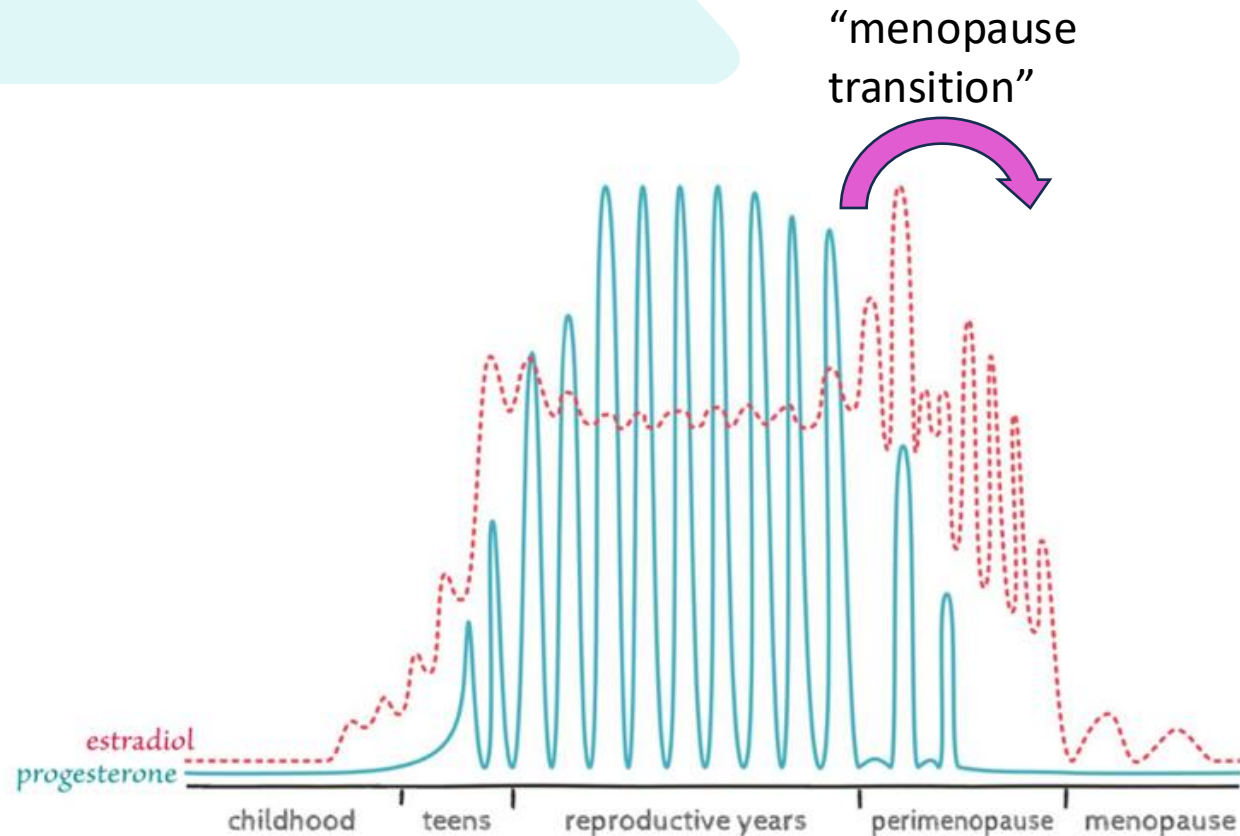


Mapping The Perimenopausal Metabolic Switch

Tanya Borowski
Head of Education

The hormonal journey

- At a young age women react strongly to oestrogen - receptors are super sensitive
- Not ovulating to counterbalance oestrogen = heavy periods in teens
- Can take up to 12 years to mature menstrual cycle
- **Perimenopause** – the isomer of menarche



Nomenclature



perimenopause / the menopause transition

noun [C]

Perimenopause is the two to twelve years before menopause. It can be the time of greatest symptoms.

menopause Also called post-menopause

noun [C]

Menopause is the life phase that begins one year after the last period. It is usually the time of almost no symptoms.

Nomenclature

The Stages of Reproductive Aging Workshop (STRAW +10) system is a defined set of nomenclature which describes the stages of ovarian ageing.

Nomenclature:- Stages of Reproductive Aging Workshop(STRAW+10)

First Period					Final Menstrual Period						
Stage	-5	-4	-3b	-3a	-2	-1	0	+1a	+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	Stabilizers 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		

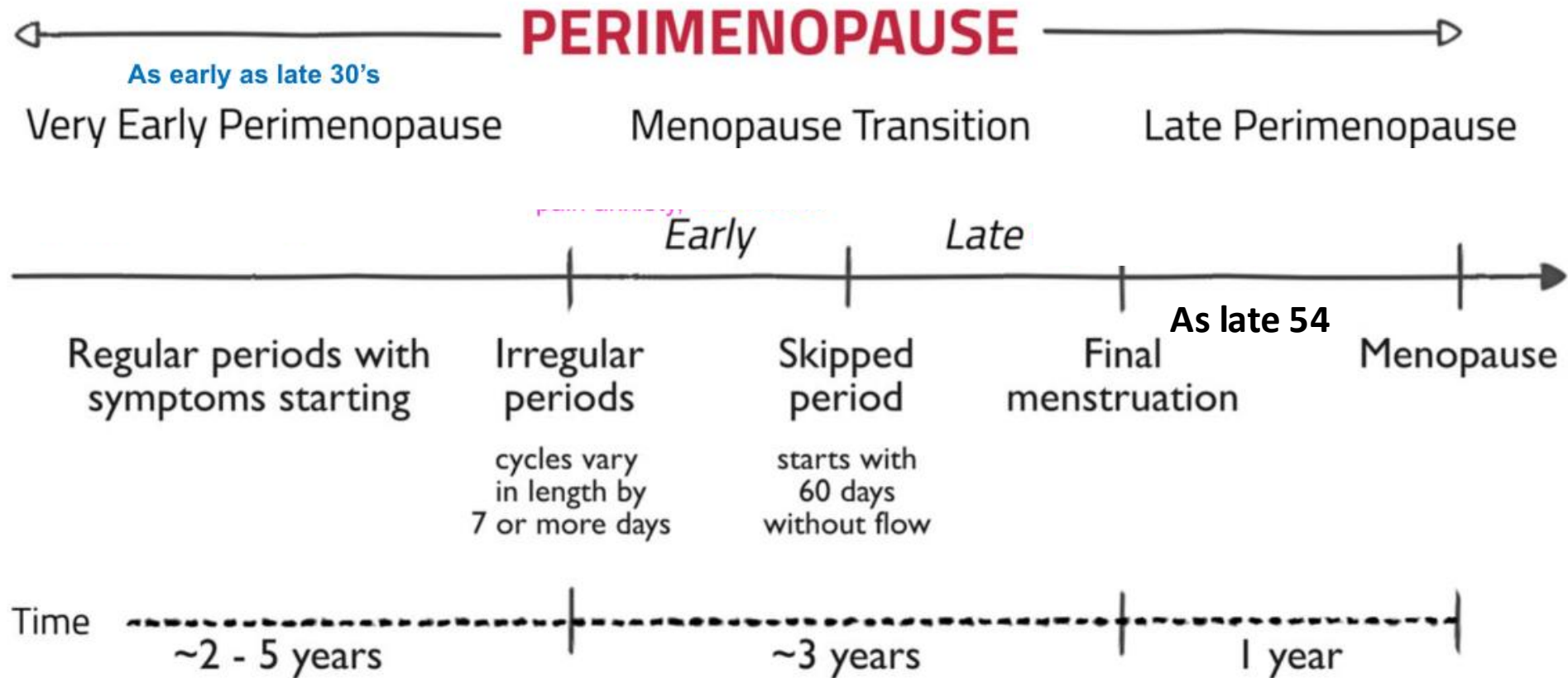
Source: Harlow, S. D., Gass, M., Hall, J. E., Lobo, R., Maki, P., Rebar, R. W., Sherman, S., Sluss, P. M., de Villiers, T. J., & STRAW+10 Collaborative Group (2012). Executive summary of the Stages of Reproductive Aging Workshop +10: addressing the unfinished agenda of staging reproductive aging. Climacteric : the journal of the International Menopause Society, 15(2), 105-114.

perimenopause
persistent
differences in
cycle length of
seven or more
days between
consecutive
cycles (Stage -2)

Menopause
12 months after
the last
menstrual
period (stage +1a)

Naming Women's Midlife

JERILYNN C. PRIOR, UBC PROF. ENDOCRINOLOGY, UBC-CEMCOR



"I feel weird"| anxious| breast pain | periods no change

Cycles start to change
Unopposed E2 symptoms ; neurological changes
(mood, hot flushes) , sleep issues , heavy flooding,
metabolic changes, bone loss.

“Women need to know that perimenopause ends in a kinder and calmer phase of life called menopause”

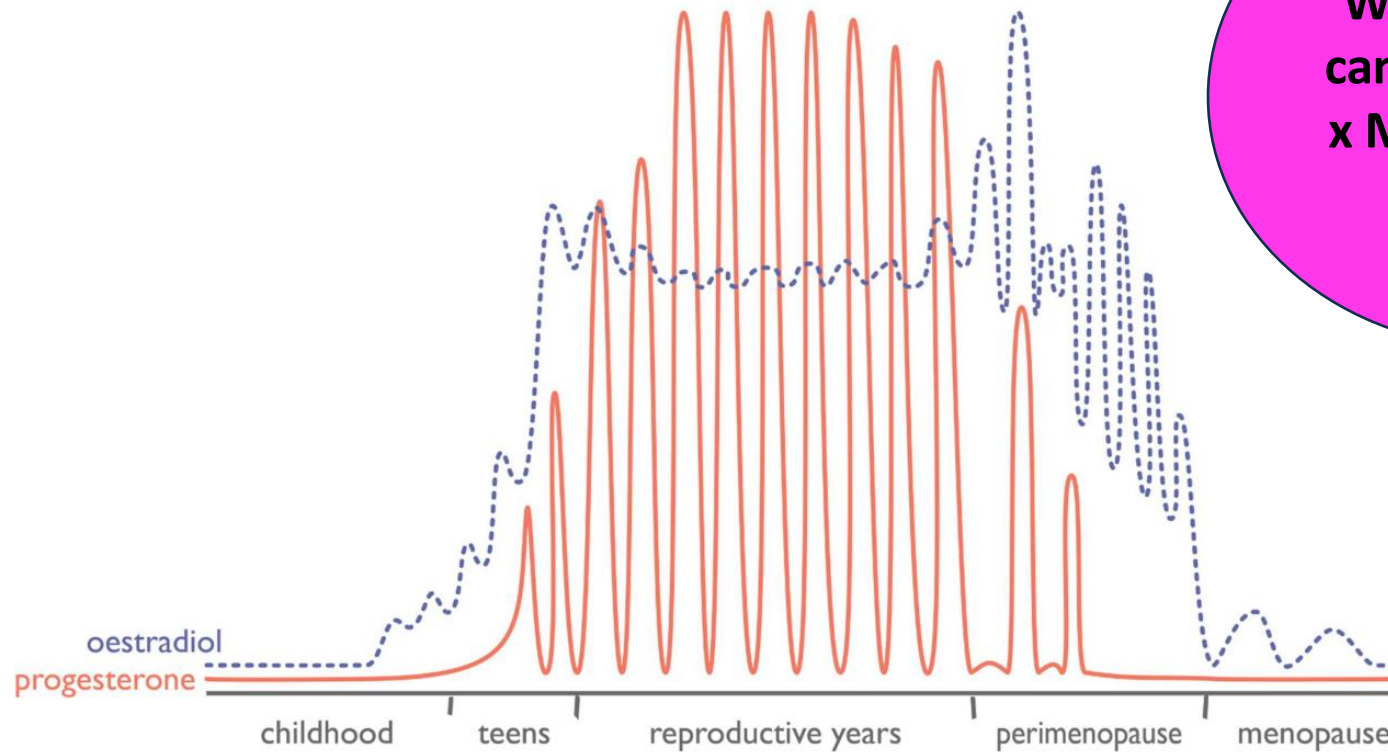
Dr Jerilynn C . Prior

Why?

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menopause transition

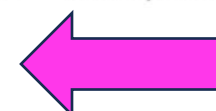
-Perimenopause-



Women in 40's
can have up to 3
x MORE E2 than
in 30's

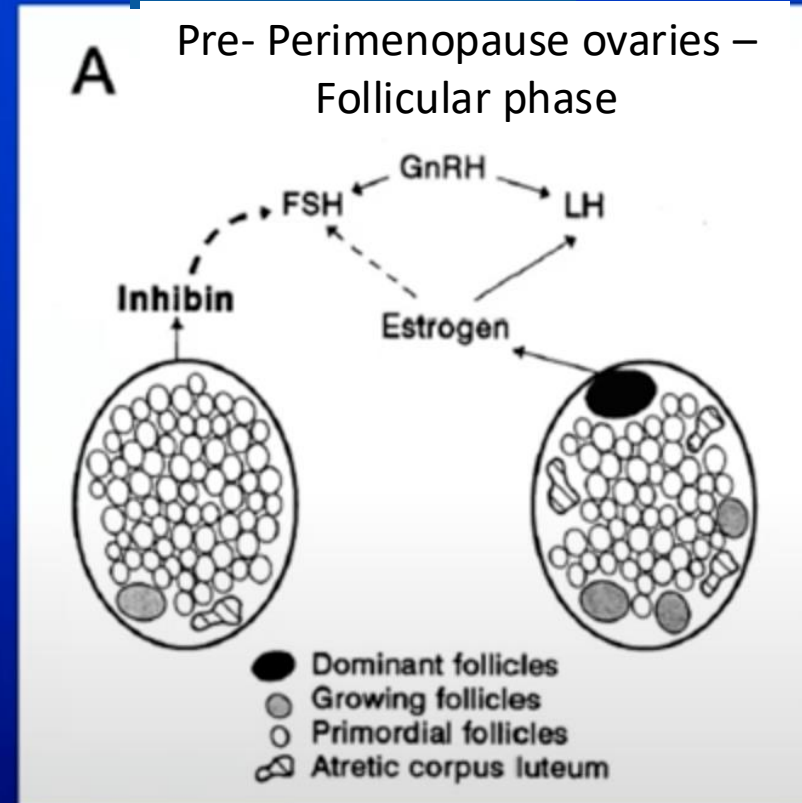


Building of metabolic reserve



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-Perimenopause –

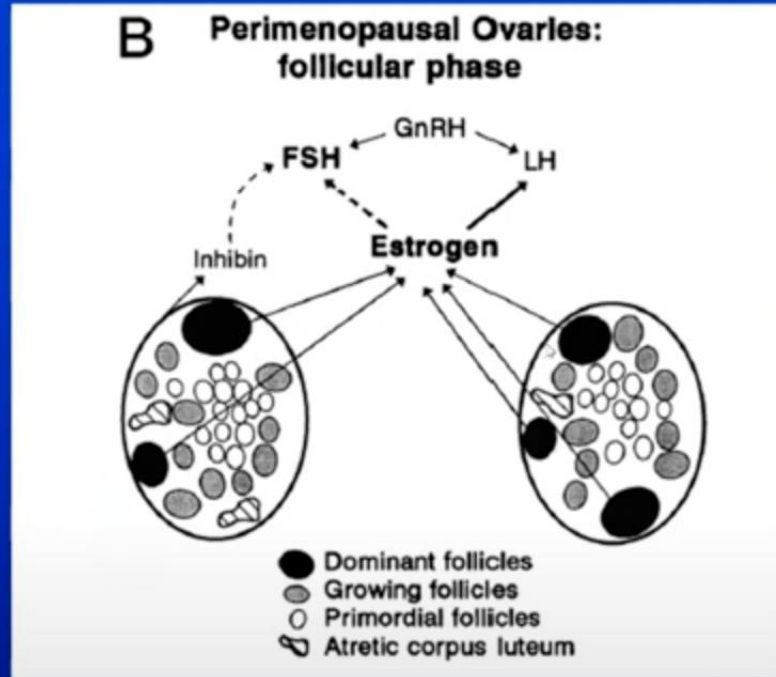


GnRH = brain control of ovaries
FSH = Pituitary Follicle Stimulating Hormone

Prior JC *Endocrine Reviews* 1998;19:397-428

JcPrior 2024

-Perimenopause –



Lower Inhibin allows the ovaries to get rid of un-needed follicles

Women in 40's can have up to 3 x MORE E2 than in 30's

Note

- >The lower follicle number
- >Much lower inhibin levels

Dominant follicles (plural) making more oestrogen – but not reliably suppressing FSH

