

# **WOMEN & CARDIOVASCULAR HEALTH**

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# Learning Objectives:

- **Recognize the link between reproduction and cardiometabolic health, acknowledging the powerful role of estrogen**
- **Discuss the impact of estrogen directly and indirectly on all cardiovascular structures and the negative effects of menopause on female cardiovascular wellbeing**
- **Summarize the inter-relationship of estrogen, the gut, the immune system, and the Circadian Rhythm and their combined impact on female cardiometabolic status**
- **Describe how to implement effective strategies to help menopausal women maintain cardiovascular wellness and metabolic homeostasis by utilizing hormonal therapy, nutritional medicine, time restricted eating, stress reduction, and sleep hygiene**

# Prime Directive of Life:

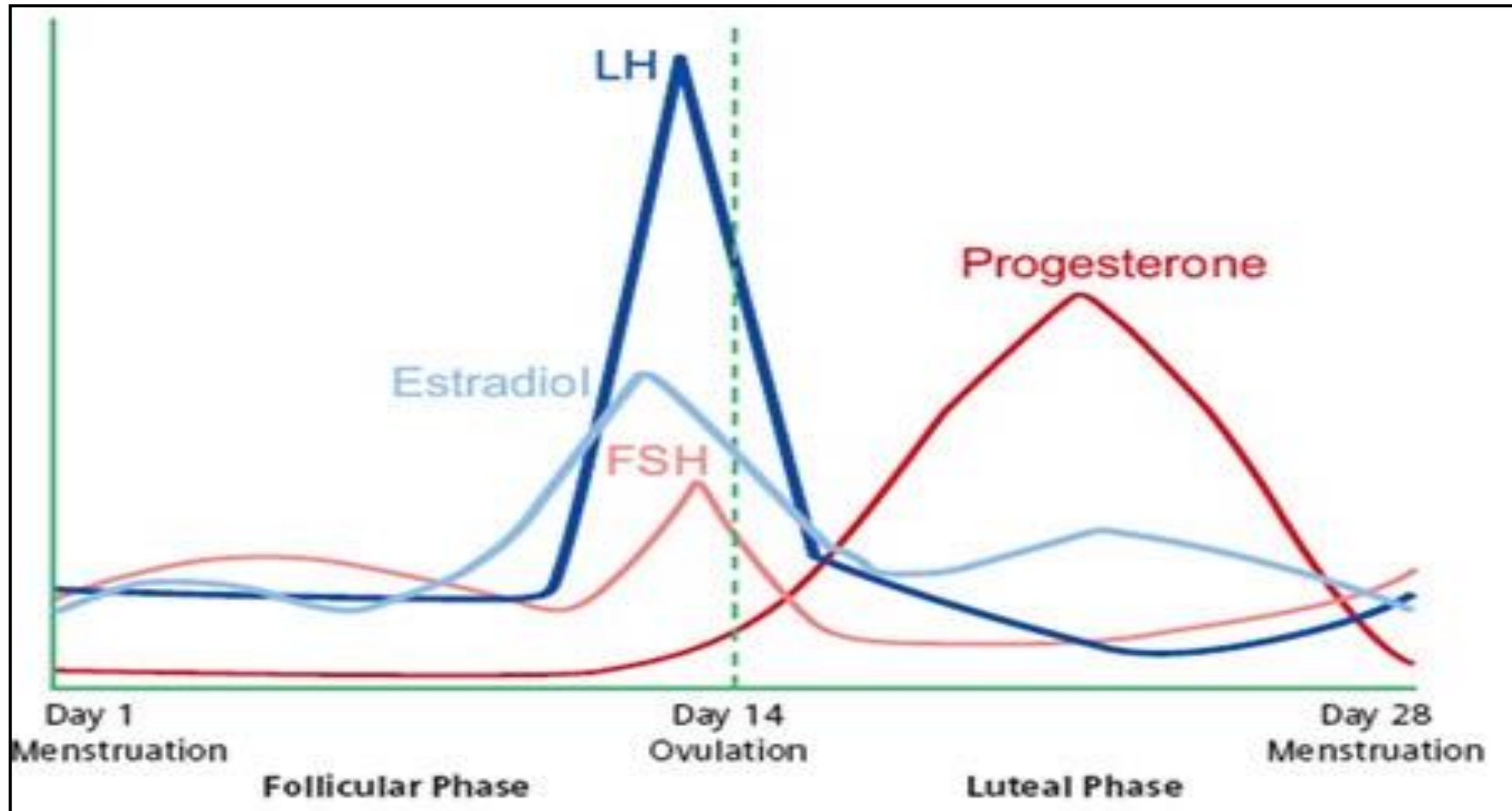
Reproduction and survival  
and then to repeat the process

...

*It is all about the  
process of making  
and raising babies!*



# The Menstrual Cycle – New Ways to Understand it

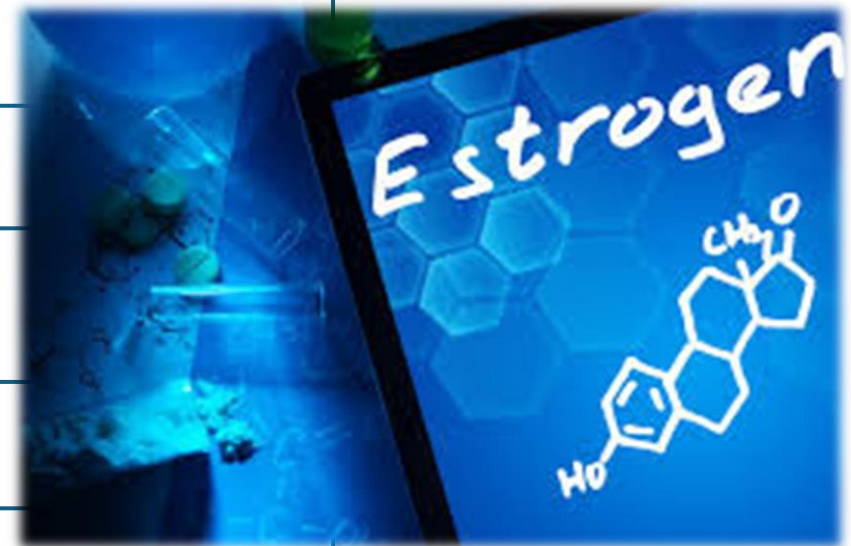


# Introducing Estrogen

“THE MOTHER HORMONE”

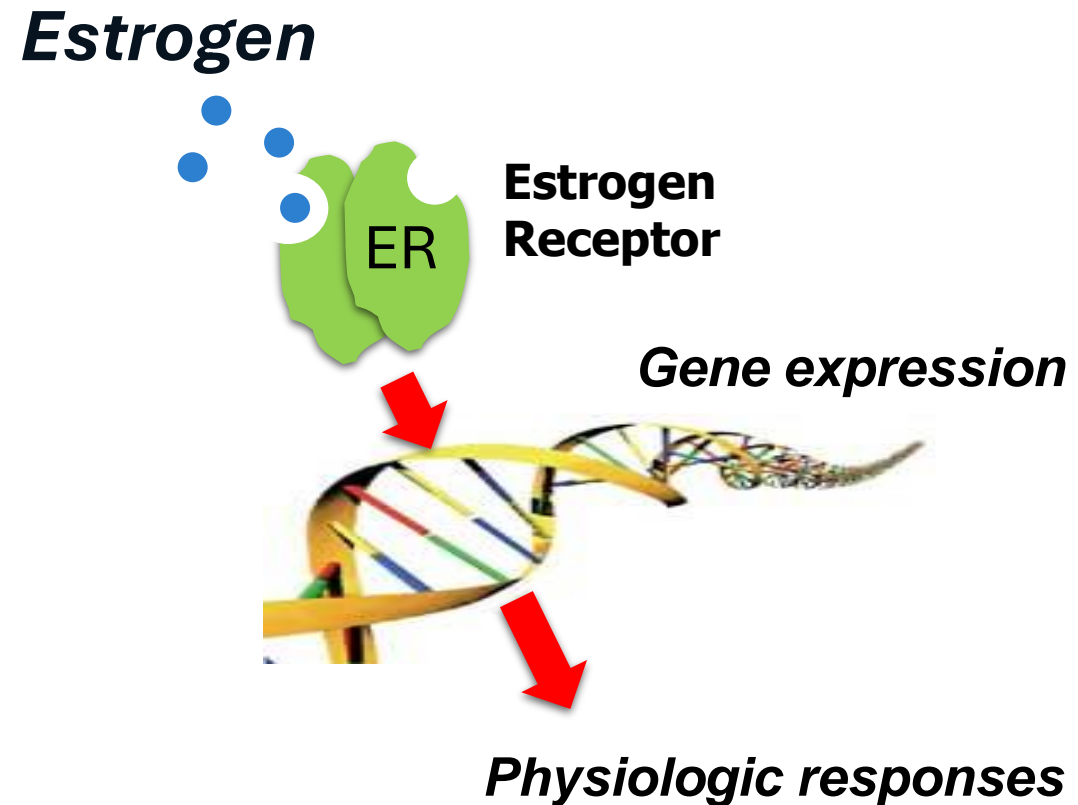
“THE LIFE HORMONE”

*Master of metabolic homeostasis*



# Functions of Estrogen: Critical roles in all extra-gonadal tissues

- Gut and Liver
- Heart
- Muscle
- Bone, cartilage, joints
- Endothelium-arteries
- Epithelium-skin
- Hematopoietic cells
- Immune cells/mitochondria
- Bladder
- Lungs
- Brain



# Estrogen Basics: An Overview

**ER alpha** → Regulates genes & membrane receptors

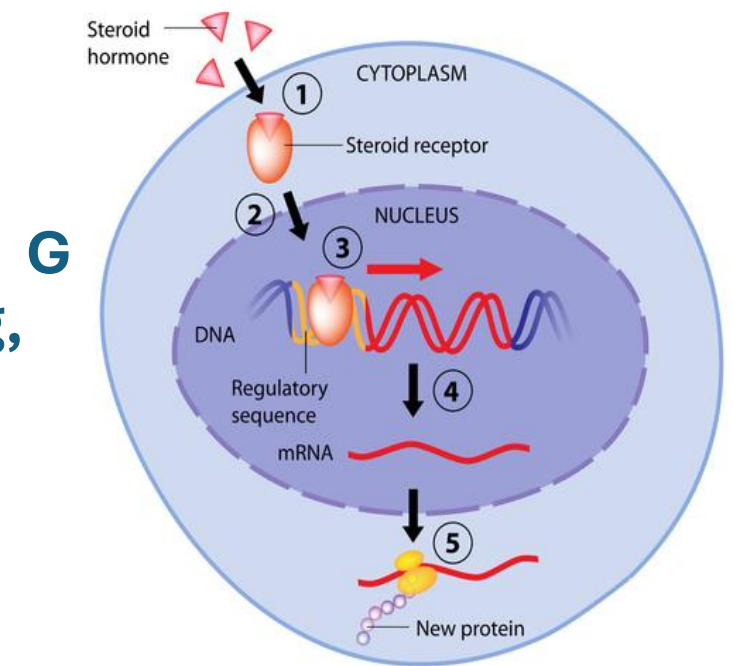
Primarily expressed in the *gonadal* organs: **Reproductive organs, breasts, bone, cardiovascular system, liver, adipose tissue, brain - hypothalamus, immune cells**

**ER beta** → Regulates genes & membrane receptors

Primarily expressed in *non-gonadal* tissues: **tract, colon, bone marrow, vascular endothelium, lung, bladder, B cells, brain, lung**

**Membrane-associated ER** →

**No effect on genes, but rapid effects on cellular signaling**



# Modulated by Estradiol ...

## Vasodilation and vasoconstriction

- Endothelial NO synthase
- Prostacyclin cyclooxygenase
- Prostacyclin synthase
- Renin and angiotensin
- Endothelin-1

## Lipid Metabolism

- Lipoprotein lipase
- Apo-lipoproteins
- Leptin
- PON 1
- LDL receptors
- HMG-CoAR activity

## Immune activity

- Vascular-cell adhesion molecule
- Cytokines (IL1, IL6, TNF $\alpha$ )
- Cytokine receptors
- Superoxide Dismutase

## Coagulation

- Fibrinogen
- Coagulation factors
- Protein S

## Angiogenesis

- Matrix metalloproteinase
- Vascular endothelial growth factor

## Non-Genomic Effects

- Fast-acting actions such as NO facilitated vasodilation





Menopause is a  
universal and natural  
event for women...  
Why address it?

