LESSON MASTER MEDICINA ESTETICA
2022

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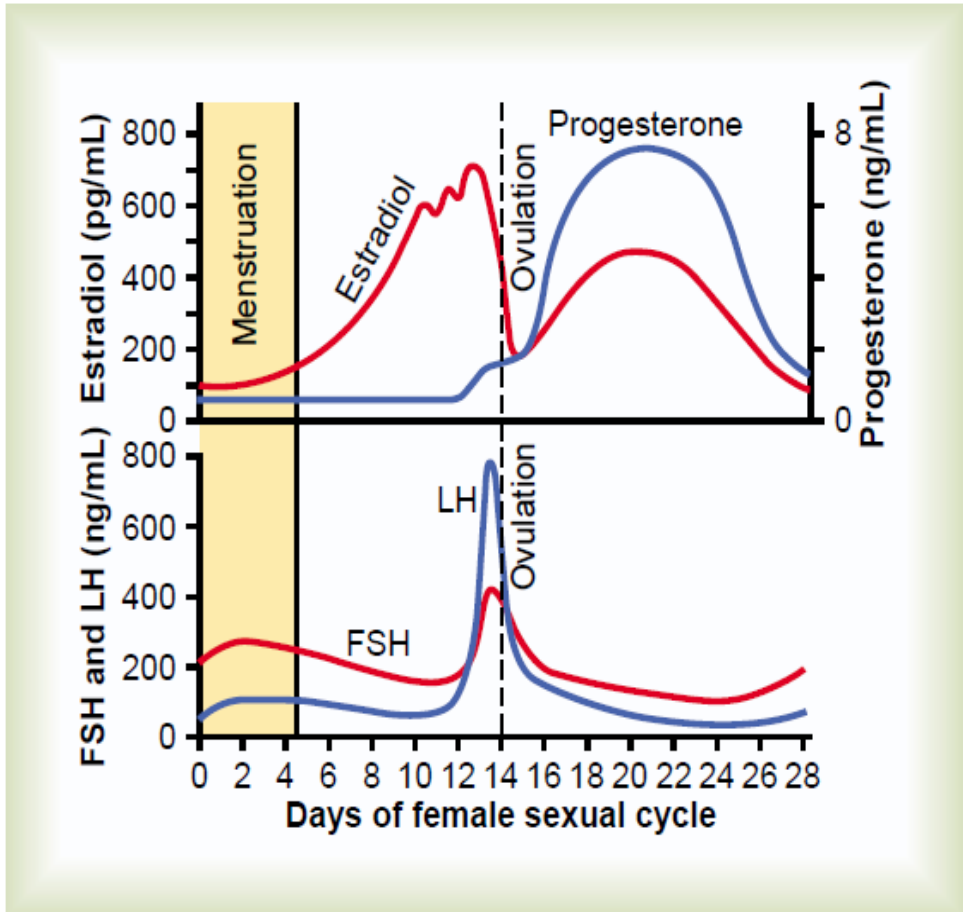
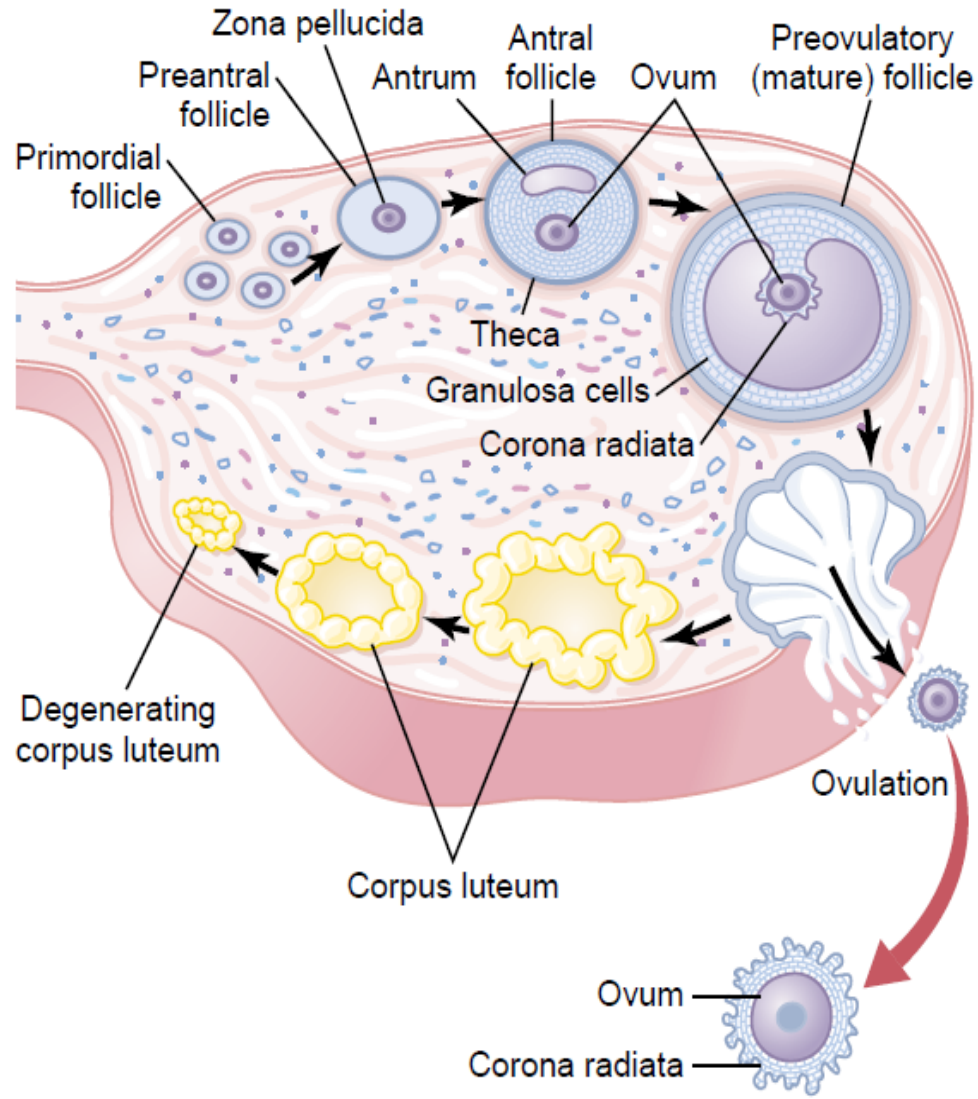
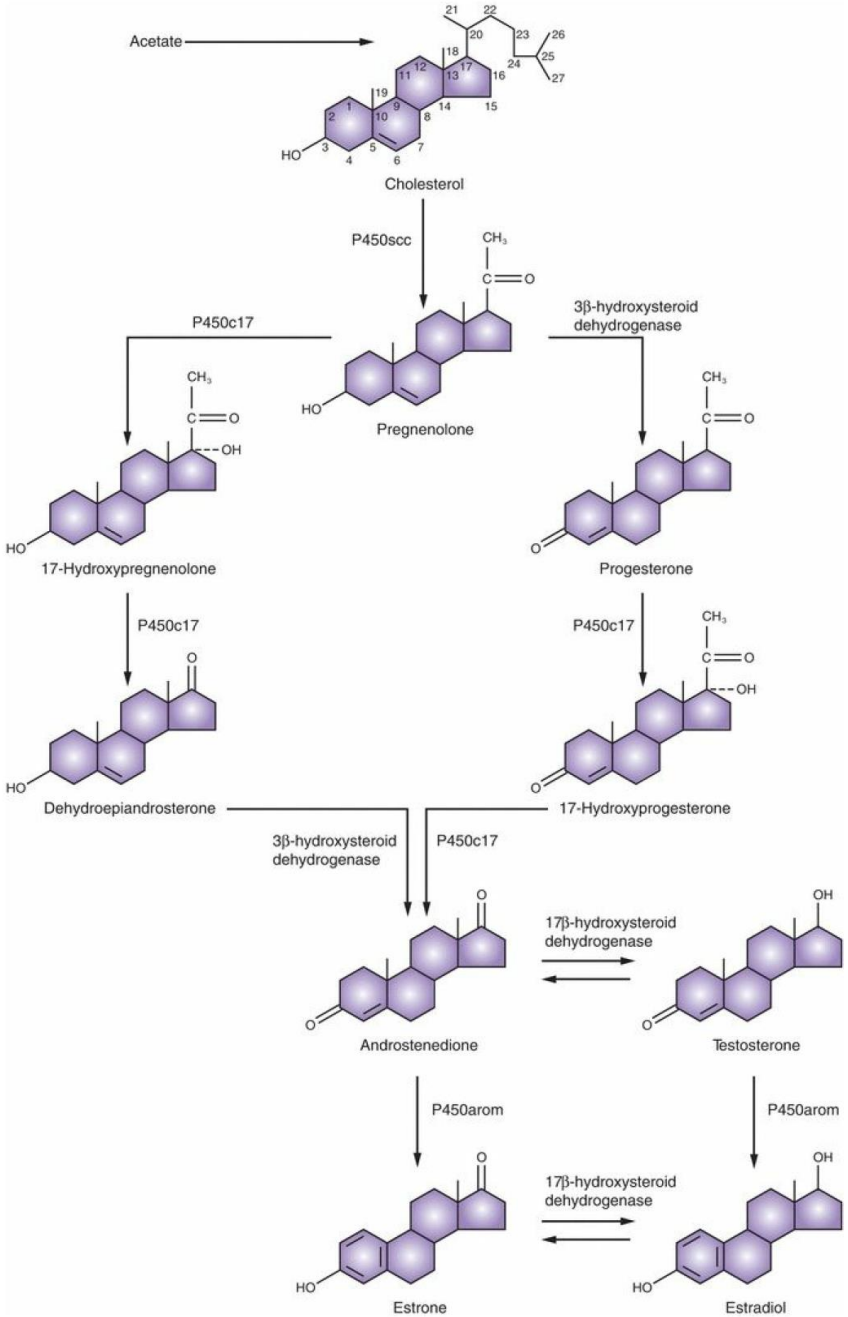
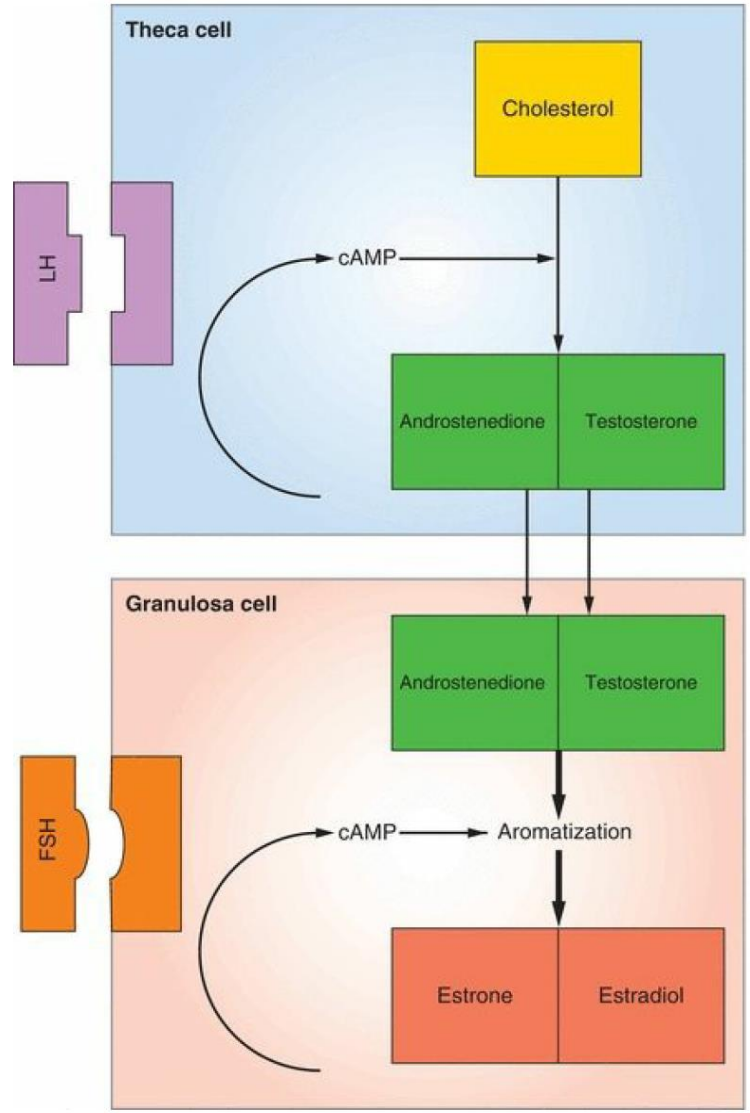
Dipartimento di Medicina dei Sistemi Università di Roma TorVergata

ESTROGENI ed INVECCHIAMENTO

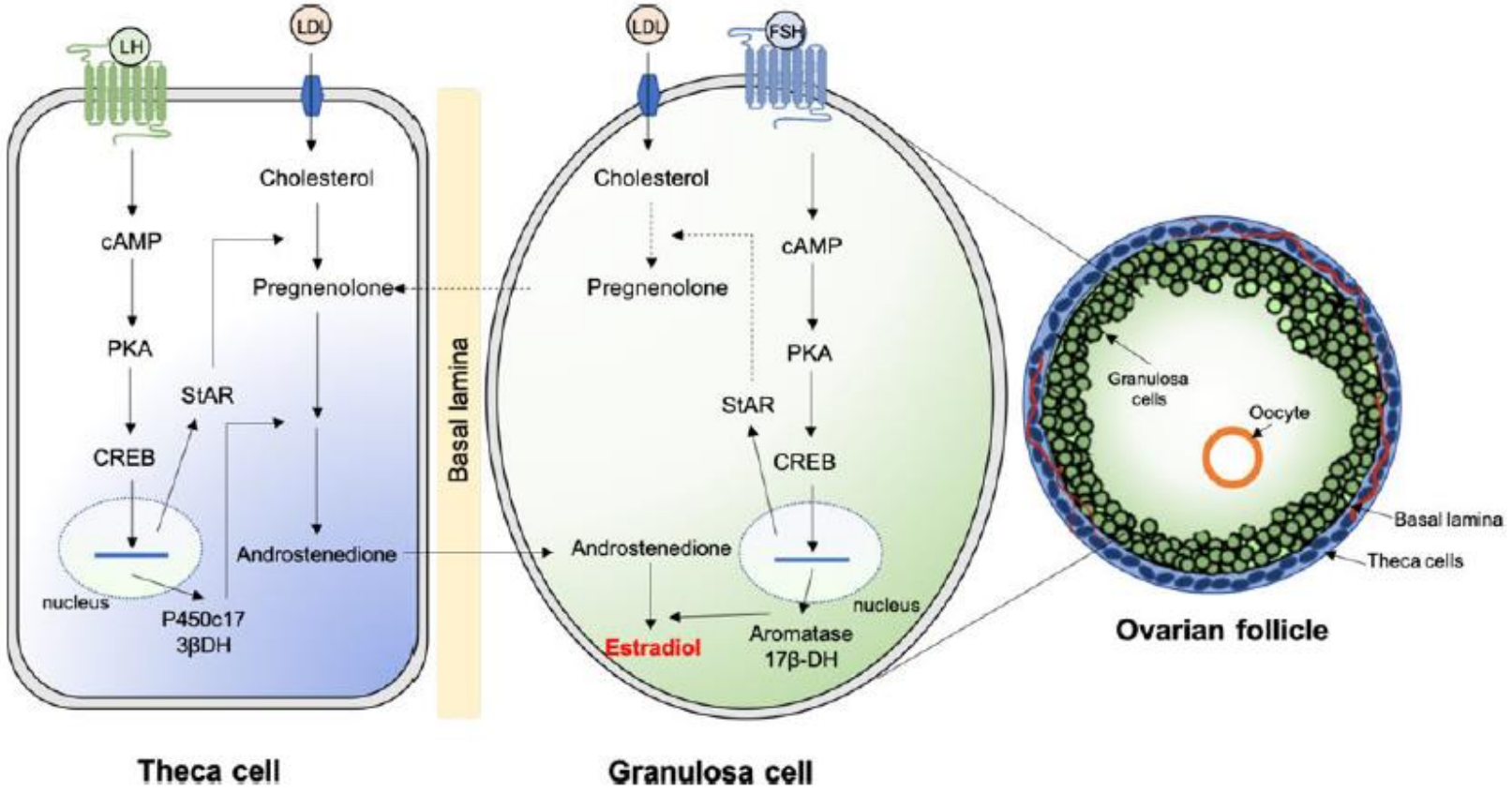

Estradiol (pg/mL)
800
600
400
200
0
Menstruation
Estradiol
Ovulation
Progesterone
8
0
Progesterone (ng/mL)
FSH and LH (ng/mL)
800
600
400
200
0
LH
Ovulation
FSH
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28
Days of female sexual cycle


Zona pellucida
Preantral follicle
Antrum
Antral follicle
Ovum
Preovulatory (mature) follicle
Primordial follicle
Theca
Granulosa cells
Corona radiata
Degenerating corpus luteum
Ovulation
Corpus luteum
Ovum
Corona radiata

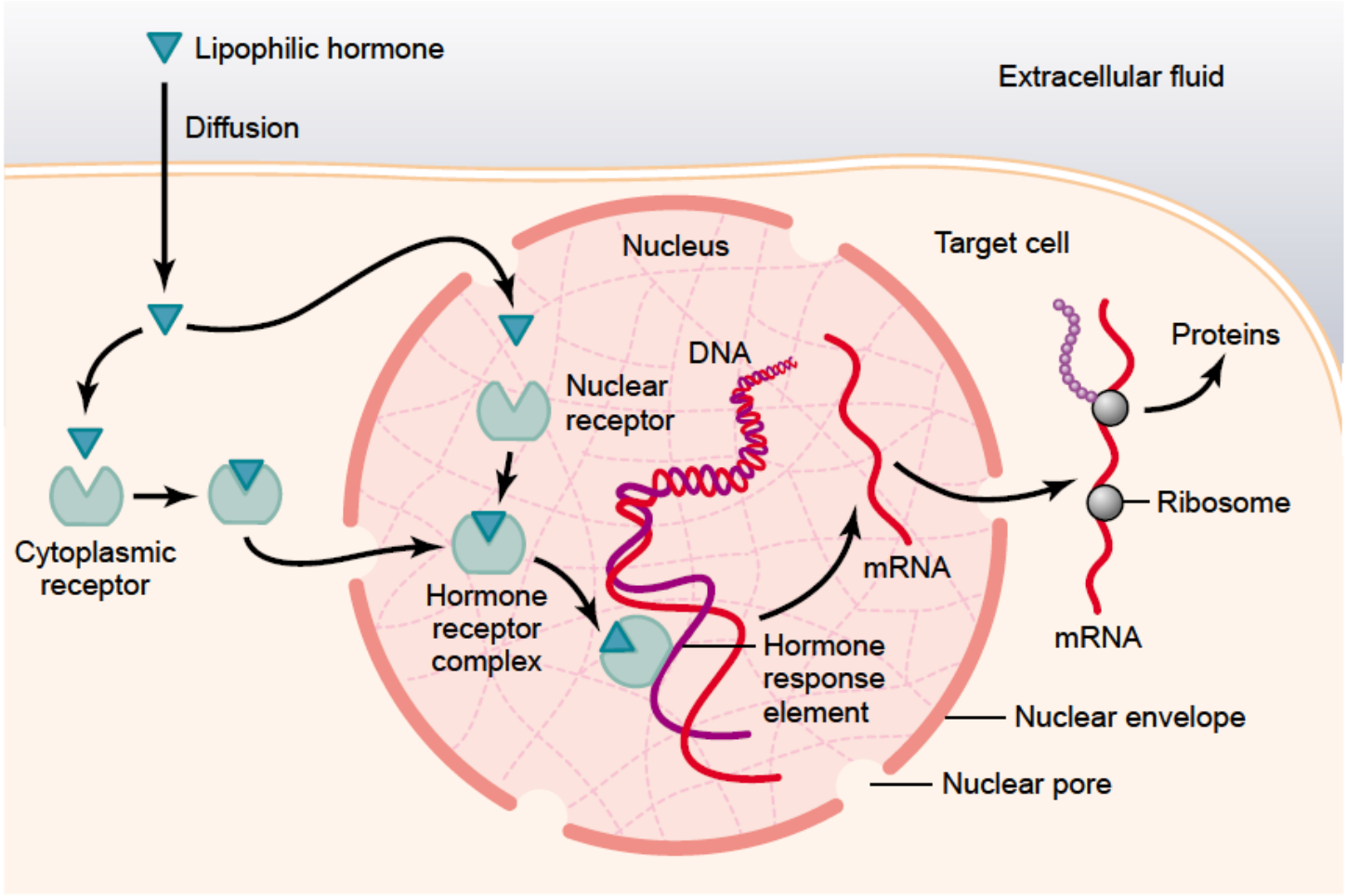

Acetate
Cholesterol
P450scc
Pregnenolone
P450c17
3β-hydroxysteroid dehydrogenase
17-Hydroxypregnenolone
Progesterone
P450c17
P450c17
Dehydroepiandrosterone
17-Hydroxyprogesterone
3β-hydroxysteroid dehydrogenase
P450c17
17β-hydroxysteroid dehydrogenase
Androstenedione
Testosterone
P450arom
P450arom
17β-hydroxysteroid dehydrogenase
Estrone
Estradiol


Theca cell
Cholesterol
LH
cAMP
Androstenedione
Testosterone
Granulosa cell
Androstenedione
Testosterone
FSH
cAMP
Aromatization
Estrone
Estradiol