Perimenopause – Unpredictable – No Definitive Test

Perimenopause is “diagnosed” by symptoms

3 of the following 9 changes

1. New – onset heavy and /or longer flow
2. Shorter menstrual cycles (<26 days)- *due to high FSH >> ovulating more rapidly*
3. New sore, swollen or lumpy breasts
4. New mid-sleep waking
5. Increased menstrual cramps
6. Onset of night sweats
7. New or increased migraine headaches
8. New or increased PMS mood swings
9. Weight gain without changes in diet

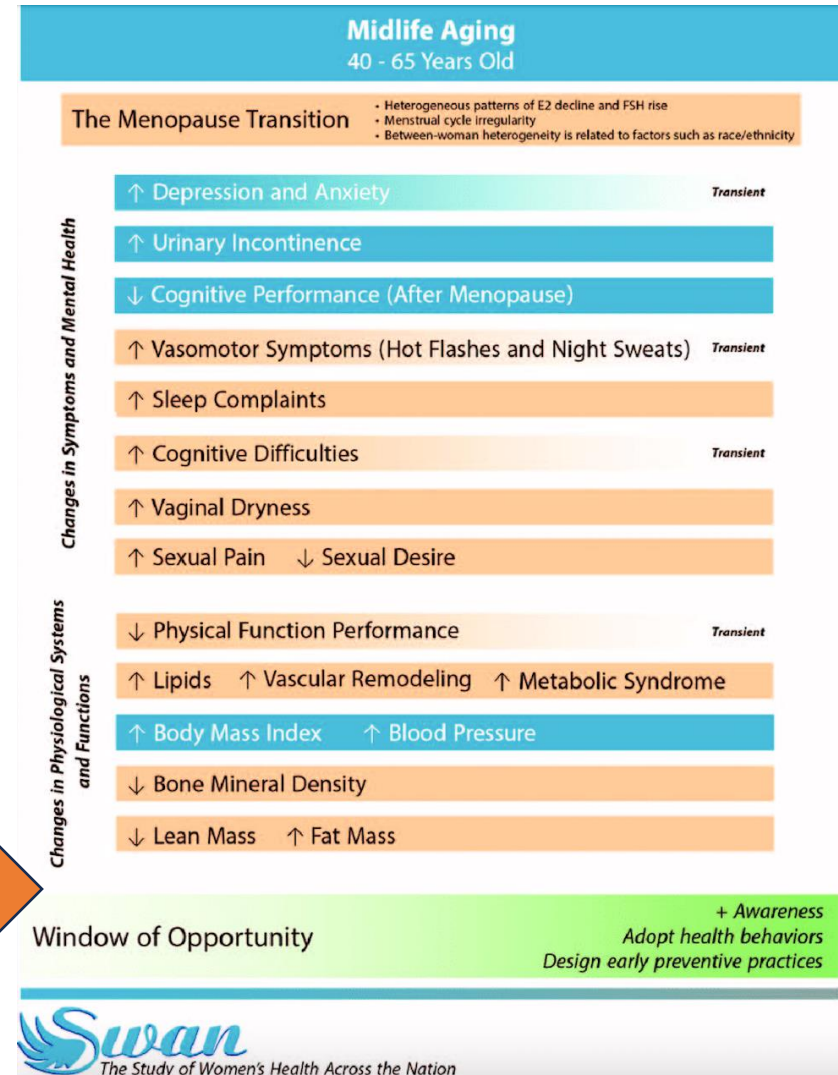
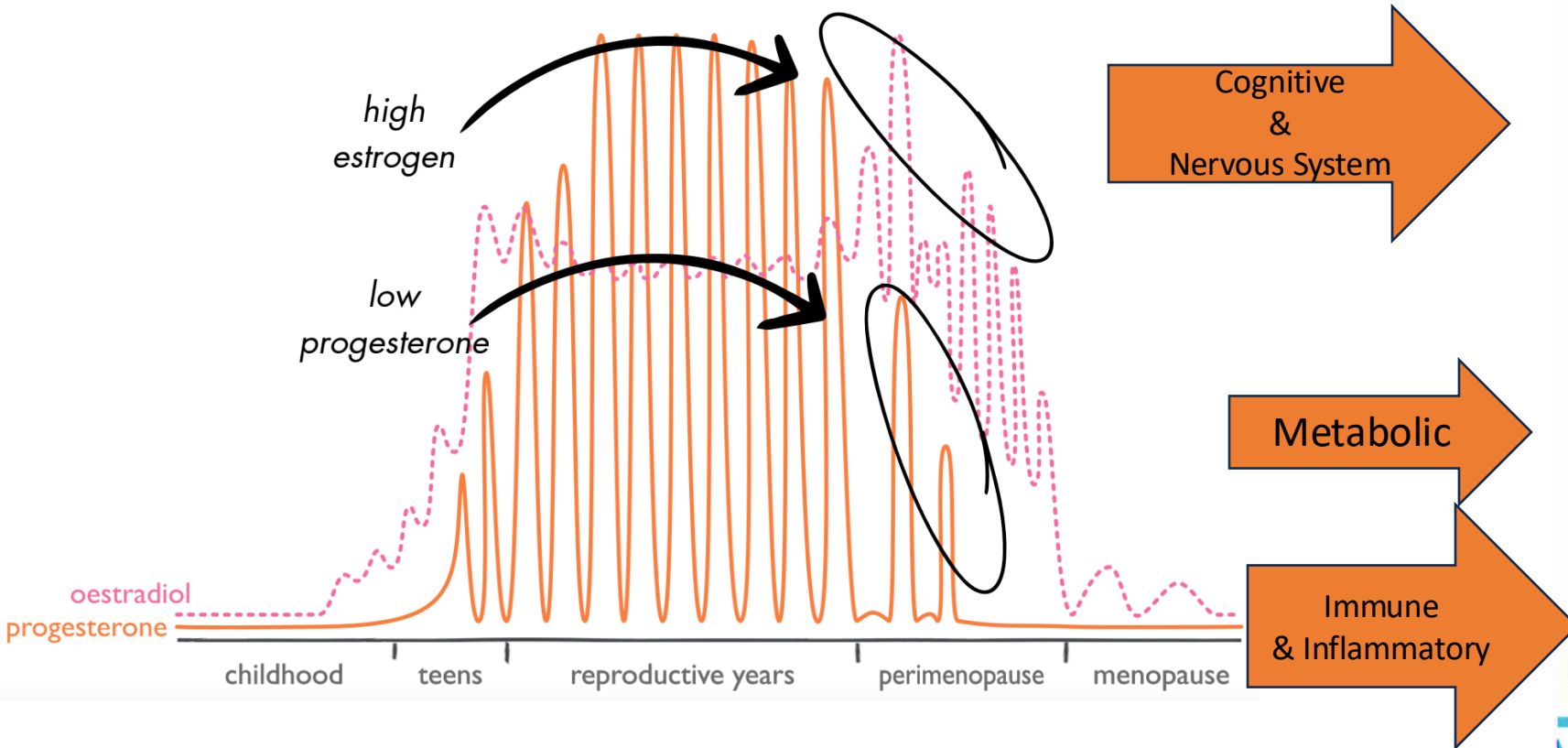
PLUS other conditions being ruled out

These symptoms result from

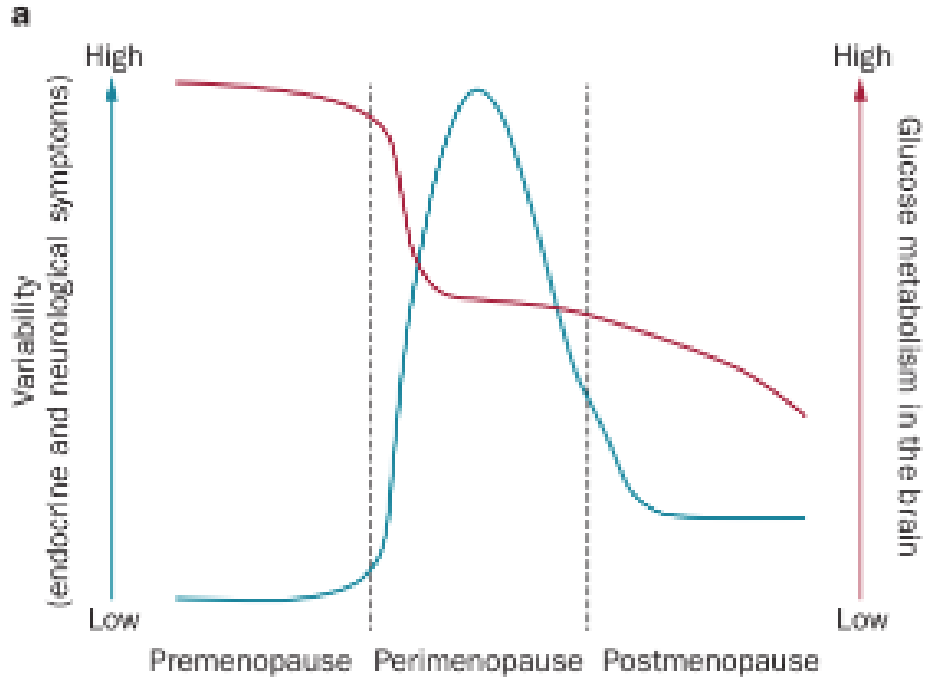
Higher E2
(In some activation mast cells)
&
Lower

Perimenopause can be a tipping point

“Window of Opportunity” SWAN



Rewiring the brain- Impact Fluctuating Oestrogen



Mosconi, L et al. Sci Rep. 2021 Jun 9;11(1):10867. PMID: 34108509

scientific reports

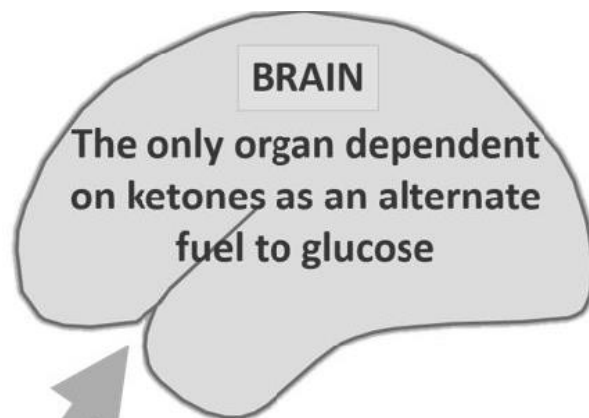
OPEN

Menopause impacts human brain structure, connectivity, energy metabolism, and amyloid deposition

Lisa Mosconi^{1,2,3,4,5}, Valentina Berti⁴, Jonathan Dyke⁶, Lacey Loughlin¹, Grace Jang¹, Aneela Rahman¹, Howard Randolph Andrews⁵, Dawn Matthews⁵, Orli Ettinger⁷, Richard Isaacson¹ & Roberta Diaz Brinton⁸

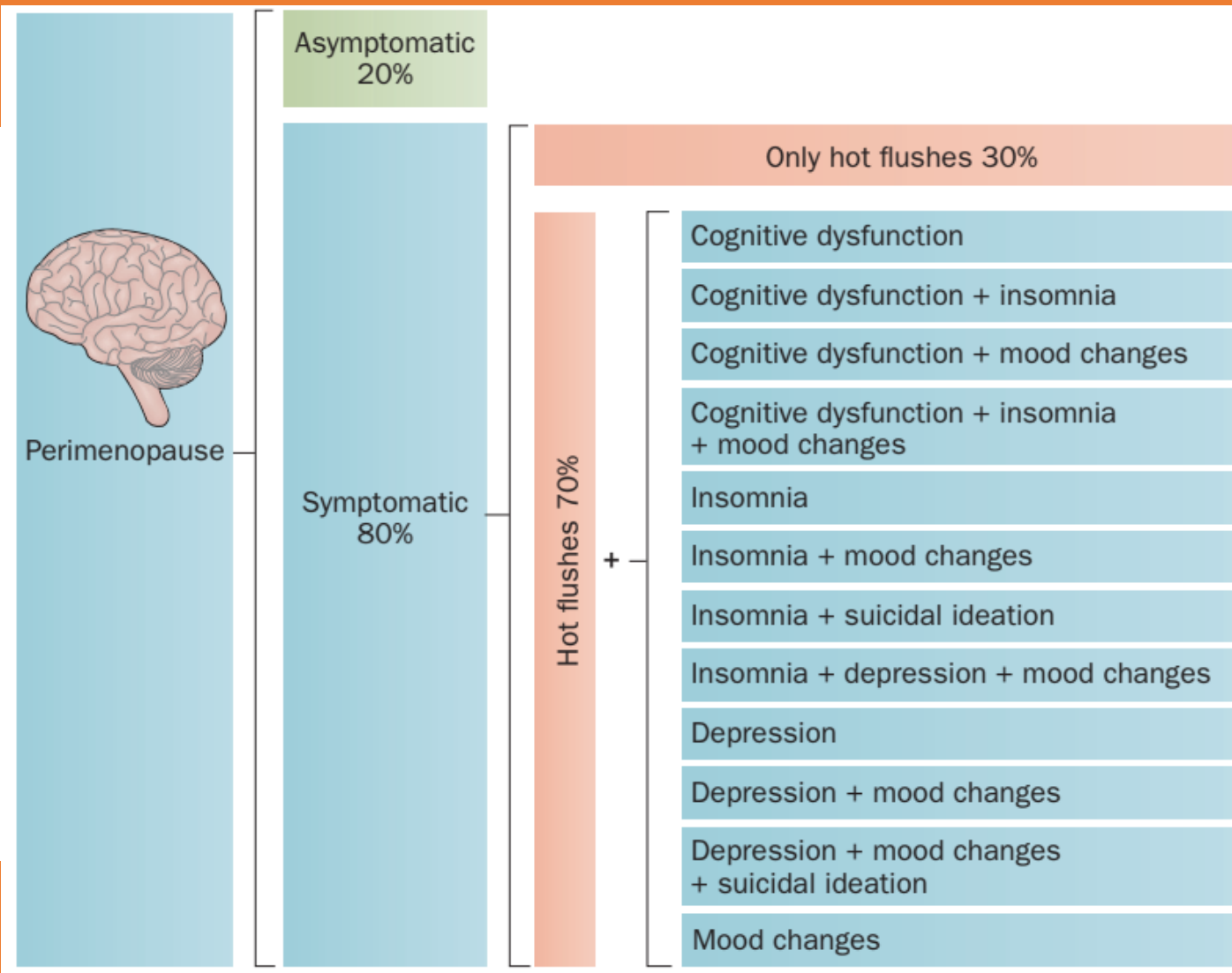
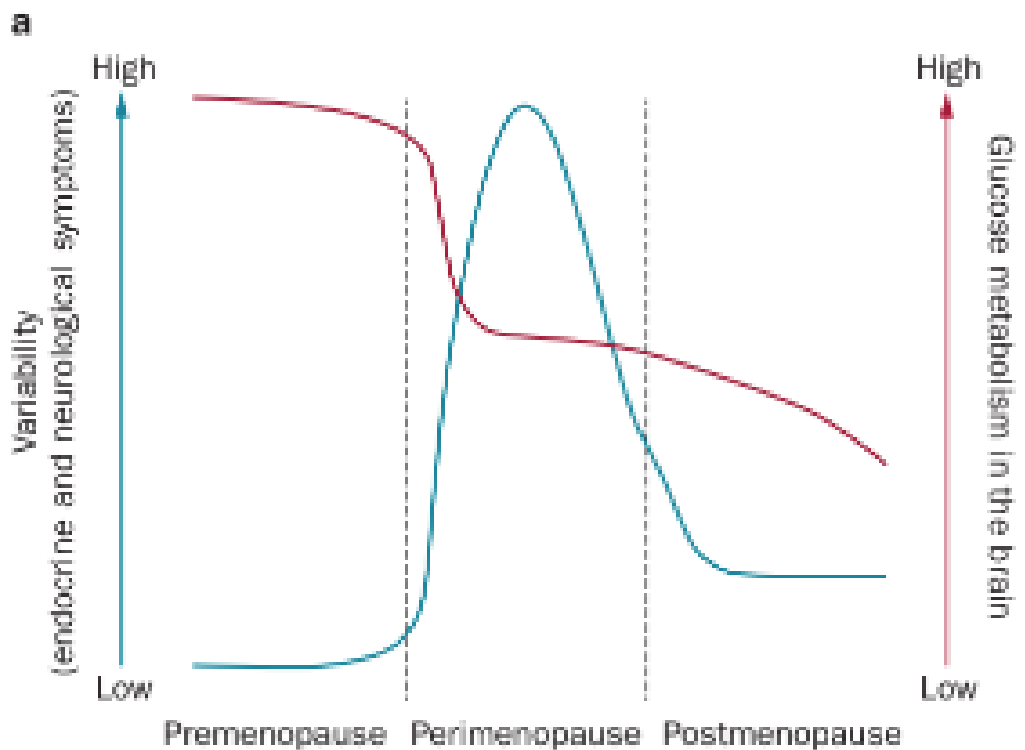
All women undergo the menopause transition (MT), a neuroendocrine process that impacts aging trajectories of multiple organ systems including brain. The MT is characterized by clinically defined stages with specific neuroendocrine, metabolic, and cognitive changes. This multi-modality neuroimaging study indicates

“...oestrogen loss... triggers a decline in [glucose metabolism] prompting an adaptive reaction to increase ketone bodies utilization...”