*Because nature is  
not always kind*



**Menopause is not just  
the loss of fertility and  
periods...**

*It is the beginning  
of a major  
metabolic shift*



# What's Going On During Menopause?

ESTROGEN

**Menopause is about estrogen loss –  
Major overlooked factor in women's  
health**

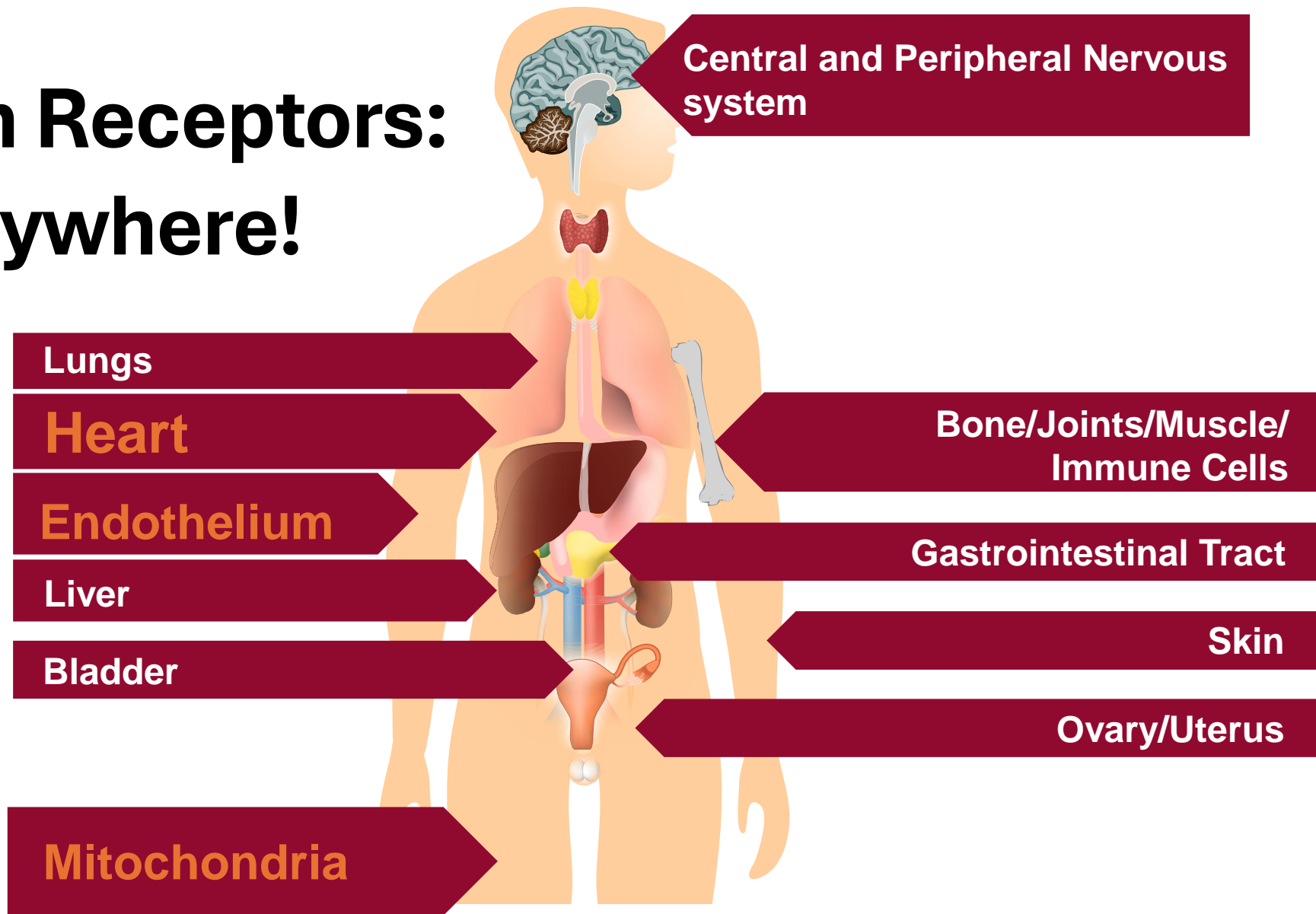


# What are the Estrogens?

- **Steroid hormones produced primarily by the ovaries and peripherally from cholesterol-derived precursors**
- **Regulate multiple functions across organs, cells, and genes**
- **Typically bind to receptors (ERs) to perform their functions**
- **Alternative ways exist for E2 to impact cell function**



# Estrogen Receptors: Everywhere!



# Estrogen Basics Remembered:

Steroid hormones - bind to receptors throughout the body - regulate a multiplicity of functions

ESTRADIOL

ESTRONE

ESTRIOL

- **Cardiometabolic Health**
- **Reproductive Health**
- **Immune Health**
- **Cognitive & Emotional Health**
- **Musculoskeletal Health**
- **Gastrointestinal Health**
- **Skin Health**

# Estrogen Related Receptor (ERR) Isoforms Expressed in Myocardium

Members of steroid hormone superfamily-  
regulate expression of genes for energy metabolism, mitochondrial  
biogenesis, fatty acid oxidation, oxidative phosphorylation

**ERR $\alpha$  and  $\gamma$**  – share target genes in myocardium

**ERR $\beta$**  – maintains proper oxygen consumption rates in myocardium

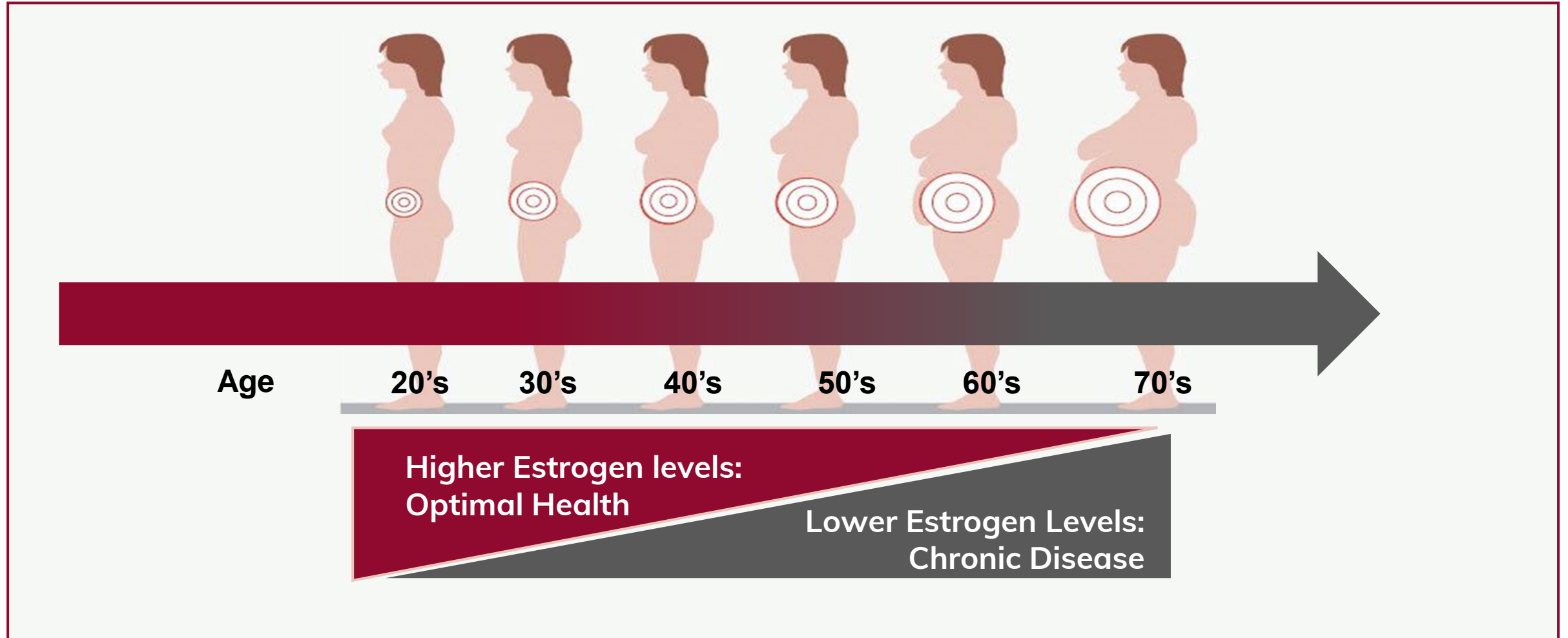


# Estrogen Metabolite – 2 Methoxy Estradiol

## Impact on CV health – not always via estrogen receptors

- **Down regulates synthesis of Angiotensin Type 1 Receptor in liver epithelial cells**
- **Down regulates Endothelin 1 in coronary artery endothelial cells**
- **Inhibits cell growth in human aortic smooth muscle cells by decreasing ERK1/2 phosphorylation – inhibits neo-intima formation and smooth muscles cell growth**

# Age-Dependent Shift in Estrogen Levels = Pro-inflammaging



# Hidden Risks of Menopause

**Estrogen receptors are everywhere and play vital roles in regulating countless physiologic functions**

## *Cardiovascular Health & Atherosclerosis*

- **Obesity & Increased Visceral Fat**
- **Metabolic Syndrome & Diabetes**
- **Musculoskeletal effects, including Osteoporosis & Osteoarthritis**
- **Alzheimer's Disease & Neuro-inflammation**
- **Cellular Health (breast, colon)**
- **Autoimmune disease**
- **Fatty Liver**
- **GI Disorders: Colon Cancer, GERD, Malabsorption & Motility**

# The Significance of Cardiovascular Health

Coronary artery disease (CAD) is the number one cause of death in women in the world

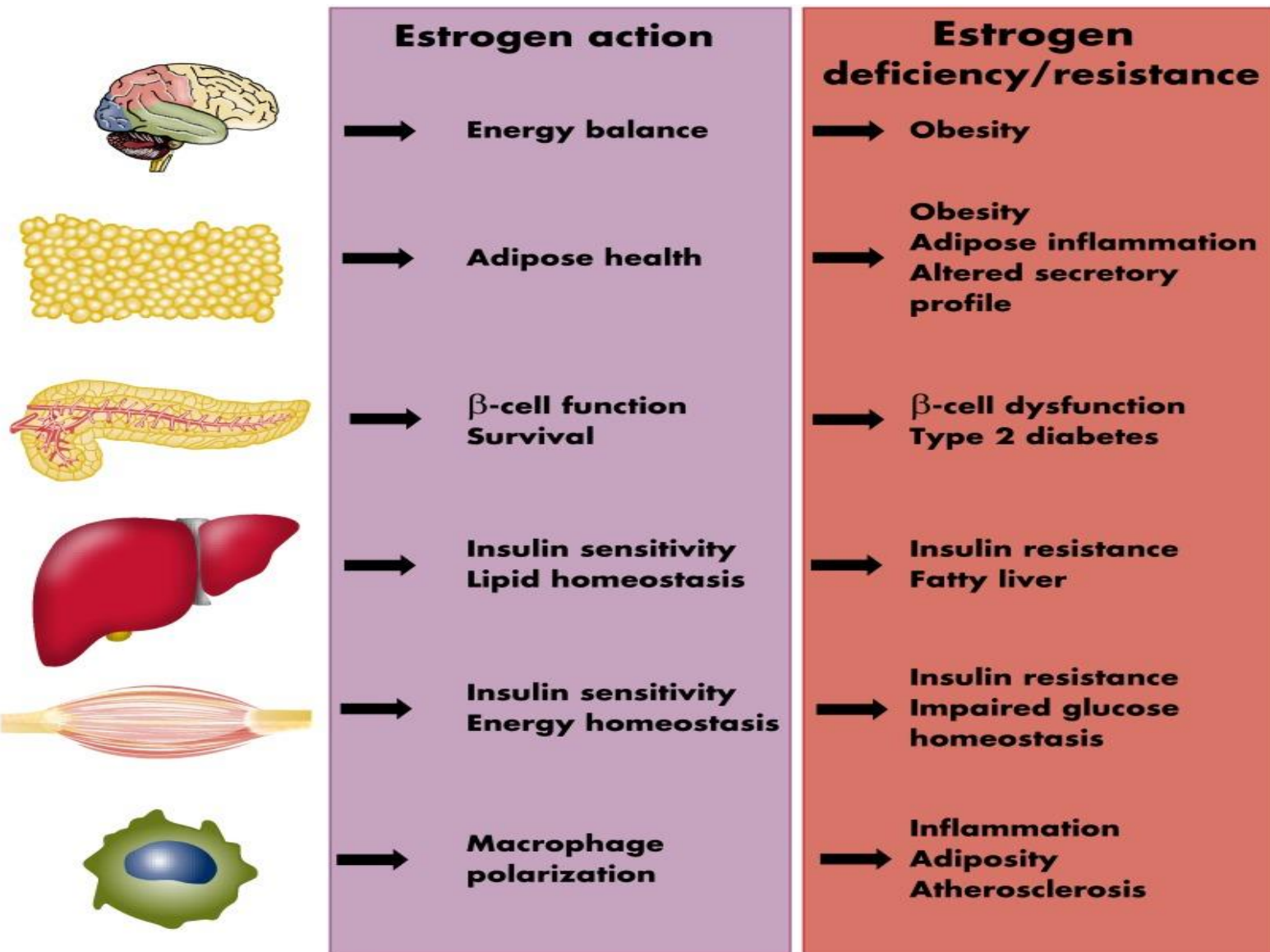
**More than cancer, diabetes, Alzheimer's & pneumonia**



# Impact of Menopause: Endothelial Function

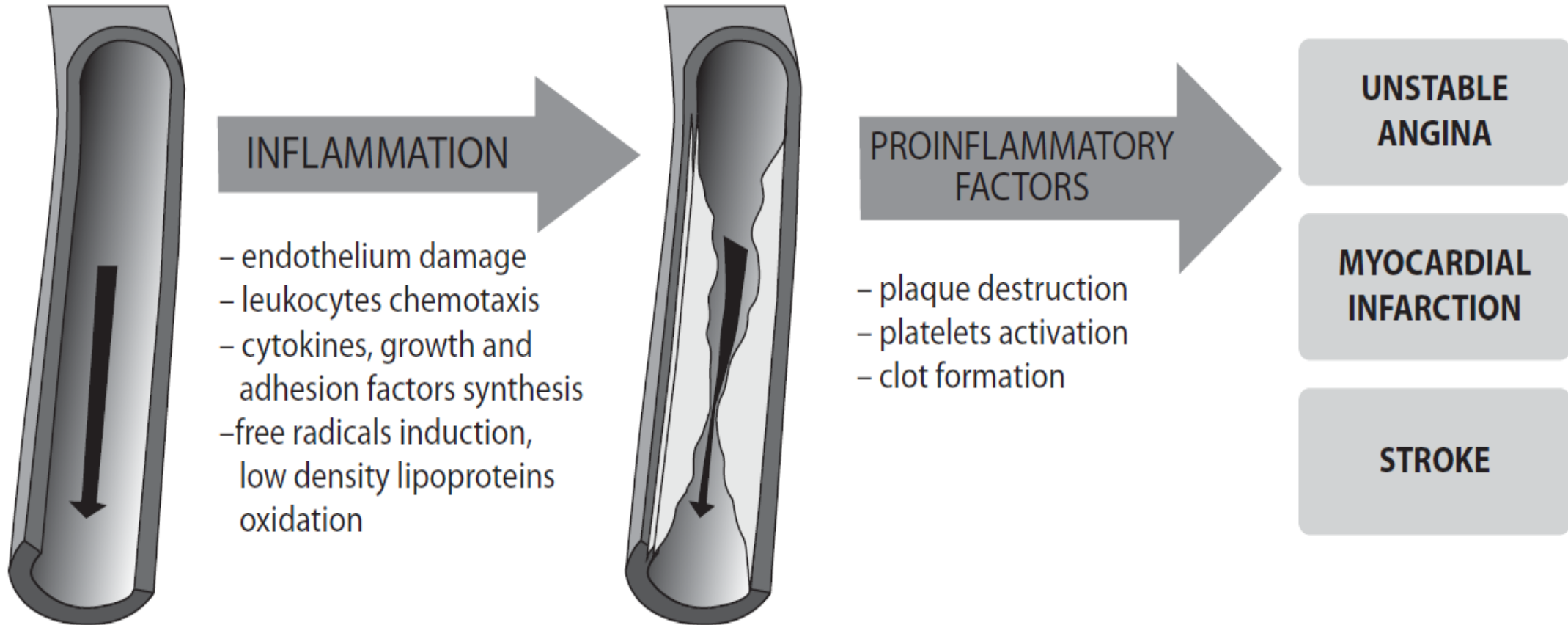
85% of all women in the US are hypertensive by the age of 75