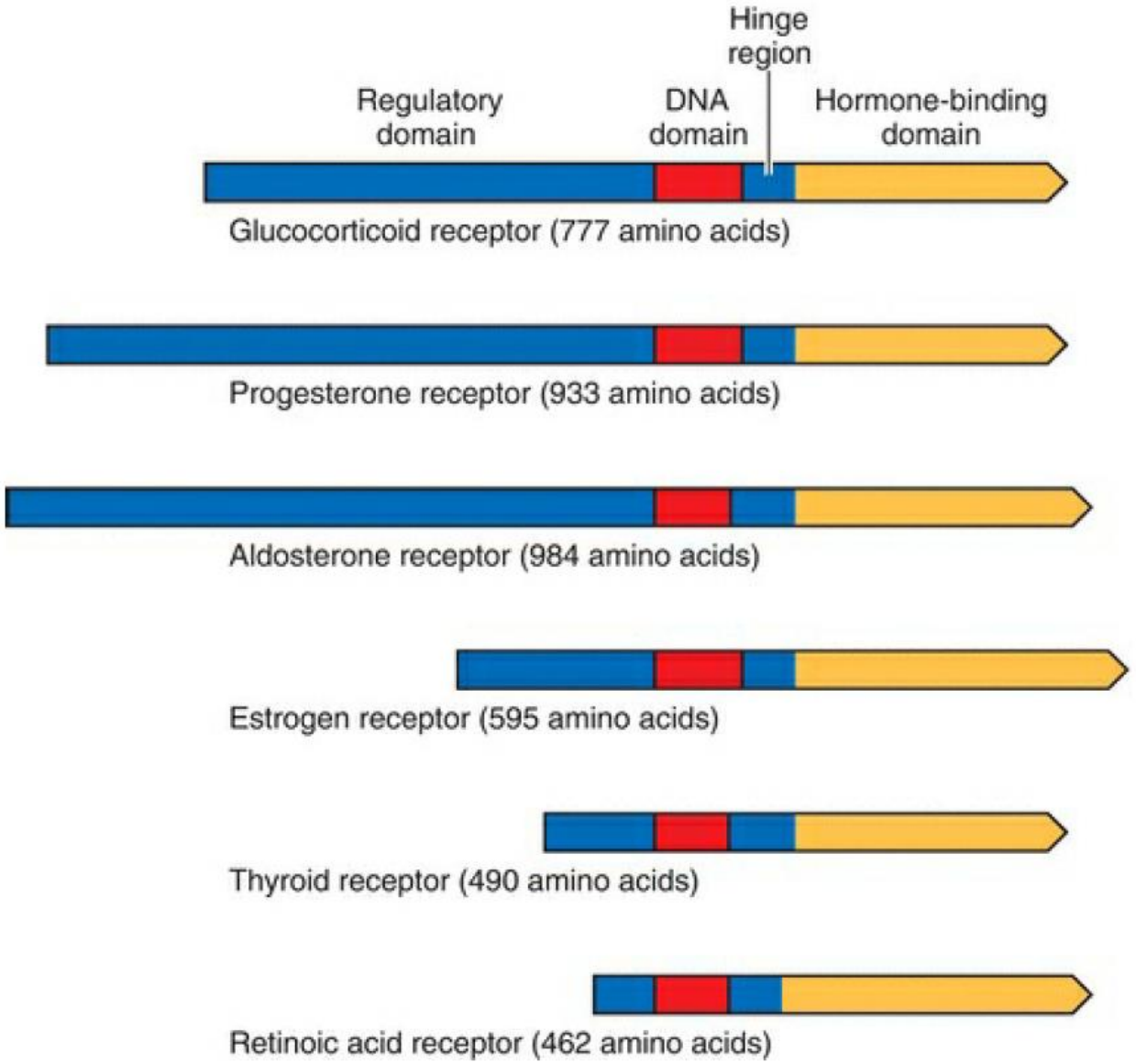
The luteinizing hormone (LH) induces the production of androgens in theca cells. The follicle-stimulating hormone (FSH) stimulates granulosa cells via aromatization of androgens to estrogens and by using cholesterol to produce pregnenolone



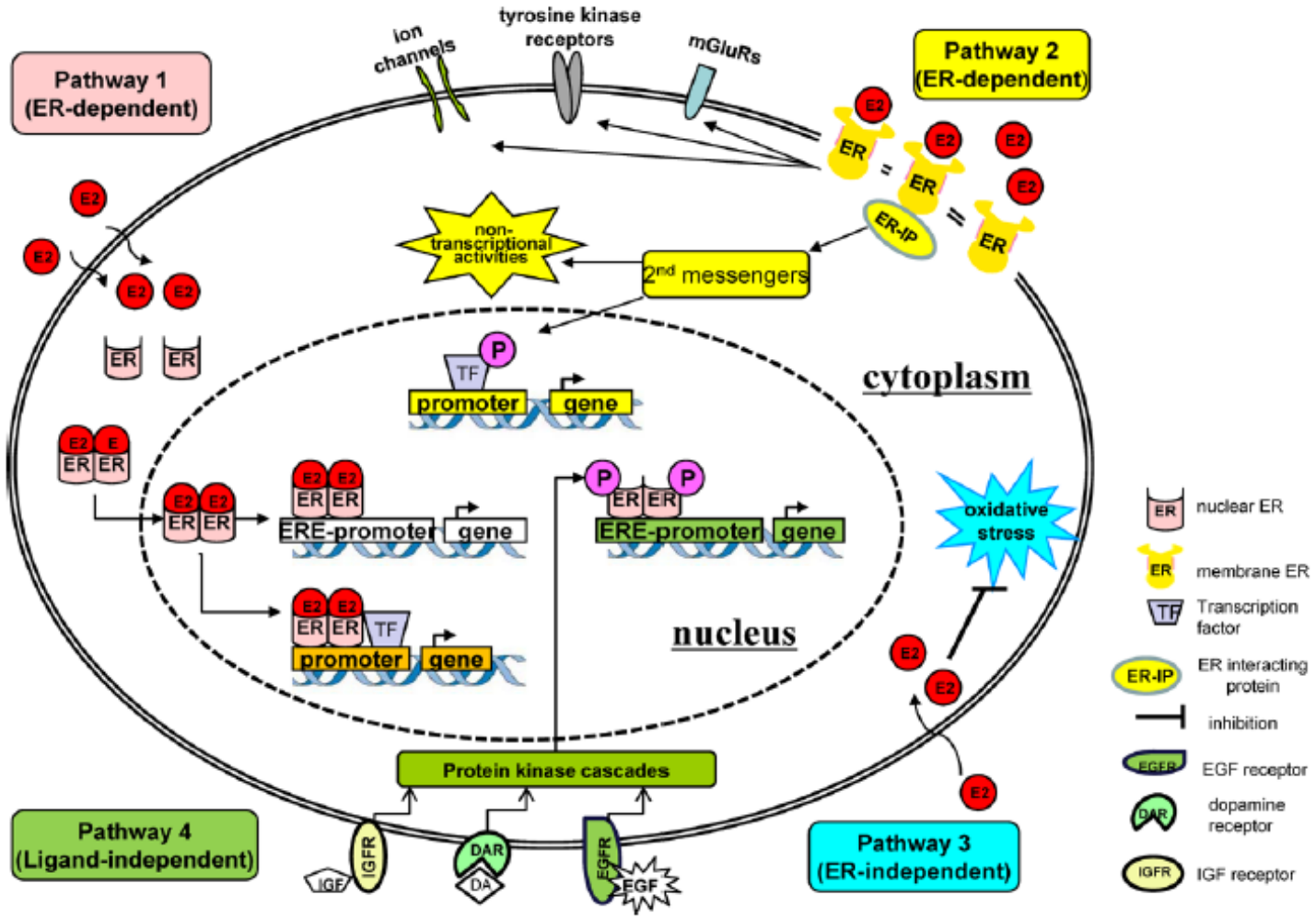
ESTROGEN SIGNAL ON THE TARGET CELL



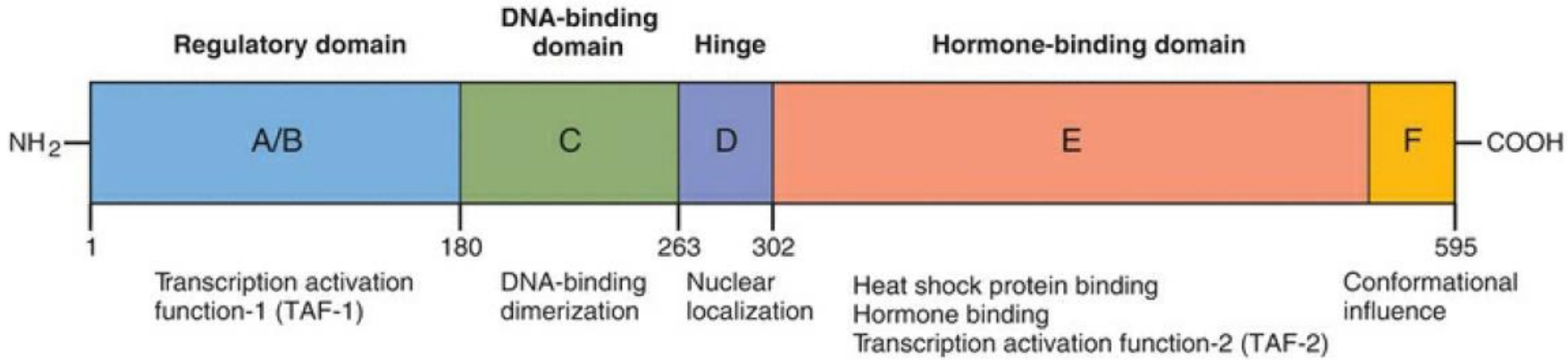
STEROID RECEPTOR SUPERFAMILY



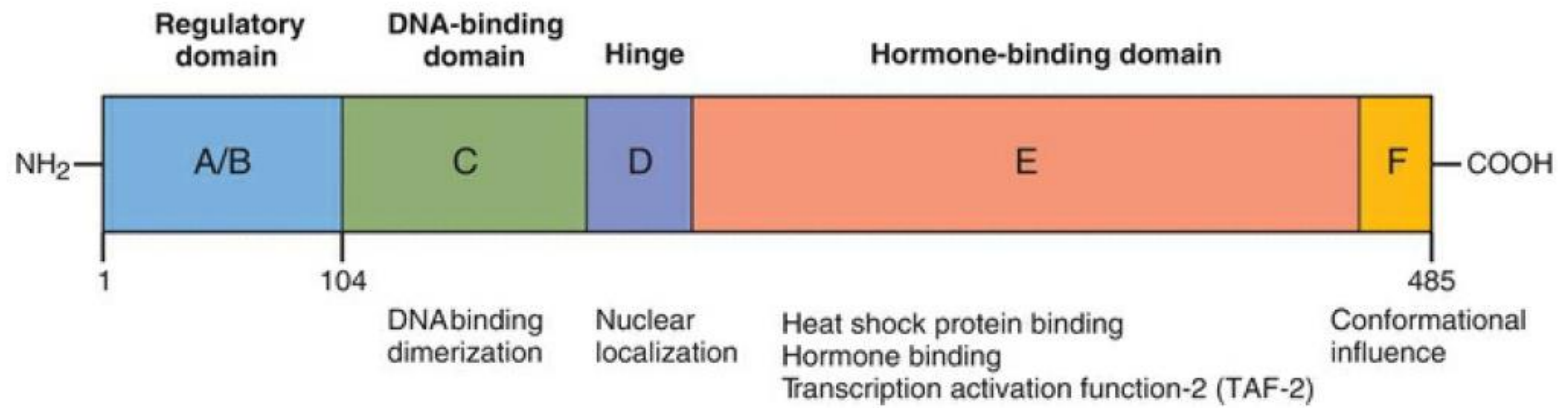
GENOMIC / NONGENOMIC ESTROGENS PATHWAYS

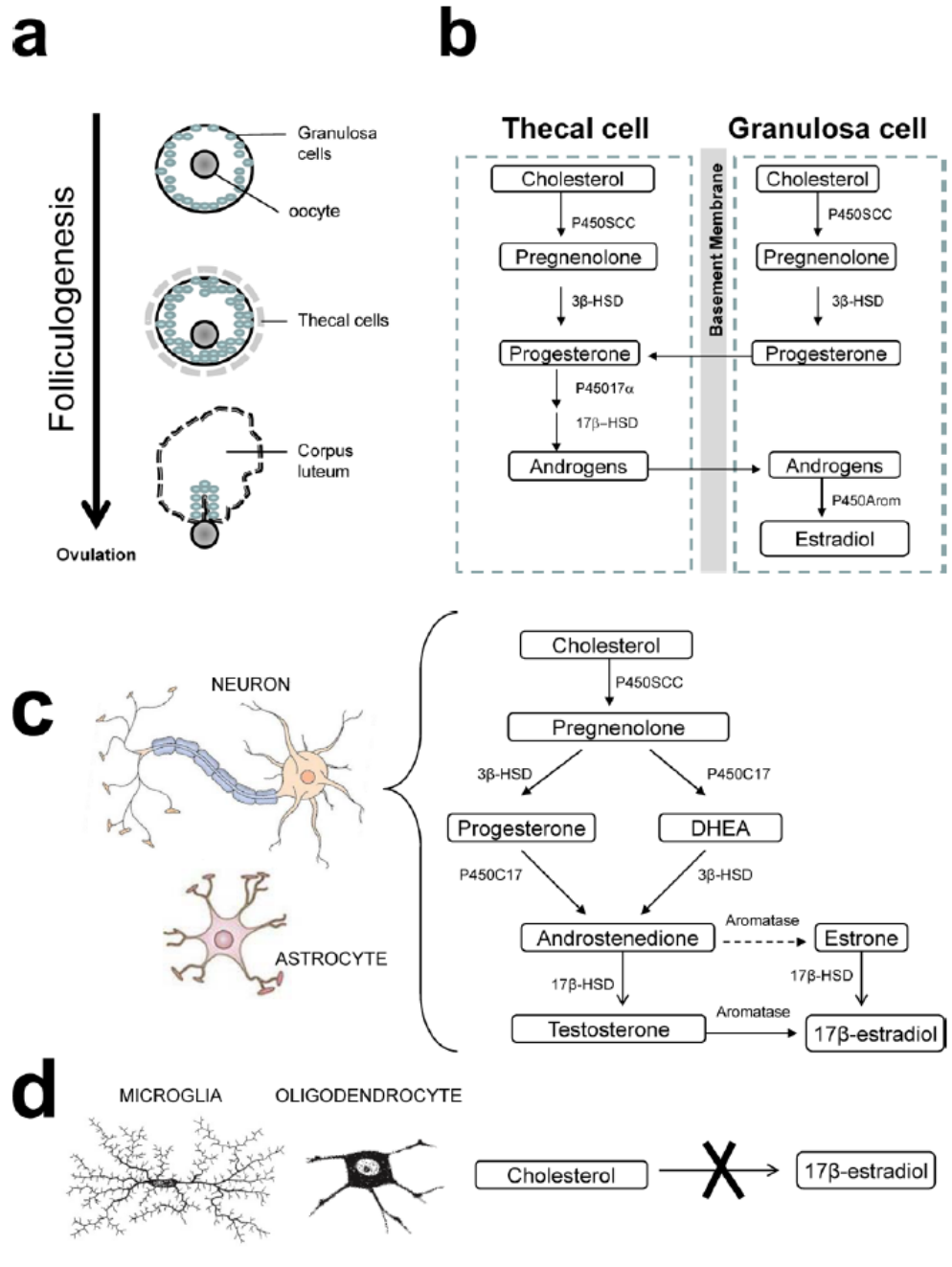


The Estrogen Receptor-Alpha

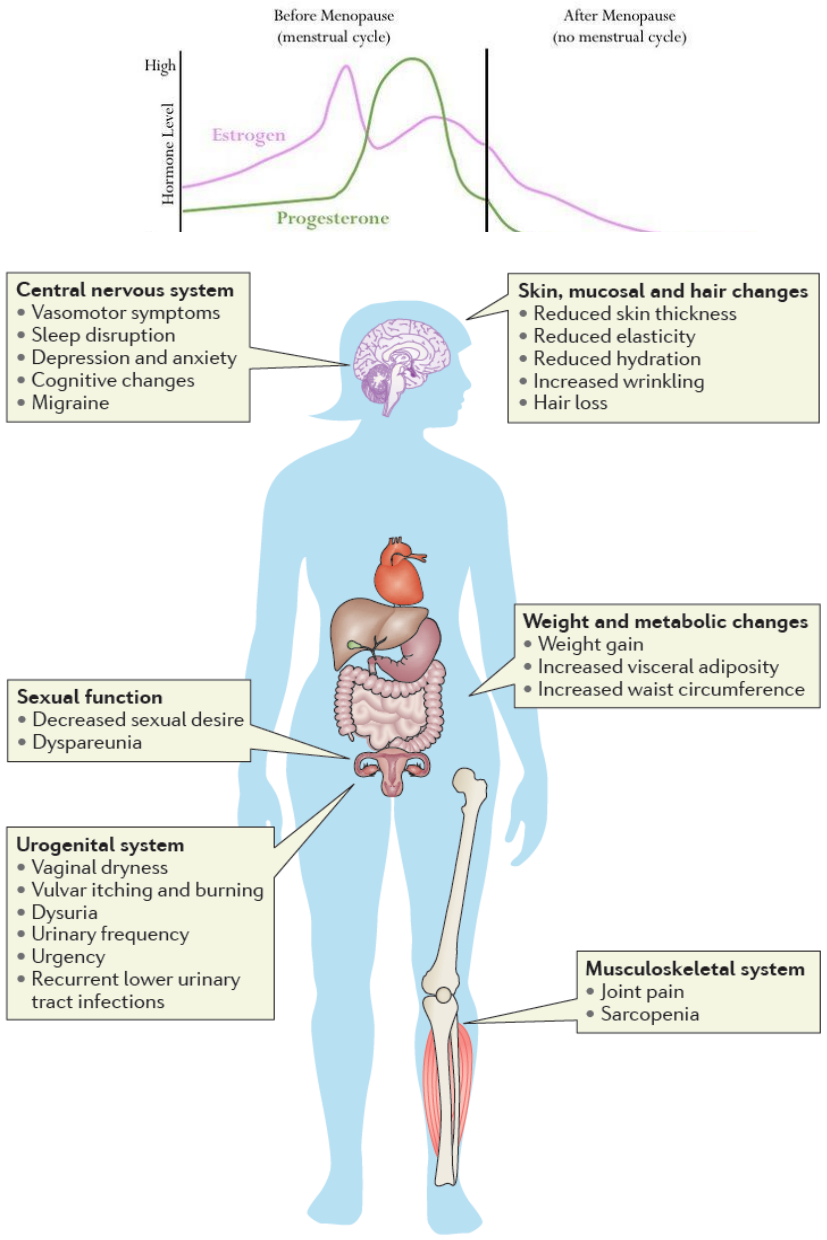


The Estrogen Receptor-Beta




a
Folliculogenesis
Granulosa cells
oocyte
Thecal cells
Corpus luteum
Ovulation
b
Thecal cell
Granulosa cell
Basement Membrane
Cholesterol
P450SCC
Pregnenolone
3β-HSD
Progesterone
P45017α
17β–HSD
Androgens
P450Arom
Estradiol
c
NEURON
ASTROCYTE
Cholesterol
P450SCC
Pregnenolone
3β-HSD
P450C17
Progesterone
DHEA
P450C17
3β-HSD
Androstenedione
Aromatase
Estrone
17β-HSD
17β-HSD
Testosterone
Aromatase
17β-estradiol
d
MICROGLIA
OLIGODENDROCYTE
Cholesterol
17β-estradiol

Menopause : change in steroid synthesis and signalling pathways



Perimenopause staging

Stage	Notes
Early menopausal transition	Persistent irregularities of the menstrual cycle
Late menopausal transition	Intermenstrual cycle ≥60 days in the prior 12 months
Early post menopause	12 months following the final menstrual period

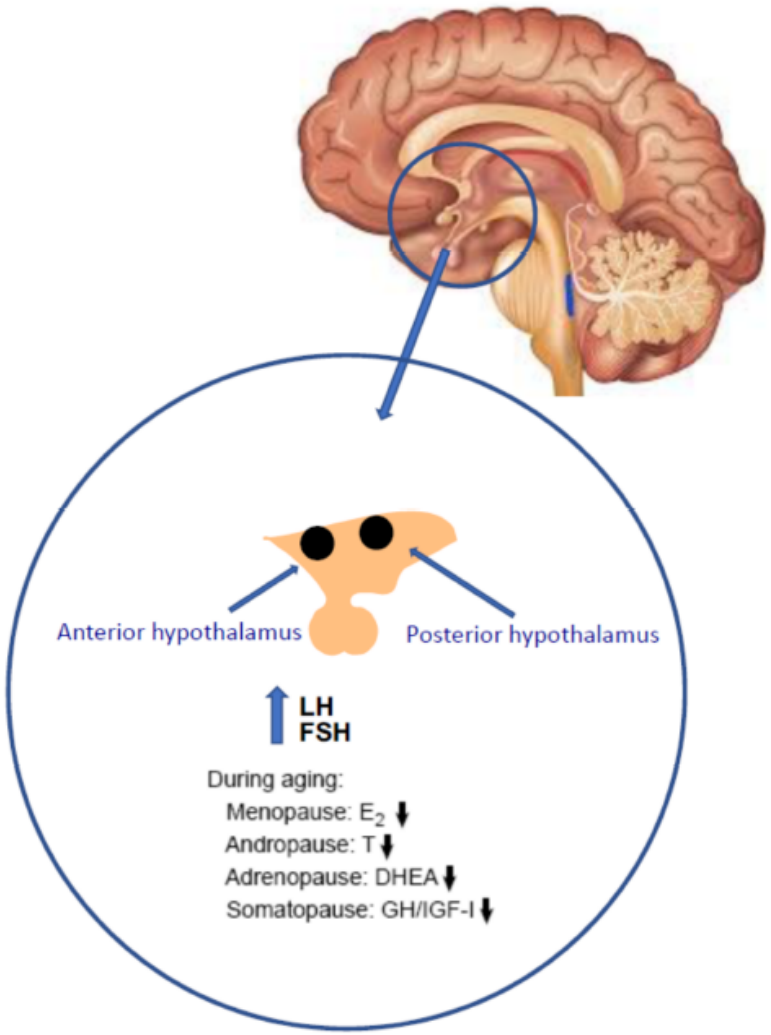
Central nervous system-related symptoms

CNS-related symptoms are those arising as a consequence of the neurobiochemical changes that occur after ovarian failure