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Menopause Is Associated With Postprandial Metabolism, Metabolic Health and Lifestyle: The ZOE PREDICT Study

18 Pages • Posted: 11 Mar 2022

[Kate Bermingham](#)

King's College London - Department of Twin Research

[Inbar Linenberg](#)

Zoe Global Limited

[More...](#)

"Menopause is a time of major metabolic upheaval."

Abstract

Background: The menopause transition is associated with unfavourable alterations in health. However, postprandial metabolic changes and their mediating factors are poorly understood.

Methods: The PREDICT 1 UK cohort (n=1002; pre- n=366, peri- n=55, and post-menopausal females n=206)

assessed phenotypic characteristics, anthropometric, diet and gut microbiome. **Bermingham et al., 2022. "Menopause is associated with postprandial metabolism, metabolic health." EBioMedicine.** postprandial (0-6h) cardiometabolic blood measurements, including continuous glucose monitoring (CGM)

Cardiometabolic Effects Perimenopause

'EARLY' PERIMENOPAUSE

Hormones*

↔ E₂ (relatively unchanged)
↑ FSH *

CVD Risk Factors

↑ C-IMT and vascular remodeling
↓ Endothelial function (FMD)



NOTE: Few studies of women in *early perimenopause* have been conducted due to the inherent difficulty in categorizing women in this earlier stage. As a result, the cardiometabolic changes that occur during *early perimenopause* have yet to be fully elucidated.

'LATE' PERIMENOPAUSE

Hormones*

↓ E₂ * and AMH
↑ FSH *

Body Composition

↑ Fat mass (abdominal fat)
↓ Fat-free (lean) mass

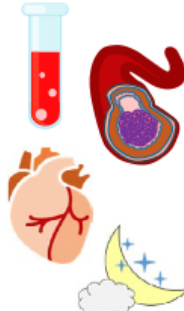


Energy Intake & Expenditure

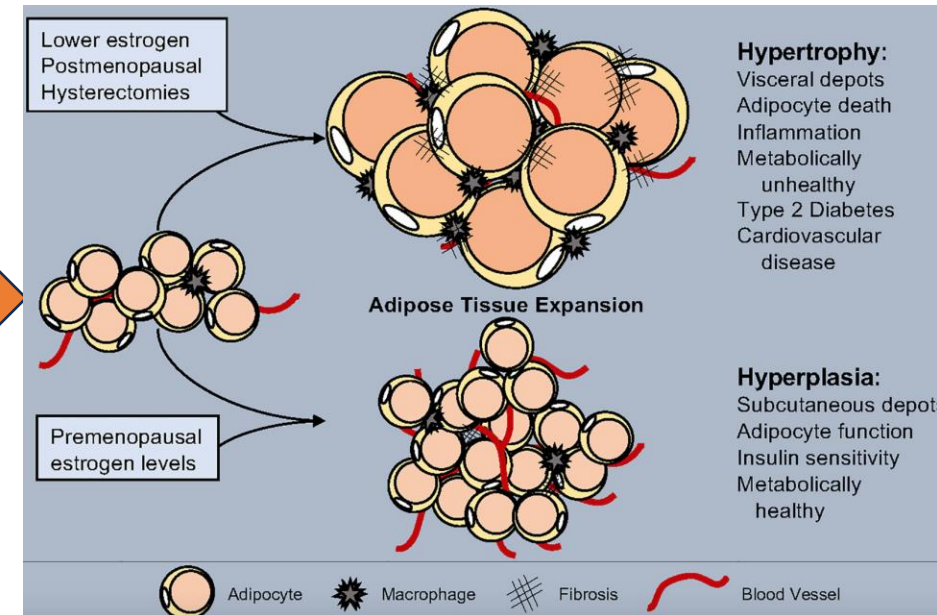
↓ 24-h, Sleep, & Physical Activity EE
↓ Resting EE (?)
↓ Fat oxidation
↓ Energy Intake

Cardiovascular Risk Factors

↑ Dyslipidemia (mostly within 1-year of FMP)
↑ C-IMT, Aortic PWV, and vascular remodeling
↓ Endothelial function (FMD) and cardiac health
↑ Insulin resistance
↑ Sleep disturbances



Adipocyte dysfunction



<https://doi.org/10.3389/fendo.2022.889923>

Subcutaneous fat

- Produces beneficial adipokines, leptin & adiponectin.
- Generally anti-inflammatory, especially gynoid fat.

Hypertrophied visceral fat

- Produces resistin and is associated with leptin resistance.
- Highly inflammatory.

Perimenopause Nervous System Vulnerability

INTERNATIONAL REVIEW OF PSYCHIATRY, 2017
VOL. 29, NO. 6, 580–596
<https://doi.org/10.1080/09540261.2017.1397607>

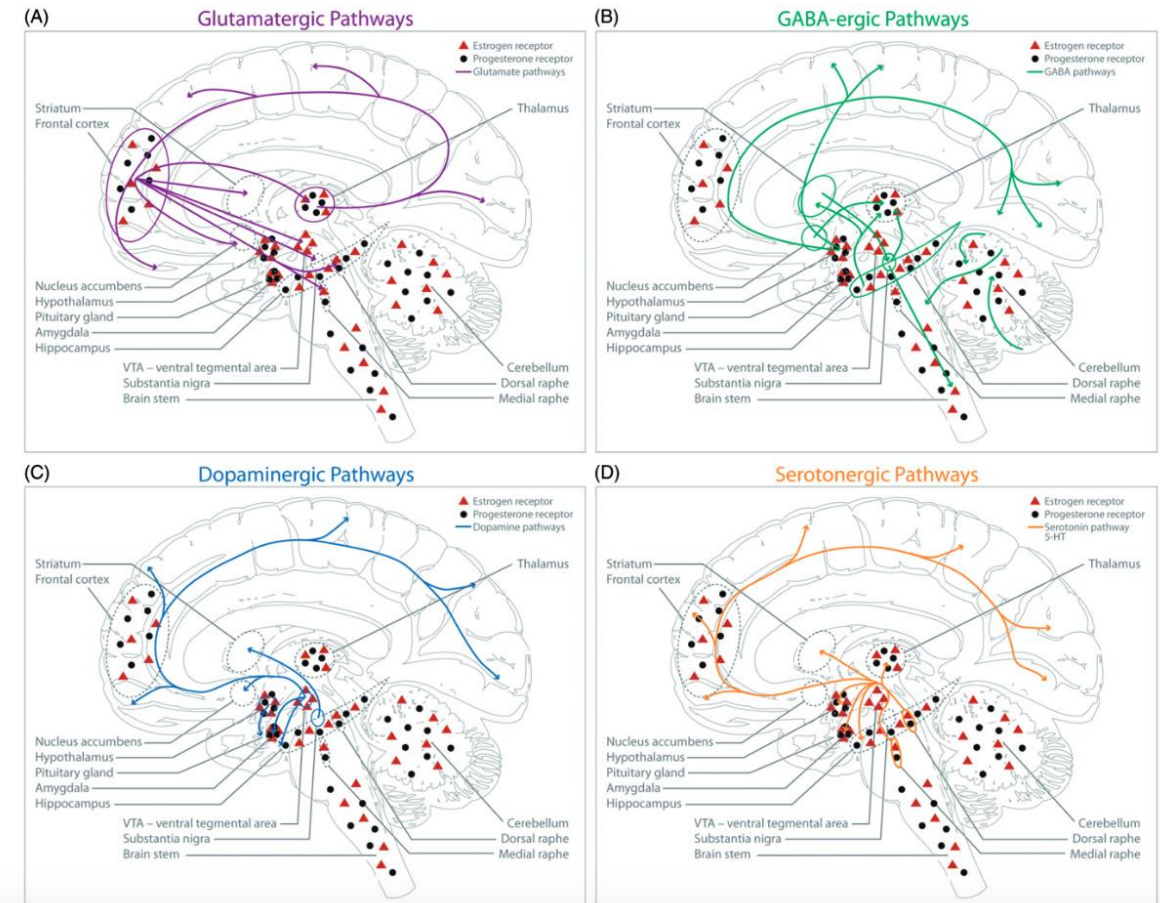
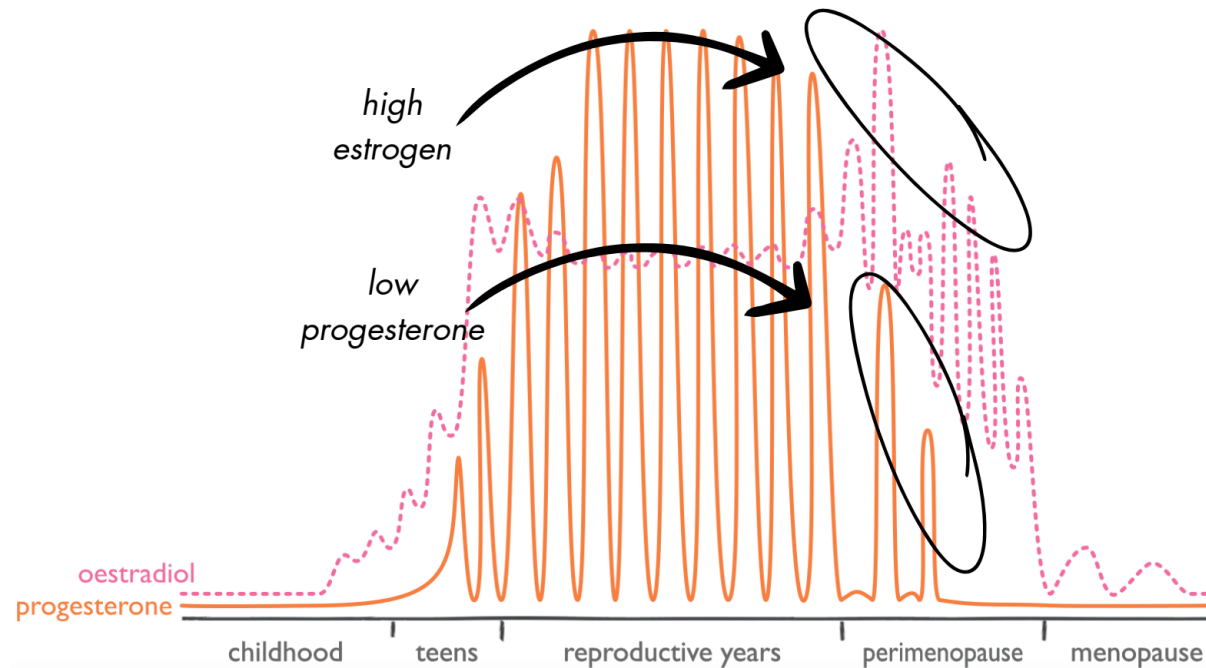
Taylor & Francis
Taylor & Francis Group

REVIEW ARTICLE

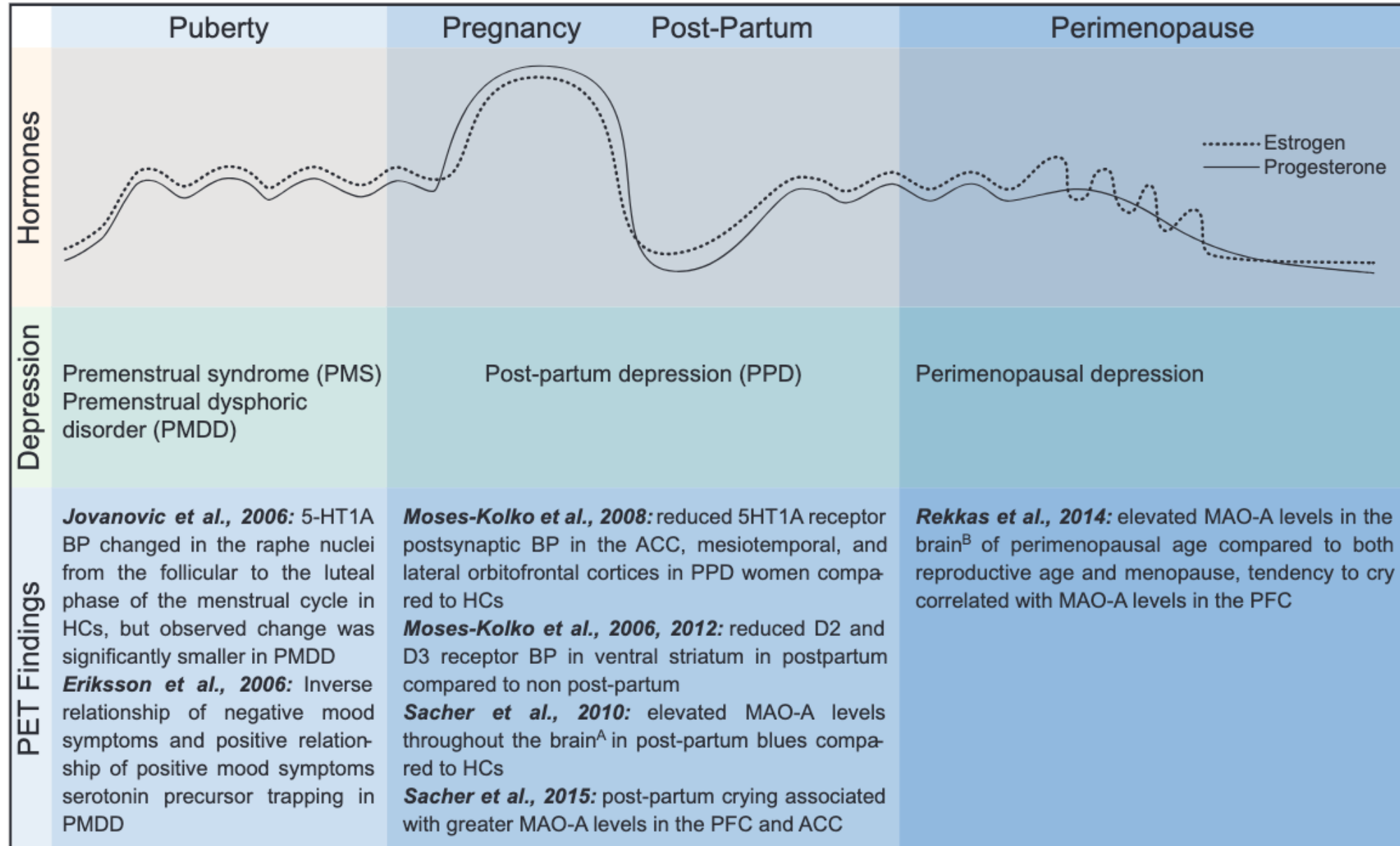
OPEN ACCESS Check for updates

Using positron emission tomography to investigate hormone-mediated neurochemical changes across the female lifespan: implications for depression

