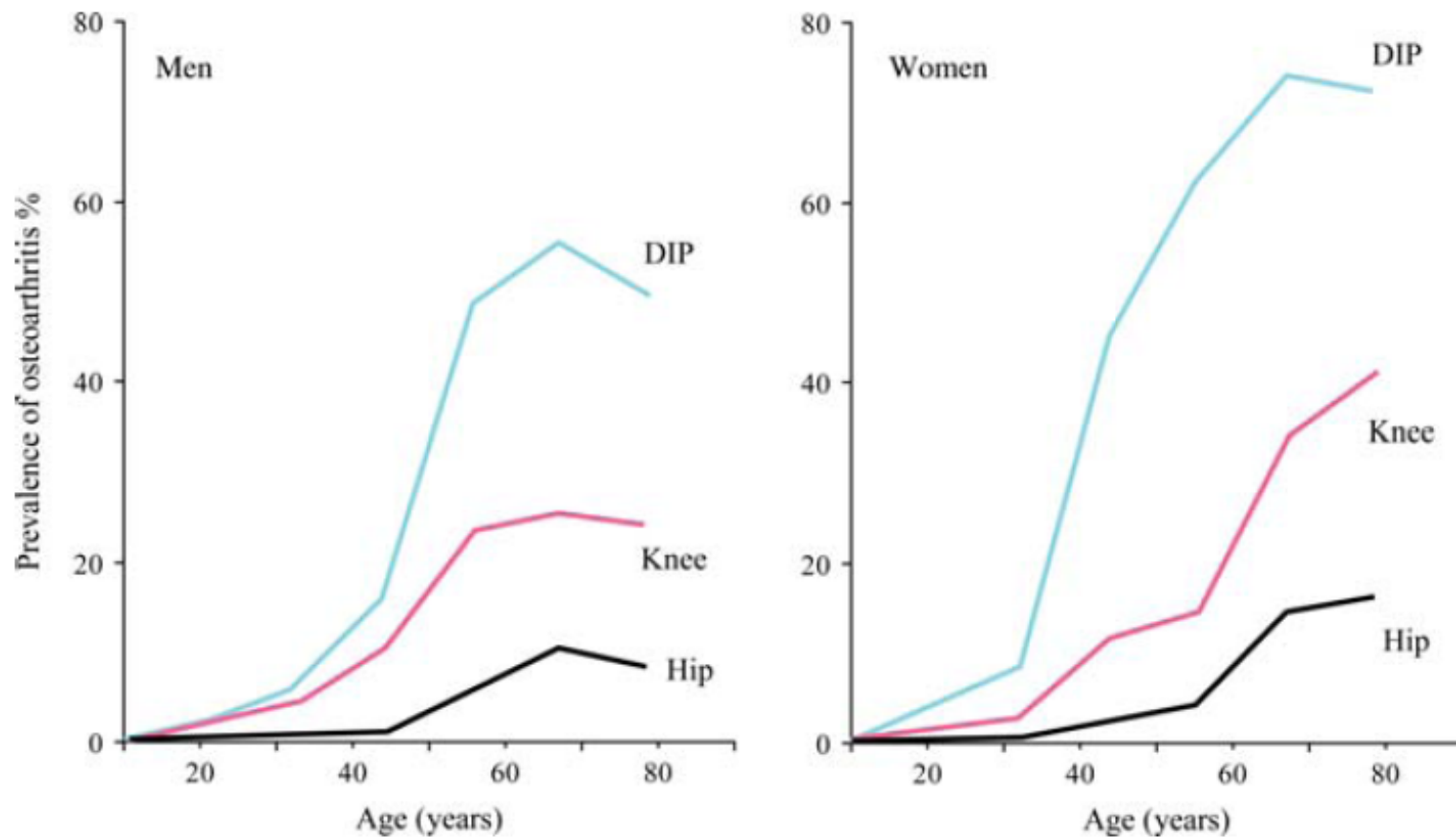
- Increased synovial levels of components of the IGF pathway in OVX monkeys
- Reversed autoimmune arthritis developed in mice
- Decreased rheumatoid factor, anti-double-stranded DNA, and anti-type II collagen serum levels in mice

Ligaments

- Contrasting effects on ACL mechanical properties in animal models
- High estrogen levels during the menstrual cycle have been associated with ACL ruptures in young women

Roman-Blas JA et al. *Arthritis Res Ther* 2009;11:241-55

Prevalence of osteoarthritis by age



Van Saase JLCM et al. *Ann Rheum Dis* 1989;48:271-80