Brain neuroendocrine changes in menopause

Vasomotor symptoms and Sleep disruption

↑FSH	↑ Noradrenaline
↑LH	↓ Dopamine
↓E_2	↓ Serotonin
	↓ β-endorphin

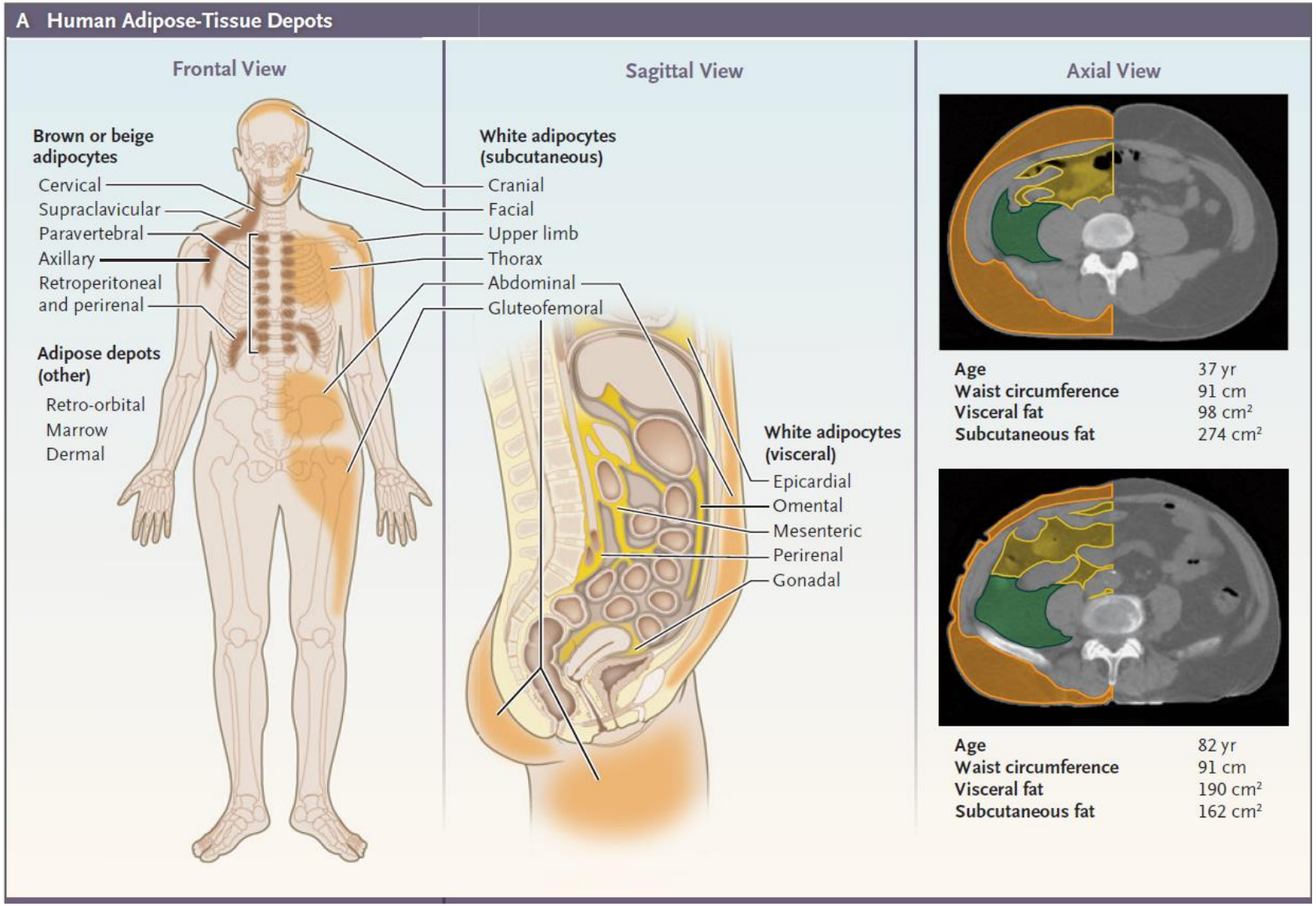


Mood and Cognitive functions
Libido and sexual arousal
Neuroendocrine activity

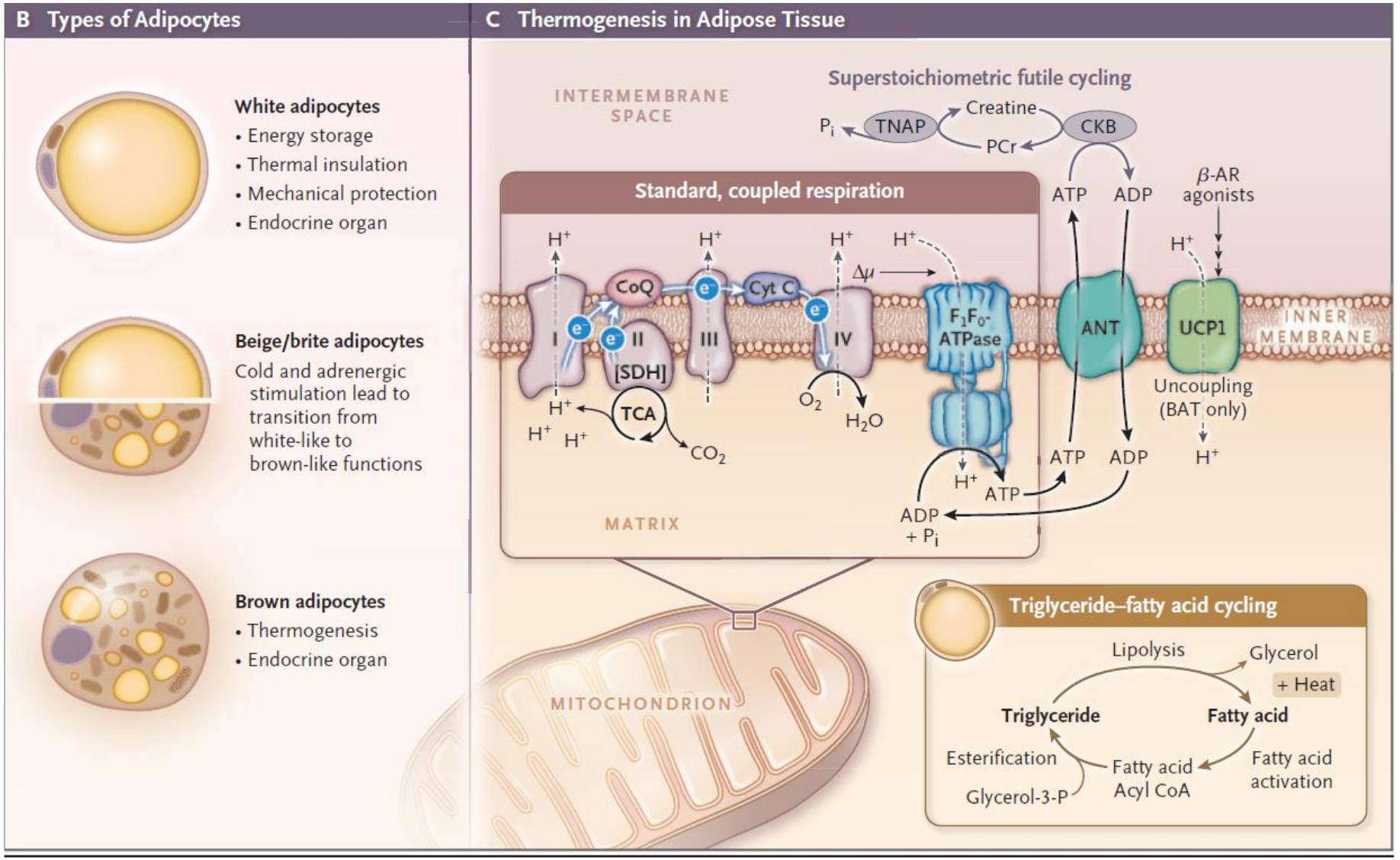
↑ FSH	↑ Noradrenaline	↓ GABA-ergic function
↑ LH	↓ Dopamine	↓ β-endorphin
= ACTH	↓ Serotonin	↓ Allopregnanolone
↓ Androstenedione		↓ DHEA
↓ Testosterone		↓ DHEAS
		↑= Cortisol
↓ E_2		↑Cortisol/DHEA

Weight and metabolic changes

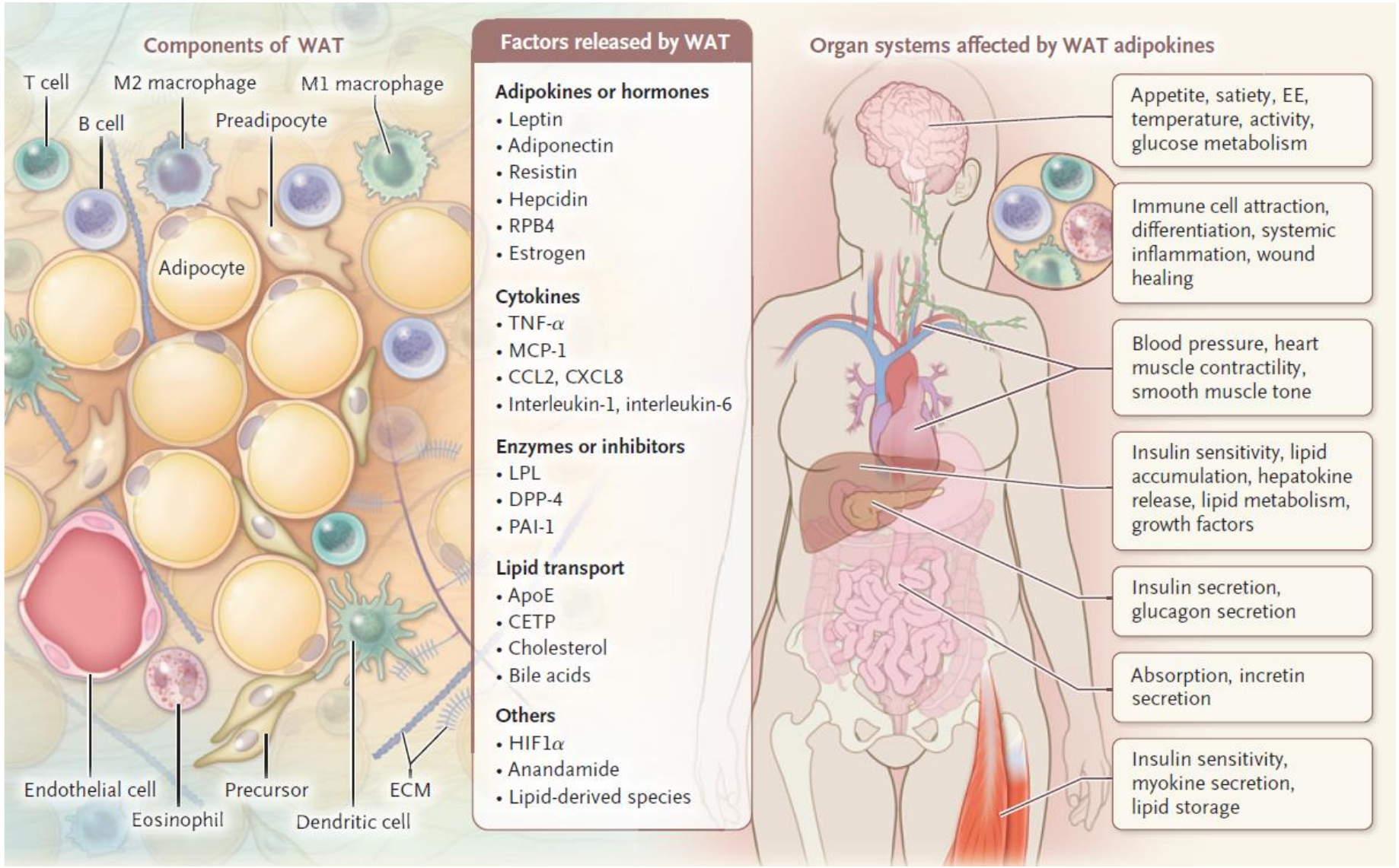
Principal human adipose-tissue depots from the frontal (left) and sagittal (center) planes



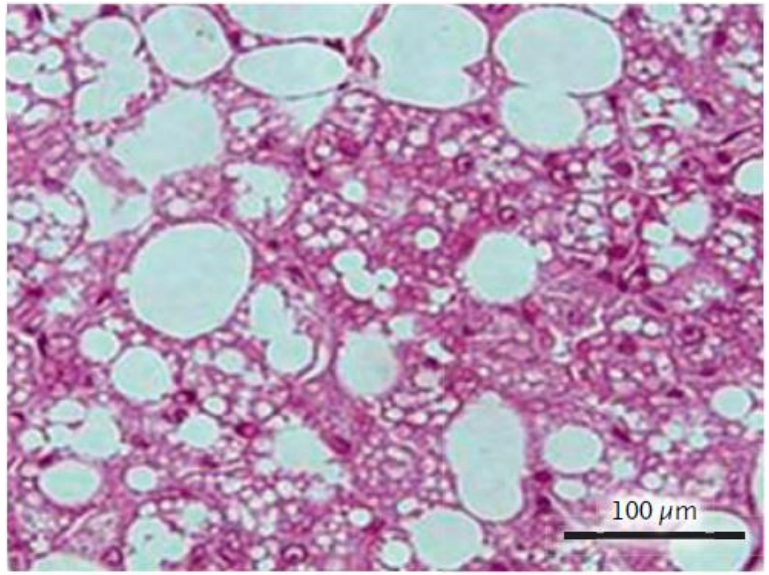
The three principal types of adipocytes and their known physiological roles. Molecular mechanisms for thermogenesis in the adipose tissue.

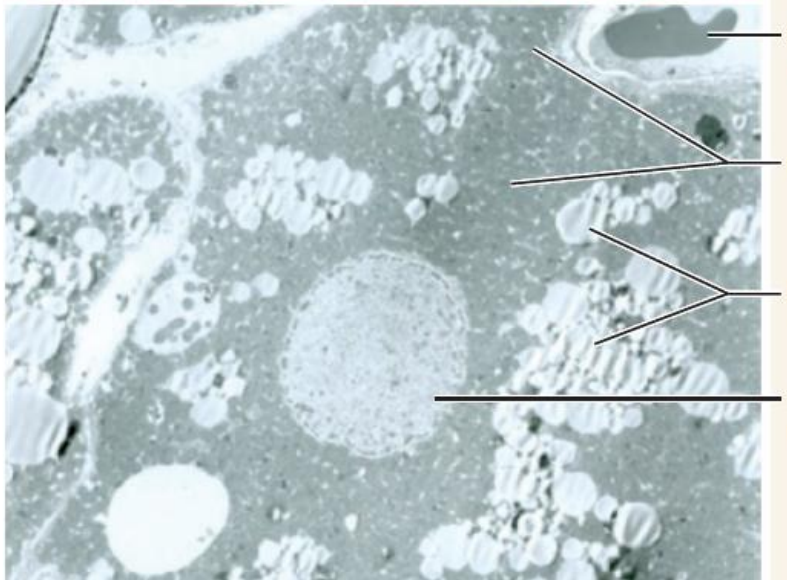


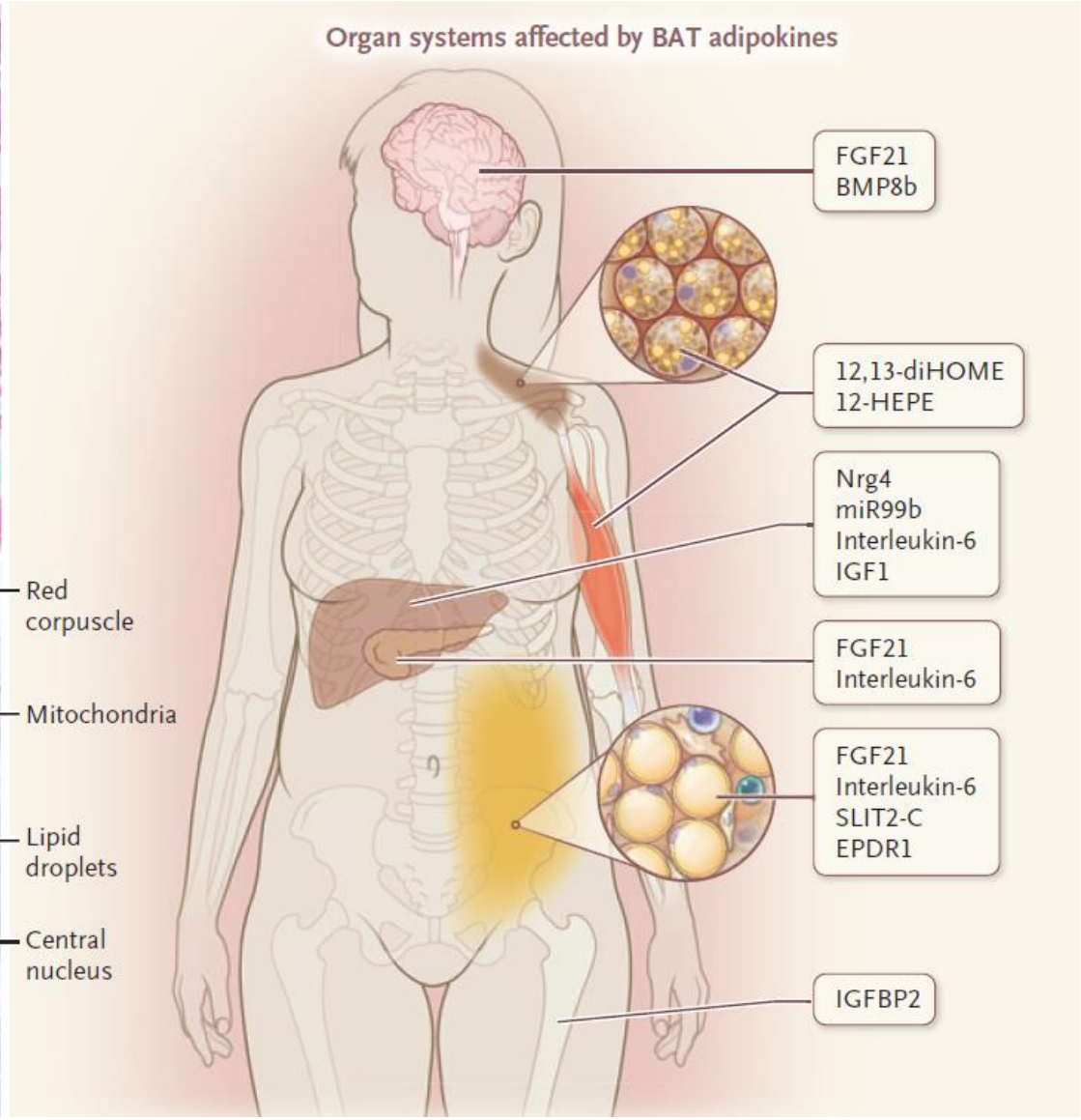
WAT Adipokines



BAT Adipokines







Definition of obesity

$$BMI = \frac{weight\ (kg)}{height\ (m^2)}$$

- Obesity is defined as abnormal or excessive fat accumulation that may impair health
- Body mass index (BMI) provides the most convenient population-level measure of overweight and obesity currently available

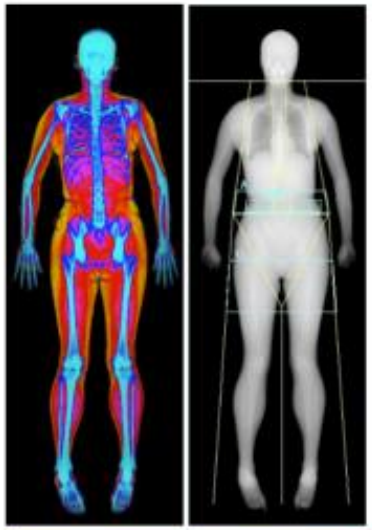
Classification	BMI (kg/m^2)
Underweight	<18.5
Normal range	≥18.5 and <25
Overweight	≥25 and <30
Obesity	≥30
Obesity class I	≥30 and <35
Obesity class II	≥35 and <40
Obesity class III	≥40

Children/Adolescents

- Sex/age-specific BMI
- BMI ≥ 95th percentile is obese
- 85th to less than 95th percentile is overweight

WHO. Factsheet 311. 2014. http://www.who.int/

Nome: Prova, Prova	Sesso: Femminile	Height: 160.0 cm
ID paziente:	Etnia: Bianco	Peso: 60.0 kg
Data di nascita: 11 Gennaio 1965		Età: 54

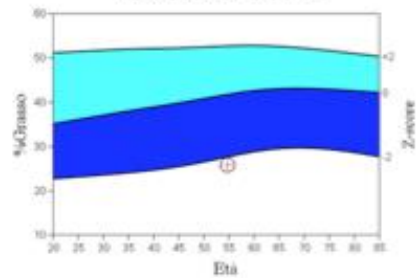


Risultati della composizione corporea

Regione	Grasso Massa (g)	Inclinato + BMC (g)	Totale Massa (g)	%Grasso	Percentile SN	% adipe AM
Braccio Sx	984	2066	3050	32.3	20	6
Braccio Dx	1094	2123	3217	34.0	28	10
Tronco	6750	20123	26874	25.1	20	4
Gamba Sx	2354	7055	9409	25.0	1	1
Gamba Dx	2525	7258	9783	25.8	1	1
Subtotale	13707	38625	52333	26.2	7	2
Testa	886	3091	3978	22.3		
Totale	**14593**	**41717**	**56310**	**25.9**	**7**	**2**
Androide (A)	1119	2853	3972	28.2		
Ginoide (G)	2626	6327	8953	29.3		

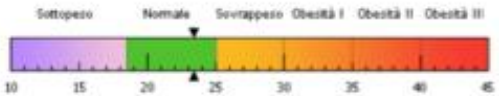
Data scansione: 25 Settembre 2019 ID: A09251904
Tipo di scansione: a Corpo Intero
Analisi: 25 Settembre 2019 00:52 Versione 13.6.0.5
Auto Whole Body Fan Beam
Operatore:
Modello: Workstation QDR (S/N: 0)
Commento:

% adipe corporeo totale



Origine: 2008 NHANES Femmina bianca

Classificazione dell'indice di massa corporea (BMI) secondo l'Organizzazione Mondiale della Sanità
BMI = 23.4 WHO Classification Normal



Il BMI presenta alcuni limiti e una diagnosi effettiva di sovrappeso o di obesità deve essere effettuata da un medico. L'obesità è associata a cardiopatie, determinati tipi di cancro, diabete di tipo 2 e altri rischi per la salute. Più il BMI di un individuo è superiore a 25, tanto maggiori sono i loro rischi correlati al peso.