Rachel G. Zsido^{a,b}, Arno Villringer^{b,c} and Julia Sacher^{a,b,c}



Hormonal Transition Periods and Mood Disorder Findings in PET in the Reproductive Years

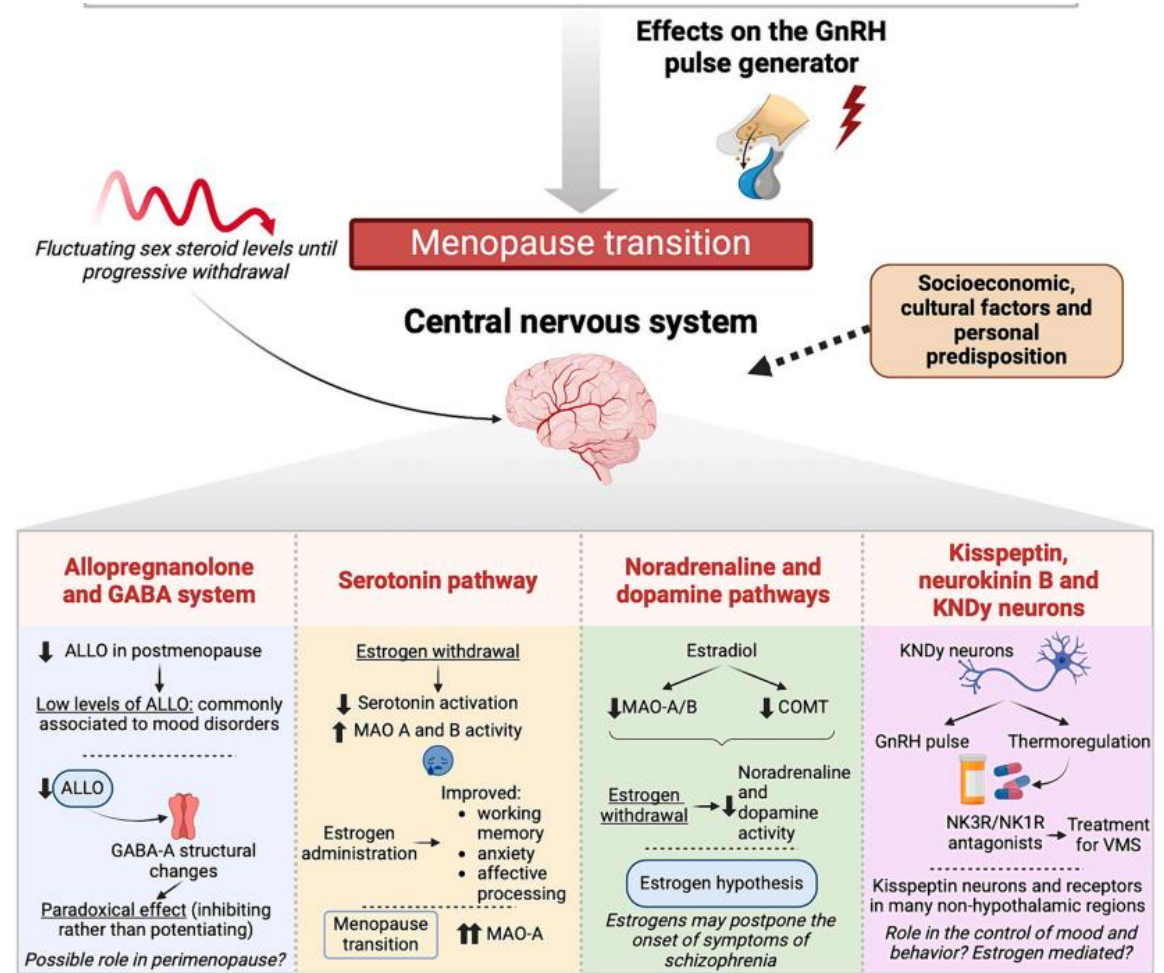
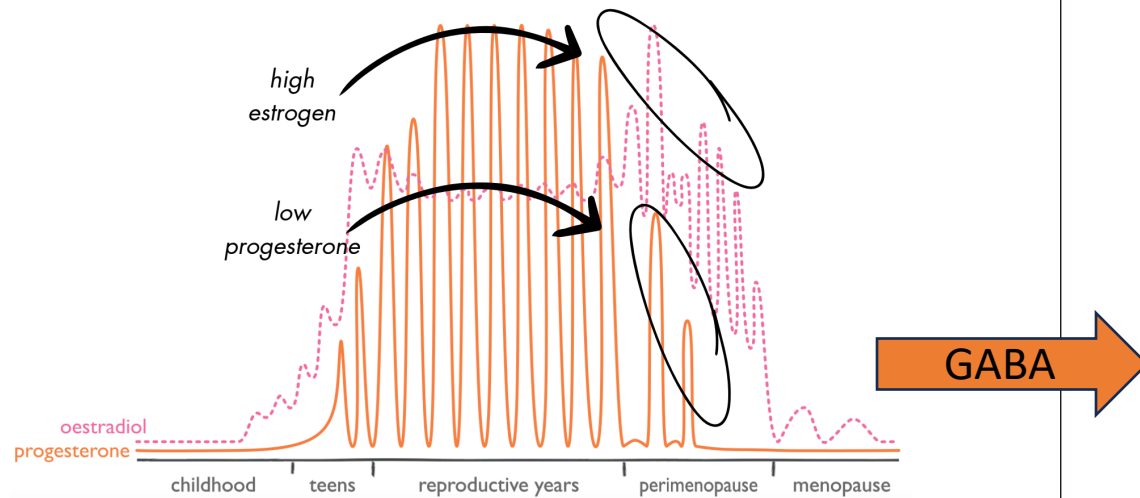


Review article

Neuroendocrine mechanisms of mood disorders during menopause transition: A narrative review and future perspectives

Tiziana Fideticchi^a, Andrea Giannini^{a,*}, Peter Chedraui^b, Stefano Luisi^a, Christian Battipaglia^c, Andrea R. Genazzani^a, Alessandro D. Genazzani^c, Tommaso Simoncini^a

^a Department of Clinical and Experimental Medicine, Division of Gynecology and Obstetrics, University of Pisa, Pisa, Italy



Neuroendocrine changes during menopausal transition may potentially contribute to increase the risk of mood symptoms in at-risk women

Perimenopause Immune Dysregulation



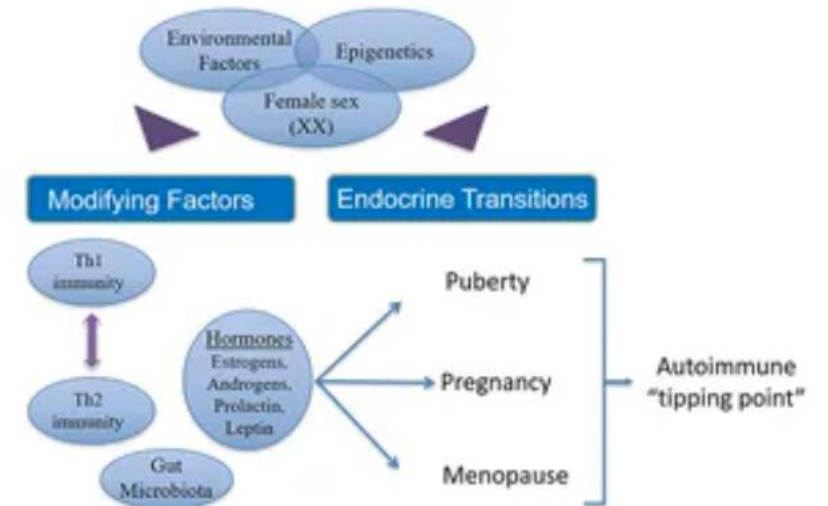
Autoimmune Disease in Women: Endocrine Transition and Risk Across the Lifespan

Maunil K. Desai¹ and Roberta Diaz Brinton²

¹ School of Pharmacy, University of Southern California, Los Angeles, CA, United States, ² School of Medicine, University of Arizona, Tucson, AZ, United States

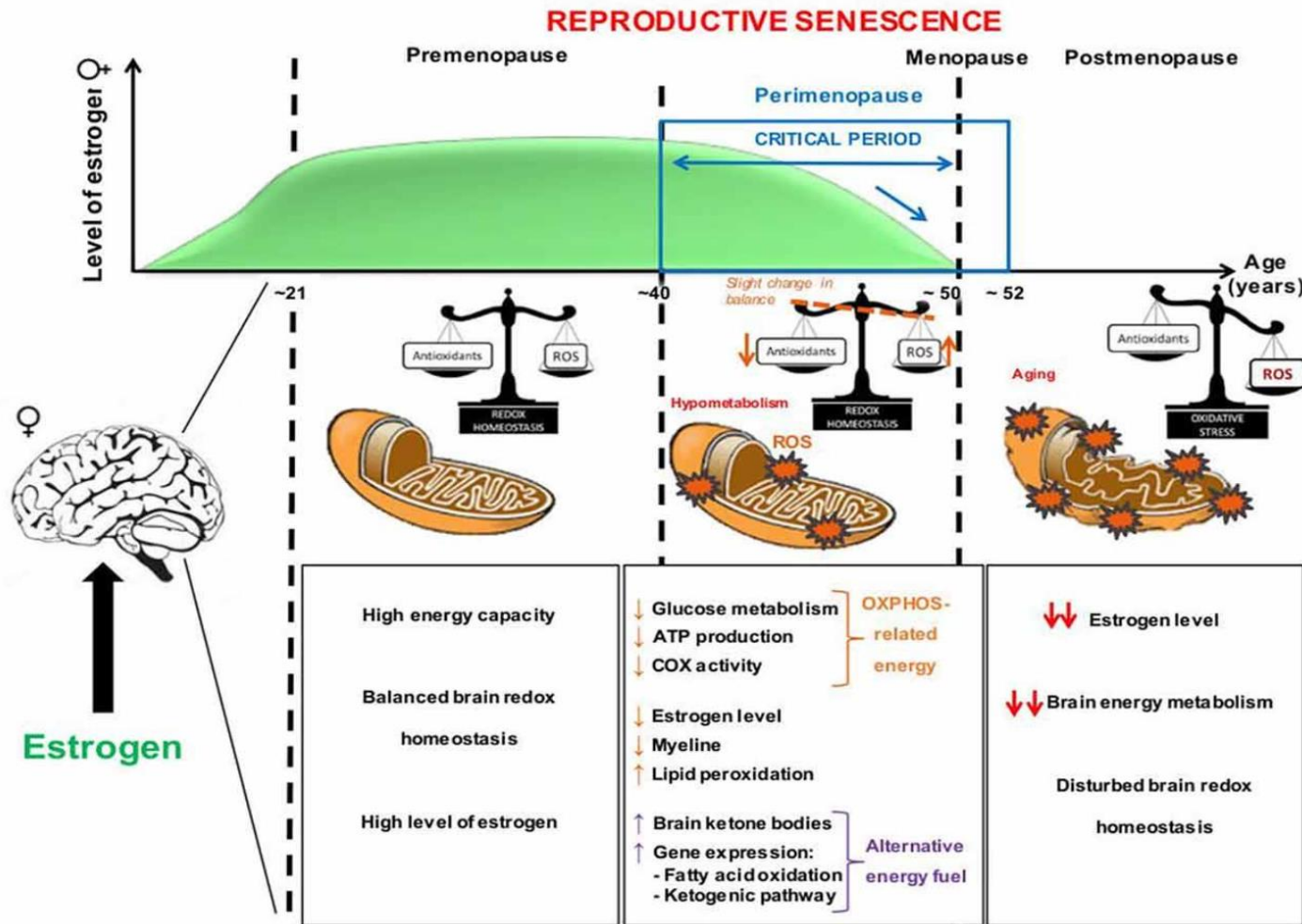
Women have a higher incidence and prevalence of autoimmune diseases than men, and 85% or more patients of multiple autoimmune diseases are female. Women undergo sweeping endocrinological changes at least once in their lifetime, during pregnancy and menopause, with many women undergoing an additional transition: pregnancy, which may or may not be accompanied by breastfeeding. These endocrinological transitions

“...hormonal flux in susceptible women may trigger downstream changes that disturb the fragile balance between inflammation and immune regulation.”



“hormonal fluctuation, immune polarization and transition states together drive susceptible women over the autoimmune “tipping point” leading to manifestation of overt clinical disease.”

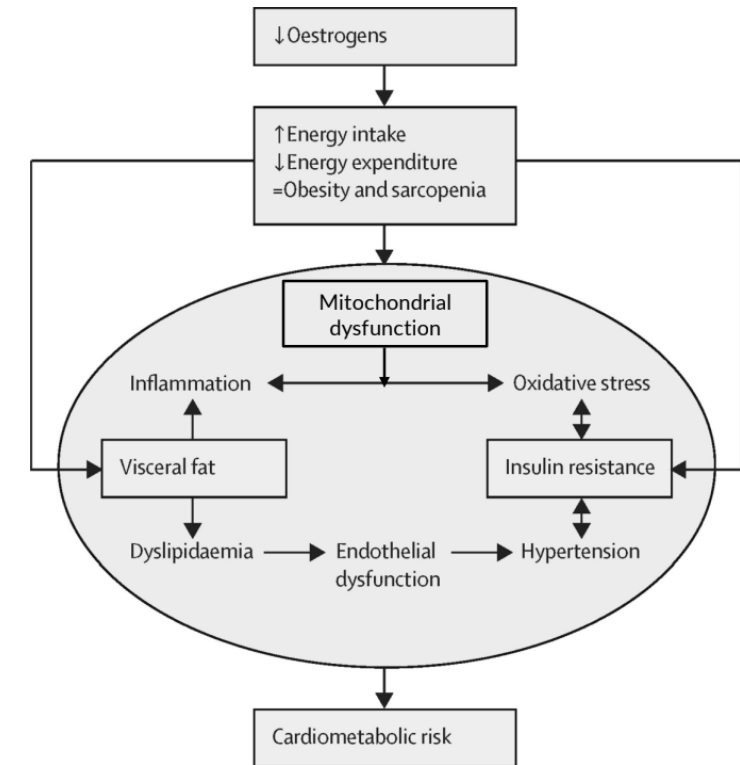
Neuro-Immune-Cardiometabolic Vicious Cycle