- **Typically expressed as systolic hypertension**
- **Often develops around menopause**
- **Attributed to the decline in estrogen**
- **Risk factor for CAD and other cardiometabolic events**

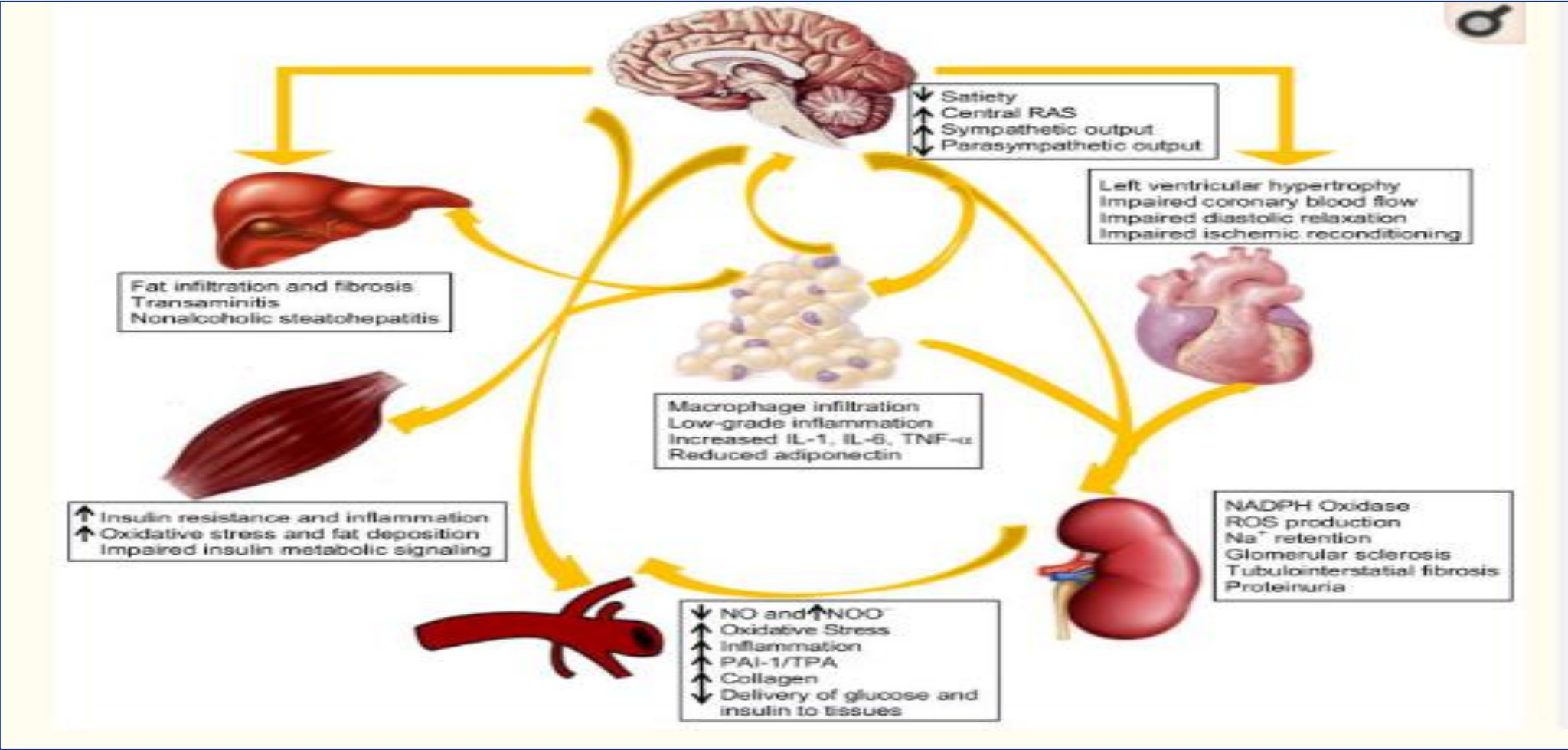


# Negative Effects of Estrogen Deficiency on Metabolism

# Inflammation Underlies Cardiovascular Events



# Cardio-Renal-Vascular-Metabolic Syndrome

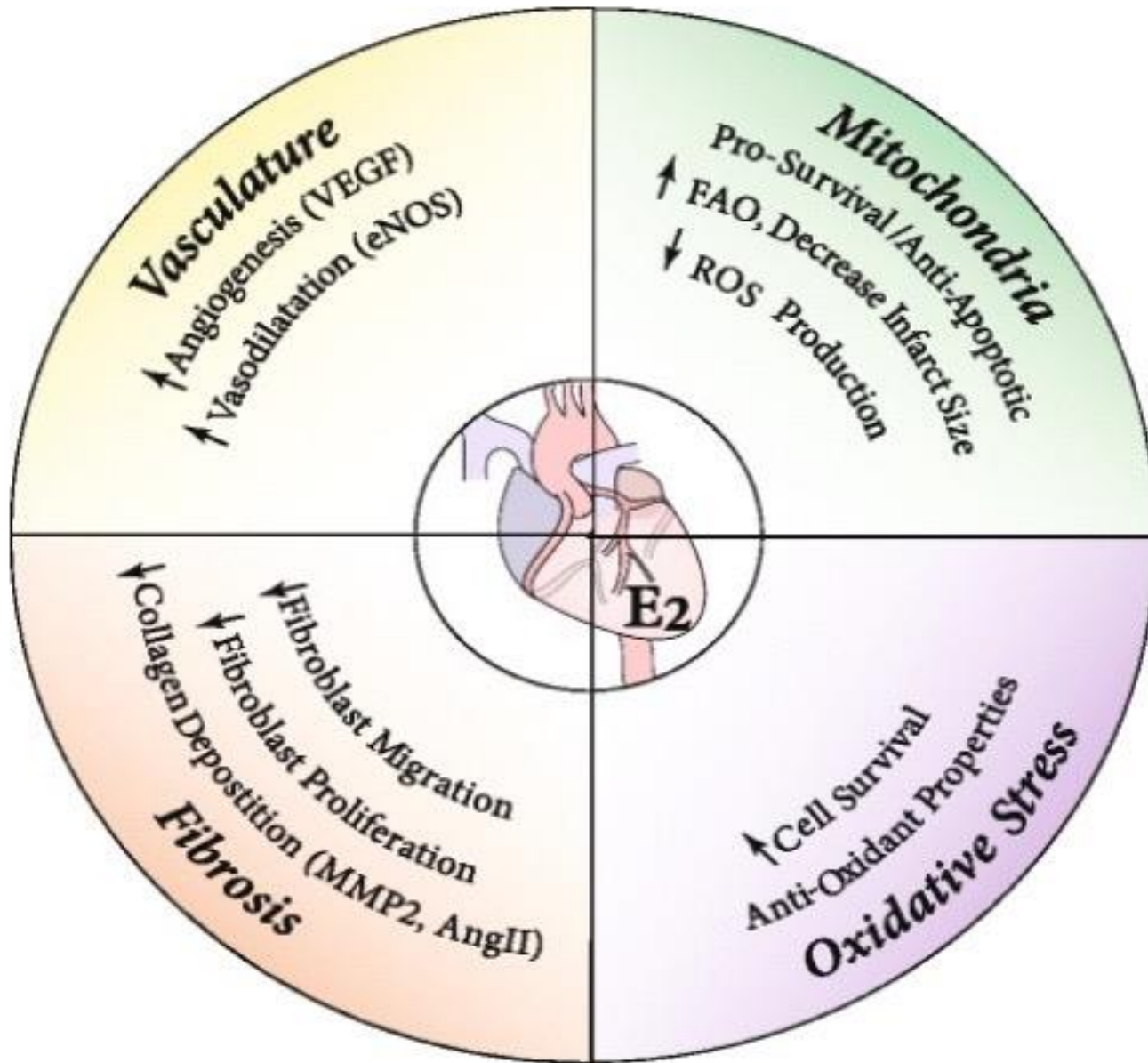




# Estradiol + Renal Angiotensin Aldosterone System (RAAS)



Estradiol – Master Immunomodulator and regulator of the RAAS



# Estradiol & the Heart - Overview

# Estrogen Alleviates Diastolic Dysfunction

**Table 2** Doppler echocardiographic diastolic indices of transmitral flow in the oestradiol and placebo groups at baseline, 90 minutes, and 12 weeks

Variable	Time point	Oestradiol	Placebo	p Value
Vel E (cm/s)	Baseline (T1)	66 (19)	63 (11)	NS
	90 minutes (T2)	68 (20)	61 (13)	NS
	12 weeks (T3)	74 (22)	61 (16)	NS
Vel A (cm/s)	Baseline (T1)	81 (21)	79 (14)	NS
	90 minutes (T2)	81 (21)	76 (11)	NS
	12 weeks (T3)	75 (23)*	73 (13)*	NS
E/A ratio	Baseline (T1)	0.8 (0.2)	0.8 (0.1)	NS
	90 minutes (T2)	0.9 (0.2)	0.8 (0.1)	NS
	12 weeks (T3)	1.0 (0.2)†	0.8 (0.2)	0.04
DTE (ms)	Baseline (T1)	260 (42)	254 (22)	NS
	90 minutes (T2)	248 (40)	245 (20)	NS
	12 weeks (T3)	238 (20)*	274 (42)*	0.01
IVRT (ms)	Baseline (T1)	127 (23)	121 (15)	NS
	90 minutes (T2)	121 (17)	120 (16)	NS
	12 weeks (T3)	106 (16)†	121 (16)	0.01

The values are expressed as mean (SD).

\* $p < 0.05$  (T1 v T3) in the same group.

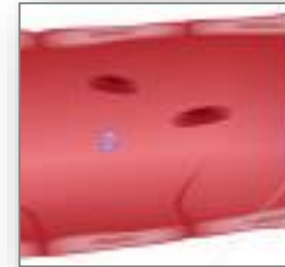
† $p < 0.001$  (T1 v T3) in the same group.

DTE, deceleration time of mitral E wave; E/A, the ratio between the peak velocity of mitral E and A wave; IVRT, isovolumic relaxation time; Vel A, peak velocity of mitral A wave; Vel E, peak velocity of mitral E wave.

# 3 Cardiovascular Benefits of Estradiol (E<sub>2</sub>)

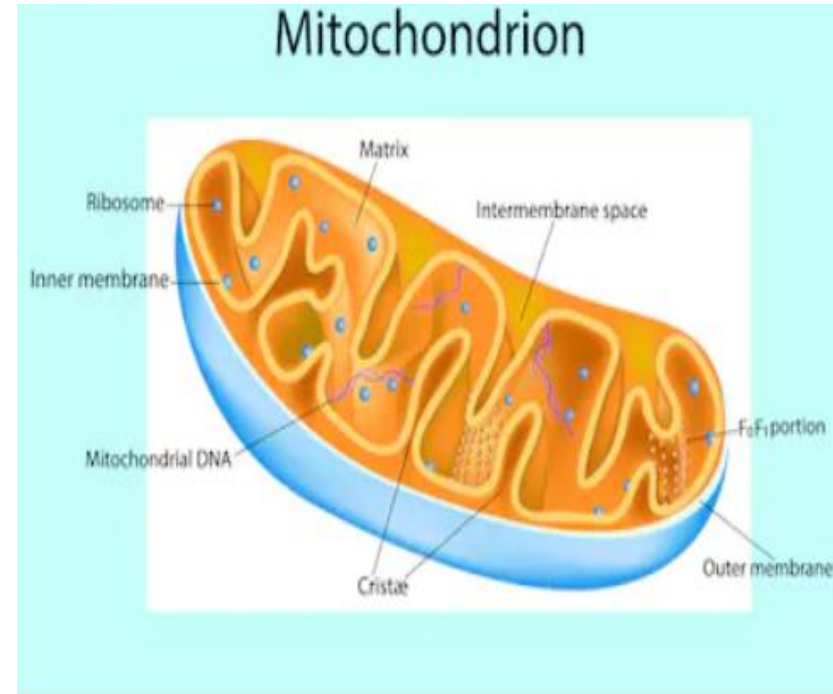
**E<sub>2</sub>**

- 1 Insulin Sensitivity & Glucose Metabolism
- 2 Lipid Profile
- 3 Endothelial Function