Indici adiposi

Misura	Risultato	Percentuale SN	Percentuale AM
% adipe corporeo totale	**25.9**	**7**	**2**
Massa grassa/altezza² (kg/m²)	5.70	14	3
Rapporto androide/ginoide	0.96		
% adipe tr/%adipe art inf	0.99	88	72
Rapporto massa adiposa tronco/arti	0.97	78	49
Est. VAT Mass (g)	145		
Est. VAT Volume (cm³)	156		
Est. VAT Area (cm²)	30.0		

Lean Indices

Misura	Risultato	Percentuale SN	Percentuale AM
Lean/Height² (kg/m²)	15.3	55	47
Appen. Lean/Height² (kg/m²)	6.76	61	61

Est. VAT = Estimated Visceral Adipose Tissue
YN = Giovane normale
AM = Corrispondente per età

Nome: Prova, Prova	Sesso: Femminile	Height: 160.0 cm
ID paziente:	Etnia: Bianco	Peso: 60.0 kg
Data di nascita: 11 Gennaio 1965		Età: 54

Informazioni sulla scansione:

Data scansione: 25 Settembre 2019 ID: A09251904
Tipo di scansione: a Corpo Intero
Analisi: 25 Settembre 2019 00:52 Versione 13.6.0.5
Auto Whole Body Fan Beam
Operatore:
Modello: Workstation QDR (S/N: 0)
Commento:

Riepilogo risultati DXA:

Regione	BMC (g)	Grasso Massa (g)	Inclinato Massa (g)	Inclinato + BMC (g)	Totale Massa (g)	%Grasso
Braccio Sx	155.58	984.5	1910.1	2065.7	3050.2	32.3
Braccio Dx	165.81	1093.8	1957.0	2122.8	3216.6	34.0
Tronco	640.64	6750.3	19482.7	20123.3	26873.6	25.1
Gamba Sx	428.59	2354.2	6626.6	7055.2	9409.4	25.0
Gamba Dx	434.66	2524.5	6823.8	7258.4	9783.0	25.8
Subtotale	1825.28	13707.3	36800.2	38625.5	52332.8	26.2
Testa	597.70	886.2	2493.7	3091.4	3977.6	22.3
Totale	**2422.98**	**14593.5**	**39293.9**	**41716.9**	**56310.4**	**25.9**

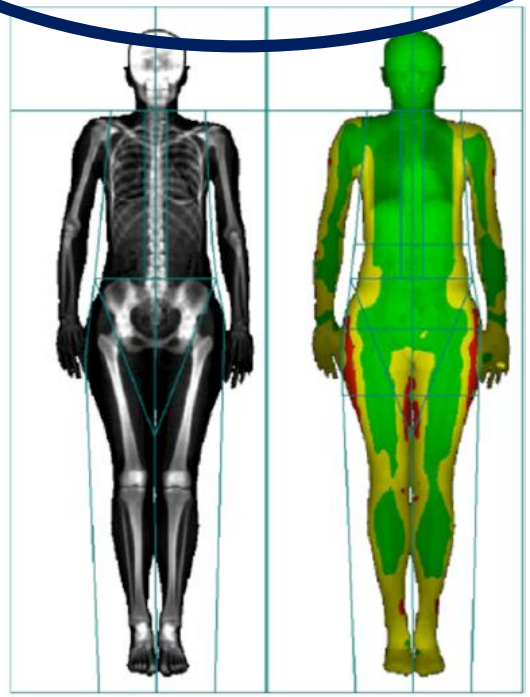
TBAR1058 - NHANES BCA calibration

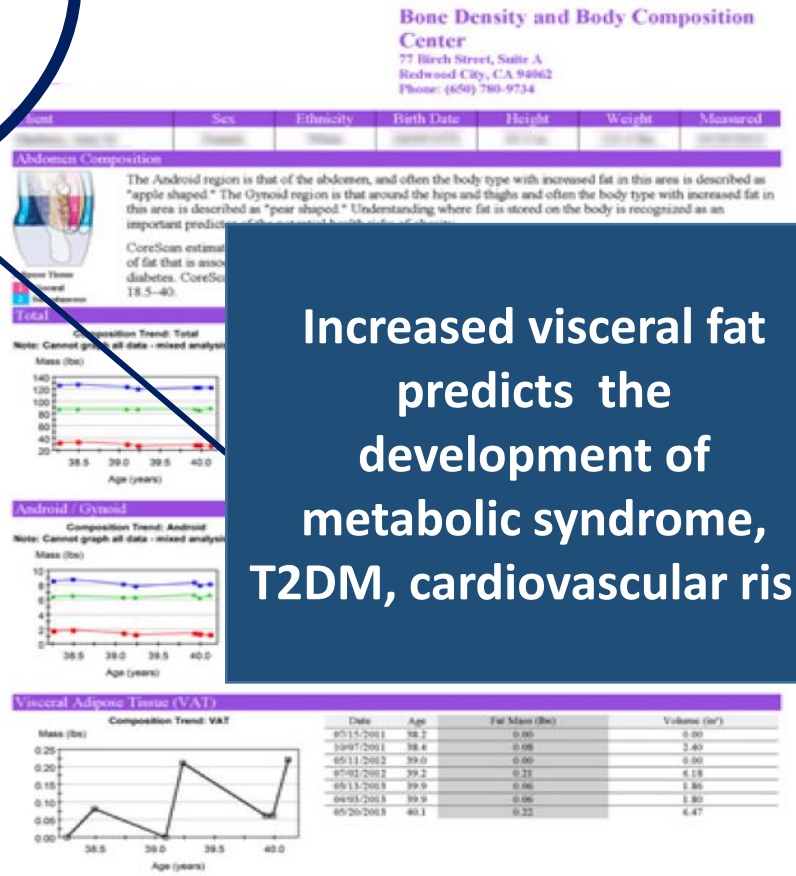
Fat/Lean weight by DXA

ROI Visceral fat

Volume 250.3±194.5 cm^3
Mass 235.9±183.1 gr
Cutoff mass 350 gr

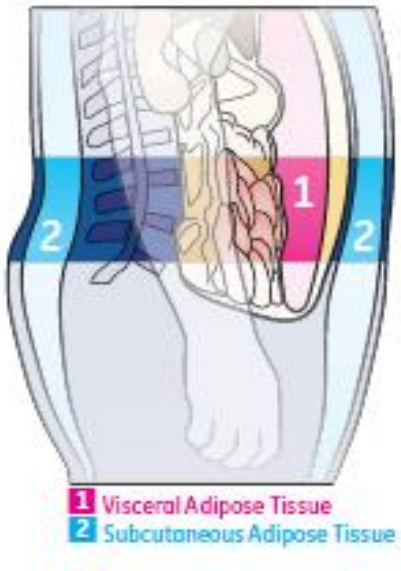
Endocrine 2014 (47)

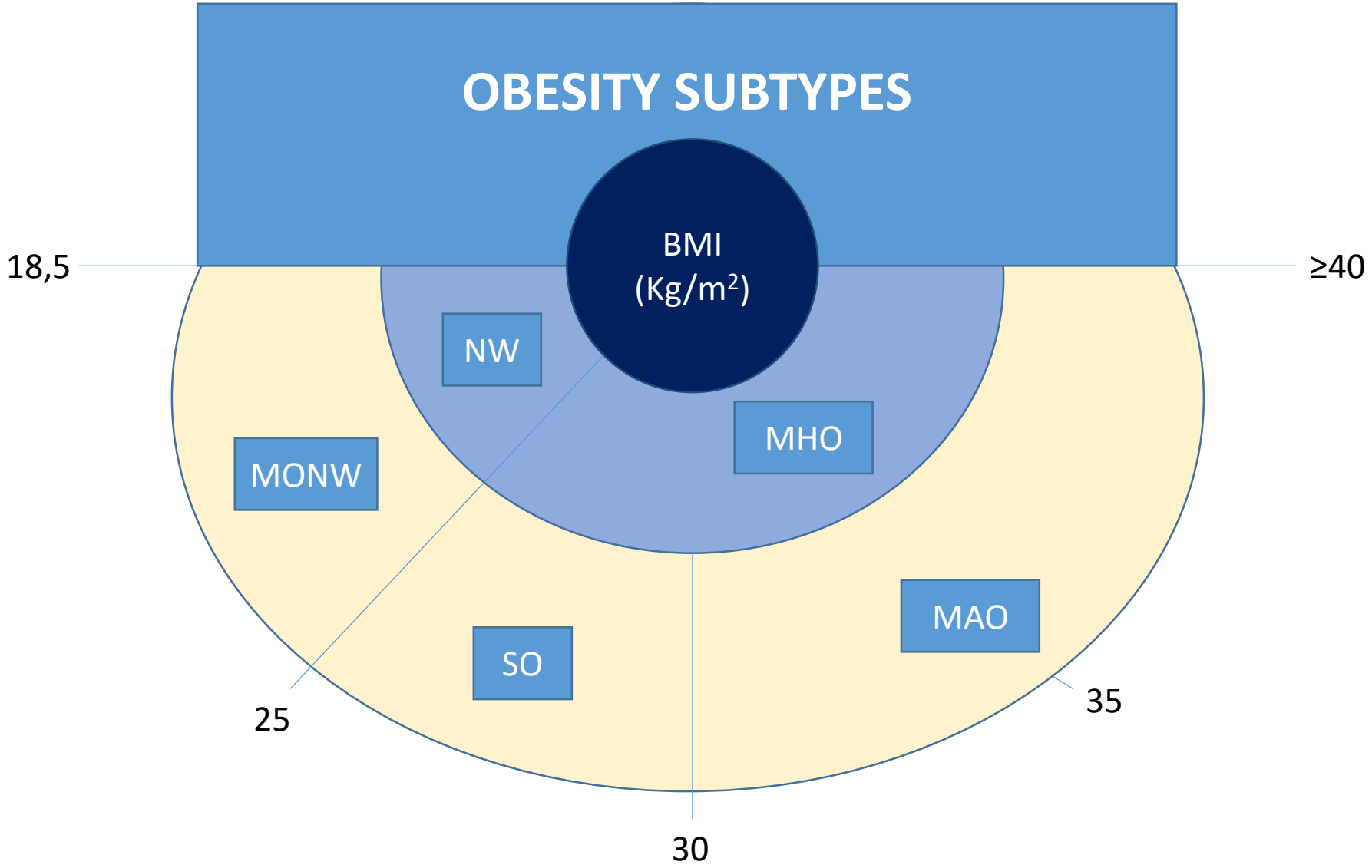




Increased visceral fat predicts the development of metabolic syndrome, T2DM, cardiovascular risk

A/G Fat





NW : normal weight metabolically healthy and normal visceral adipose tissue (VAT)
MHO : metabolically healthy obese : high BMI and healthy metabolic profile+low VAT
MAO : metabolically abnormal obese : high BMI, abnormal metabolic profile, high VAT
SO : sarcopenically obese, loss of muscle mass, high VAT, high risk of metabolic alteration
MONW : metabolically obese normal weight : high VAT and normal BMI

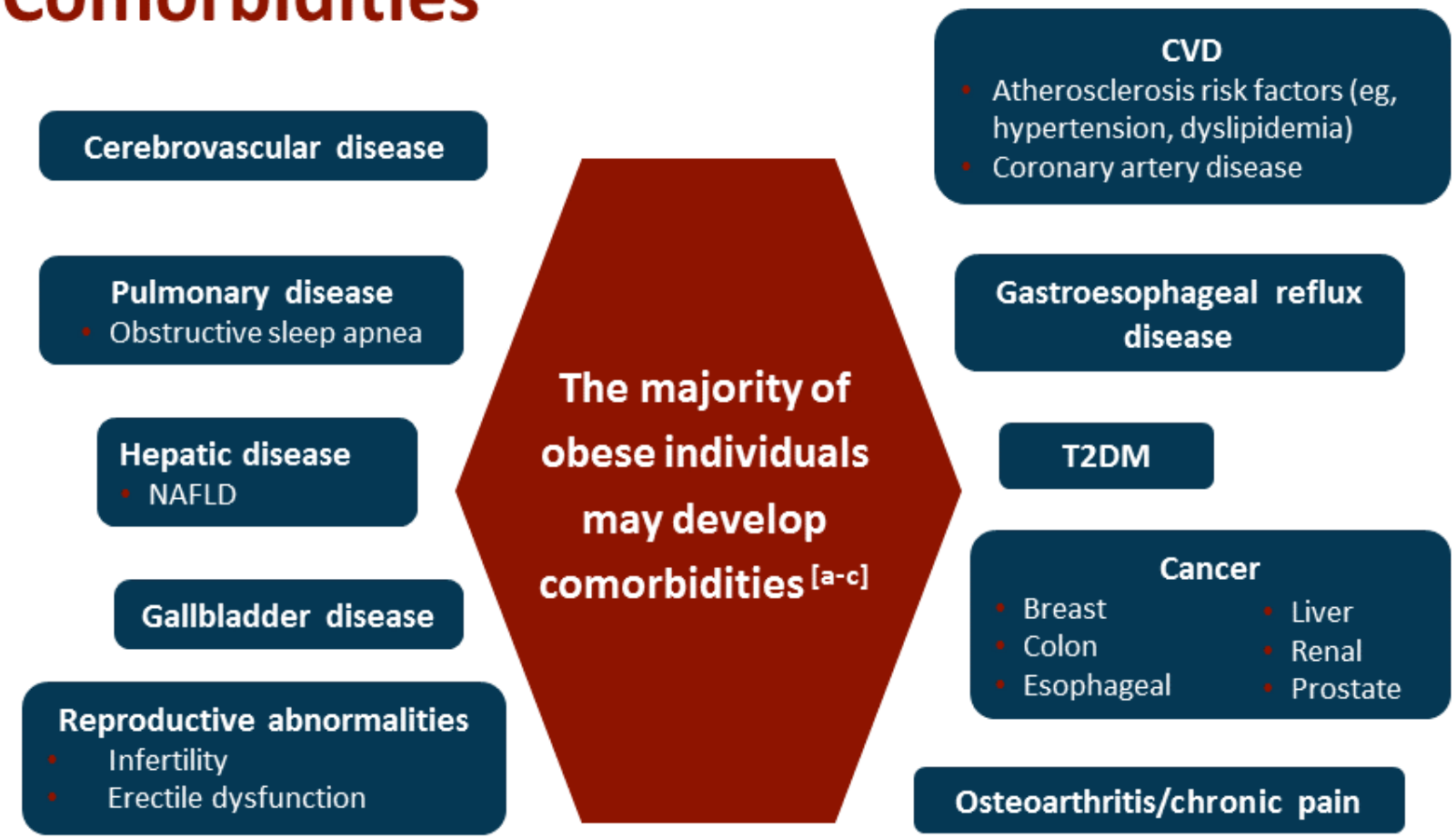
Mayoral etal. *Ind J Med Res* 2020

Obesity is a complex disease
Drivers of obesity

Physiological[1]	Genetic[2]	Environmental[1]
• **Central nervous system pathways** – Hunger and reward • **Neuroendocrine signals** – Long-term – Short-term	• **High heritability** of body weight, especially at BMI extremes • **Genes** in hypothalamus leptin-melanocortin pathway • **Single genetic mutations** leading to obesity are rare, but variations in many genes may predispose to obesity	• **Socio-cultural factors** – Traditions, belief systems, peer pressure • **Socio-economic factors** – Education level – Affordability of healthy food • **Food environment** – Availability of inexpensive, highly palatable food with high fat, sugar and salt content

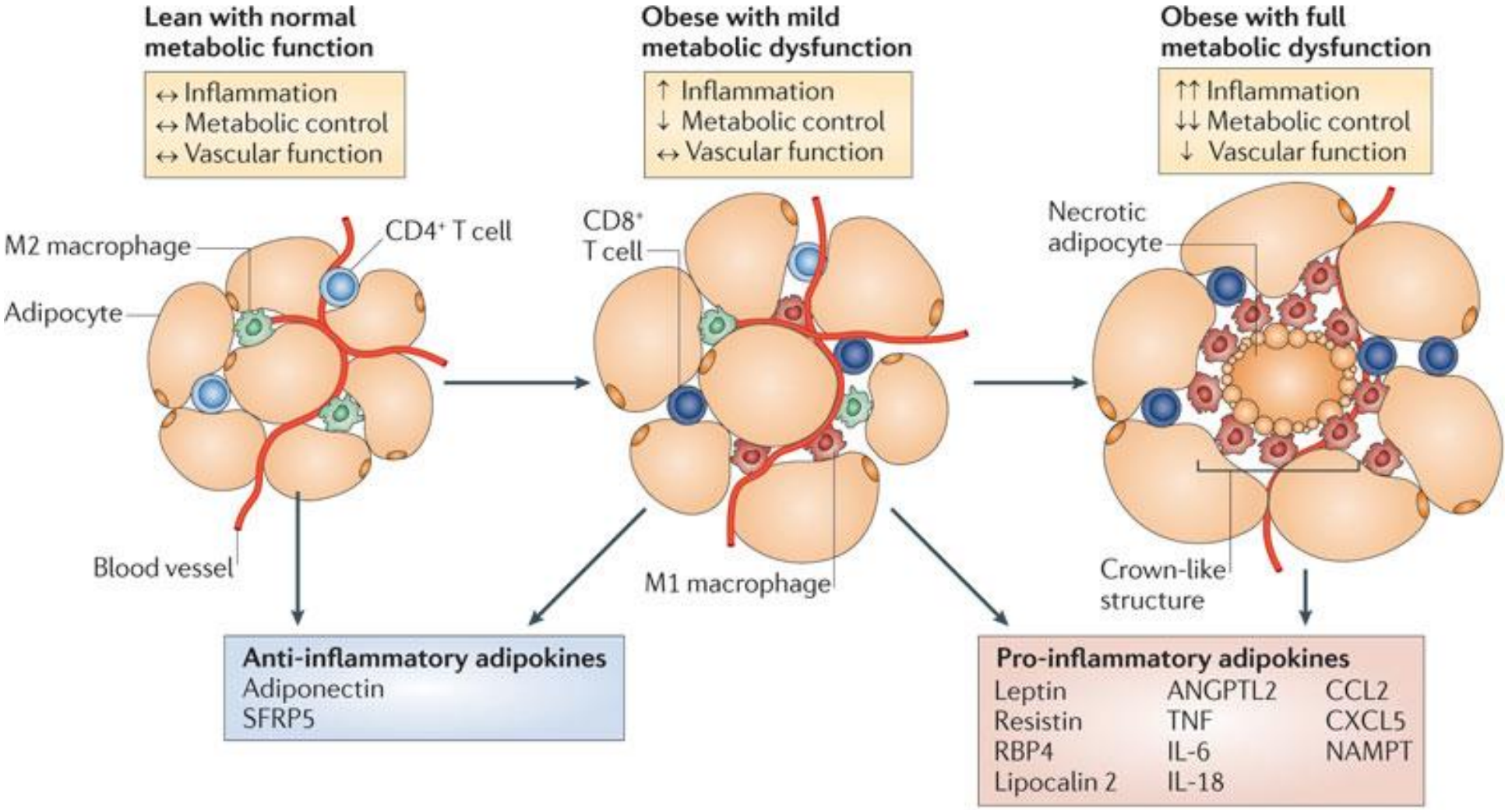
1. Sharma AM et al. *Obes Rev* 2010;11:362–370;
2. Chesi A et al. *Trends Endocrinol Metab* 2015;26:711–721

Obesity Is Associated With Multiple Comorbidities

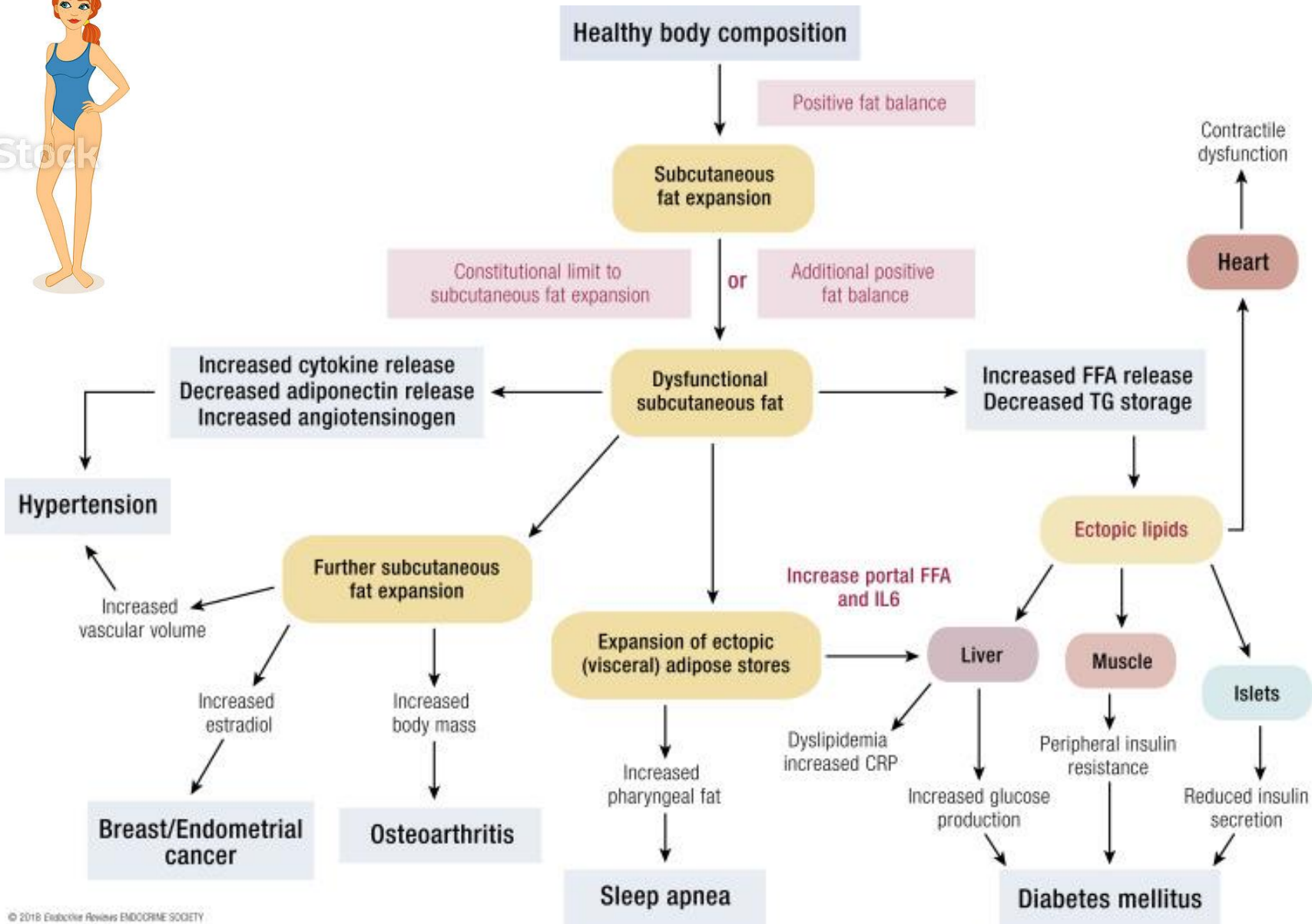


a. Catenacci VA et al. *Clin Chest Med*. 2009;30:415-444.
b. Calle EE et al. *N Engl J Med*. 2003;348:1625-1638.
c. Bluher M. *Exp Clin Endocrinol Diabetes*. 2009;117:241-250.