Menopause: a cardiometabolic transition

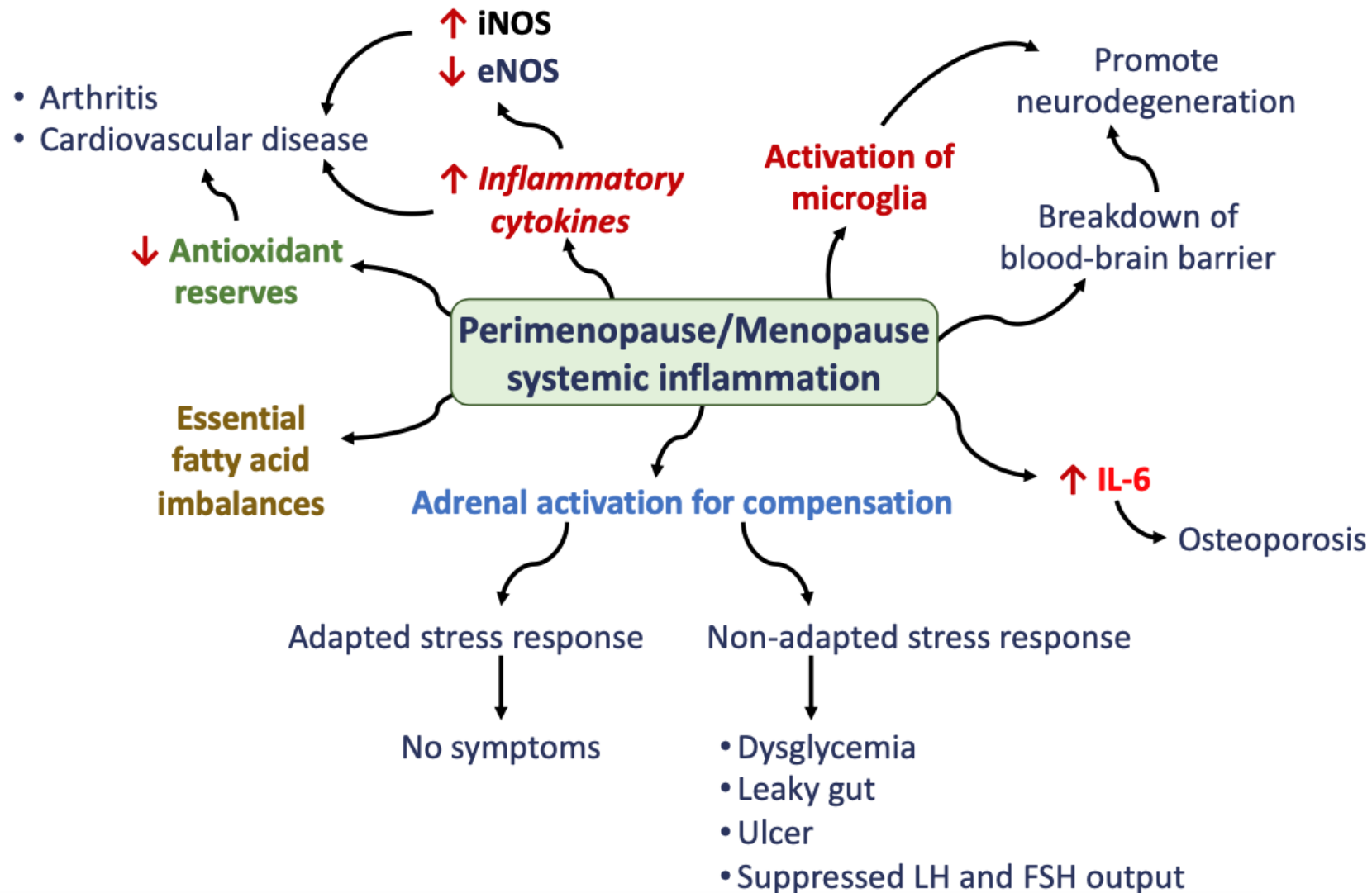
Prof Rossella E Nappi, MD • Prof Peter Chedraui, MD • Prof Irene Lambrinoudaki, MD • Prof Tommaso Simoncini, MD

Published: May 05, 2022 • DOI: [https://doi.org/10.1016/S2213-8587\(22\)00076-6](https://doi.org/10.1016/S2213-8587(22)00076-6) • [Check for updates](#)

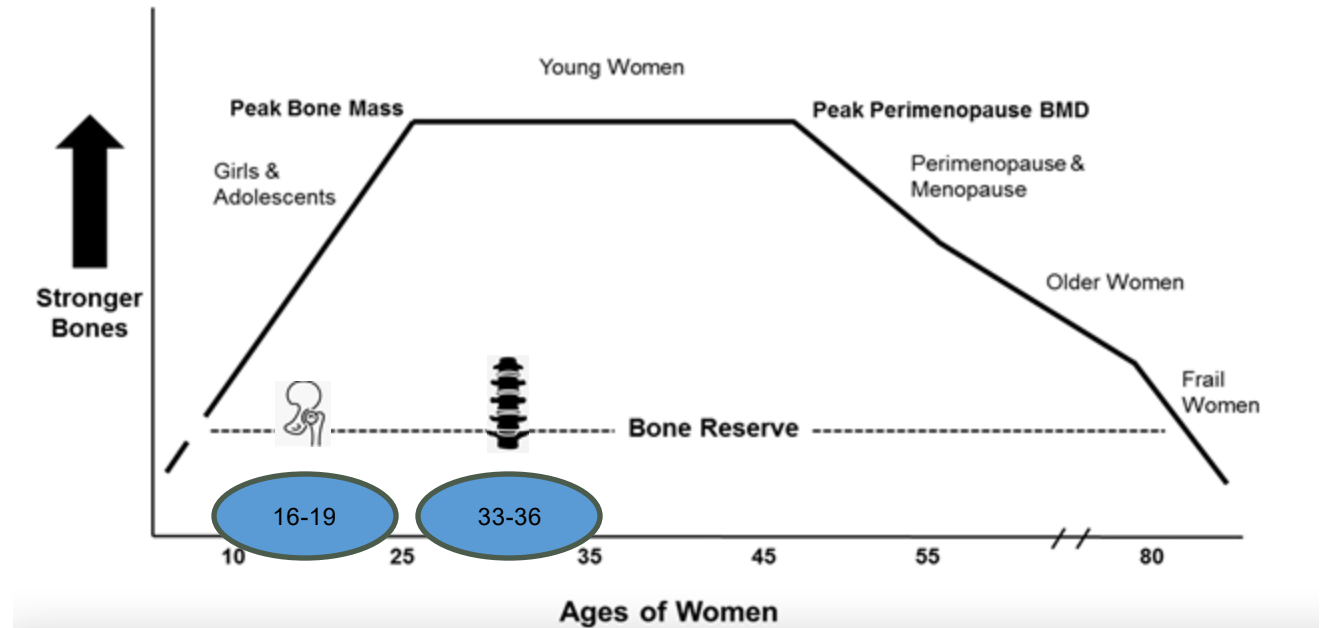
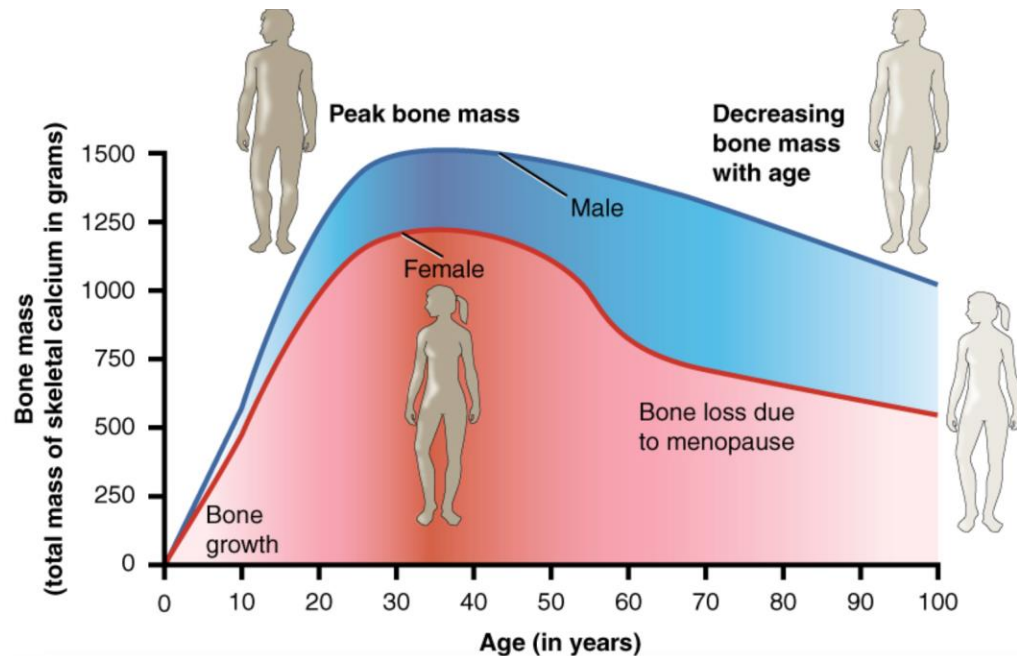


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Impact Systemic Inflammation in Perimenopause

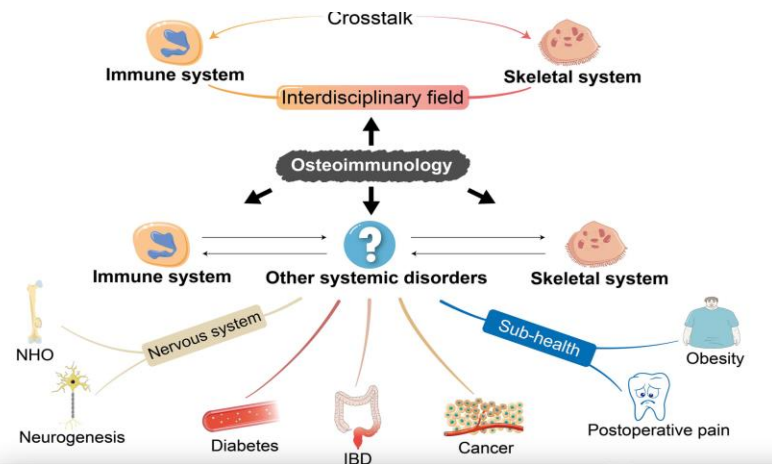
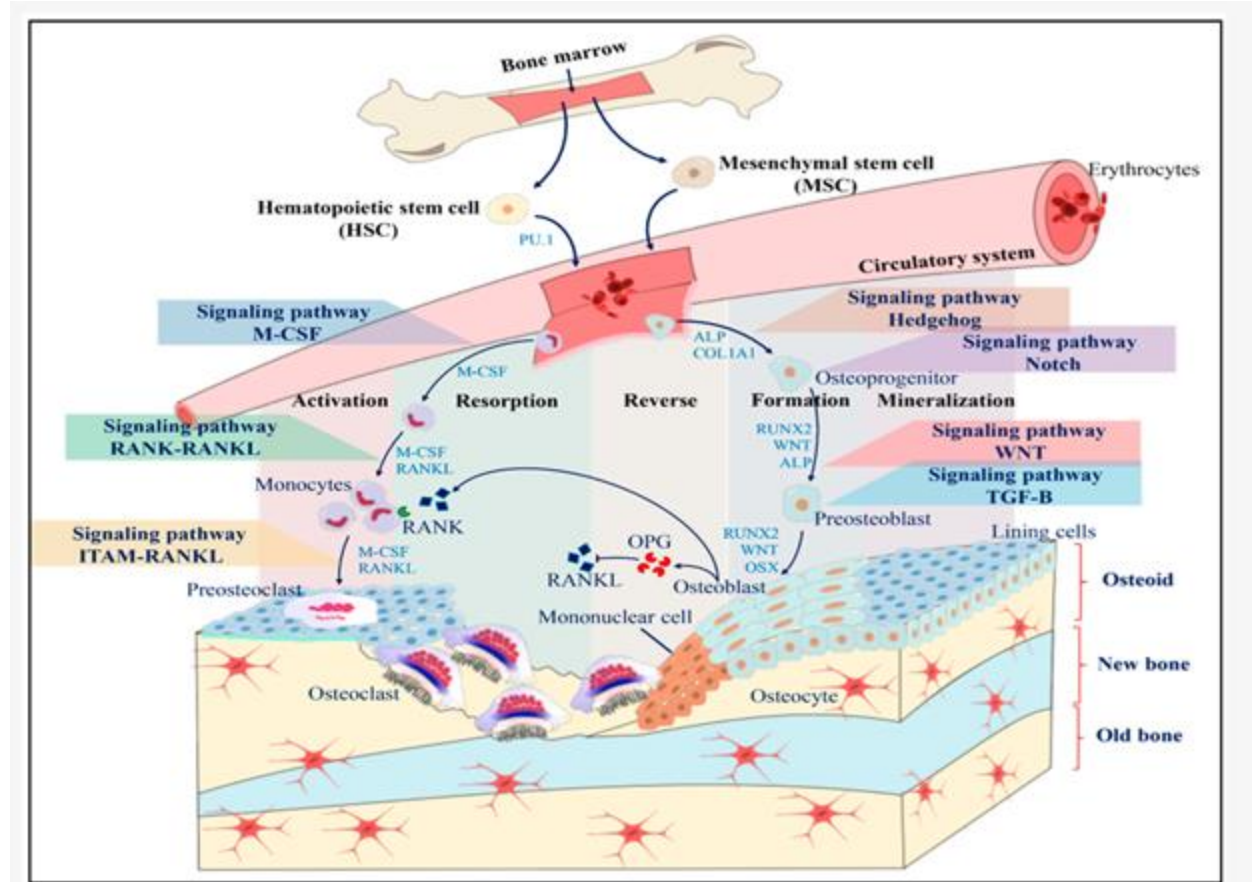
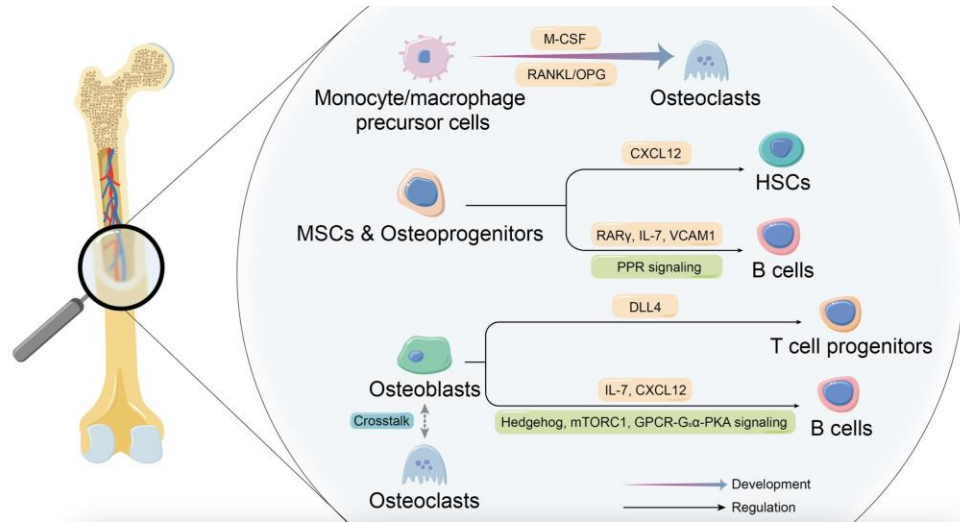