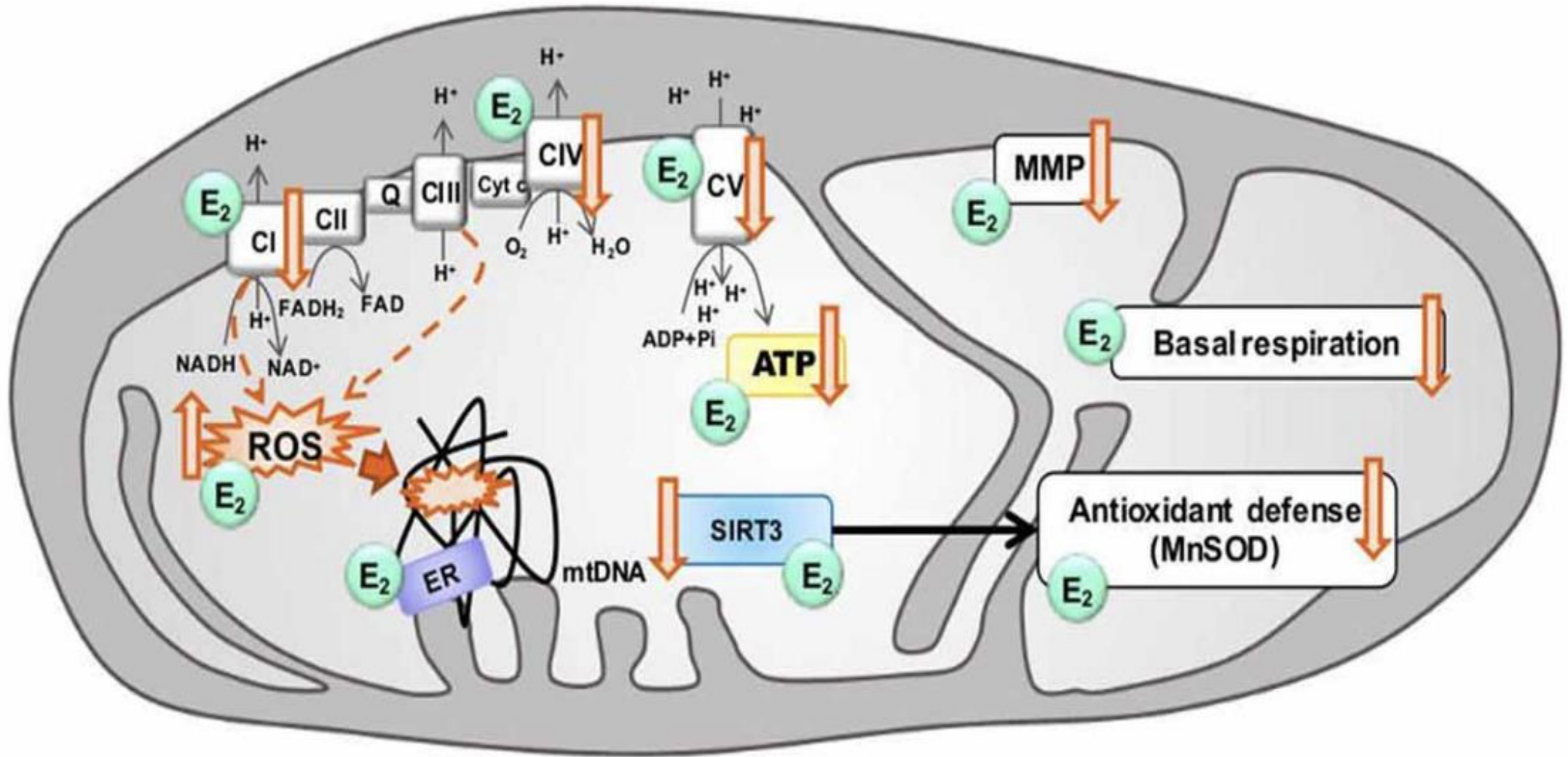
# Estrogen Supports Mitochondrial Health

There is a growing understanding of the role which E2 plays in metabolism via its regulation of mitochondrial function



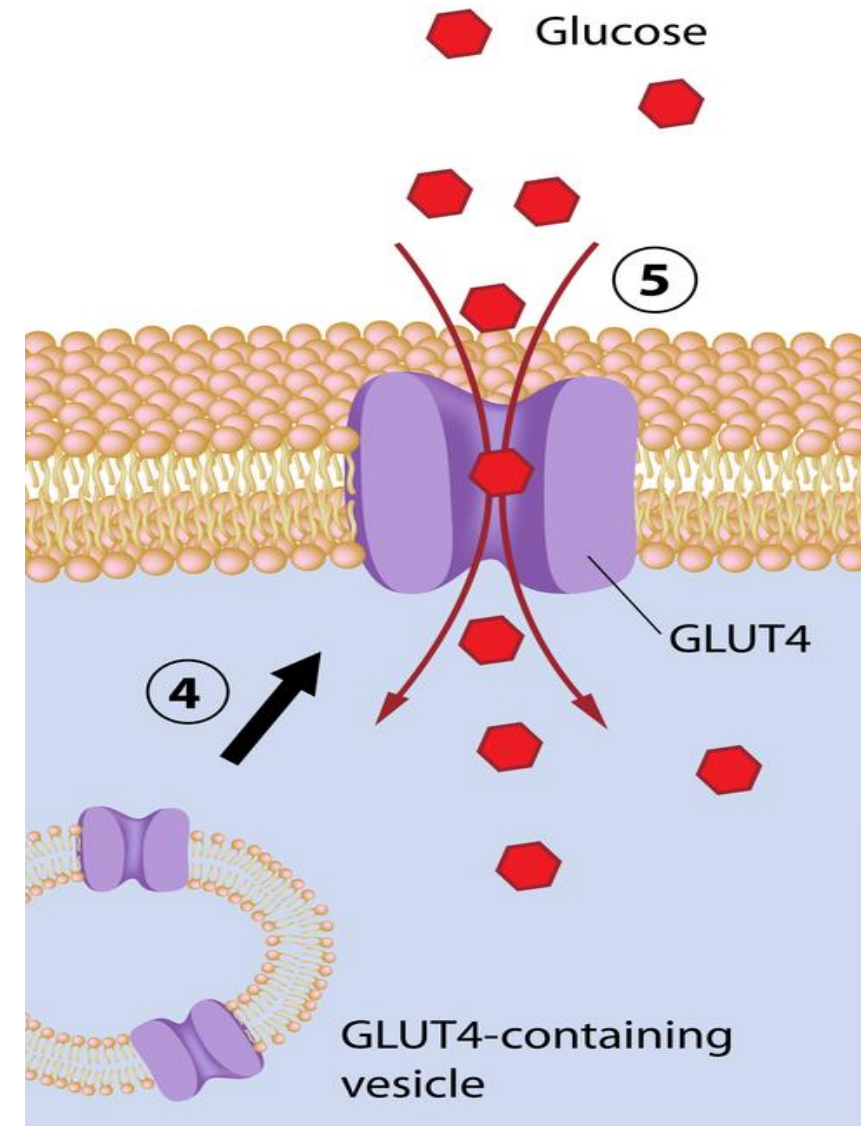
Duckles et al. Molecular Interventions, 2006;Vol 6, No1, pp26-35  
Wang et al. J Neurochemistry, 2001; Vol 77, No.3; pp 804-11

# Estrogen-Mitochondria-SIRT3 Link



# Estrogen Supports Insulin Sensitivity

- Supports glucose transporter (GLUT3, GLUT4) function
- Enhances glucose-stimulated insulin biosynthesis
- Promotes  $\beta$  cell survival



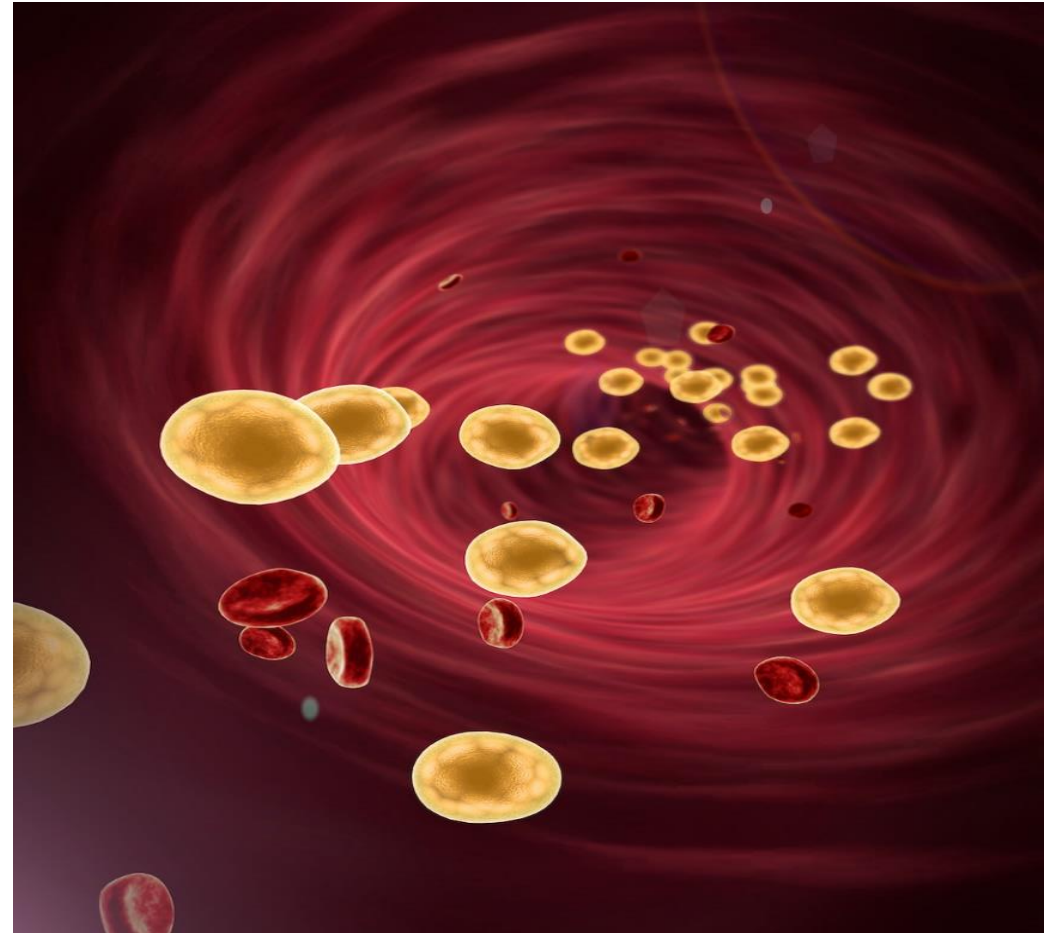
# Lipid Metabolism: Cholesterol

- **Compared to men, during reproductive years, women have:**
  - Lower LDL levels
  - Higher HDL levels
  - Lower total lipid levels
- **Estradiol upregulates the expression of:**
  - Apolipoprotein A1
  - LDL receptors – responsible for the uptake of lipoprotein
- **Estradiol decreases:**
  - Lipoprotein lipase
  - HMG-CoA Reductase activity



# Estrogen Supports a Healthy Lipid Profile

- **Supports HDL levels by promoting apolipoprotein A-I and moderating hepatic lipase activity**
- **Moderates LDL levels by promoting levels of hepatic LDL receptors**



# Estrogen and Paraoxonase (PON 1)

- Oxidized low-density lipoproteins (oxLDL) involved in initiation of atherosclerosis
- PON 1 located on HDL – protects against oxidation of HDL and LDL by hydrolysing lipid peroxides
- Oxidative status reduces PON 1 activity, increases oxLDL

***Estrogen increases PON 1 activity***

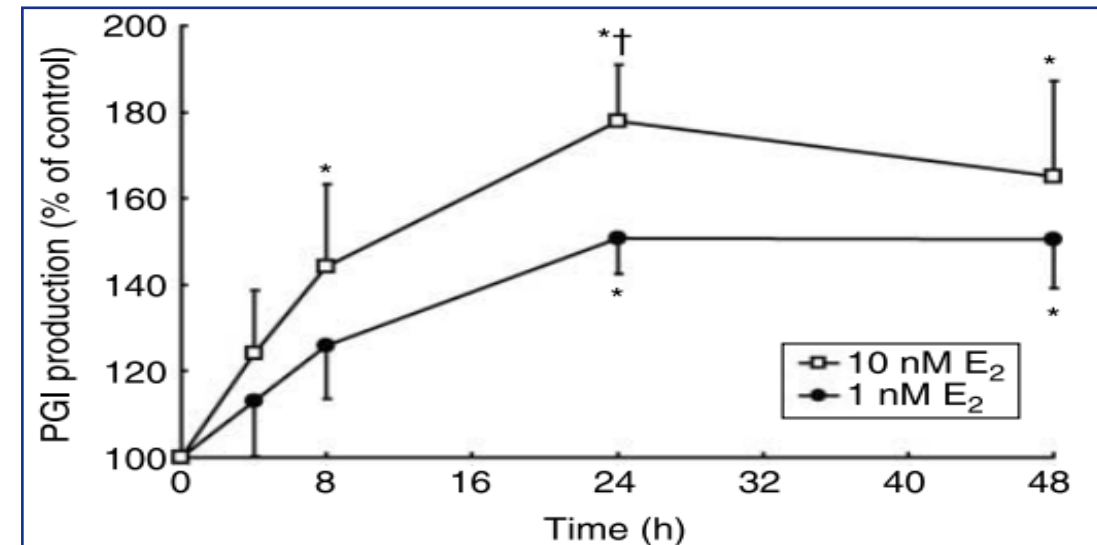
# Estradiol Promotes Prostacyclin Expression

Produced by endothelial and vascular smooth muscle cells

- Major anti-atherogenic prostanoid
- Counter effects thromboxane – important balance in cardiovascular homeostasis