Metabolic dysfunction: the metaflammation

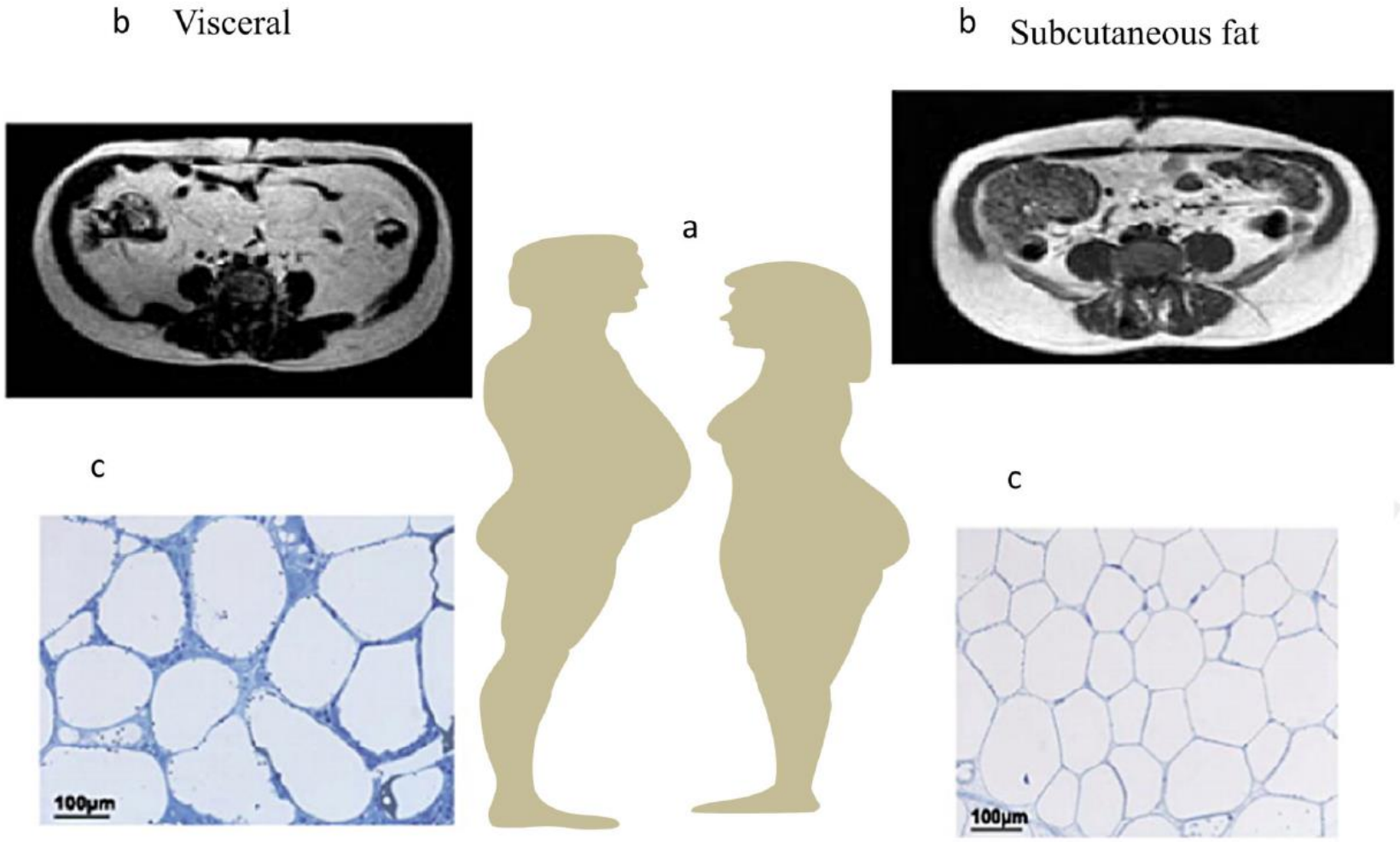


Nature Reviews | Immunology

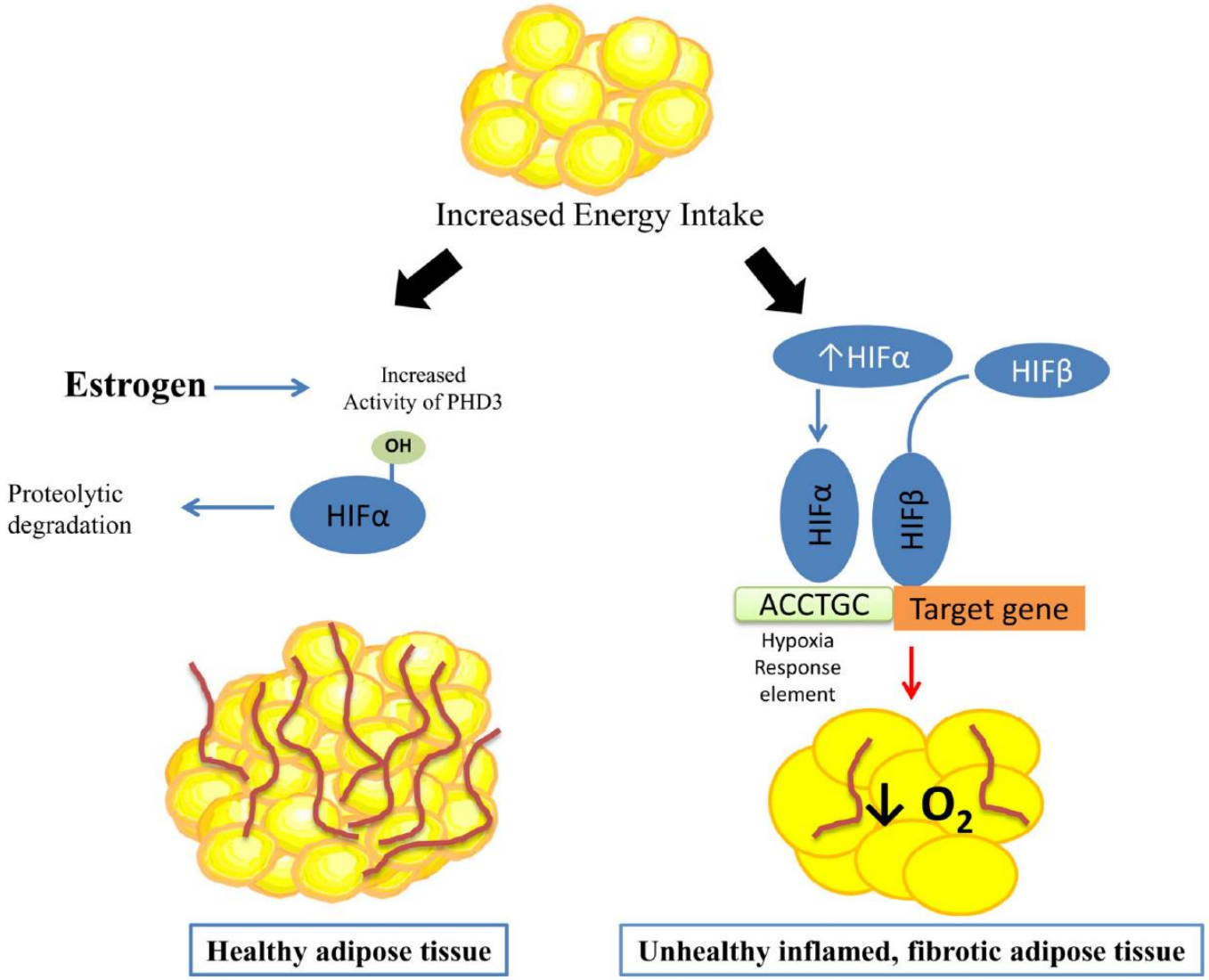


Bray et al. *Endocrine Review* 2018

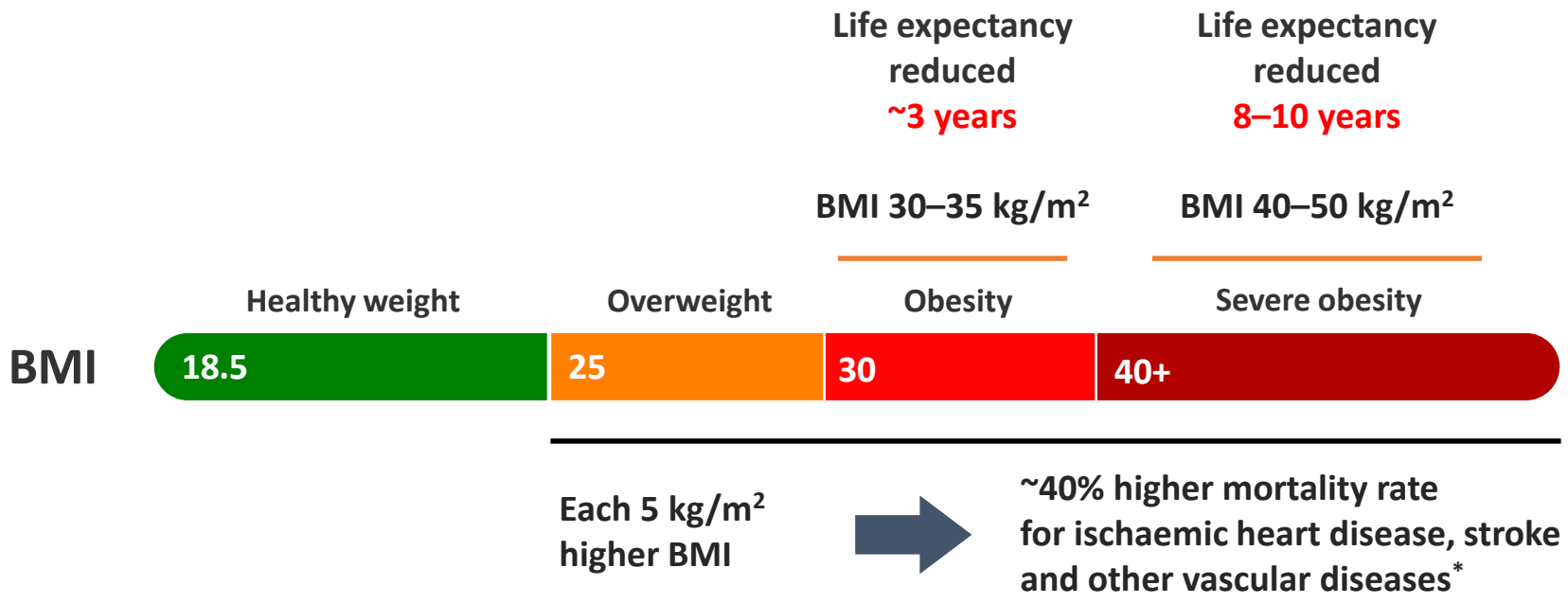
Approximately 80% of all body fat is in the subcutaneous depot and lies just under the skin primarily around the waist, in the subscapular area, and in the gluteal and femoral (thigh) areas. Visceral fat, accounting for 10–20% of total fat, is in the abdomen primarily in the omentum and mesentery but also in perirenal, gonadal, epicardial, and retroperitoneal depots



E2/ERα regulates HIF-1 activity in adipose tissues by promoting transcription of a specific prolyl hydroxylase domain enzyme (PHD3)



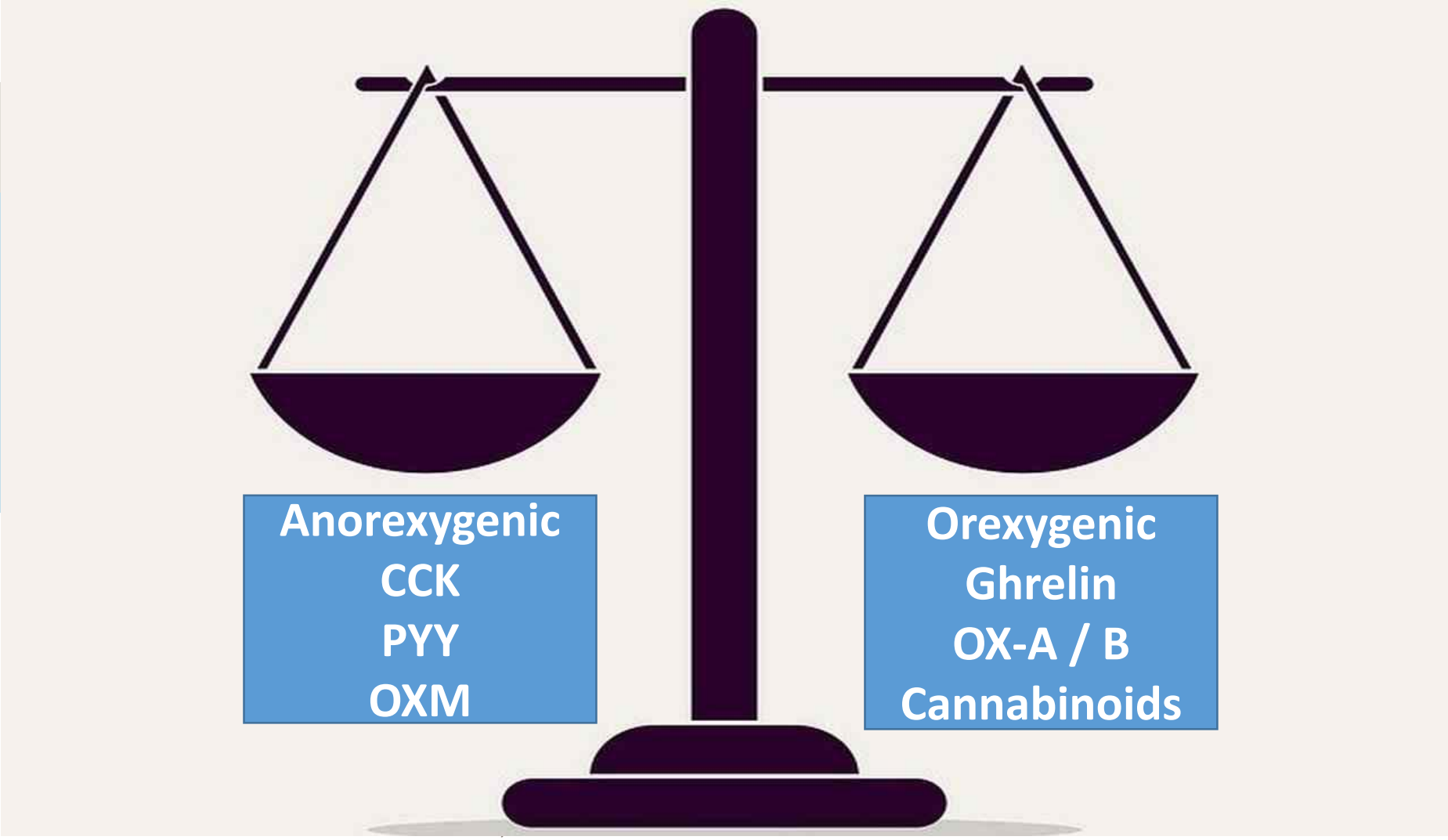
Obesity is a chronic condition/disease with serious implications for life expectancy[1]



*Based on a meta-analysis of 57 international prospective studies predominantly based in Europe, the United States, Israel and Australia, including BMI information for
894,576 adults. BMI, body mass index

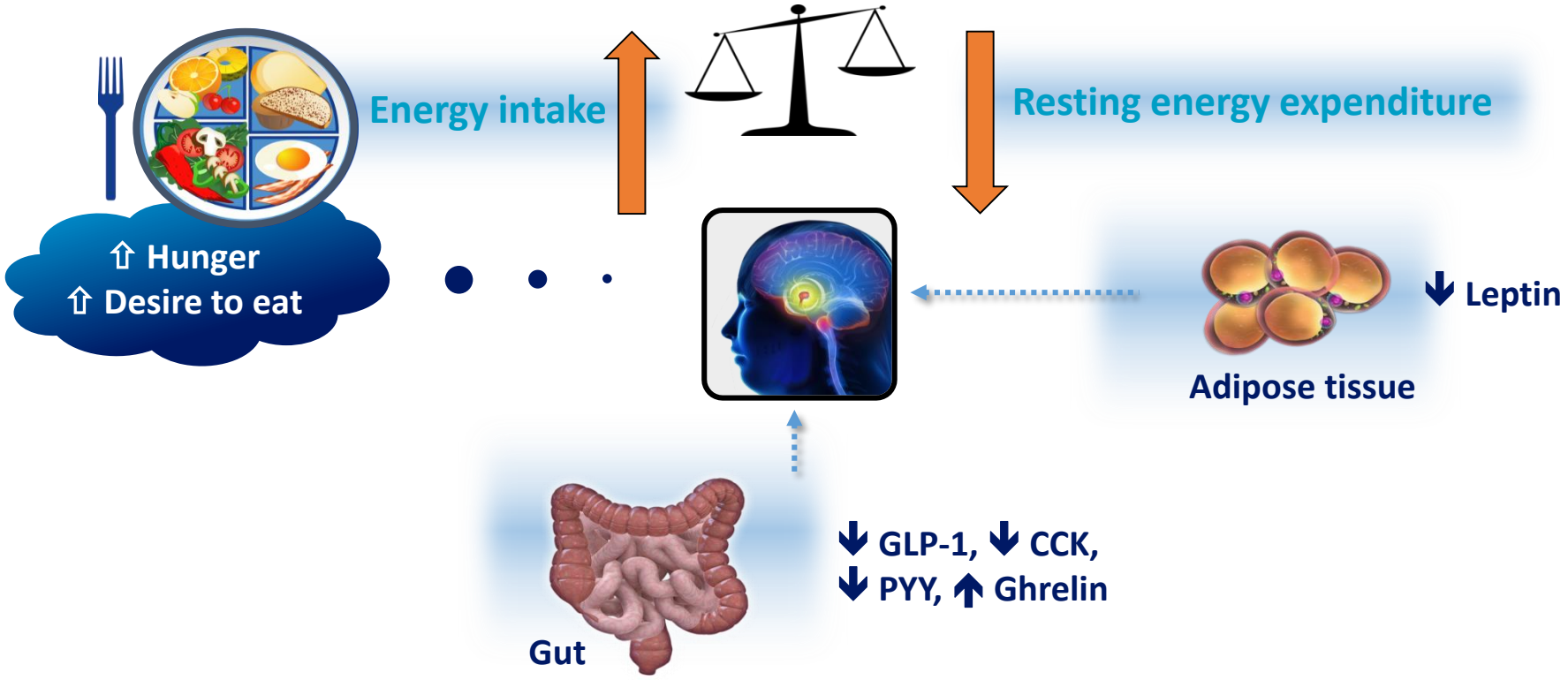
1. Prospective Studies Collaboration. *Lancet* 2009;373:1083–1096

Homeostatic regulation of appetite



mphetamine-
otide Y; OXM,
5 receptor
et al. J Clin

Physiological responses to weight loss favour weight regain

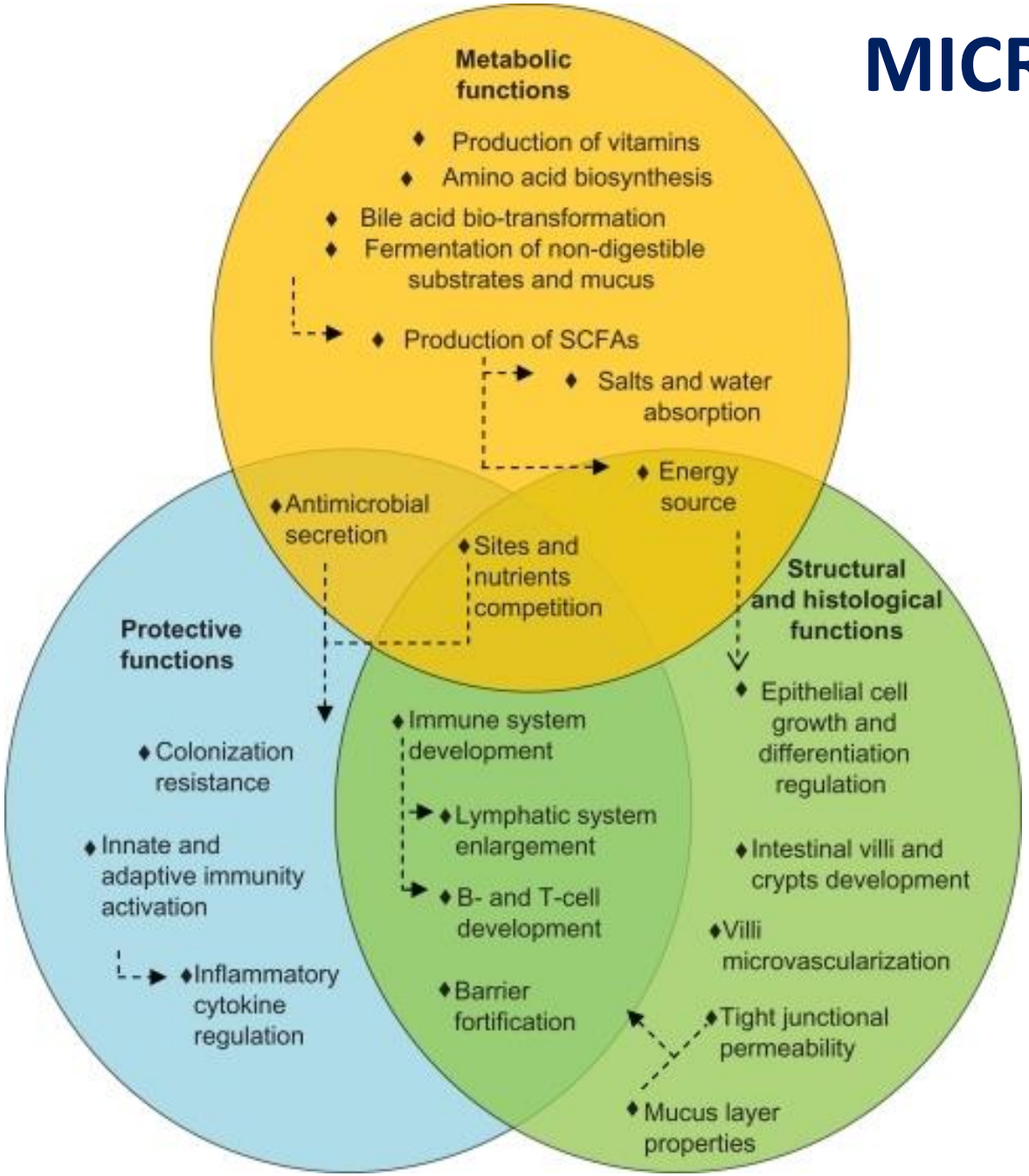


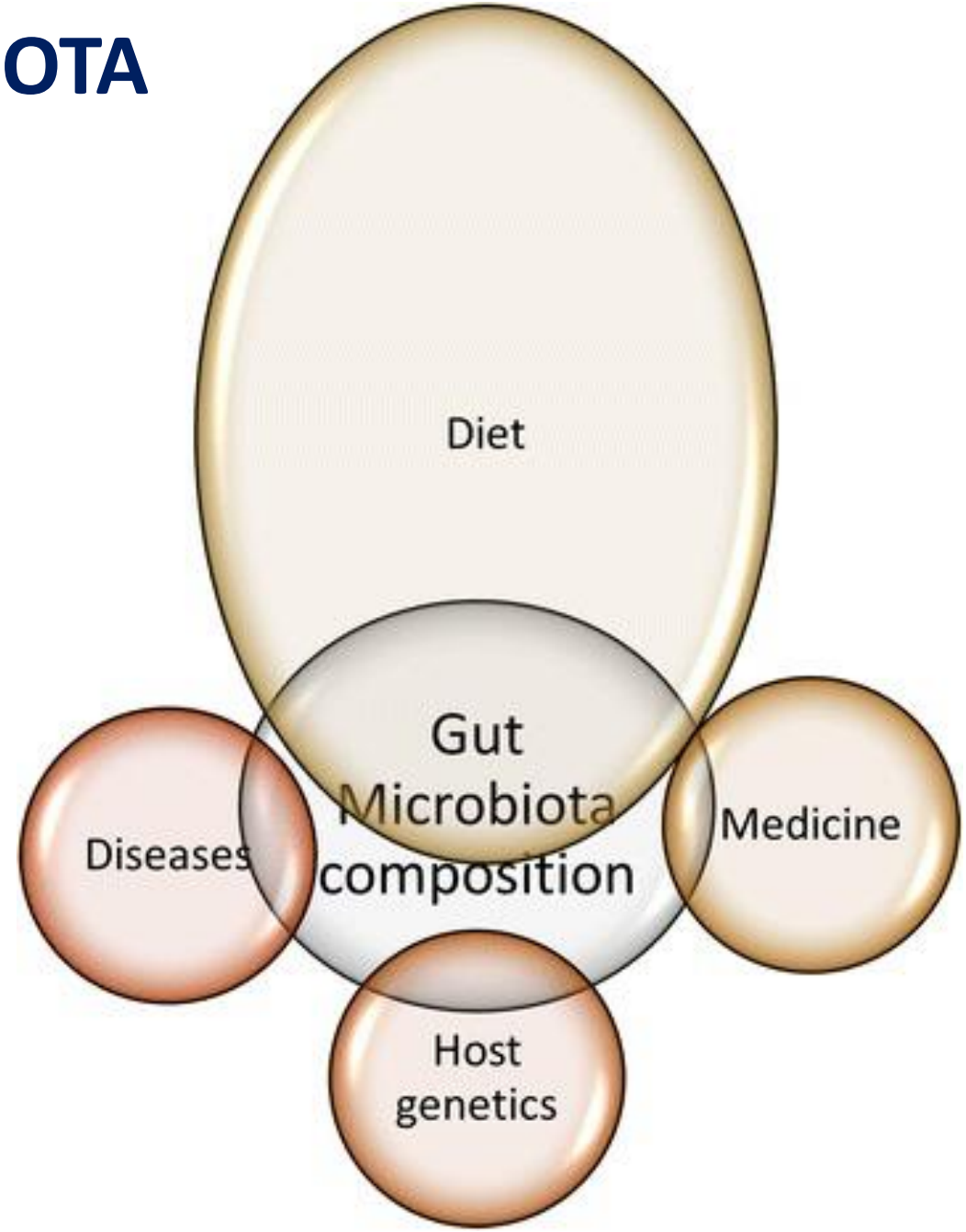
CCK, cholecystokinin; GLP-1, glucagon-like peptide-1; PYY, peptide YY