Peak Bone Mineral Density



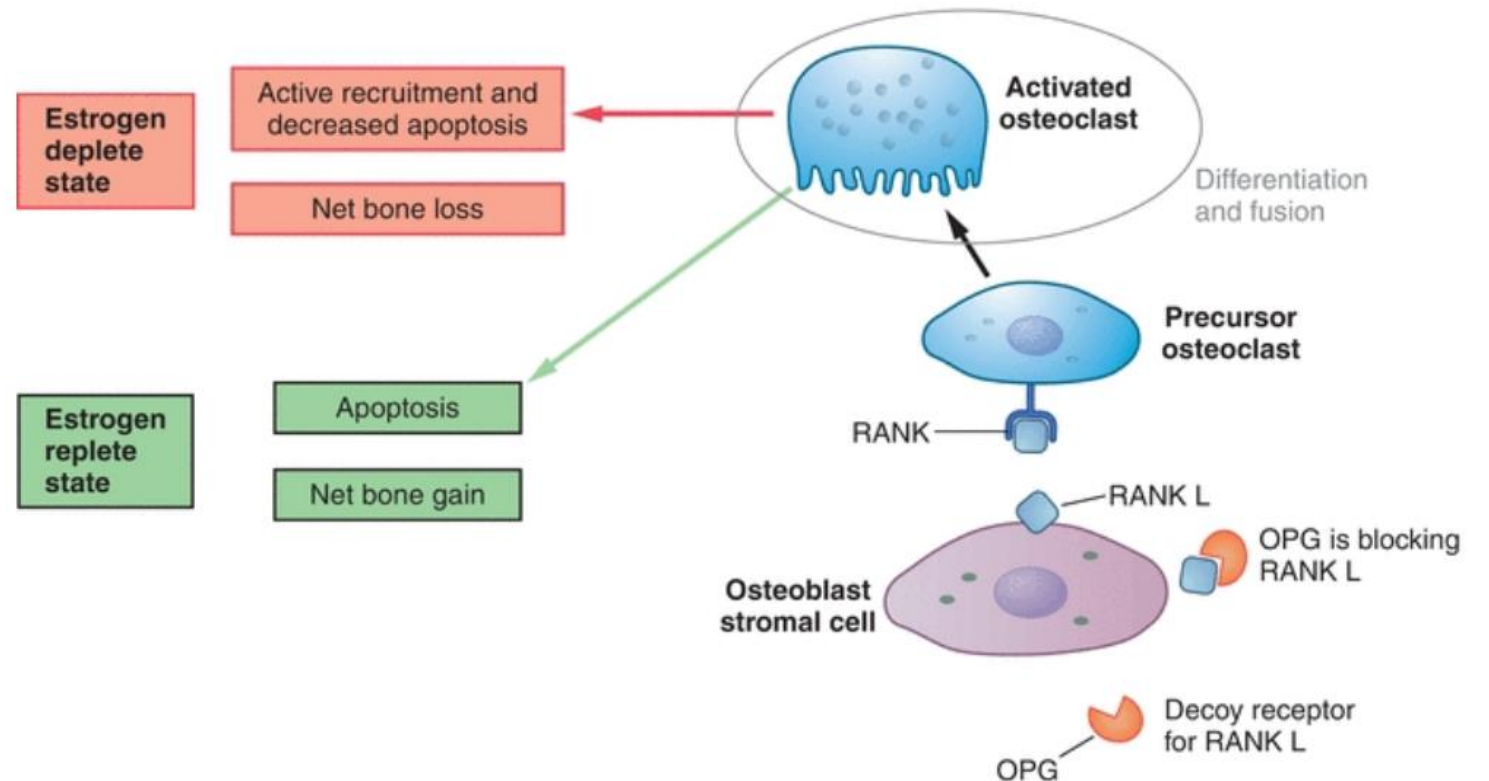
Peak hip & femoral neck 16-19yrs
Lumbar spine 33 yrs

Osteoimmunology – speak the same language



Perimenopause

E2 exerts a tonic suppression of remodeling by directing activated osteoclasts toward apoptosis; in the absence of E2, osteoclastic activity predominates, resulting in net bone resorption.



Window Oppourtunity Summary

Losing progesterone

- Lowered GABAergic tone
- Destabilization of HPA axis
- Anxiety, hot flushes , insomnia, migraines

High & Fluctuating E2

- *Immune* – dysregulation >> Autoimmune window
- *Nervous System* - Oestrogen withdrawal; cognition changes, memory loss, brain fog
hot flushes headaches , heavy periods & breast pain
- *Metabolism*- Insulin resistance > body shape change
- *Nervous System*- temporary 25% drop in brain energy
- Inflammatory – Bone density

Perimenopause high-risk stage



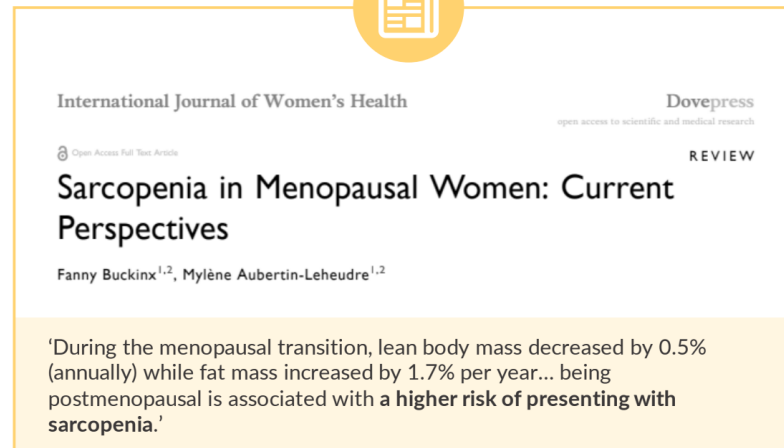
Metabolic dysfunction
& Insulin Resistance



Sarcopenic
Obesity

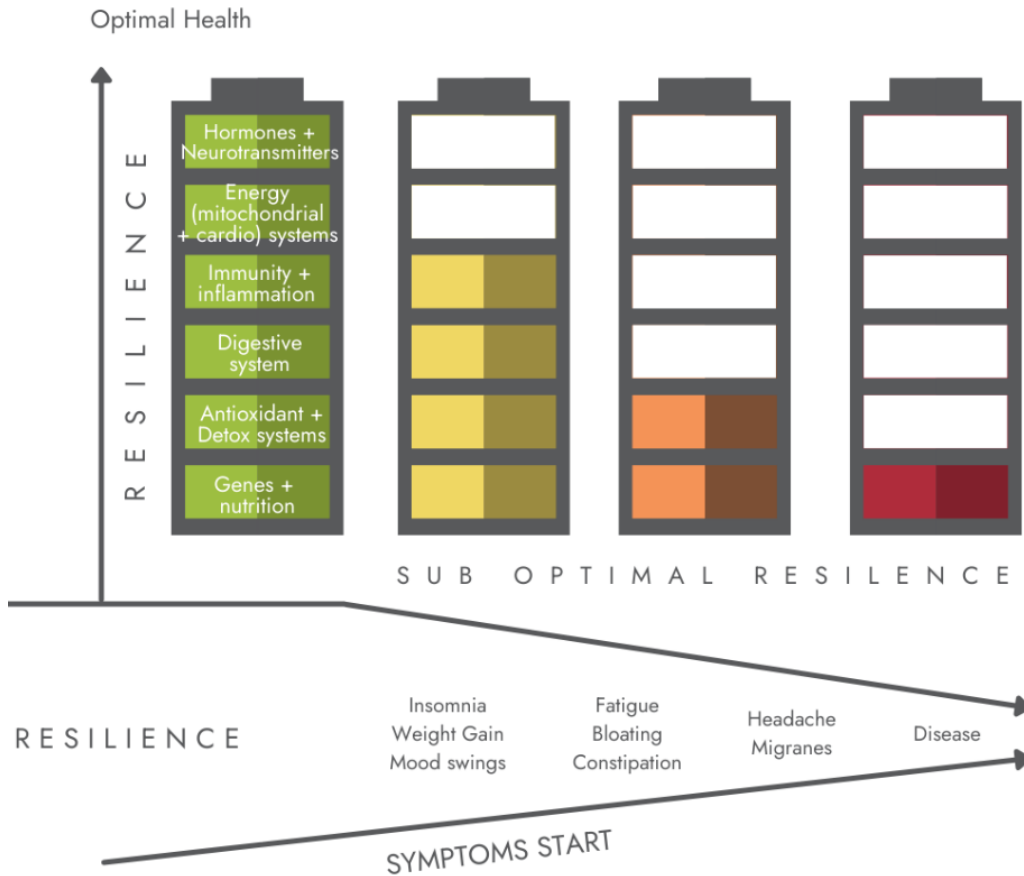


Chronic Inflammation



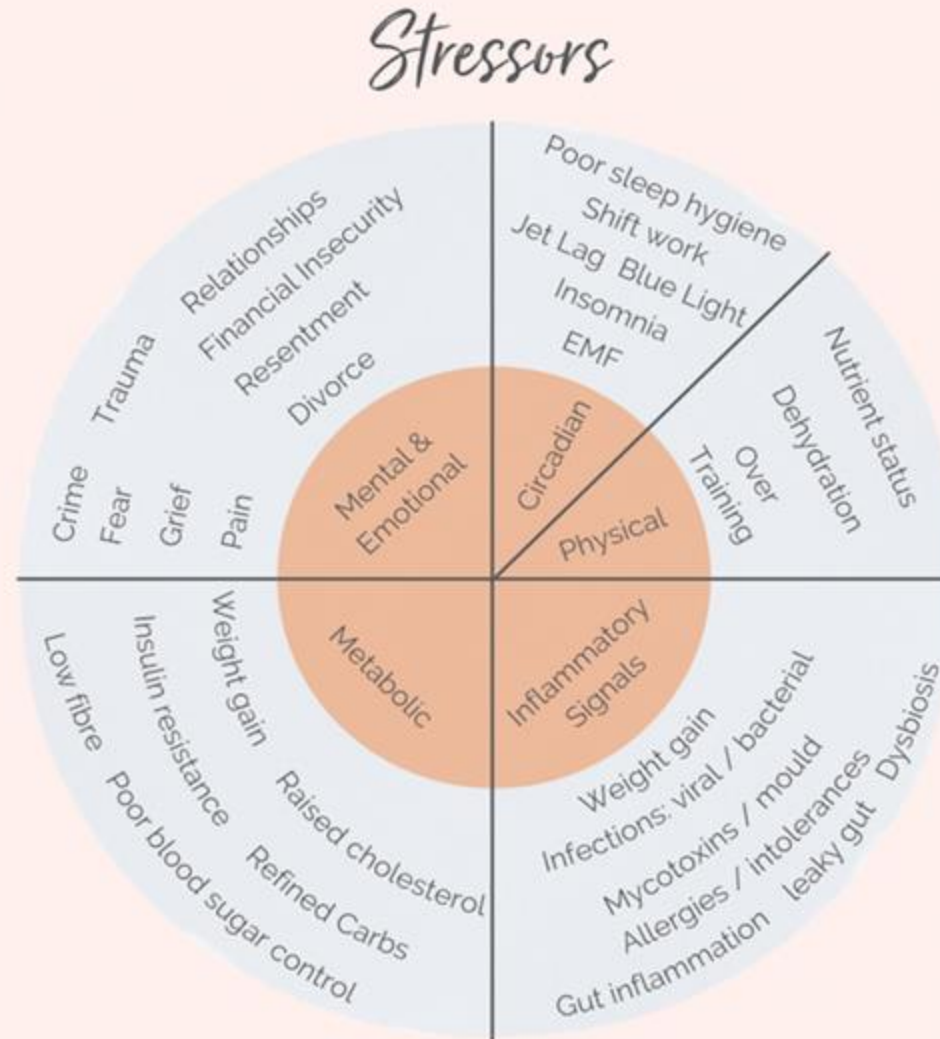
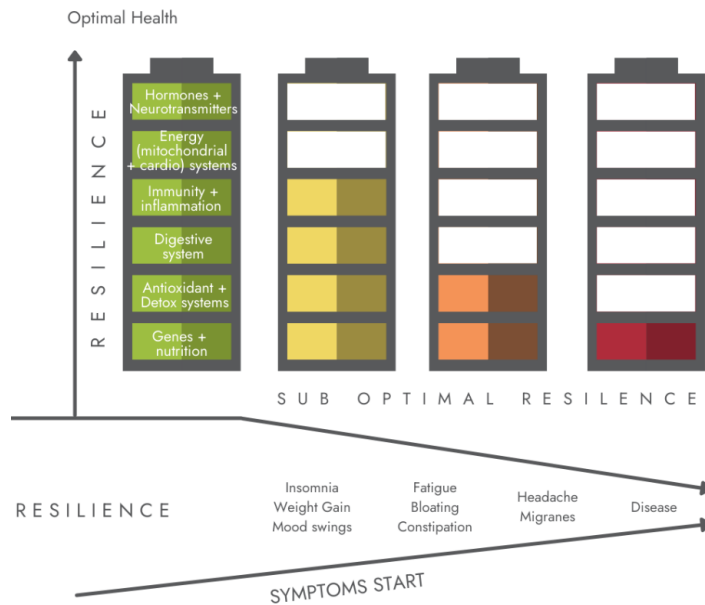
Nutritional Therapy has a Tool Kit for all the above

Metabolic Reserve



- Cell membrane integrity & receptor sensitivity
- Antioxidant Capacity
- Micronutrient reserves
- Mitochondrial capacity & health
- Digestive system and barriers
- Immune system
- Neuro-Endocrine systems
- Liver Detoxification
- Nutrigenomics

Stressors & Metabolic Reserve



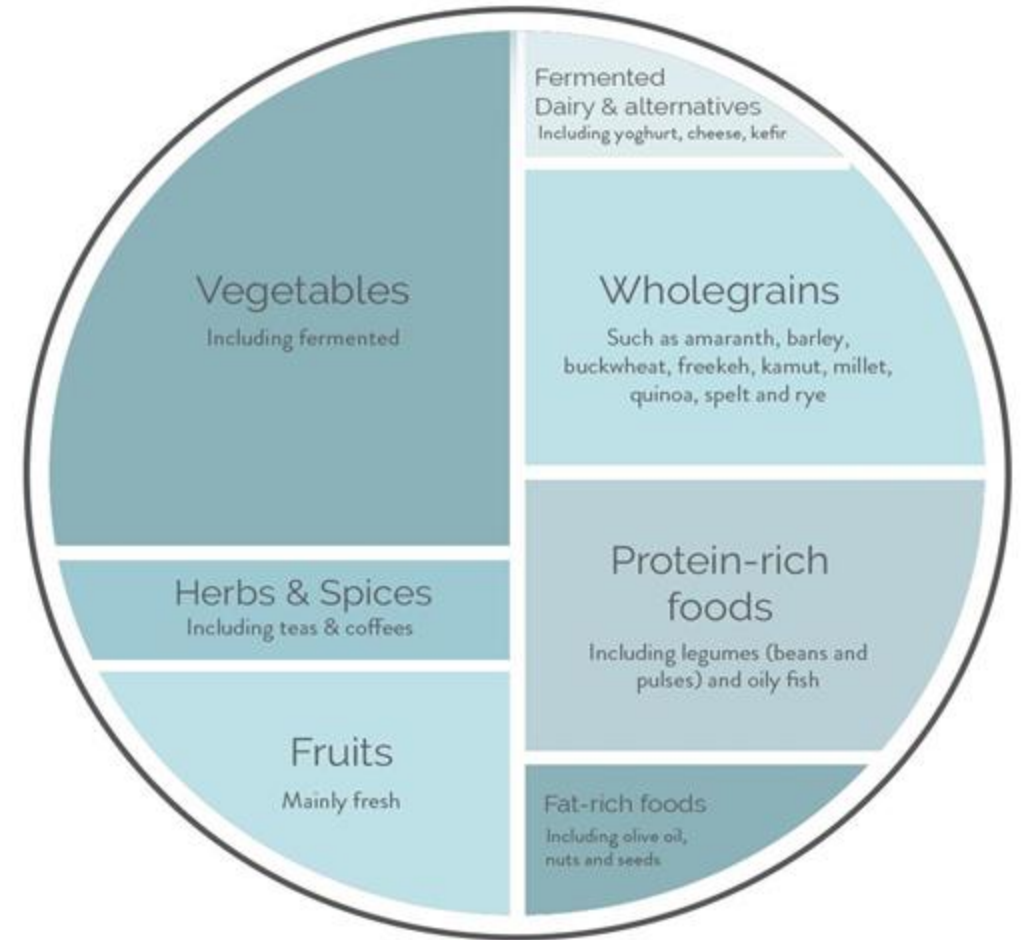
Food ALWAYS first

- Mostly Plants(Complex carbs)
- Whole and natural vs CRAP
(colourless, refined & Processed)
- Herb & Spice up your plate
- Protein