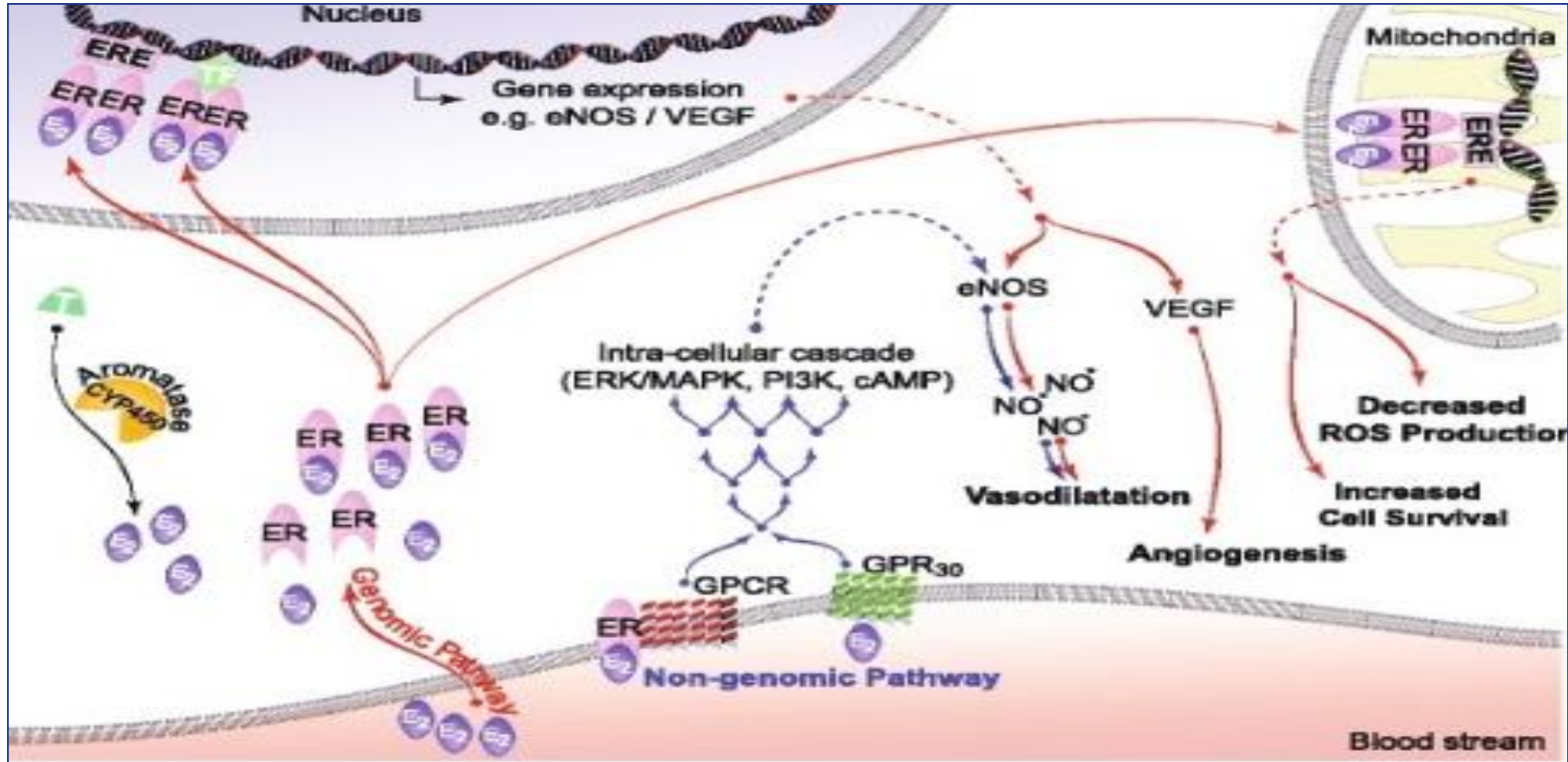
**E2 promotes vasodilation through release of prostanoids (and others)**

- E2 binds to ER $\alpha$  to up-regulate (Cyclooxygenases and PGI Synthase and PGI expression)

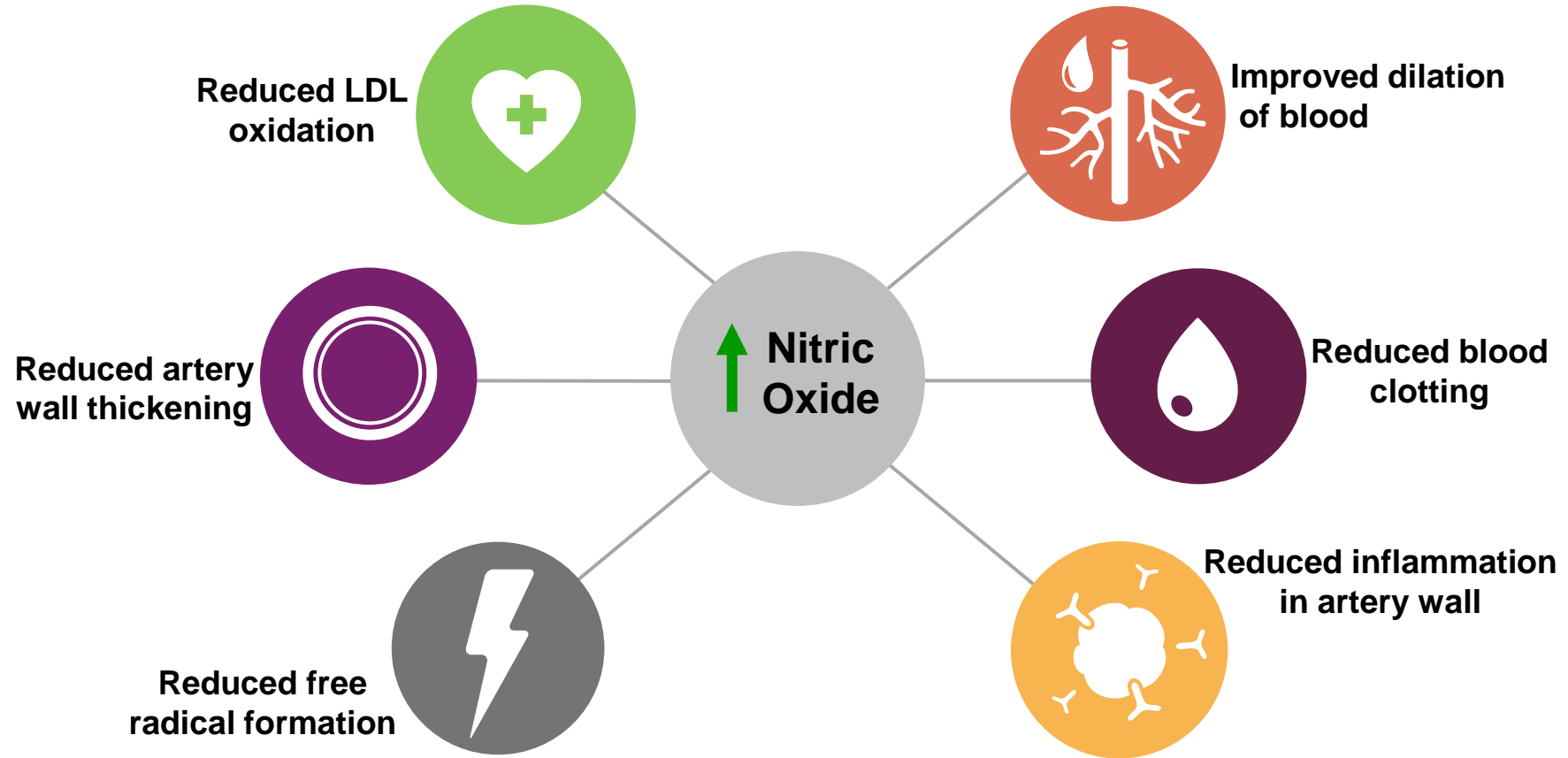


**Endothelial cells treated with E2:  
induces PGI production in a dose  
dependent manner**

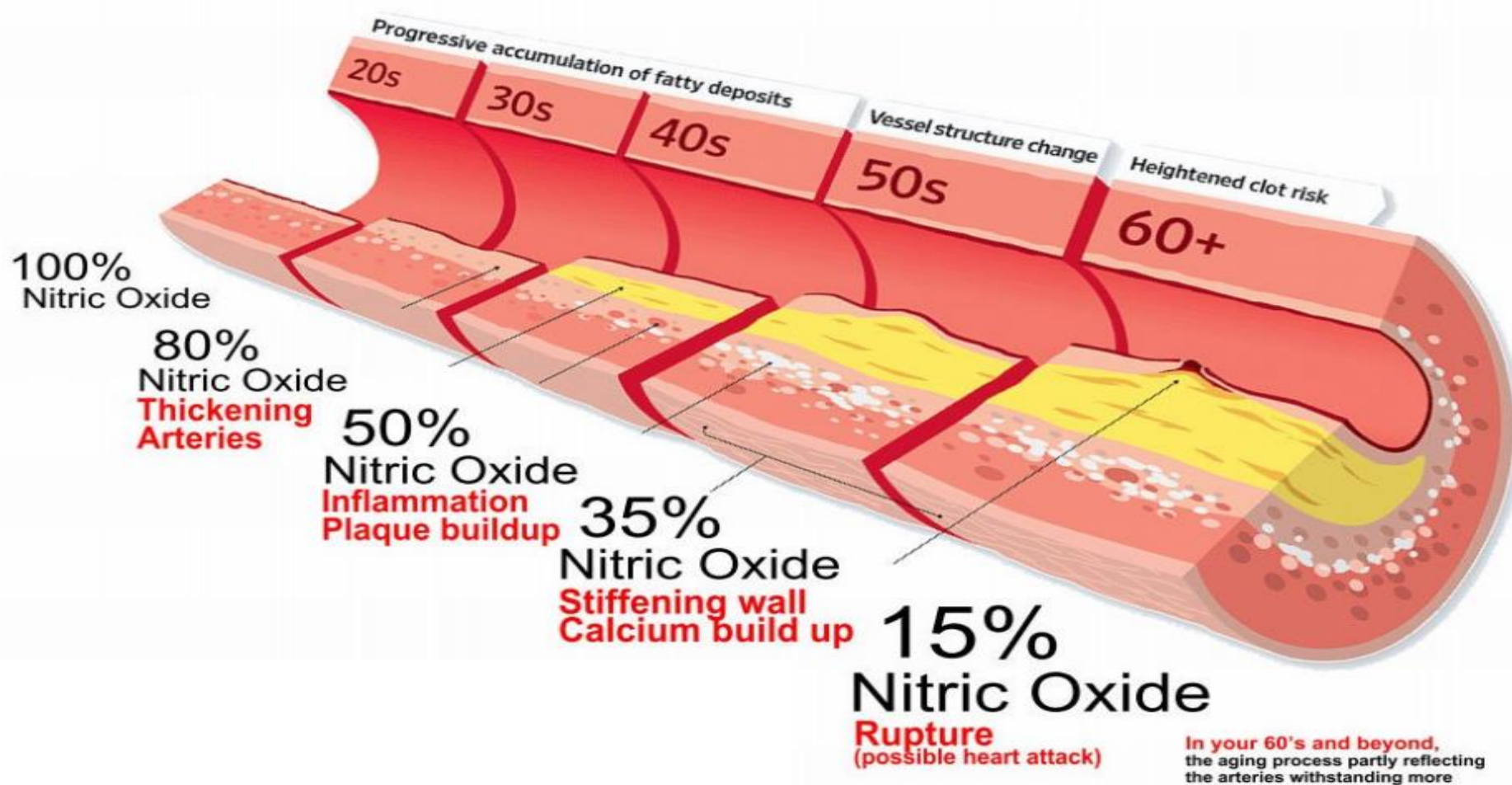
# Estradiol and Arterial Health – Production of Nitric Oxide



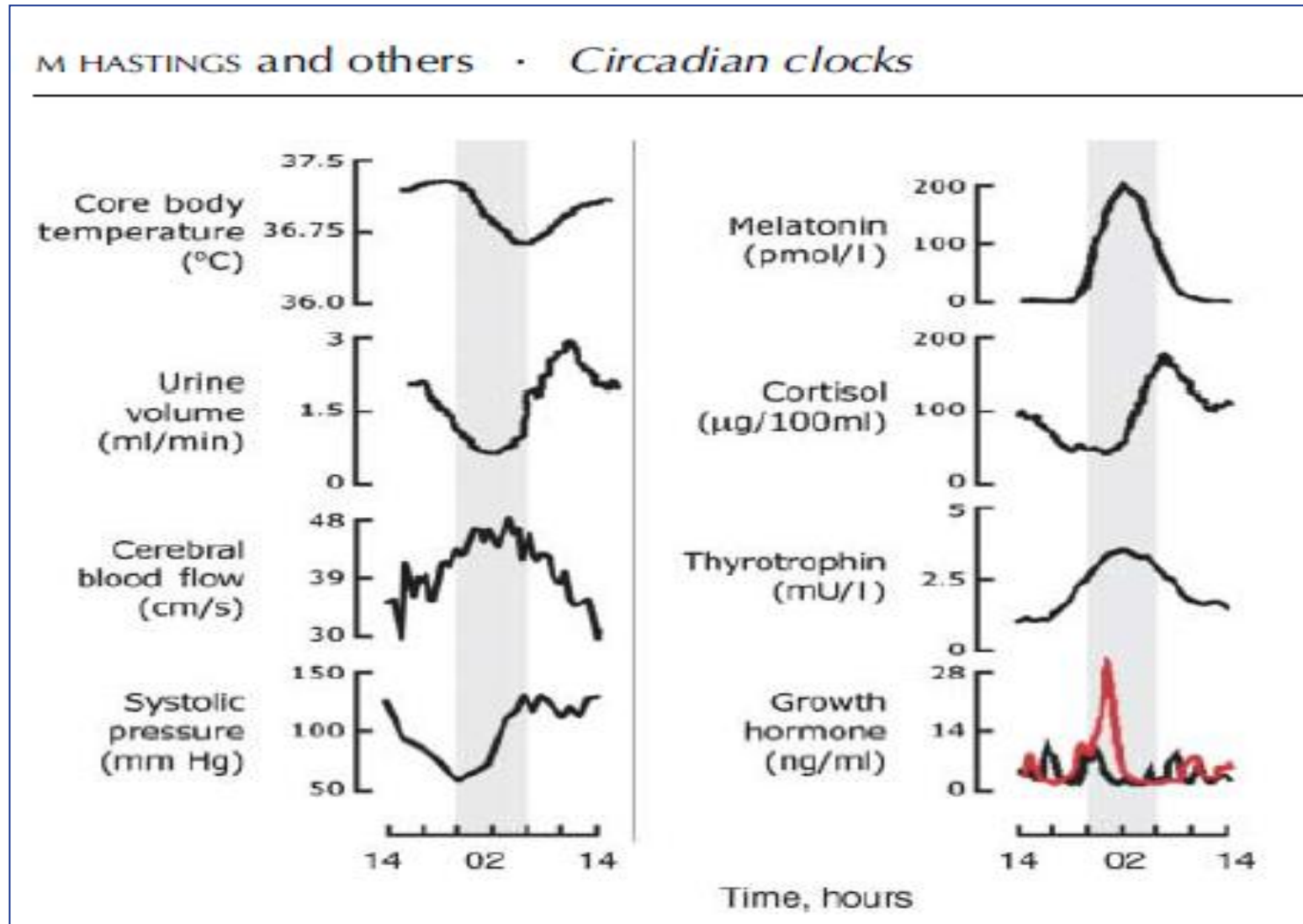
# Nitric Oxide Maintains Endothelial Health