Schwartz A et al. *Obes Rev* 2010;11:531–547; Sumithran P et al. *N Engl J Med* 2011;365:1597–1604

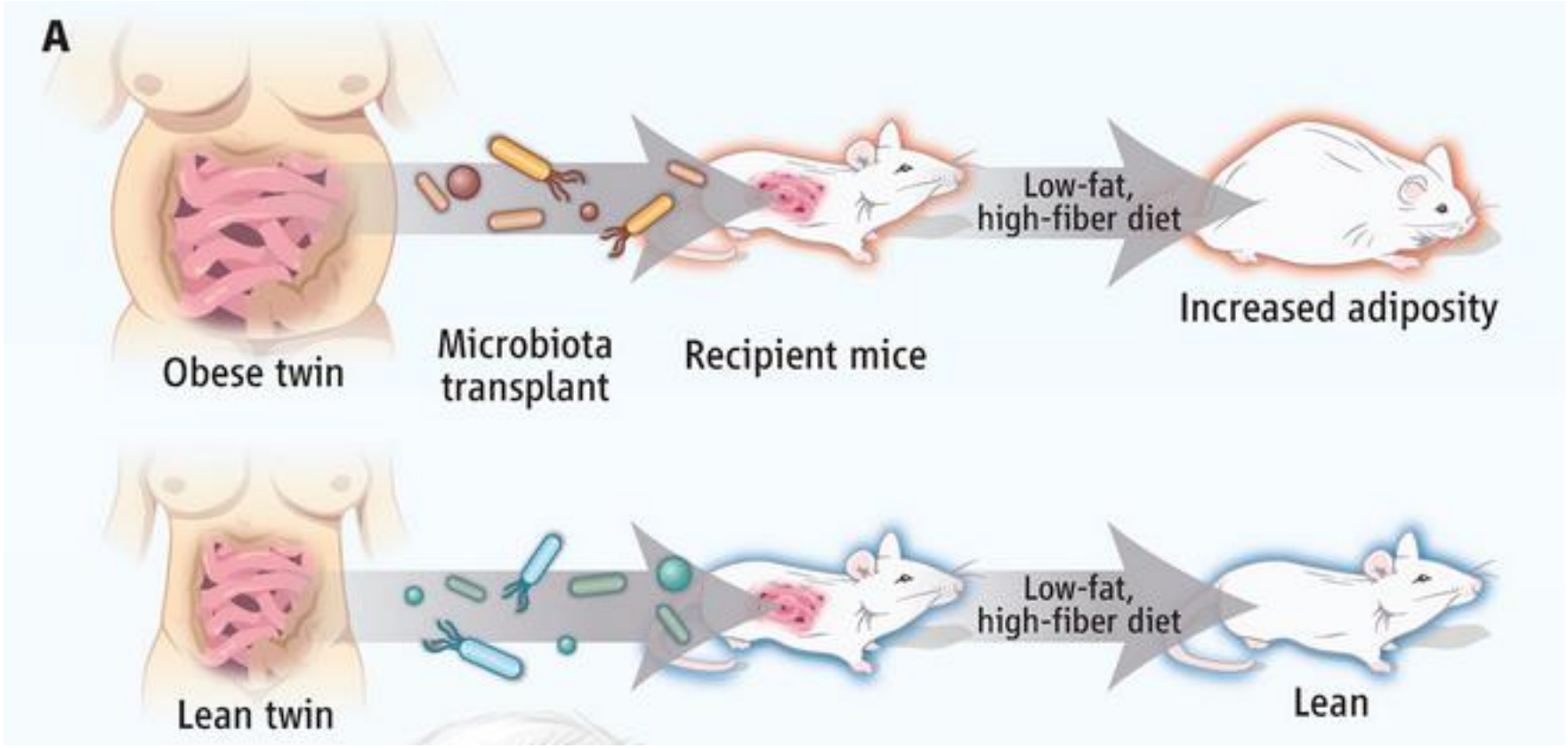
A new actor on stage : the gut microbiota

MICROBIOTA


Metabolic functions
Production of vitamins
Amino acid biosynthesis
Bile acid bio-transformation
Fermentation of non-digestible substrates and mucus
Production of SCFAs
Salts and water absorption
Energy source
Antimicrobial secretion
Sites and nutrients competition
Protective functions
Colonization resistance
Innate and adaptive immunity activation
Inflammatory cytokine regulation
Immune system development
Lymphatic system enlargement
B- and T-cell development
Barrier fortification
Structural and histological functions
Epithelial cell growth and differentiation regulation
Intestinal villi and crypts development
Villi microvascularization
Tight junctional permeability
Mucus layer properties

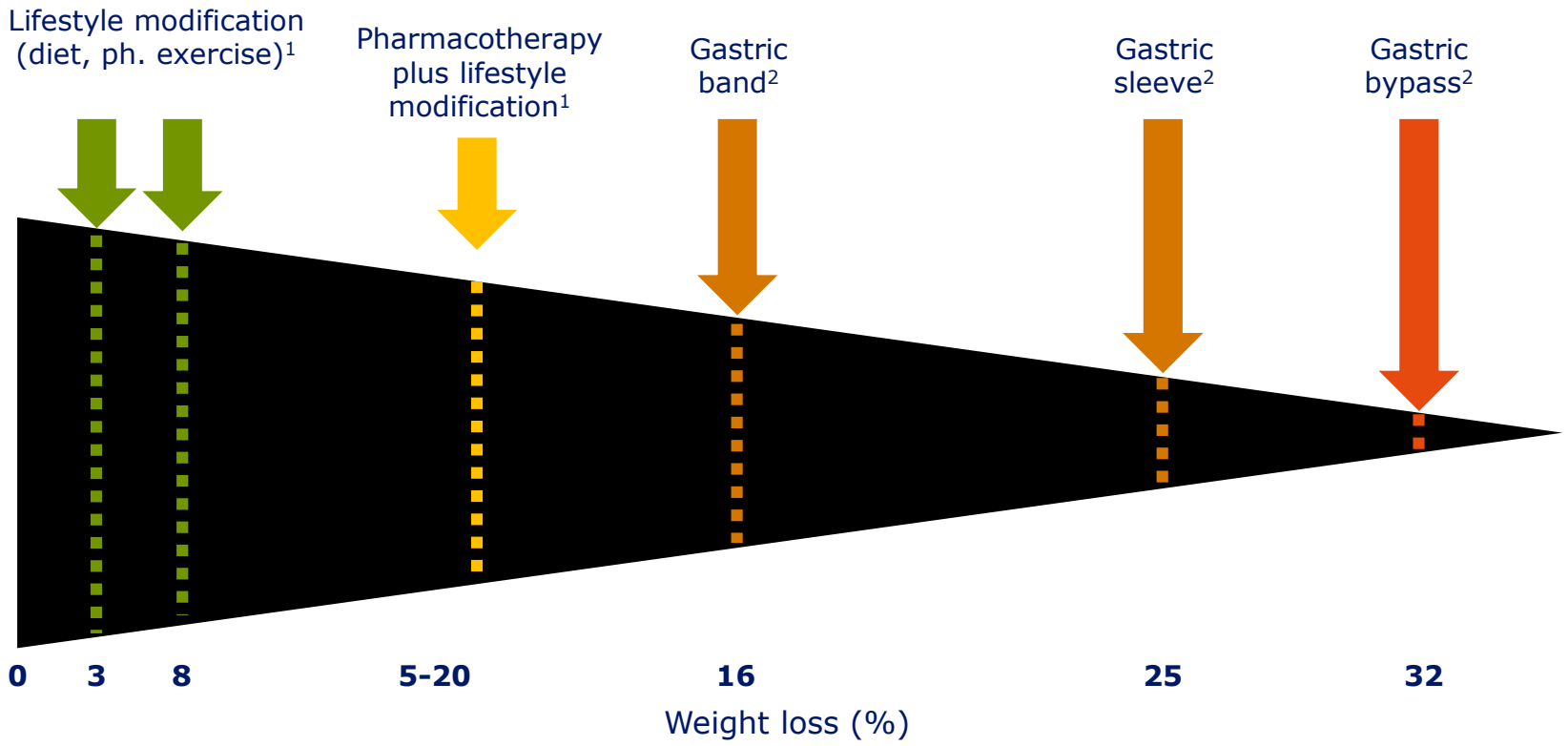

Diet
Gut Microbiota composition
Diseases
Medicine
Host genetics

Microbiota and obesity : the mouse model



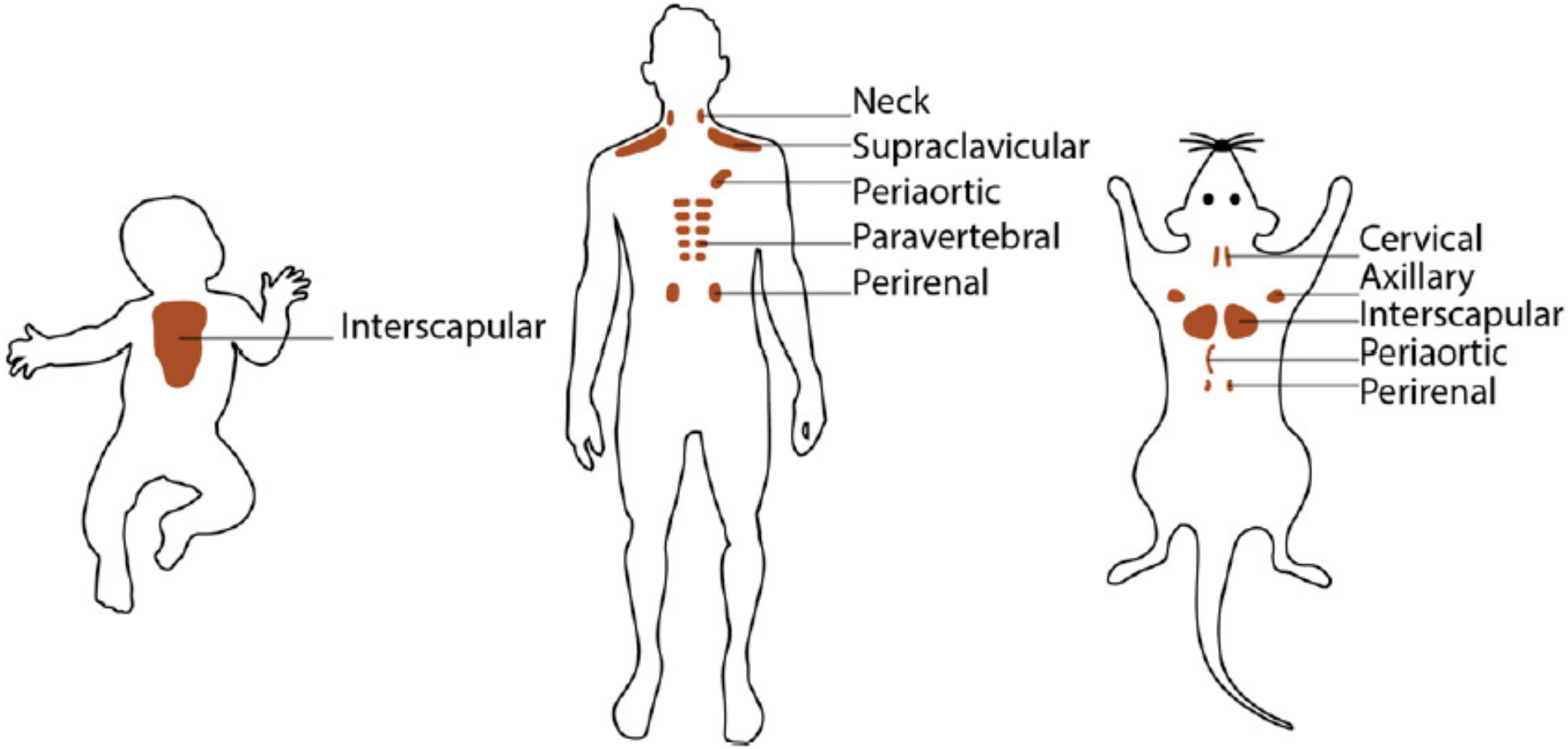
Treatment options

Treatment options for people with obesity: weigh loss target



1. Jensen MD *et al. Circulation* 2014;129(25 Suppl. 2):S102–38; 2. Courcoulas AP *et al. JAMA* 2013;310:2416–2425

DEPOSIT LOCATIONS OF BROWN FAT TISSUE IN HUMAN AND MOUSE

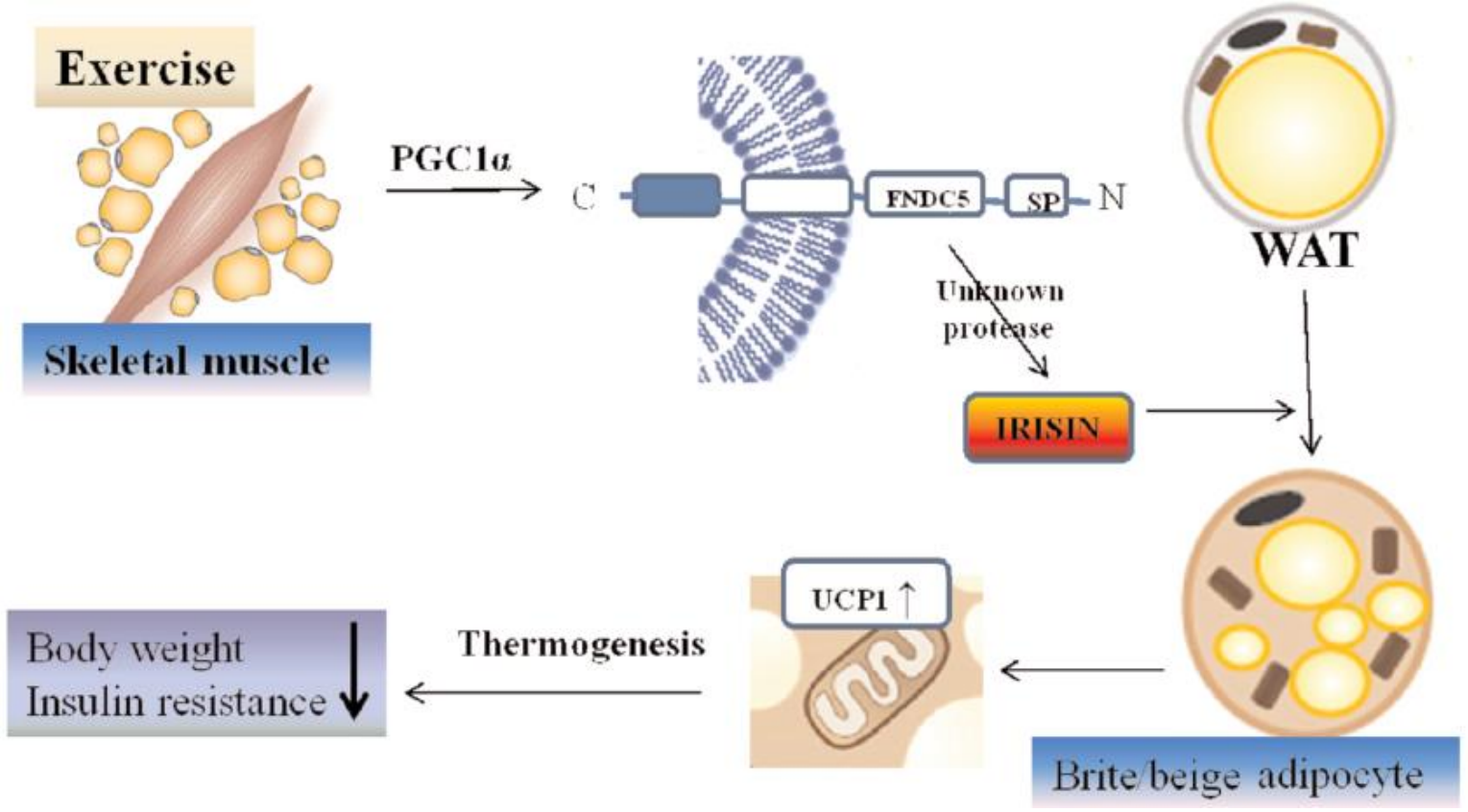


Van den Berg SM et al. *Endocrine Review* 38:46-68,2017

IRISIN

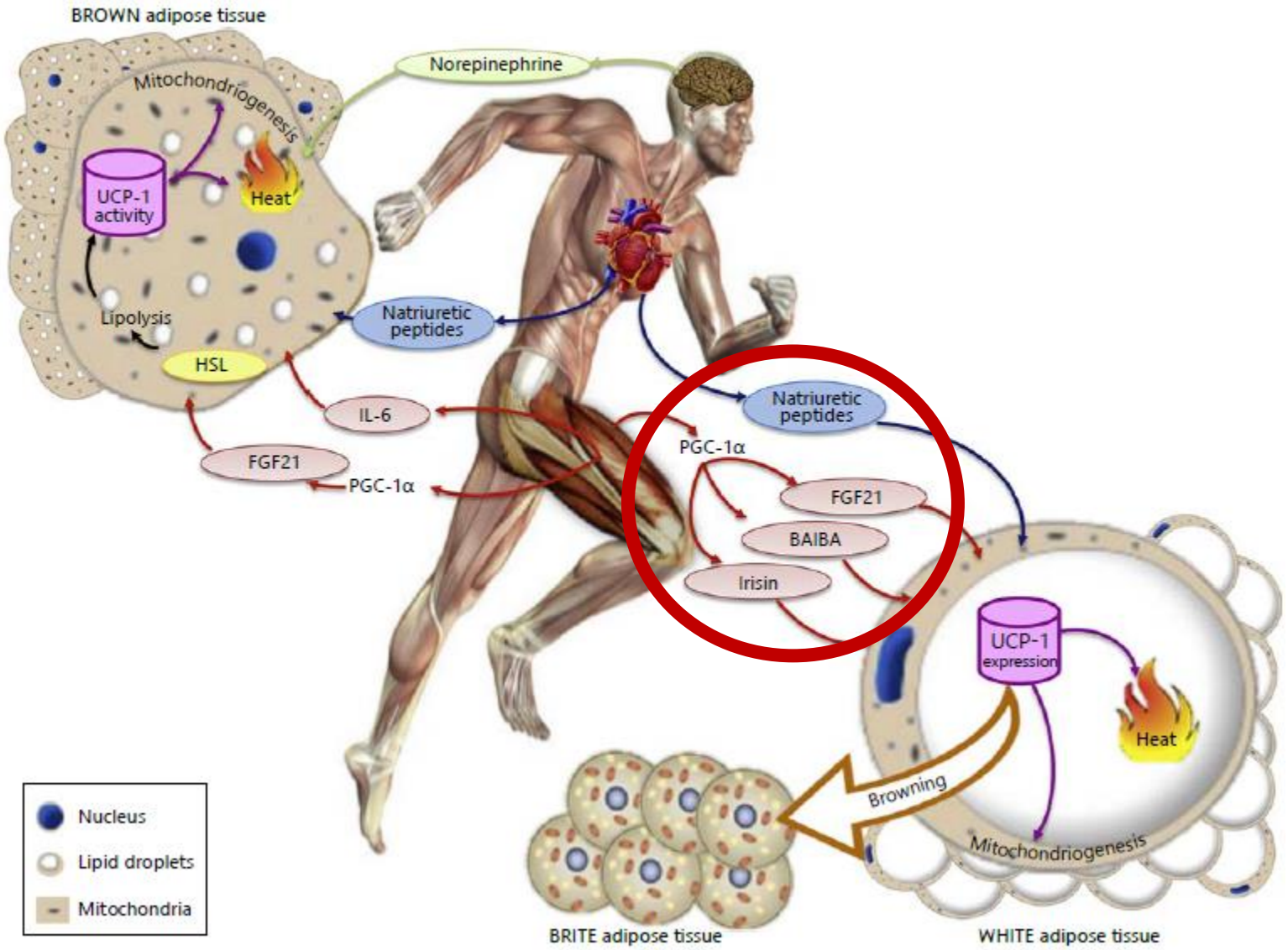
The health promoting hormone

PHYSICAL EXERCISE INDUCES THE RELEASE OF **PPARγ coactivator-1α (PGC1α)** FROM THE SKELETAL MUSCLE TISSUE THAT INCREASES THE EXPRESSION OF **FIBRONECTIN TYPE III DOMAIN 5 (FNDC5)** WHOSE CLIVAGE BY UNKNOWN PROTEASE INDUCES **IRISIN** RELEASE



Panati K et al. *ERMPS* 2016

EXERCISE MODULATES THE ENDOCRINE CROSSTALK BETWEEN MUSCLE AND ADIPOSE TISSUE



How much activity do I need?

Moderate-intensity aerobic activity

Anything that gets your heart beating faster counts.