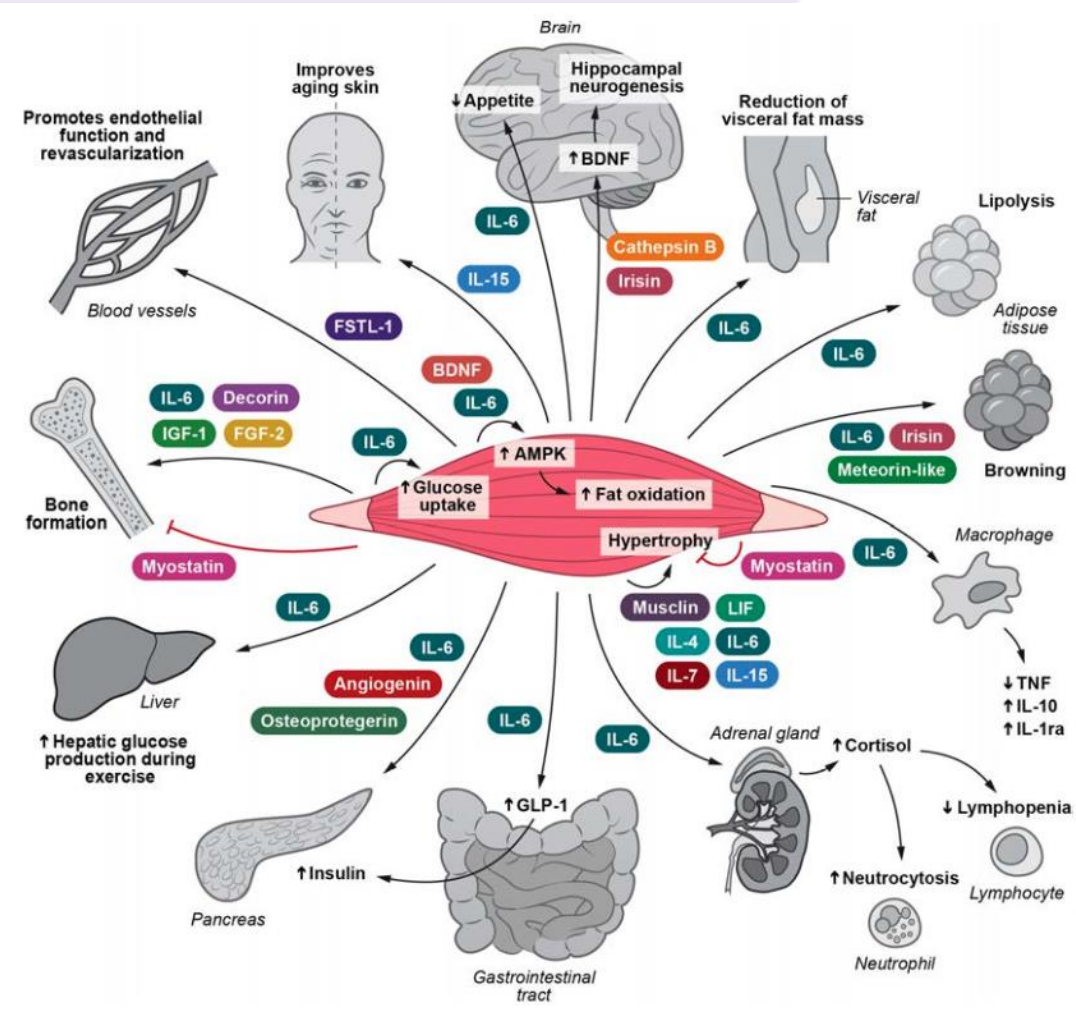
For perimenopause women 1.0 grams per kg of body weight per day
(bones and muscle)

- If “fasting” *BREAK*fast @ 9-10am =14-15 hr fast
- 800-1200g(osteo Dx) **dietary** calcium day
 - ❖ *Mineral* Water- 1- ½ litres (ca,k bones)
 - ❖ **Move** at least 30 mins every day!
- ENJOY- this is not a restrictive elimination DIET.....

Way of long, fulfilling healthy life



Movement :-Muscle Activation & Immuno-metabolic Modulation

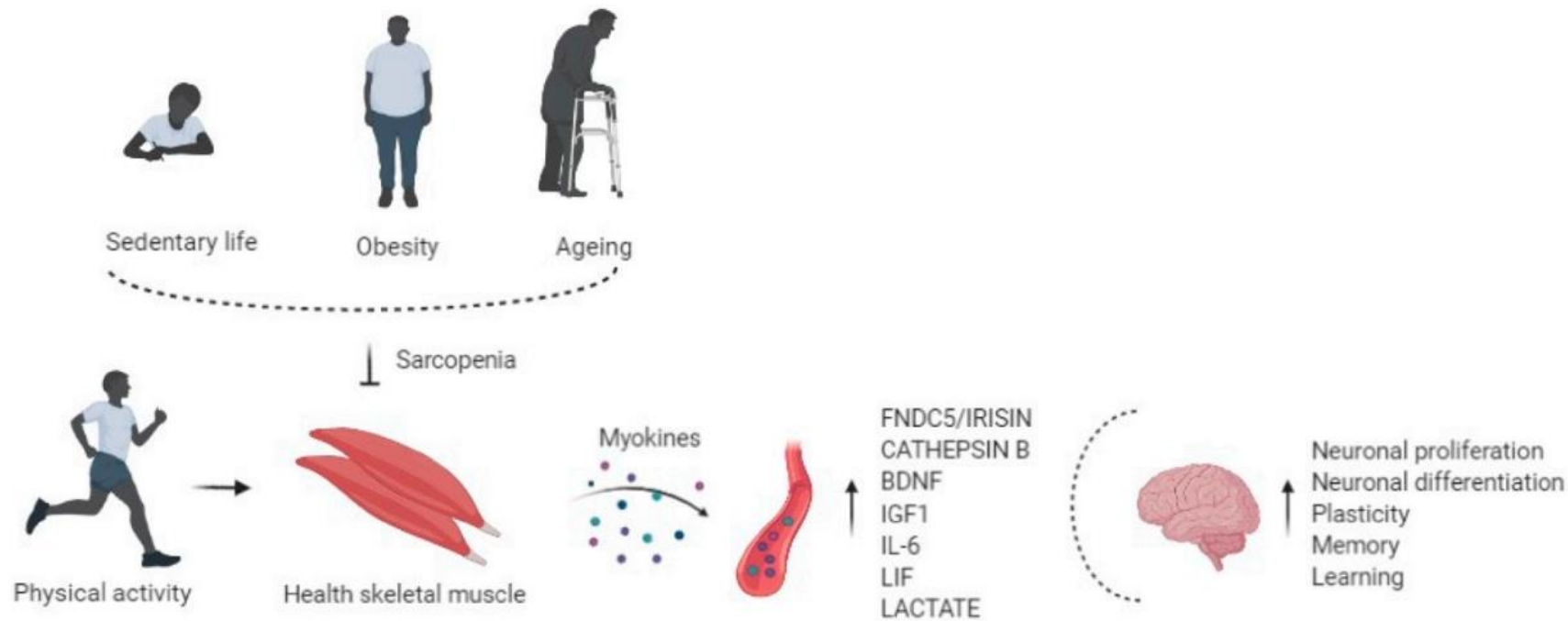


Muscle-Organ Crosstalk: Focus on Immunometabolism

Immunometabolism.
Front. Physiol. 11:567881.



Muscle – Myokines – Brain Functionality



“Physical activity enhances circulating levels of myokines in the bloodstream, affects the brain regulating neuronal proliferation and differentiation, plasticity, memory, and learning.”

Benefits Exercise

Progressive Weight Bearing

- AB crunch 3x 12-15
Leg curl 1 x 8-10 1 x 12-15
Leg press 1 x 8-12 1 x 12-20
Lateral raise 2 x 10-12 1 x 12-15
Single arm high row 1 x 8-12
1x 12-15
Barbell row 1x 10 1 x 10-15

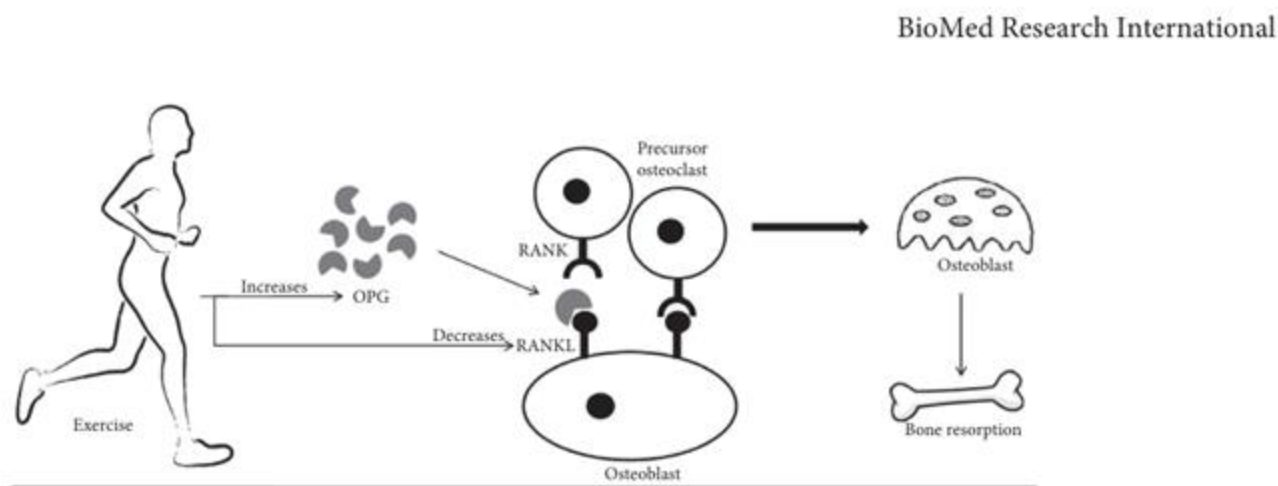


FIGURE 1: Interaction of exercise and RANKL/RANK/OPG biomolecular pathway. OPG: osteoprotegerin; RANK: receptor activator of nuclear factor κ B; RANKL: receptor activator of NF- κ B ligand.

Strength

Deadlift 3 x 5-10
Lat pulldown 3 x 10-12
Lat raise 1 x 10-12
Bench press 3 x 5
Leg curl 1 x 12-15
Squat 3 x 5

Myo-inositol

Inositols in Midlife

Kalra, Sanjay; Kalra, Bharti¹

[Author Information](#) ✓

Journal of Mid-life Health 9(1):p 36-38, Jan–Mar 2018. | DOI: 10.4103/jmh.JMH_52_16

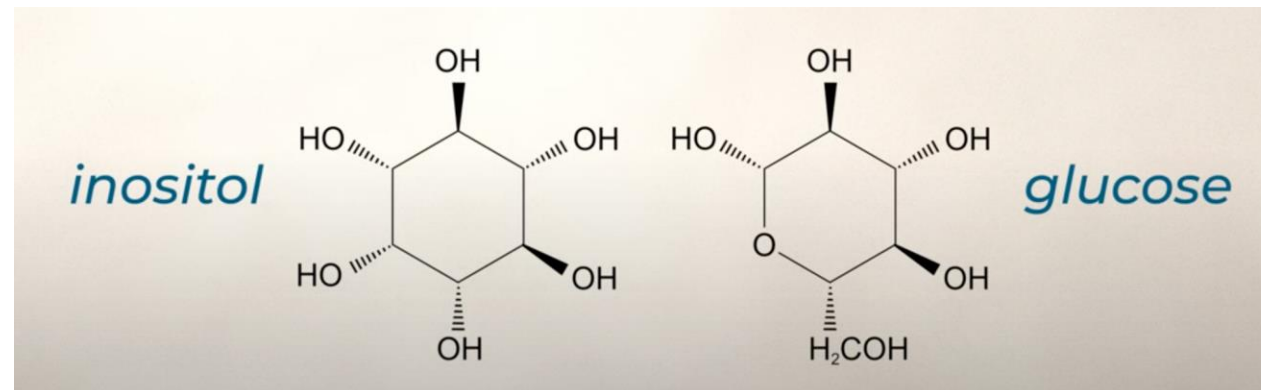
This review describes the mechanistic, animal, and clinical data related to the use of inositols in midlife. It covers studies related to the mechanism of action of myo-inositol and D-chiro-inositol and randomized controlled trials conducted in postmenopausal women with metabolic syndrome and supports these data with the results of *in vitro* and animal studies on inositol in nephropathy and other related conditions. Recent advances related to biochemistry, pharmaceutical science, and genetics are discussed. It concludes that inositols have a potential role to play in maintaining metabolic health in postmenopausal women.



Myo-inositol

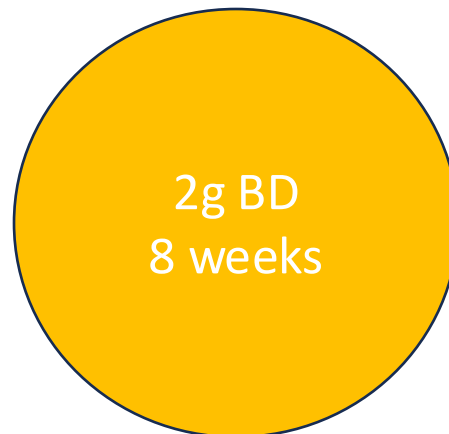
Inositols are small molecules similar to sugar

- myo-inositol is the most abundant isomer makes up 95% in the body
- myo-inositol is an intracellular 2nd messenger for hormones, especially insulin, FSH and TSH
- Being a 2nd messenger for insulin facilitates a normal response to insulin and thereby improving insulin sensitivity



Myo-inositol supplementation improves cardiometabolic factors, anthropometric measures, and liver function in obese patients with non-alcoholic fatty liver disease

Sara Arefhosseini¹, Neda Roshanravan², Helda Tutunchi³,
Somayyeh Rostami¹, Manuchehr Khoshbaten⁴ and
Mehrangiz Ebrahimi-Mameghani^{5*}



- Anthropometric measures decreased significantly
- Weight reduction ($P=0.049$)
- Systolic blood pressure ($P=0.006$)
- Reductions in serum fasting insulin ($p=0.008$)
- Reductions in HOMA-IR ($P=0.046$)
- Significant improvements in lipid profile, liver enzymes, AST, ALT and serum ferritin

Myo-Inositol Thyroid & BMI

Specifically, myo-inositol may help with weight loss in several ways:

- By supporting and balancing thyroid function
- By Improving sensitivity to thyroid hormone
- By reducing insulin resistance and lowering blood sugar levels
- By reducing the increases in insulin after glucose intake

Body Mass Index

Obesity Science and Practice

Open Access



REVIEW | [Open Access](#) |

Inositol supplementation and body mass index: A systematic review and meta-analysis of randomized clinical trials

Meysam Zarezadeh , Azadeh Dehghani, Amir Hossein Faghfour, Nima Radkhah, Mohammad Naemi Kermanshahi, Fatemeh Hamed Kalajahi ... [See all authors](#) ▾

First published: 10 October 2021 | <https://doi.org/10.1002/osp4.569> | Citations: 3

Thyroid Dysfunction

frontiers
in Endocrinology

REVIEW
published: 10 May 2021
doi: 10.3389/fendo.2021.662582



The Role of Inositol in Thyroid Physiology and in Subclinical Hypothyroidism Management

Salvatore Benvenga^{1,2}, Maurizio Nordio^{2,3}, Antonio Simone Laganà^{2,4} and Vittorio Unfer^{2,5*}

amrita

Magnesium

- ✓ Fuels mitochondria- ATP production
- ✓ Improves glucose homeostasis and insulin sensitivity
- ✓ Supports oestrogen detoxification
- ✓ Supports thyroid health
- ✓ Stabilises the HPA axis
- ✓ Increases vitamin D uptake
- ✓ Calms the nervous system