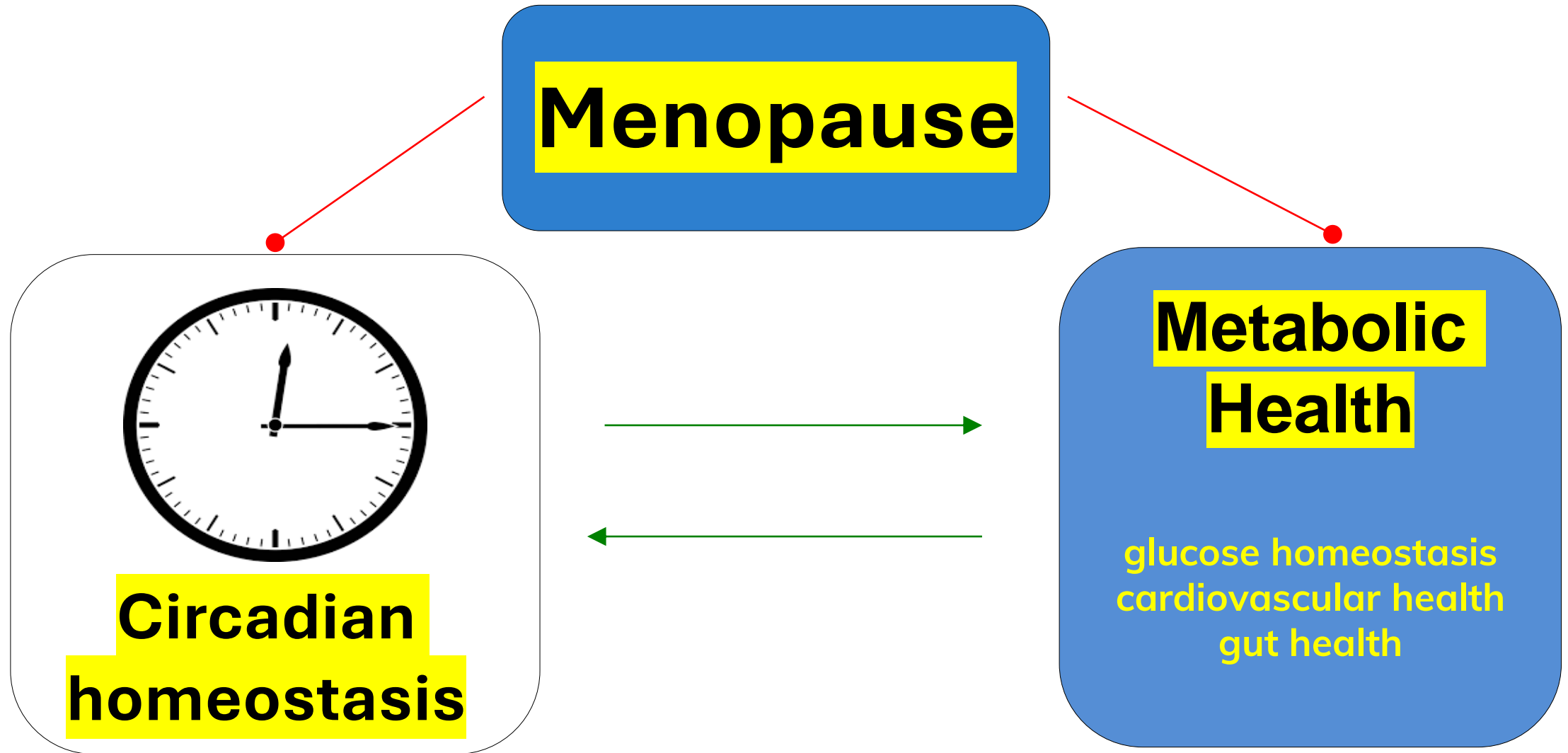
# Progression with Age: a NO Perspective