AND

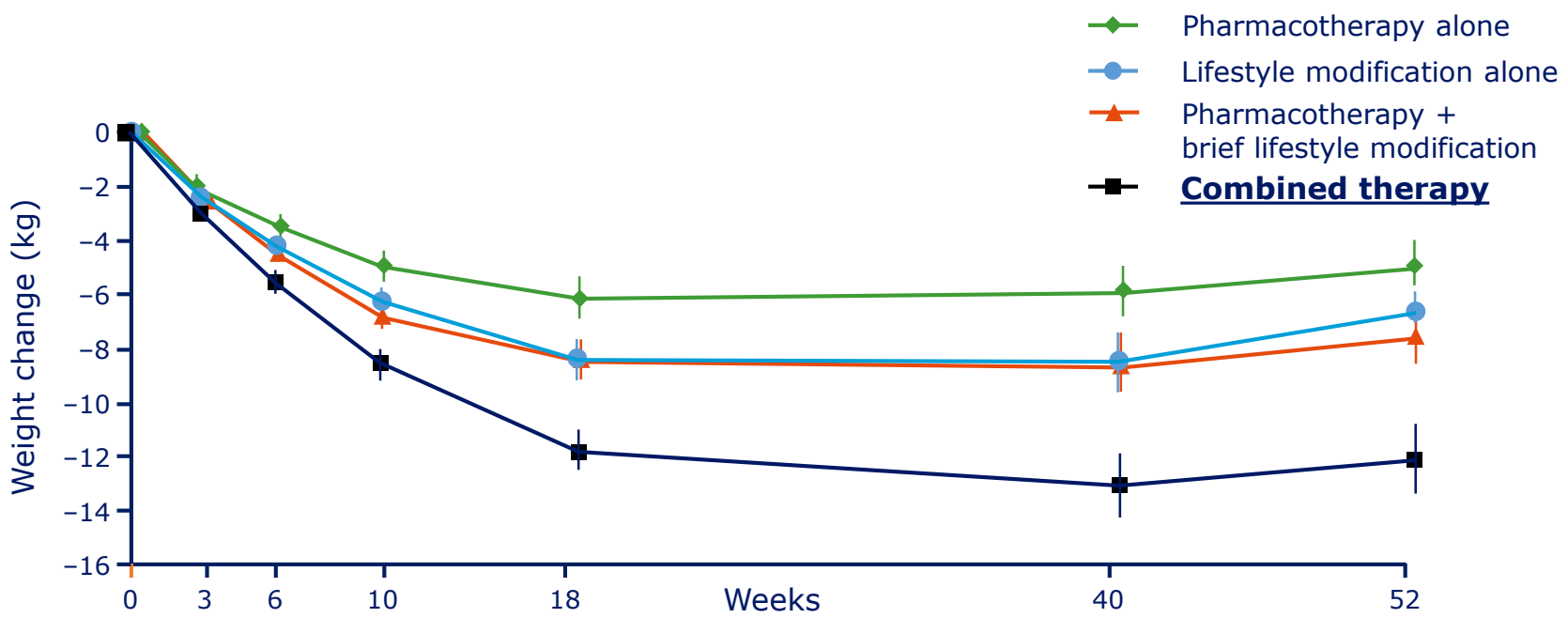
Muscle-strengthening activity

Do activities that make your muscles work harder than usual.

Tight on time this week? **Start with just 5 minutes.** It all adds up!

Or get the same benefits in half the time. If you step it up to **vigorous-intensity** aerobic activity, aim for at least **75 minutes** a week.

Pharmacotherapy in addition to diet and exercise can help patients achieve clinically relevant weight loss

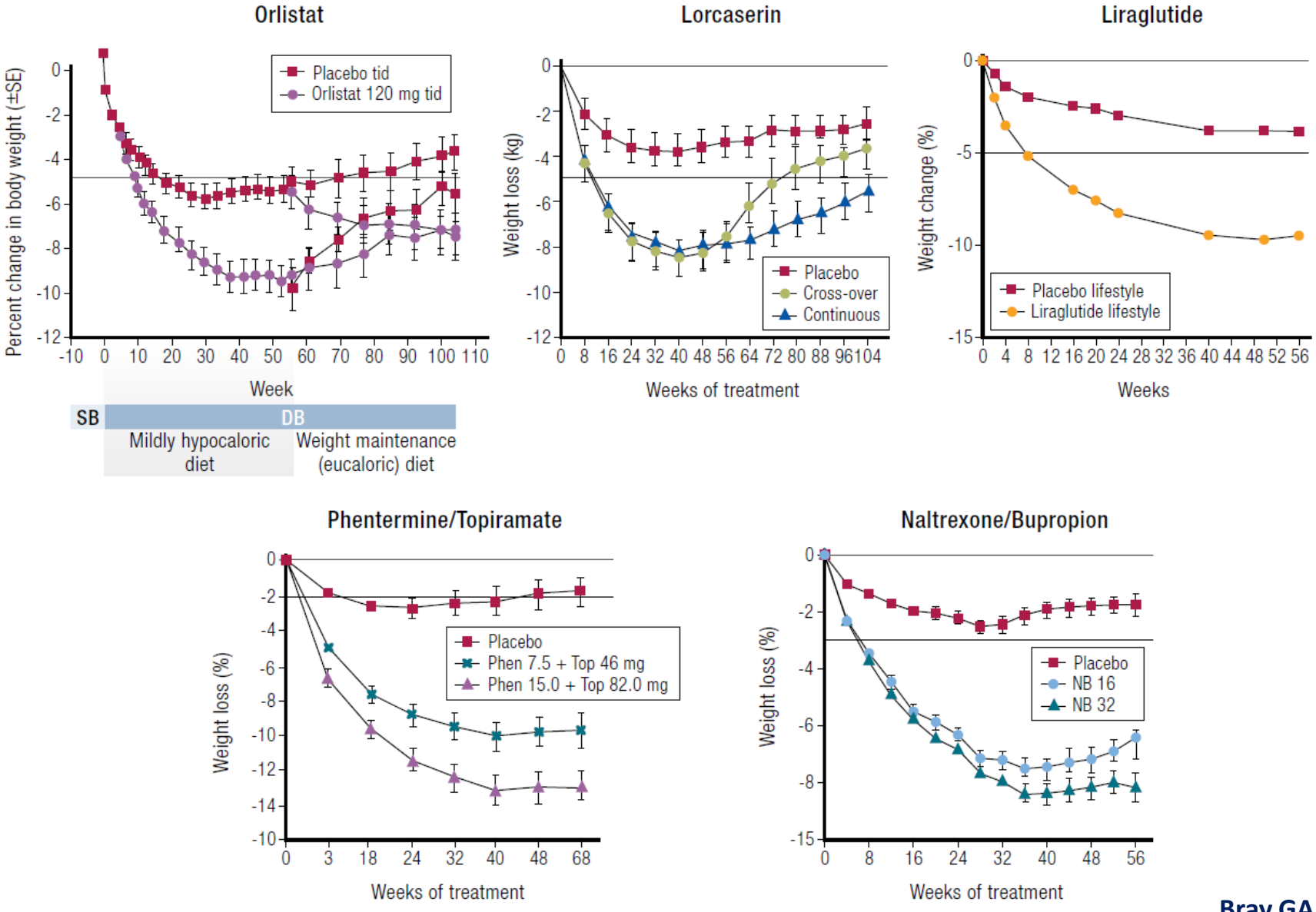


Data are mean ± standard error
Pharmacotherapy: Sibutramine; Pharmacotherapy alone: Patients received a daily dose of 15 mg/day; Lifestyle modification alone: Patients attended 30 lifestyle
counselling sessions; Pharmacotherapy + brief therapy: Patients were given sibutramine and received brief lifestyle counselling; Combined therapy: Patients received sibutramine and attended 30 lifestyle counselling sessions

Wadden TA *et al. N Engl J Med* 2005;353:2111–2120

Sibutramine is not approved for weight management in the EU

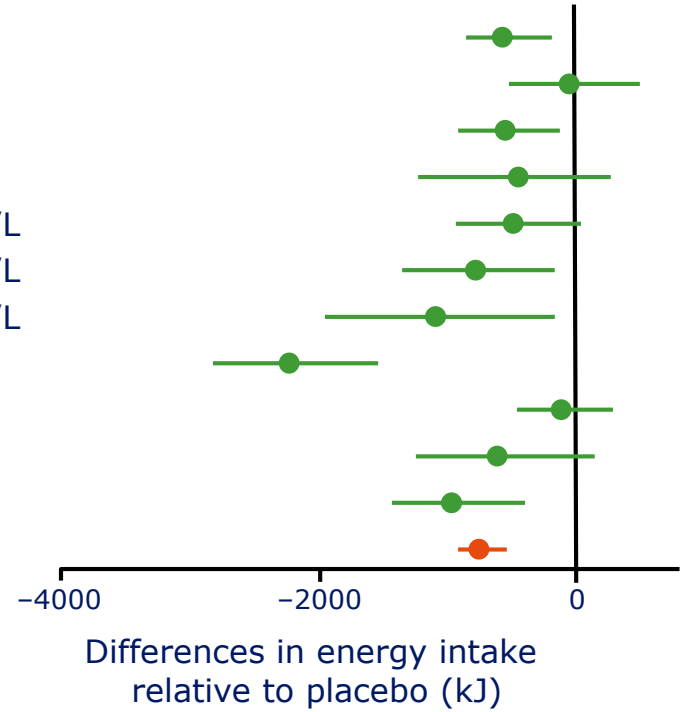
Randomized controlled trial data and weight loss



Bray GA et al. *Endoc Review* 2017

GLP-1 reduces energy intake in humans

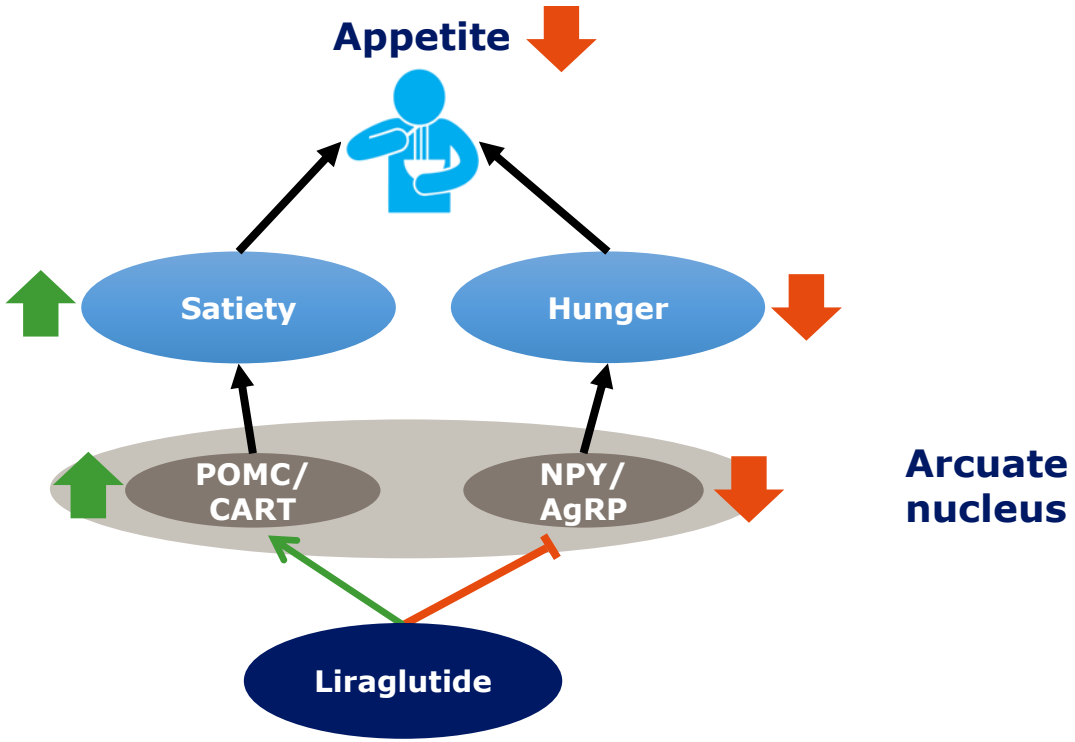
Flint *et al.* 1998 (n=19)
Näslund *et al.* 1998 (n=6)
Näslund *et al.* 1999 (n=8)
Long *et al.* 1999 (n=10)
Gutzwiller *et al.* 1999a (n=16); 0.38 pmol/L
Gutzwiller *et al.* 1999a (n=16); 0.75 pmol/L
Gutzwiller *et al.* 1999a (n=16); 1.50 pmol/L
Gutzwiller *et al.* 1999b (n=12)
Flint *et al.* 2001 (n=17)
Beglinger *et al.* (unpublished b) (n=12)
Beglinger *et al.* (unpublished a) (n=15)
Meta-analysis



On average, energy intake was **reduced by 727 kJ** (95% CI: 548–908 kJ) during GLP-1 infusion, corresponding to a **reduction of ~12%**

Data are mean and 95% CI
CI, confidence interval; GLP-1, glucagon-like peptide-1
Adapted from: Verdich C *et al. J Clin Endocrinol Metab* 2001;86:4382–4389

Liraglutide reduces hunger and increases satiety via neurons in the arcuate nucleus

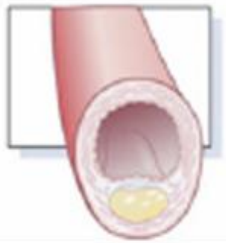
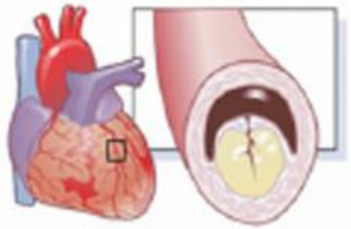
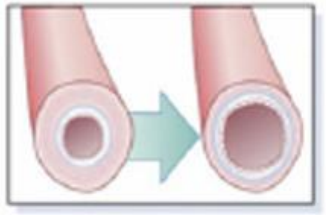


AgRP, agouti-related peptide; CART, cocaine- and amphetamine-regulated transcript; NPY, neuropeptide Y; POMC, pro-opiomelanocortin

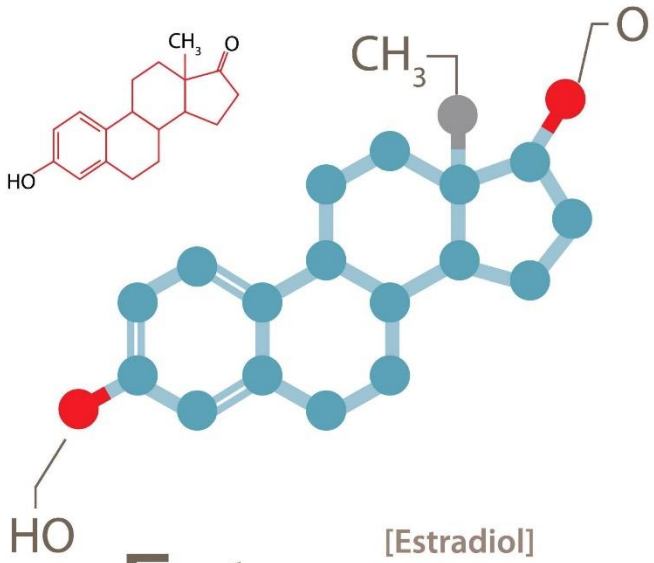
Secher A *et al. J Clin Invest* 2014;124:4473–4488; van Can J et al. *Int J Obes* (Lond) 2014;38:784–793

Cardiovascular changes

Atherosclerosis and risk of adverse cardiovascular events increase in postmenopausal women due to VAT production of proinflammatory cytokines and adipokins

Estrogens		Progestins
↓ LDL oxidation ↓ LDL binding ↑↓ lipoprotein* *** ↑ blood pressure ↓ oxidation damage ↓ VSMC proliferation ↓ glucose tolerance***	**Atherosclerosis** 	↑↓ HDL effect* ** ↑↓ blood pressure** ↑ glucose tolerance**
↑ coagulation factors ↓ platelet aggregation	**Thrombosis** 	↑ coagulation factors ↓ platelet aggregation ↓ nitric oxide**
↑ nitric oxide ↓ endothelin ↑ Cox-2 ↓ neuroendocrine response ↓ VSMC proliferation	**Vasomotion** 	↑ vasoconstriction** ↓ nitric oxide**
↑ QT prolongation	**Arrhythmogenesis** 	↓ QT prolongation

Urogenital Symptoms and sexual dysfunction



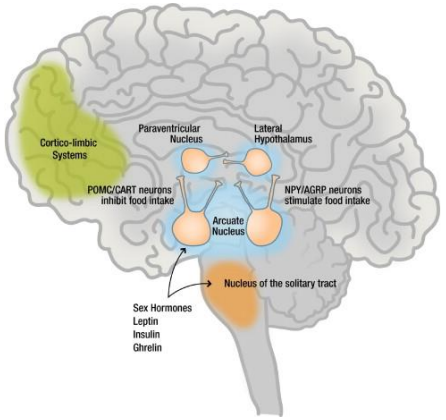
[Estradiol]

Estrogen

structure

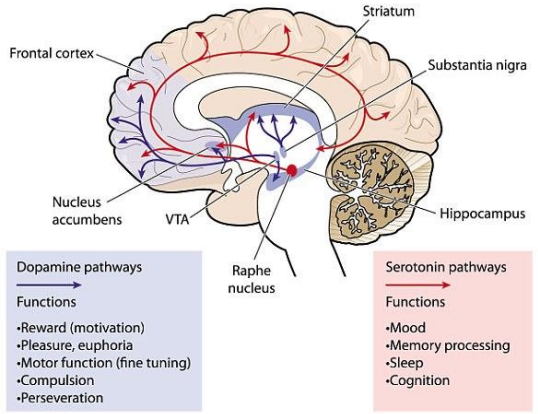
Excitatory Systems of the Brain

Opioids

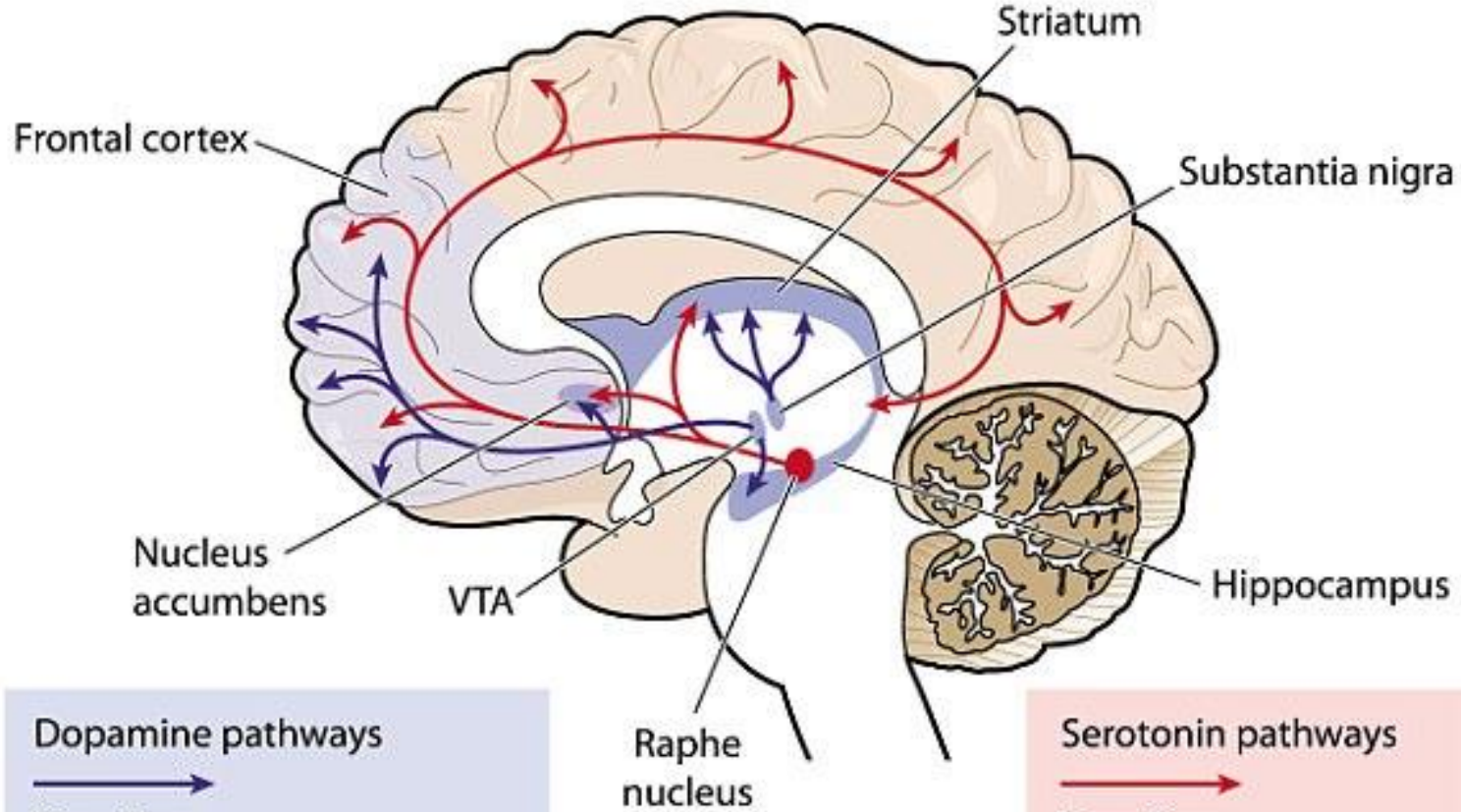


Cell bodies in the periarcuate regions of hypothalamus and brainstem
Diffused projections to hypothalmic limbic, cortical, midbrain and brainstem regions

Serotonin (5-HT)



Cell bodies in the raphe nuclei
Ascending projections to hypothlmic limbic and cortical regions
Descending projections to spinal cord



Dopamine pathways →

Functions

- Reward (motivation)
- Pleasure, euphoria
- Motor function (fine tuning)
- Compulsion
- Perseveration