300-600mg
glycinate daily

Magnesium Research

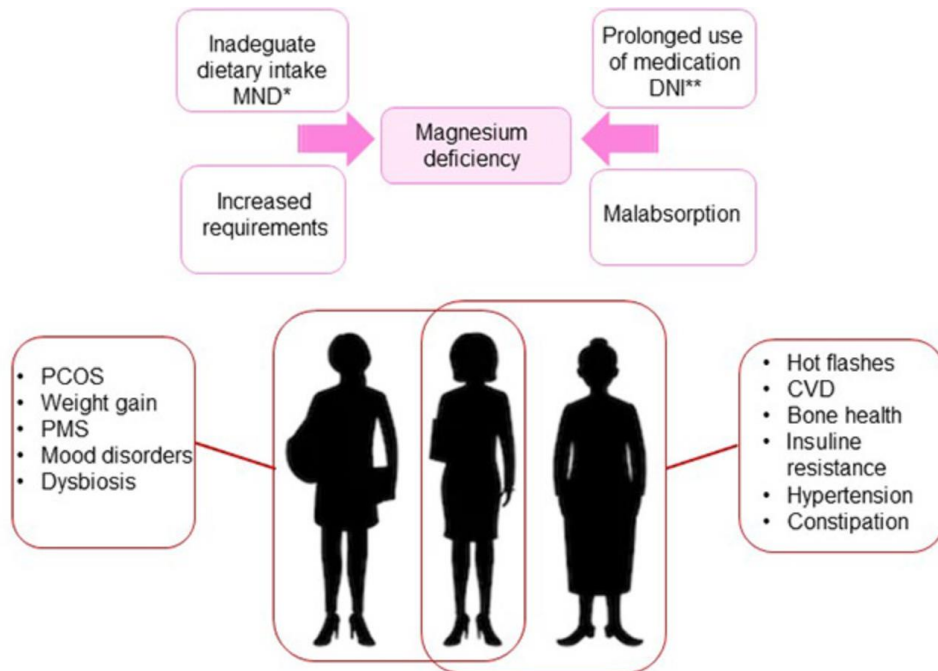


ELSEVIER

Effect of magnesium supplementation on women's health and well-being

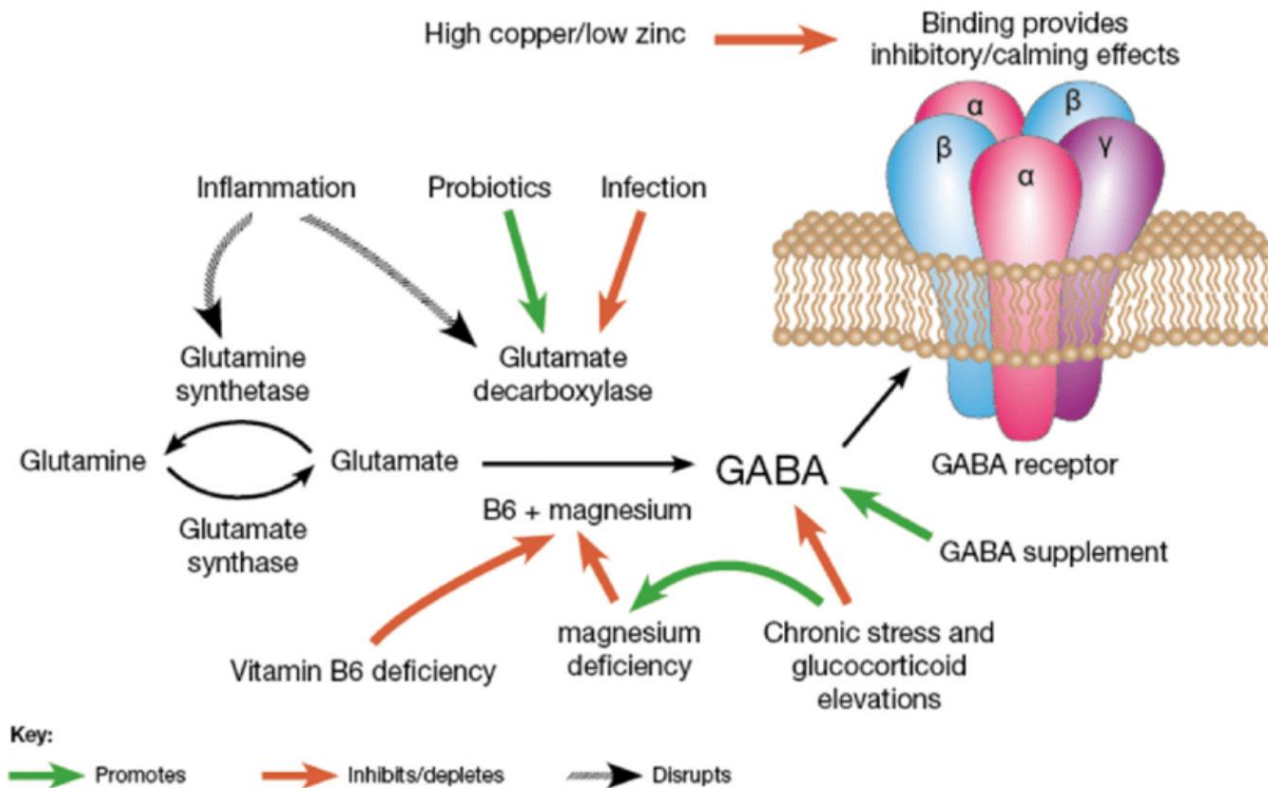
Debora Porri^{a,*}, Hans K. Biesalski^b, Antonio Limitone^c, Laura Bertuzzo^c, Hellas Cena^{a,d}

^a Laboratory of Dietetics and Clinical Nutrition, Department of Public Health, Experimental and Forensic Medicine, University of Pavia, 27100 Pavia, Italy



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Magnesium Research



Taurine

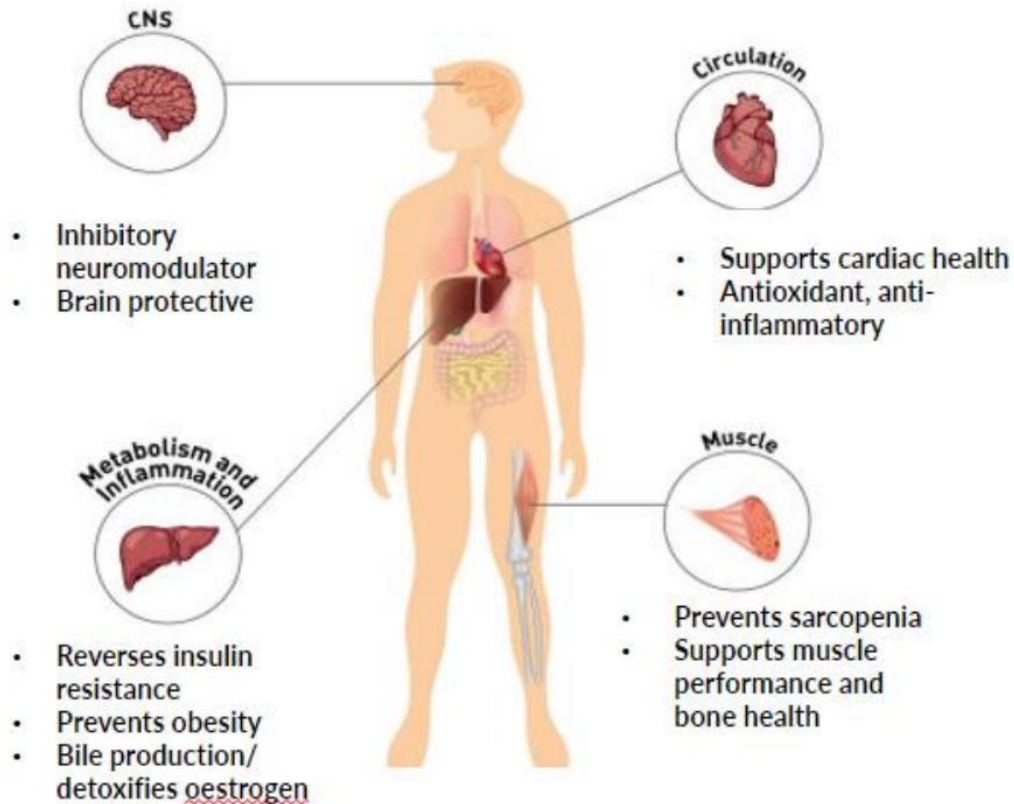
- ✓ Supports mitochondrial function; inhibits ROS
- ✓ Improves insulin sensitivity
- ✓ Anti-inflammatory, quenches oxidative stress
- ✓ Counteracts bone mineral density loss



2-4g daily

amrita

Taurine Research



Amino Acids
<https://doi.org/10.1007/s00726-020-02859-8>

ORIGINAL ARTICLE



The effects of taurine supplementation on glycemic control and serum lipid profile in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled trial

Vahid Maleki^{1,2} · Mohammad Alizadeh³ · Fatemeh Esmaeili² · Reza Mahdavi³

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After 8 weeks:

- ✓ Fasting blood sugar ($p=0.01$)
- ✓ Insulin ($p=0.01$)
- ✓ HOMA-IR ($p=0.003$)
- ✓ Total cholesterol ($p=0.013$)
- ✓ LDL-C ($p=0.041$)



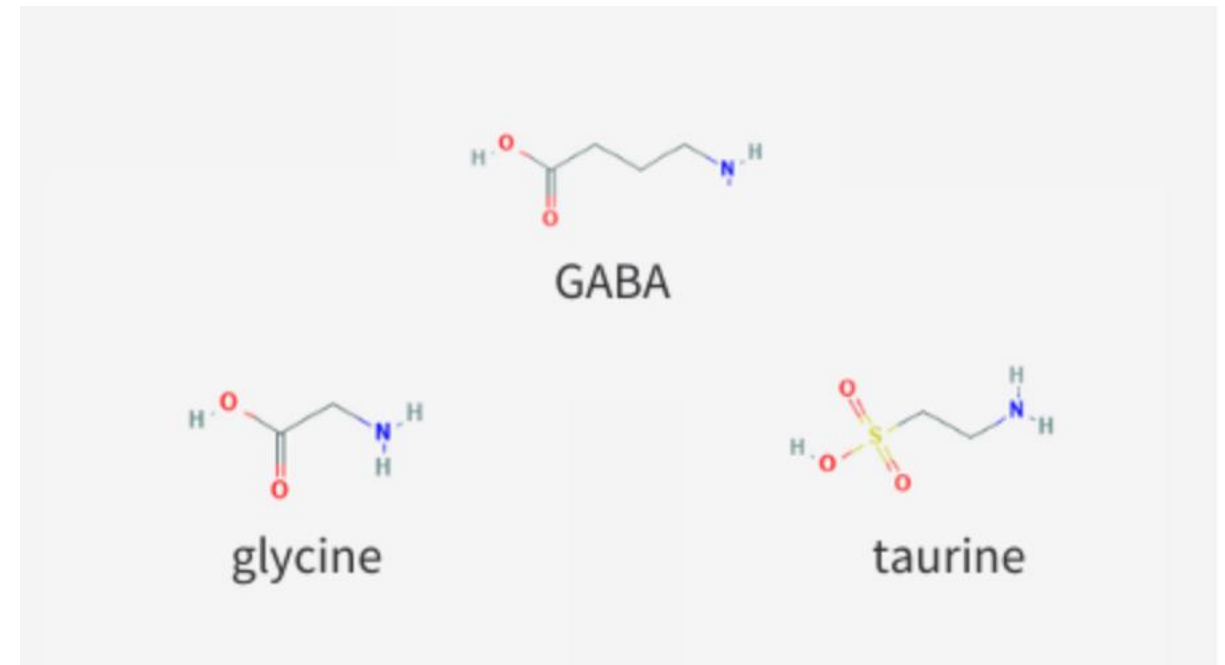
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Taurine is a ["calming" neurotransmitter similar in structure to GABA](#) (gamma-aminobutyric acid) & Glycine — the brain's other two calming neurotransmitters.

By interacting with GABA receptors, taurine helps to support beneficial "GABAergic" tone or overall GABA activity, thereby improving sleep, preventing migraines & relieving perimenopausal mood symptoms.



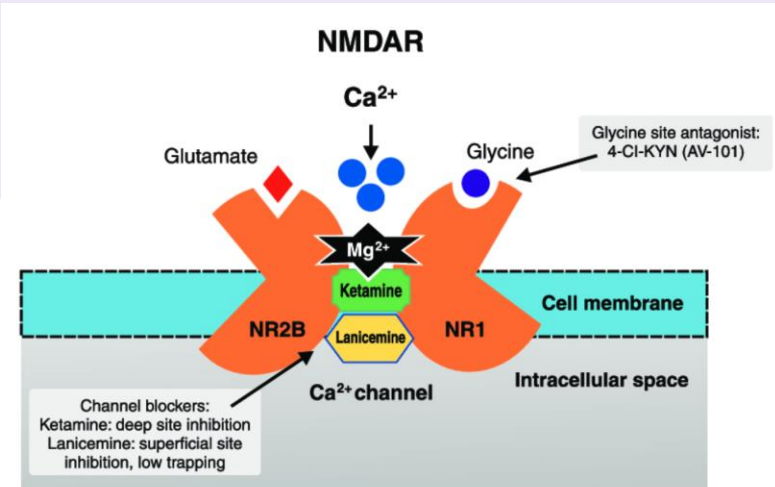
Glycine

- ✓ Induces deeper REM restorative sleep
- ✓ Deficiency is associated with obesity and NAFLD
- ✓ Lowers markers of oxidative stress
- ✓ Improves liver detoxification- glutathione synthesis
- ✓ Calms the brain by inhibiting glutamate
- ✓ May control food intake



2-6g daily in
divided doses.
3g to promote
sleep

Glycine Research

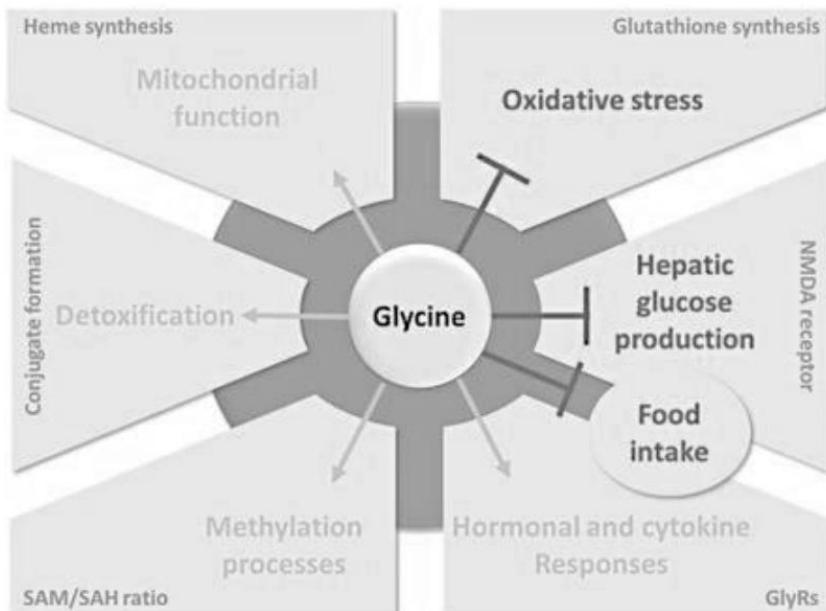


Review

Glycine Metabolism and Its Alterations in Obesity and Metabolic Diseases

Anaïs Alves¹, Arthur Bassot¹, Anne-Laure Bulteau², Luciano Pirola¹ and Béatrice Morio^{1,3,*}

The study also suggested that decreased plasma glycine concentration was associated with hepatic insulin resistance. This finding is supported by a recent meta-analysis, which showed that plasma glycine concentration is consistently lower in patients with obesity and T2DM compared to healthy individuals (−11 and −15%, respectively) [72]. Another meta-analysis showed that plasma glycine concentration has a very significant inverse association with the risk of developing T2DM [8]. In addition



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Nutraceuticals



Nutraceuticals



Nutraceuticals



Magnesium glycinate dihydrate
equiv. Magnesium
equiv. Glycine

Glycine
Total Glycine

Taurine

Passiflora incarnata herb ext dry conc (Passionflower)
equiv. from Passiflora incarnata herb dry

Melissa officinalis leaf ext dry conc (Lemon Balm)
equiv. from Melissa officinalis leaf dry





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