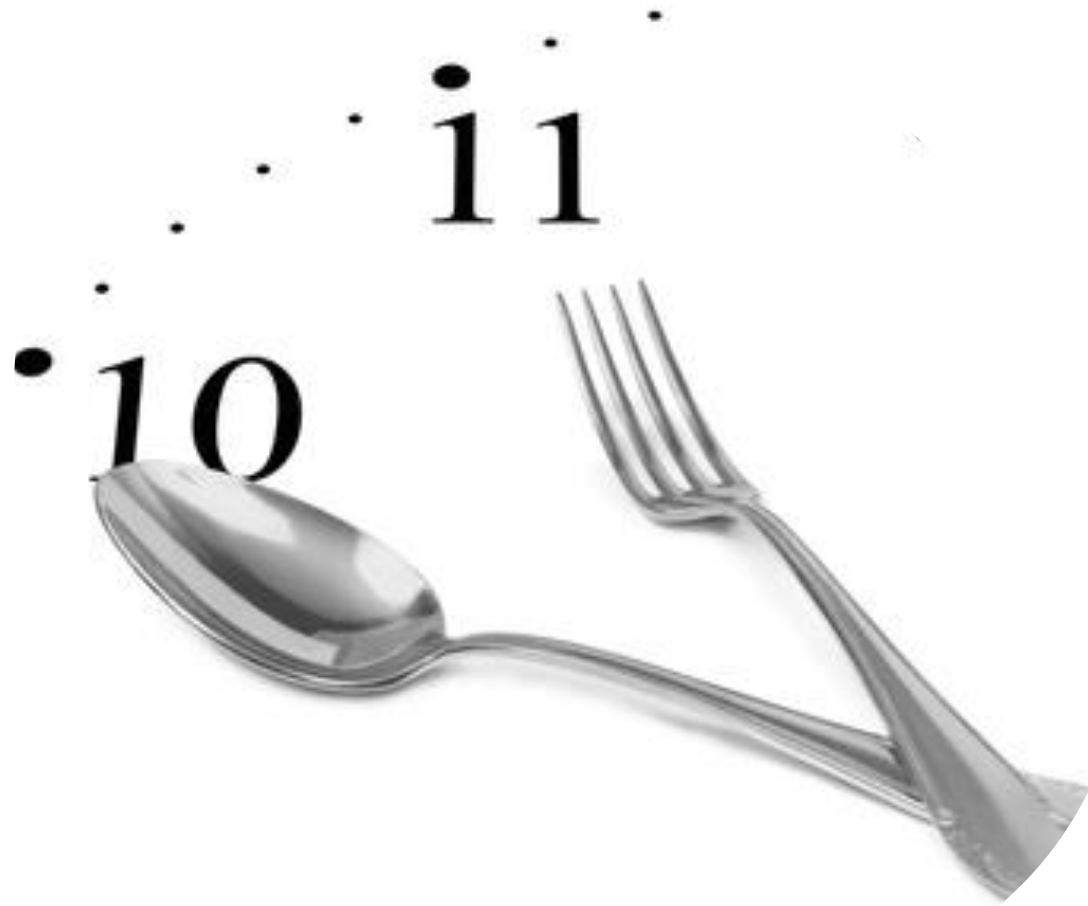
# Importance of the Circadian Rhythm



# Menopause-Circadian-Metabolic Triad:





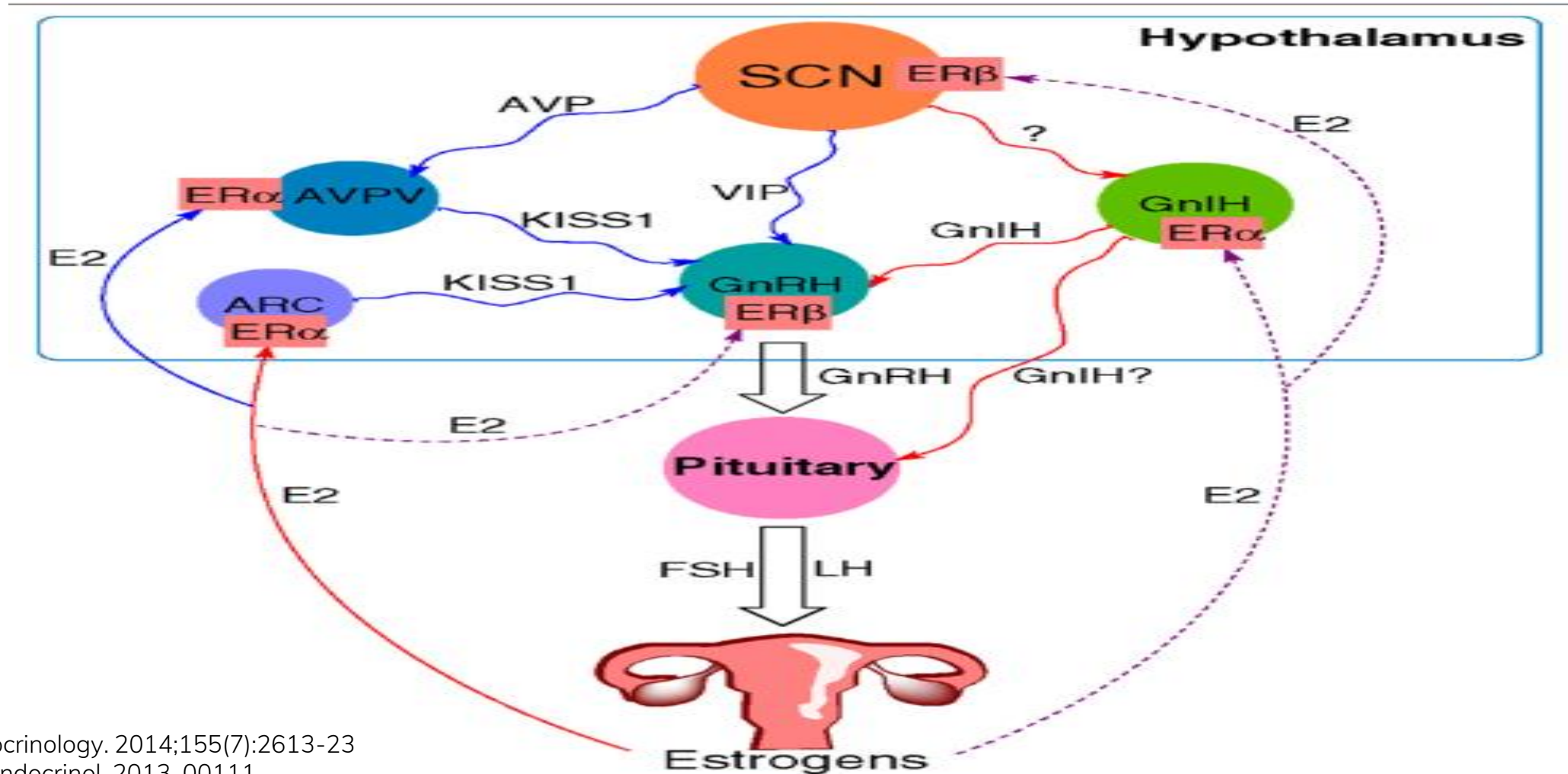


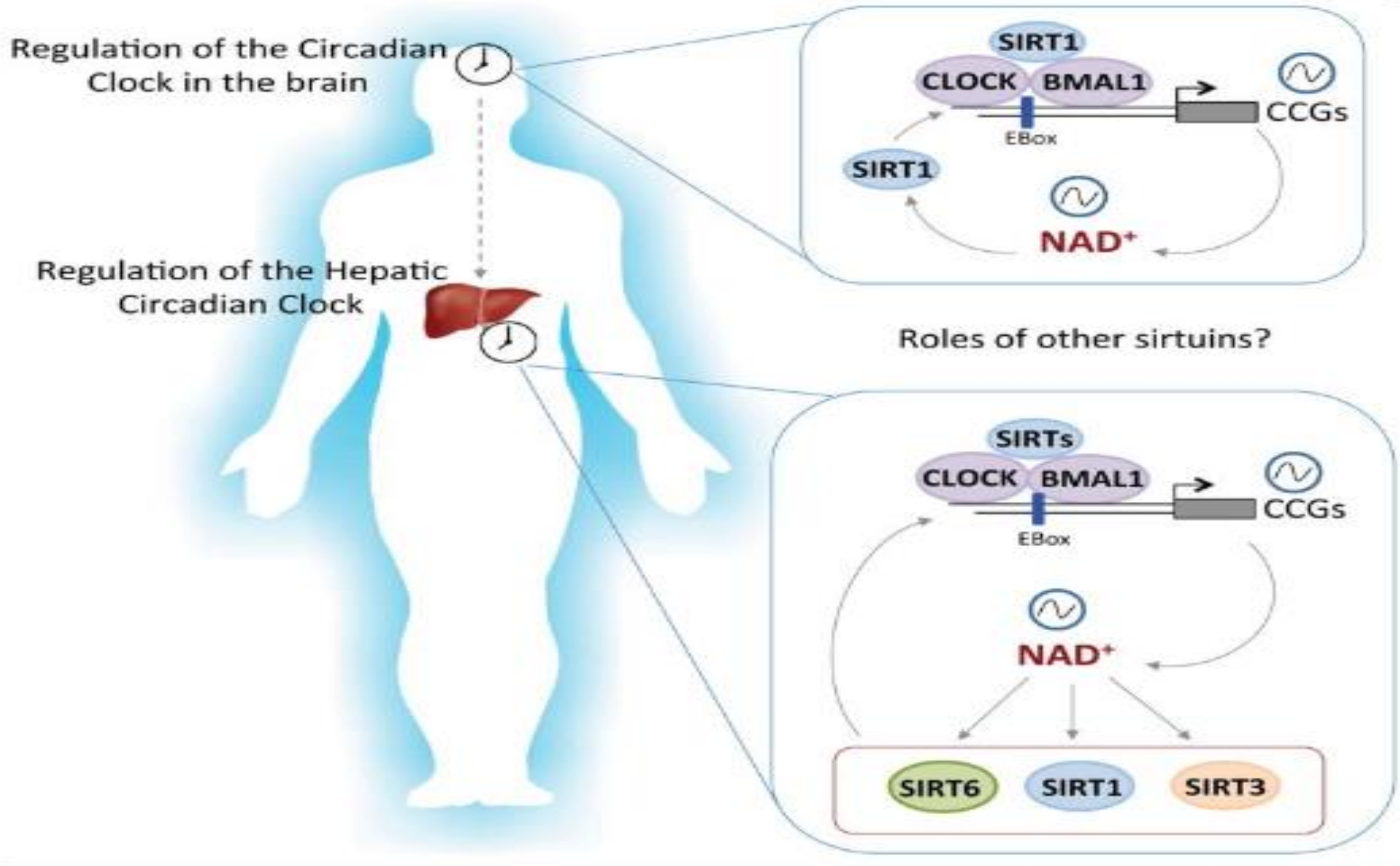
## **Redefining Menopause:**

*It's like living a life of jetlag – and that is a major challenge!!*

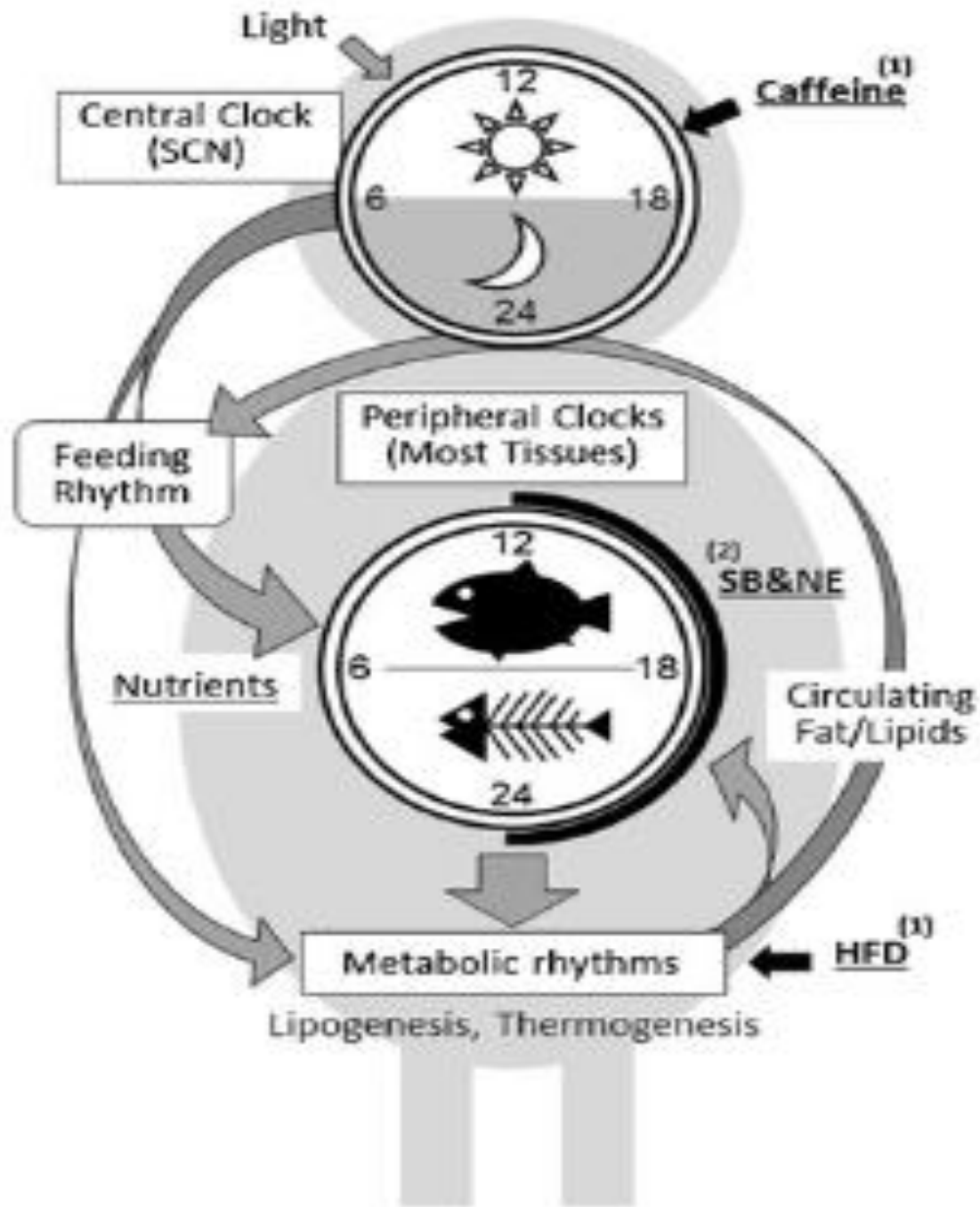
*Lifestyle Approaches to Optimize  
Cardiovascular Health*

# Coordination of Reproduction & Metabolism: Optimal Health



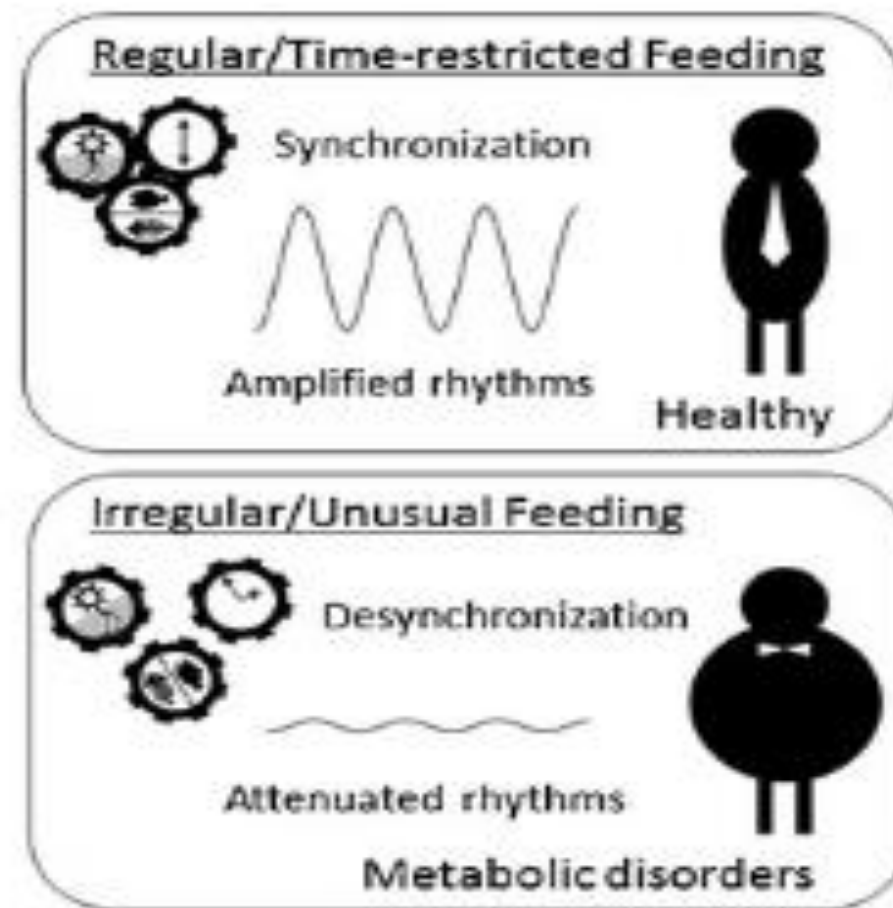


**Sirtuin-dependent control of the circadian clock in the brain and periphery**



## Chrono-nutrition

- (1) Clock regulation  
ex. High-fat diet (HFD), Caffeine
- (2) Meal-time effects  
ex. Skipping breakfast (SB)  
Nocturnal eating (NE)



# Poor diet + Estrogen Deficiency *drives Dysbiosis*

## Dysbiosis → Systemic Inflammation

### High fat/high sugar diet leads to gut dysbiosis

...

### & Circadian Rhythm Dysfunction



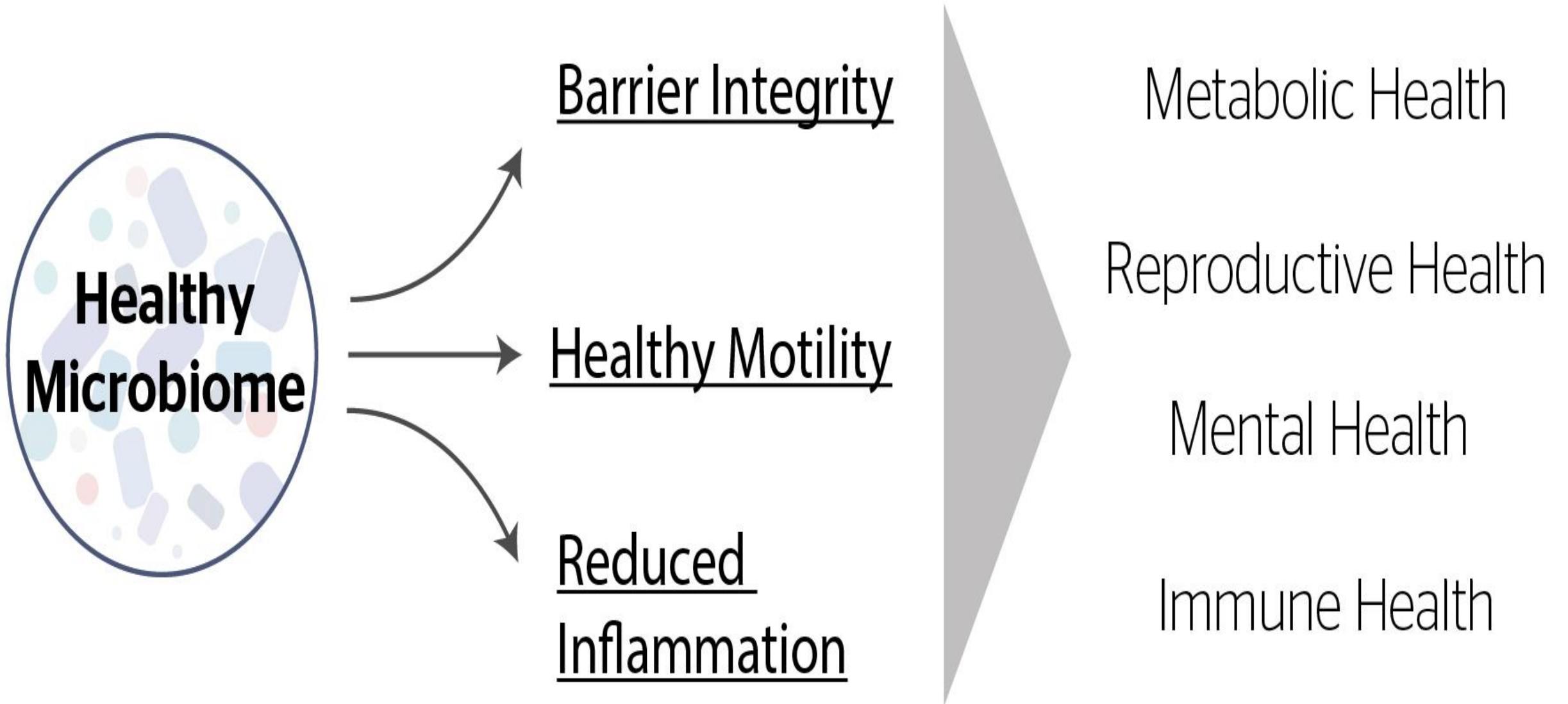
Guinane CM et al. Tole of the gut microbiota inhealth and chronic gastrointestinal disease.