Serotonin pathways →

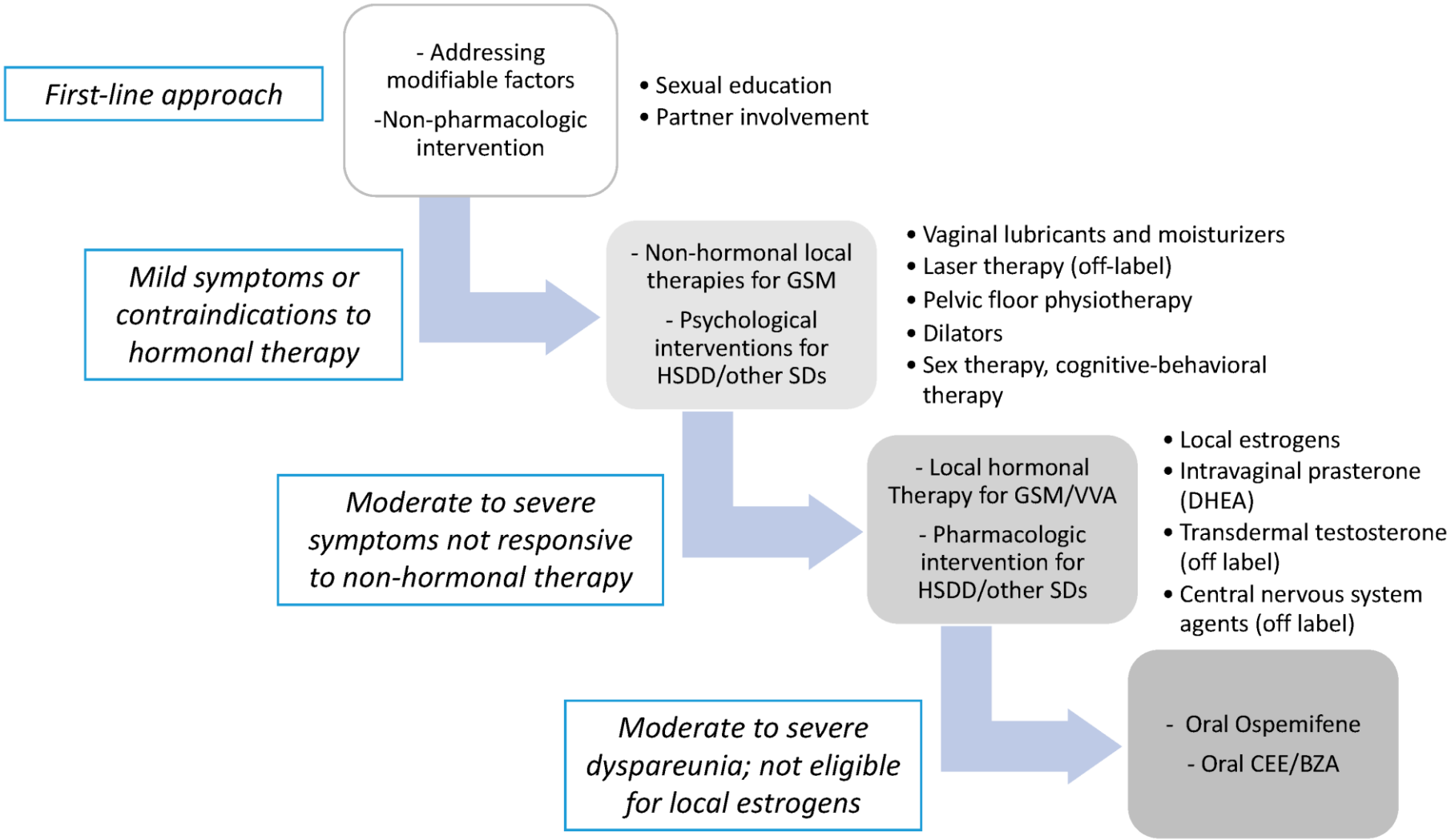
Functions

- Mood
- Memory processing
- Sleep
- Cognition

Hypoactive Sexual Desire Disorder HSDD

Increased activation of prefrontal cortex → increased inhibition of sexual desire

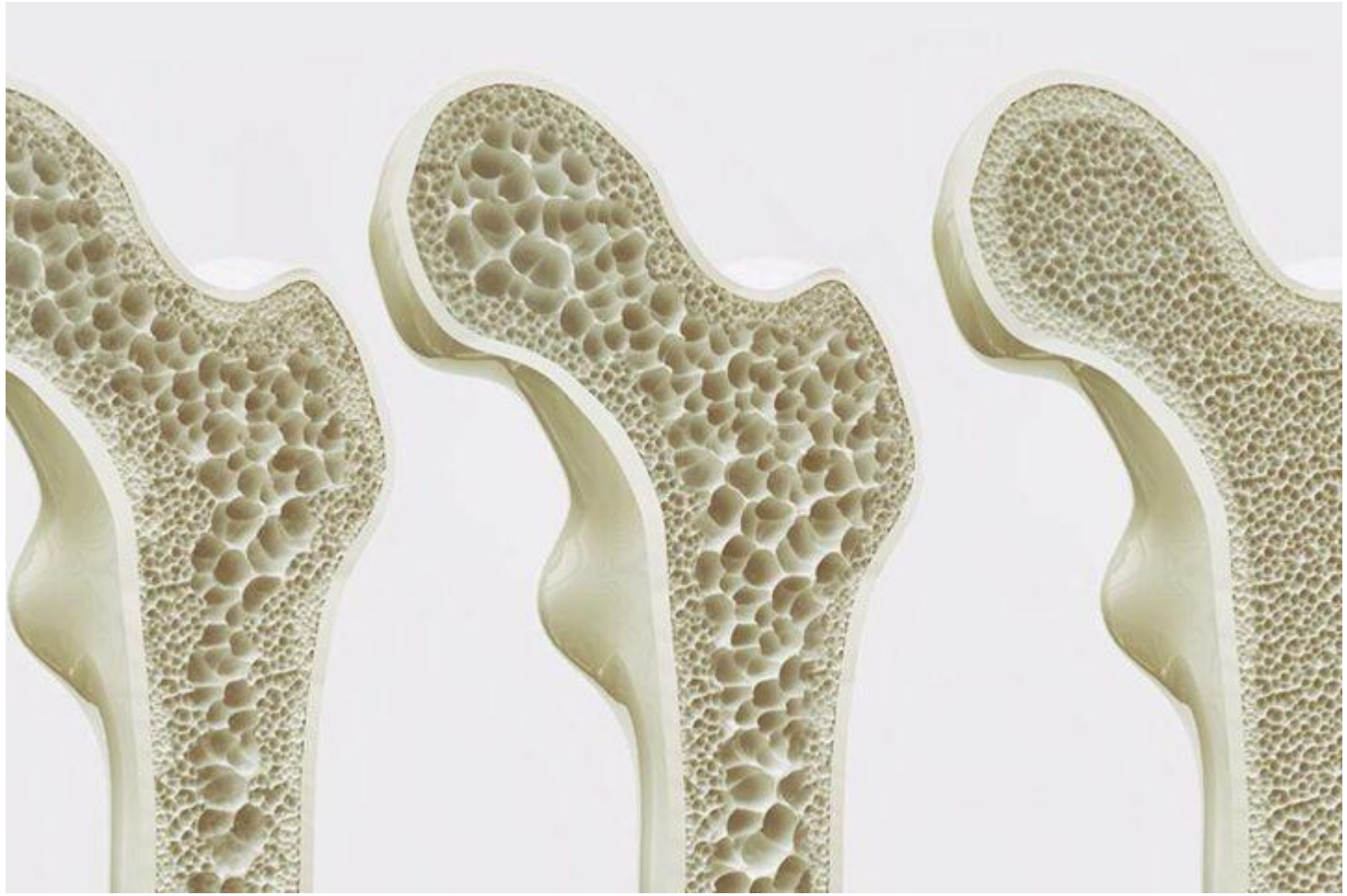
Proposed flow chart for the management of sexual dysfunction in menopause



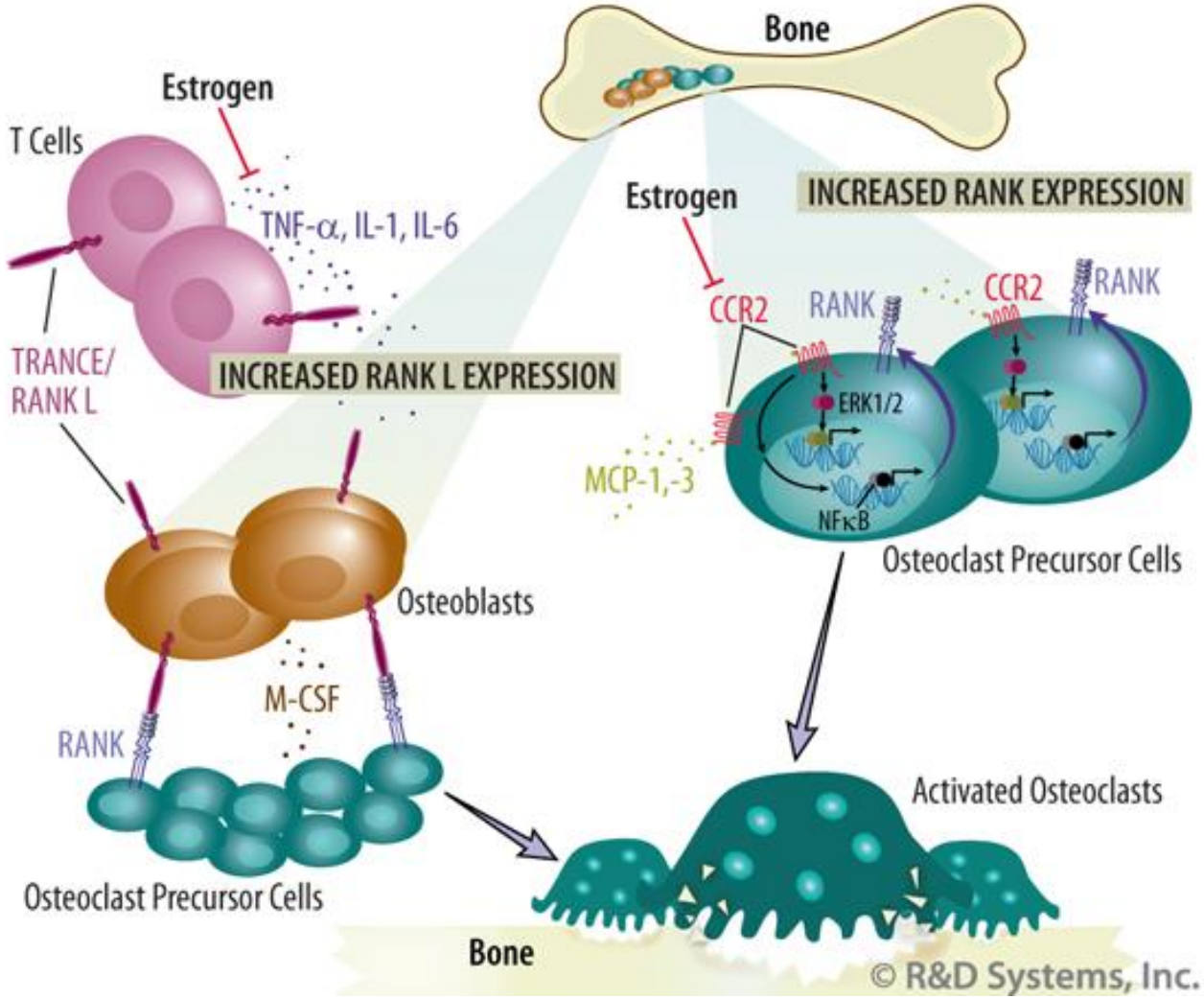
Scavello et al. Medicina 2019

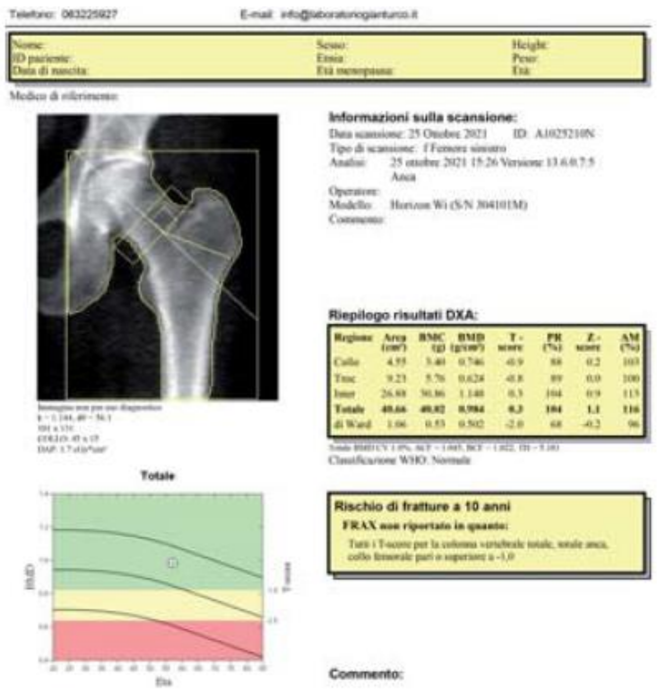
Muscoloskeletal symptoms

Postmenopausal osteoporosis



Proinflammatory Cytokines & CCR2 Promote Estrogen-deficient Bone Loss





Telefono: 063225927 E-mail: info@laboratoriogianturco.it

Nome:	Sesso:	Height:
ID paziente:	Etnia:	Peso:
Data di nascita:	Età menopausa:	Età:

Medico di riferimento:

Informazioni sulla scansione:

Data scansione: 25 Ottobre 2021 ID: A1025210N
Tipo di scansione: f Femore sinistro
Analisi: 25 ottobre 2021 15:26 Versione 13.6.0.7:5
Anca
Operatore:
Modello: Horizon Wi (S/N 304101M)
Commento:

Immagine non per uso diagnostico

Riepilogo risultati DXA:

Regione	Area (cm²)	BMC (g)	BMD (g/cm²)	T - score	PR (%)	Z - score	AM (%)
Collo	4.55	3.40	0.746	-0.9	88	0.2	103
Troc	9.23	5.76	0.624	-0.8	89	0.0	100
Inter	26.88	30.86	1.148	0.3	104	0.9	113
Totale	**40.66**	**40.02**	**0.984**	**0.3**	**104**	**1.1**	**116**
di Ward	1.06	0.53	0.502	-2.0	68	-0.2	96

Classificazione WHO: Normale

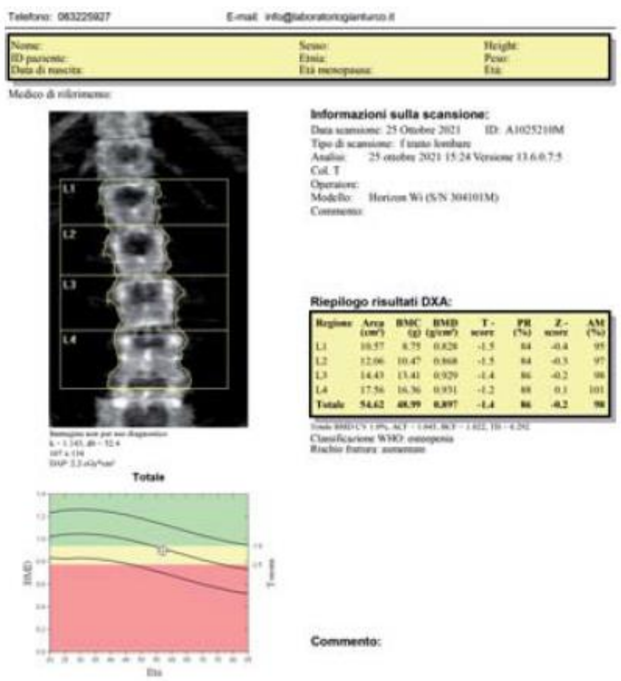
Totale

Rischio di fratture a 10 anni

FRAX non riportato in quanto:

Tutti i T-score per la colonna vertebrale totale, totale anca, collo femorale pari o superiore a -1,0

Commento:



Telefono: 063225927 E-mail: info@laboratoriogianturco.it

Nome:	Sesso:	Height:
ID paziente:	Etnia:	Peso:
Data di nascita:	Età menopausa:	Età:

Medico di riferimento:

Informazioni sulla scansione:

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Tipo di scansione: f tratto lombare
Analisi: 25 ottobre 2021 15:24 Versione 13.6.0.7:5
Col. T
Operatore:
Modello: Horizon Wi (S/N 304101M)
Commento:

Immagine non per uso diagnostico

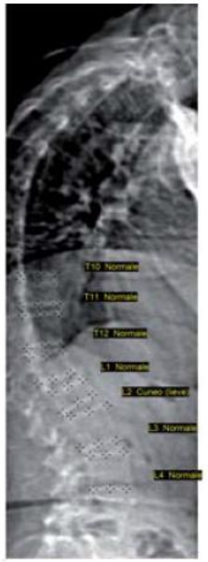
Riepilogo risultati DXA:

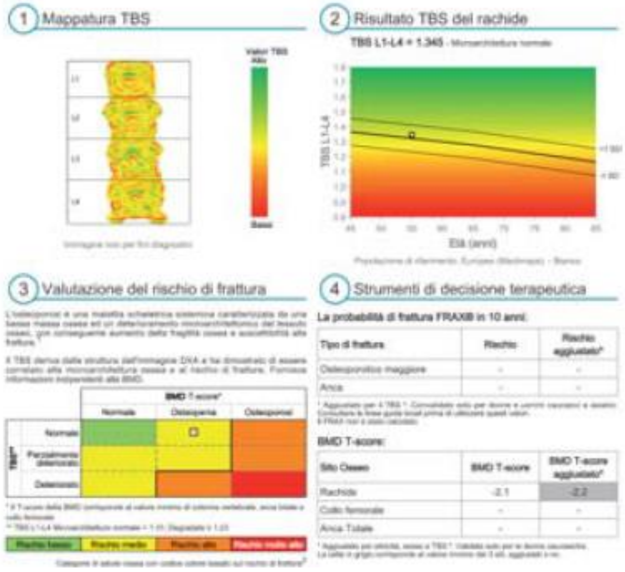
Regione	Area (cm²)	BMC (g)	BMD (g/cm²)	T - score	PR (%)	Z - score	AM (%)
L1	10.57	8.75	0.828	-1.5	84	-0.4	95
L2	12.06	10.47	0.868	-1.5	84	-0.3	97
L3	14.43	13.41	0.929	-1.4	86	-0.2	98
L4	17.56	16.36	0.931	-1.2	88	0.1	101
Totale	**54.62**	**48.99**	**0.897**	**-1.4**	**86**	**-0.2**	**98**

Classificazione WHO: osteopenia

Totale

Commento:





1 Mappatura TBS

2 Risultato TBS del rachide

TBS L1-L4 = 1.345

Età (anni)

3 Valutazione del rischio di frattura

4 Strumenti di decisione terapeutica

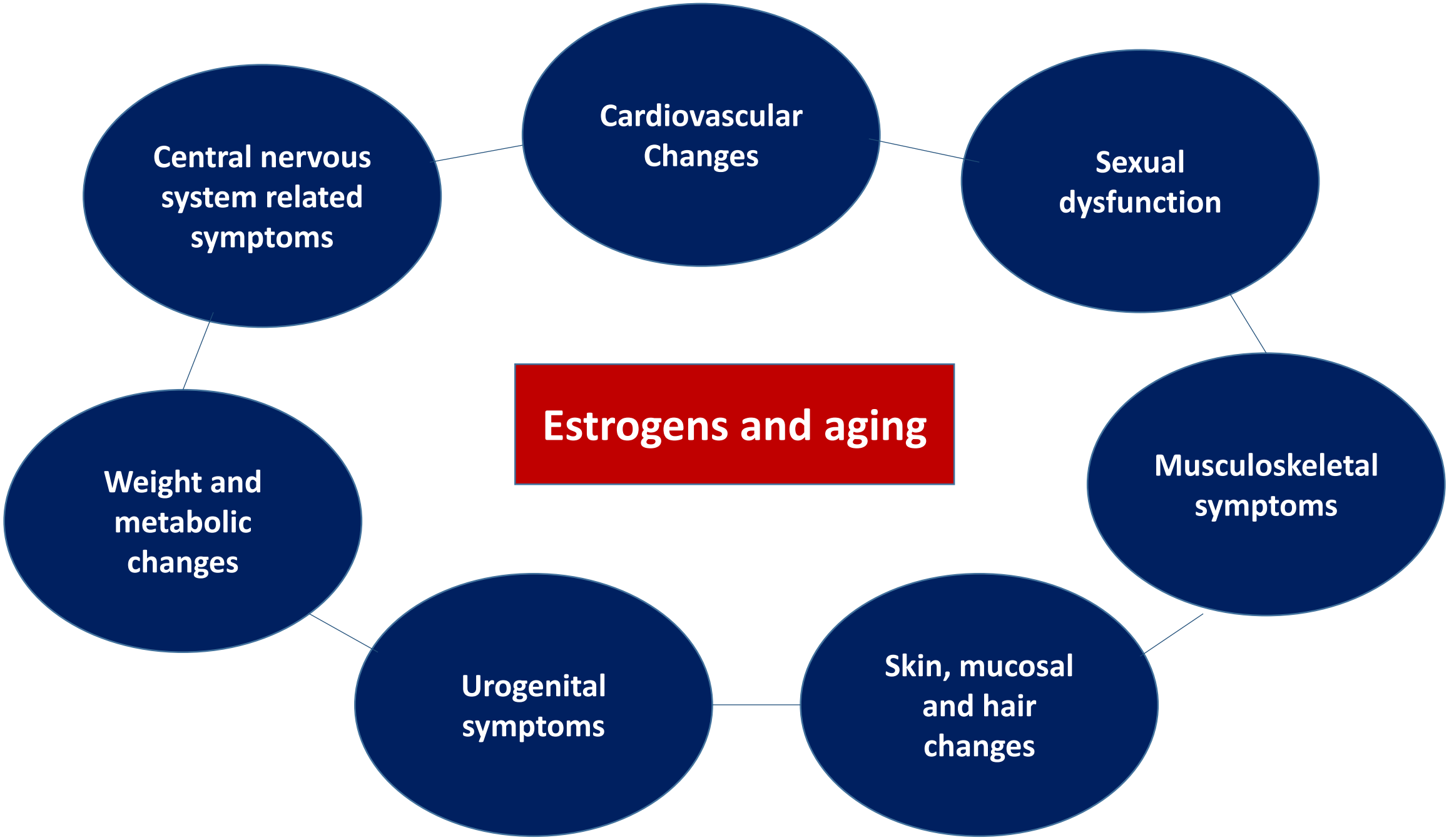
La probabilità di frattura FRAX® in 10 anni

Tipo di frattura	Rischio	Rischio aggiustato*
Osteoporotica maggiore	-	-
Anca	-	-

BMD T-score:

Sito Osseo	BMD T-score	BMD T-score aggiustato
Rachide	-2.1	-2.2
Collo femorale	-	-
Anca Totale	-	-

	Normale	Osteopenia	Osteoporosi
Normale			
Parzialmente deteriorata			
Deteriorata			


Estrogens and aging
Cardiovascular Changes
Sexual dysfunction
Musculoskeletal symptoms
Skin, mucosal and hair changes
Urogenital symptoms
Weight and metabolic changes
Central nervous system related symptoms

KEY POINTS

1. Lack of estrogens in aging has a substantial effect on the quality of life on women and on performance at the workplace; increased awareness of symptoms and acquisition of coping strategies might help
2. Certain symptoms might serve as markers for future health; severe vasomotors symptoms and sleep disorders may increase cardiovascular risk, whereas severe vasomotor symtoms and depression might affect cognitive function
3. Individual factors such us ethnicity, personal history, current helth status (body composition) and socioeconomic condition considerably worsen a woman's experience of estrogen depletion in aging
4. Health-care providers should offer education to women on improving modifiable lifestyle factors to reduce the risk of future illness
5. Loss of estrogens is linked to the ageing process