Therp Adv Gastroenterol 2013; 6: 295-308

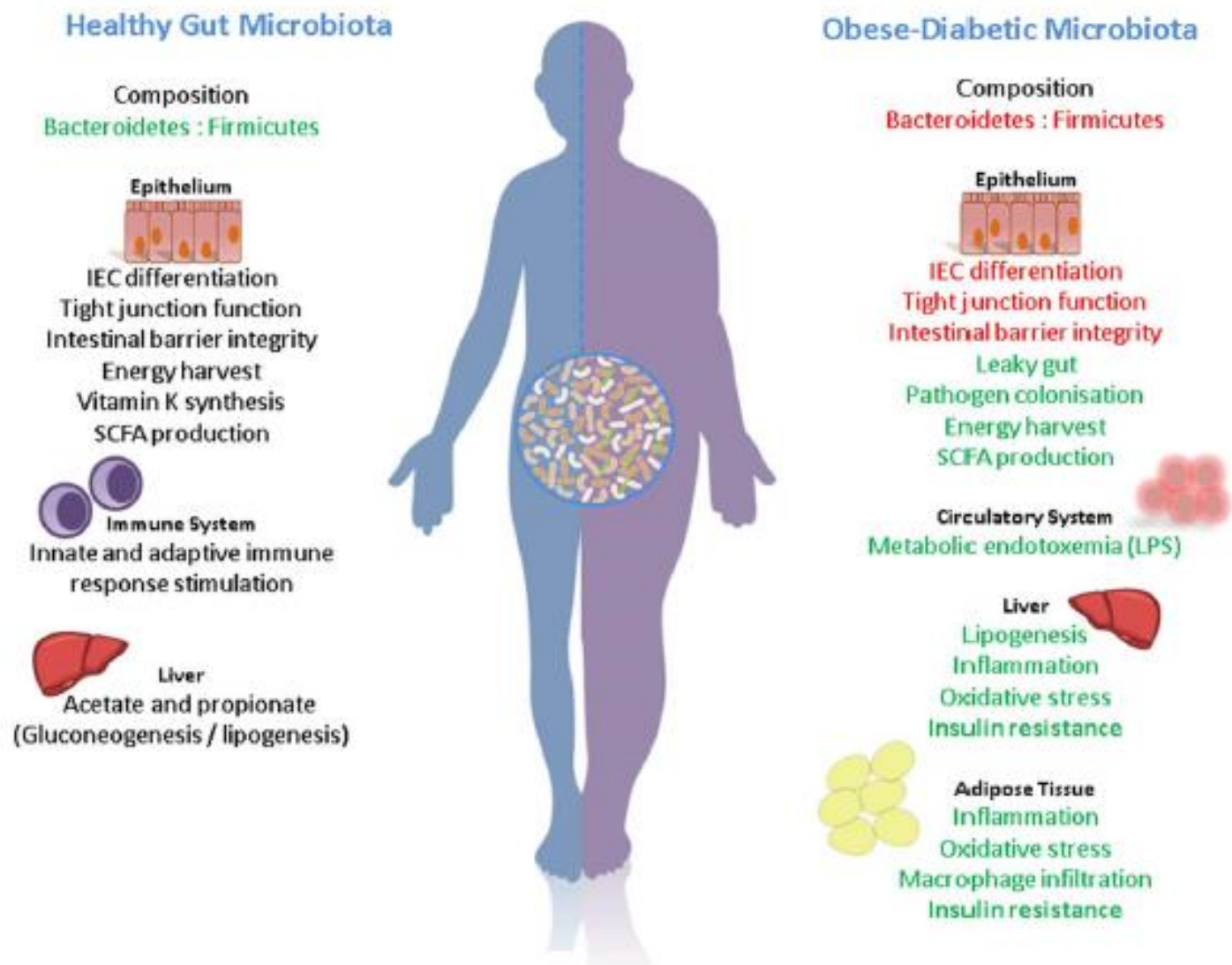
Turnbaugh PJ et al. Diet-induced obesity is linked to marked but reversible alterations in the mouse distal gut microbiome.

Cell Host Microbe 2008; 3: 213-223

# Healthy Microbiome Supports all Systems

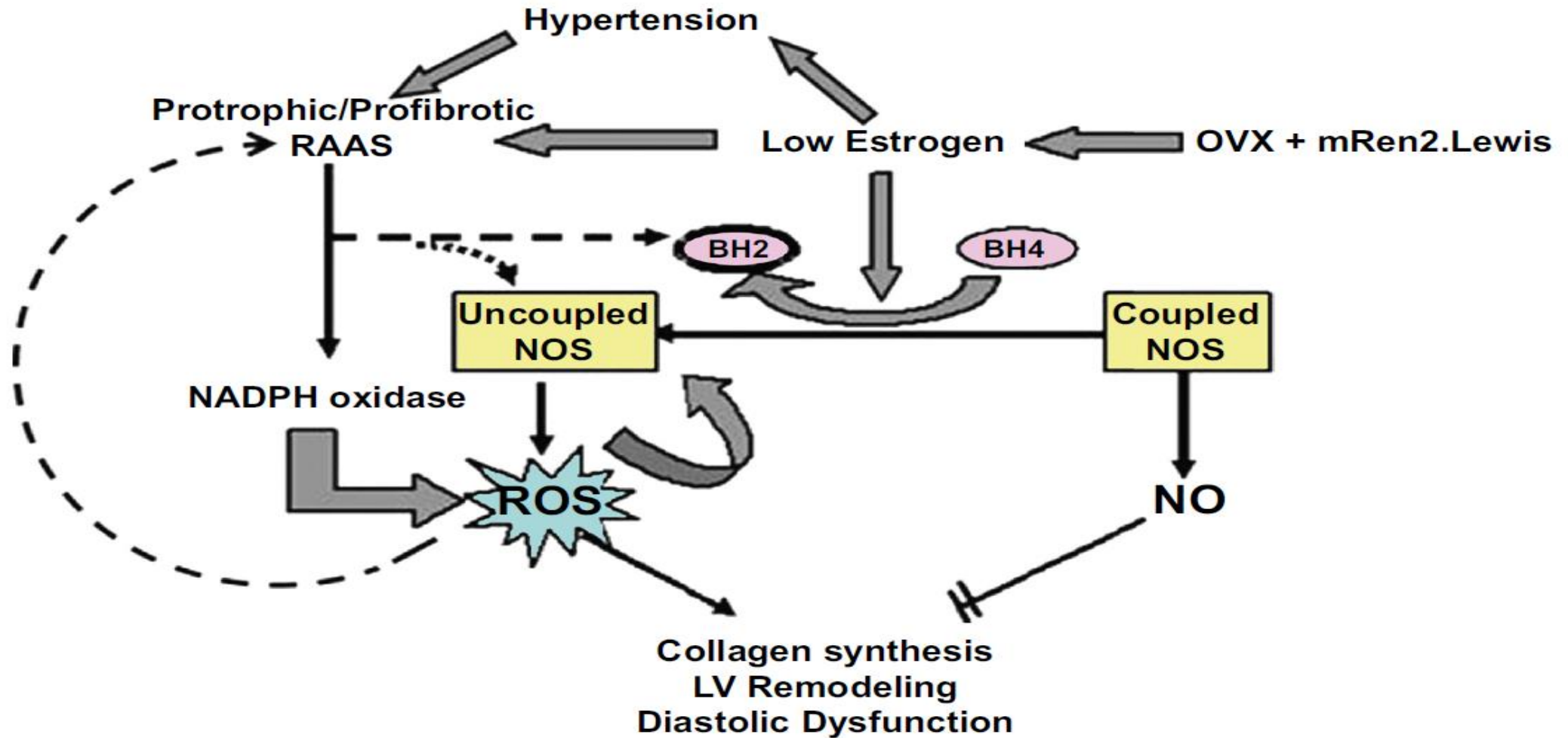


Review



**Figure 1** Compositional and functional alterations in the healthy gut microbiota versus the obese-diabetic microbiota. The metabolic processes in peripheral organs leading to increased adiposity, inflammation, oxidative stress, insulin resistance and lipogenesis are associated with the altered microbiota profile associated with the obese-diabetic phenotype. IEC, intestinal epithelial cell; LPS, lipopolysaccharide; SCFA, short chain fatty acid.

# Your patient is menopausal ... NOW WHAT DO YOU DO??





# Motivation & Compliance

- **Set the expectation: Accept "better"**
- **Each woman can set her own pace**
- **Help your patient make health a priority**



# Key Cardiovascular Testing Options

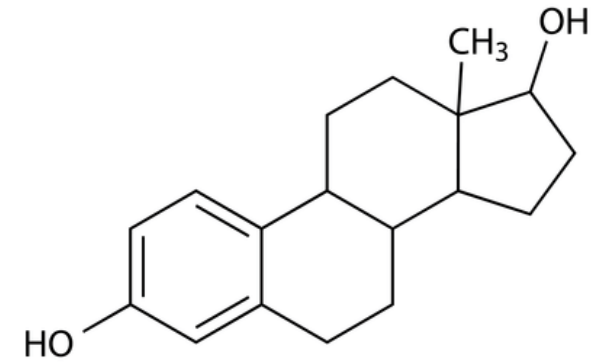
- ADMA
- Advanced lipid profile, Oxidized LDL
- Insulin and HbA1c
- Inflammatory markers: hsCRP, MPO, F2isoprostane, LpPLA2
- ApoE, MTHFR
- Hormones
- Thyroid
- Ferritin
- CBC, CMP
- Micronutrients
- Microalbumin
- Heavy metals
- Gut microbiome testing



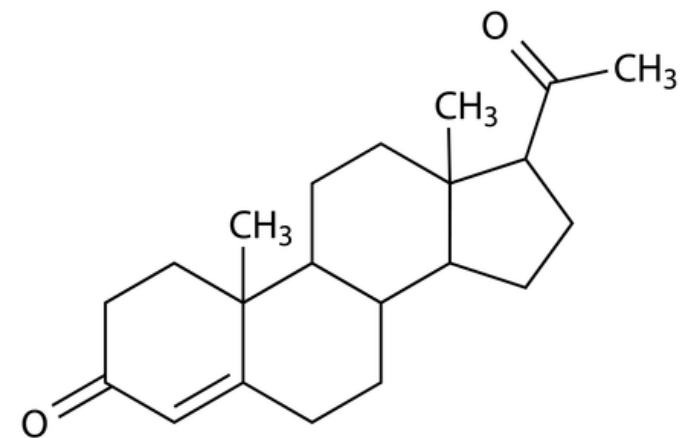


# Hormone Therapy Revisited: Hormones are Beneficial

- **Estradiol patch or gel**
- **Oral micronized progesterone (preferably cyclic)**
- **Compounded Estradiol + progesterone creams**



Estradiol



Progesterone

# Estrogen: Concentration Matters

- “E2 has a bi-potential effect on monocytes and macrophages.
- Low doses enhance the production of pro-inflammatory cytokines while high doses reduce the production of these cytokines”

*Modulating inflammation is a  
key function of ESTROGEN!*

# Supplements that May Support Cardiovascular Health

Nitric Oxide  
Support

Berberine

Bergamot

Quercetin

Magnesium

Omega 3

Curcumin

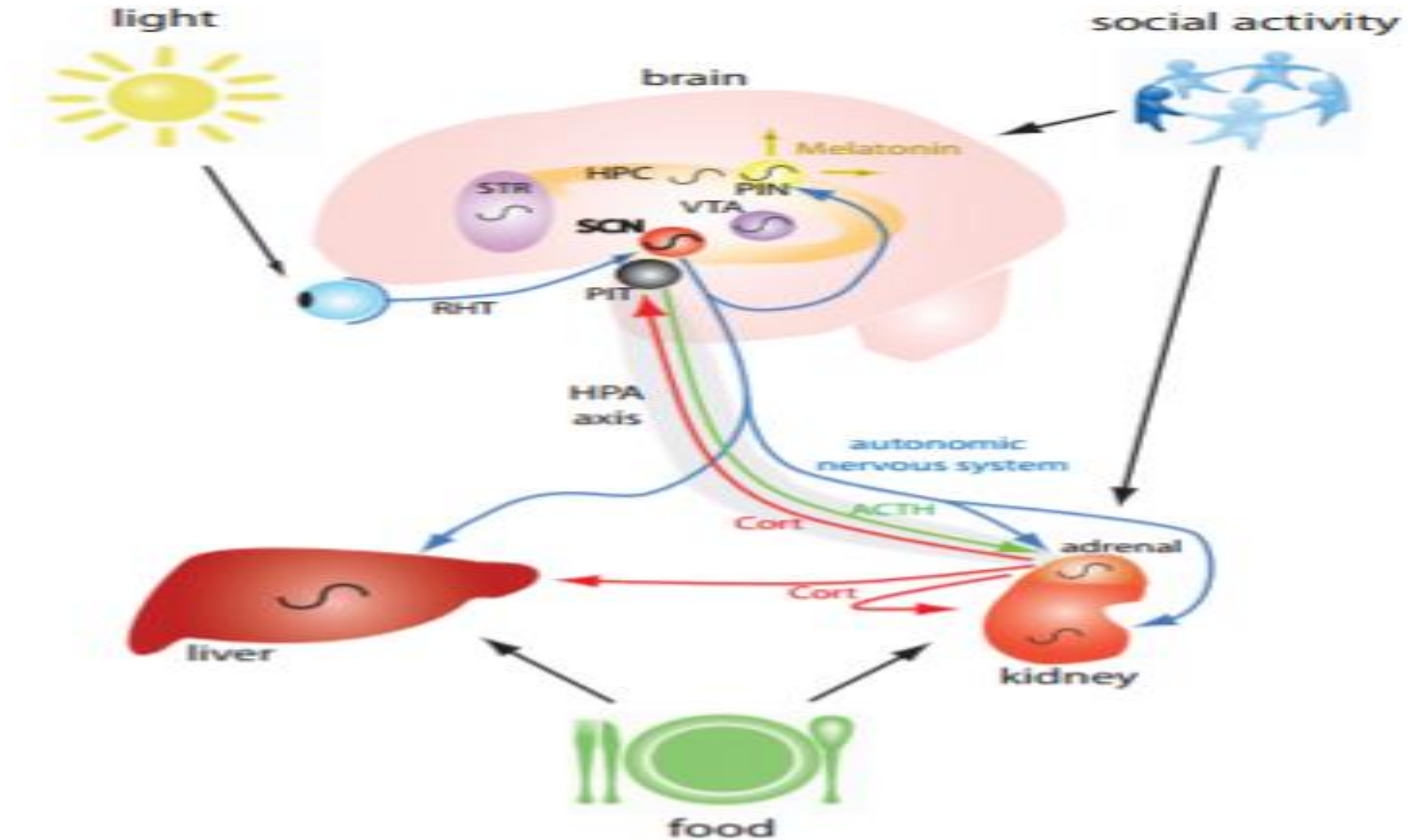
Ubiquinol/COQ10

Probiotics and  
Prebiotics

Multivitamin

Supplements	Details
<ul style="list-style-type: none"><li>Berberine</li><li>Resveratrol</li></ul>	Supports healthy insulin function and glucose homeostasis
<ul style="list-style-type: none"><li>EPA &amp; DHA rich fish oils</li></ul>	Supports healthy TGs and lipid metabolism, maintains healthy blood flow, and supports healthy platelet function
<ul style="list-style-type: none"><li>French maritime pine bark extract</li></ul>	A source proanthocyanidins support vascular endothelial integrity
<ul style="list-style-type: none"><li>Hawthorn extract</li><li>Cranberry and grape seed extract</li></ul>	Supports healthy vascular relaxation and circulatory function for heart health

# Menopausal Metabolic & Cardiovascular Health





# THANKS SO MUCH!



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