

# WHY WEIGHT MATTERS

Manage the Patient and not only the Disease



**Driving** | **in**  
**change** | **obesity**

Dr Riaz Motara  
Physician  
Cardiologist

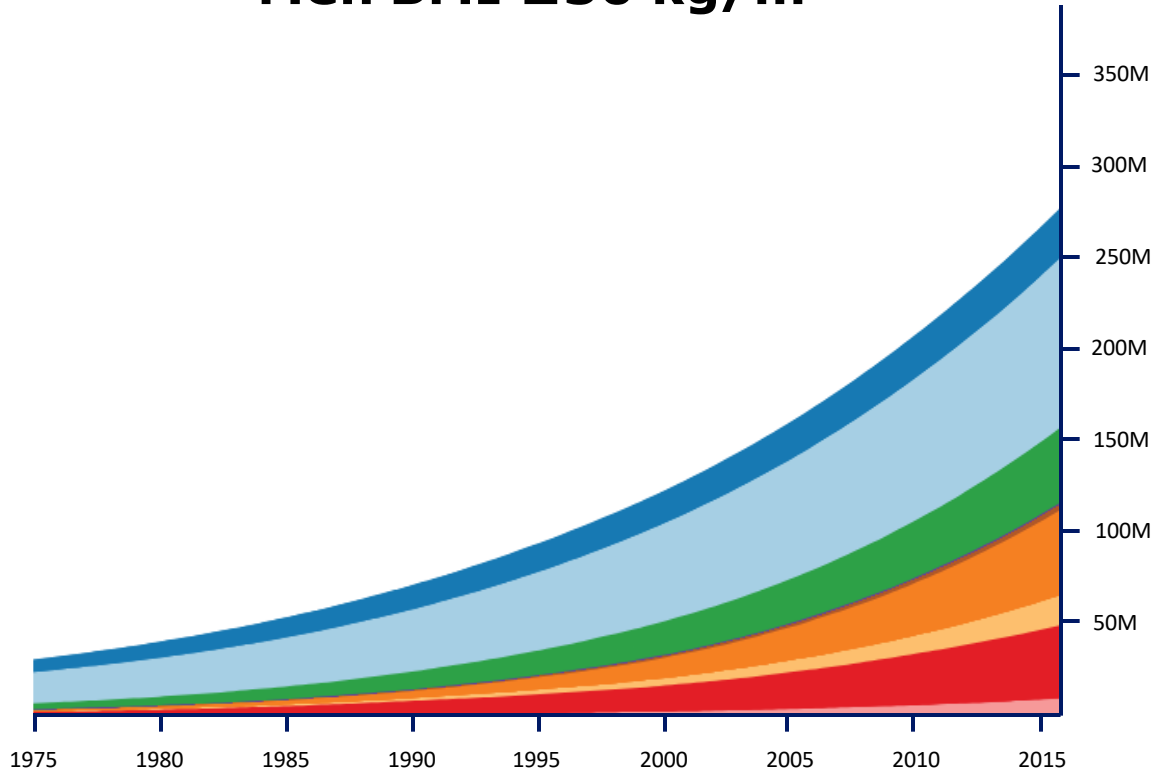
# Disclosures

<b>SPEAKER'S NAME and credentials</b>	<b>Roaz Motara</b> Specialist Physician and Cardiologist MBBCh, FCP(SA)
<b>RELATIONSHIPS WITH COMMERCIAL INTERESTS</b>	
<b>Grants/Research Support:</b>	Nil
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<b>Consulting Fees:</b>	Nil

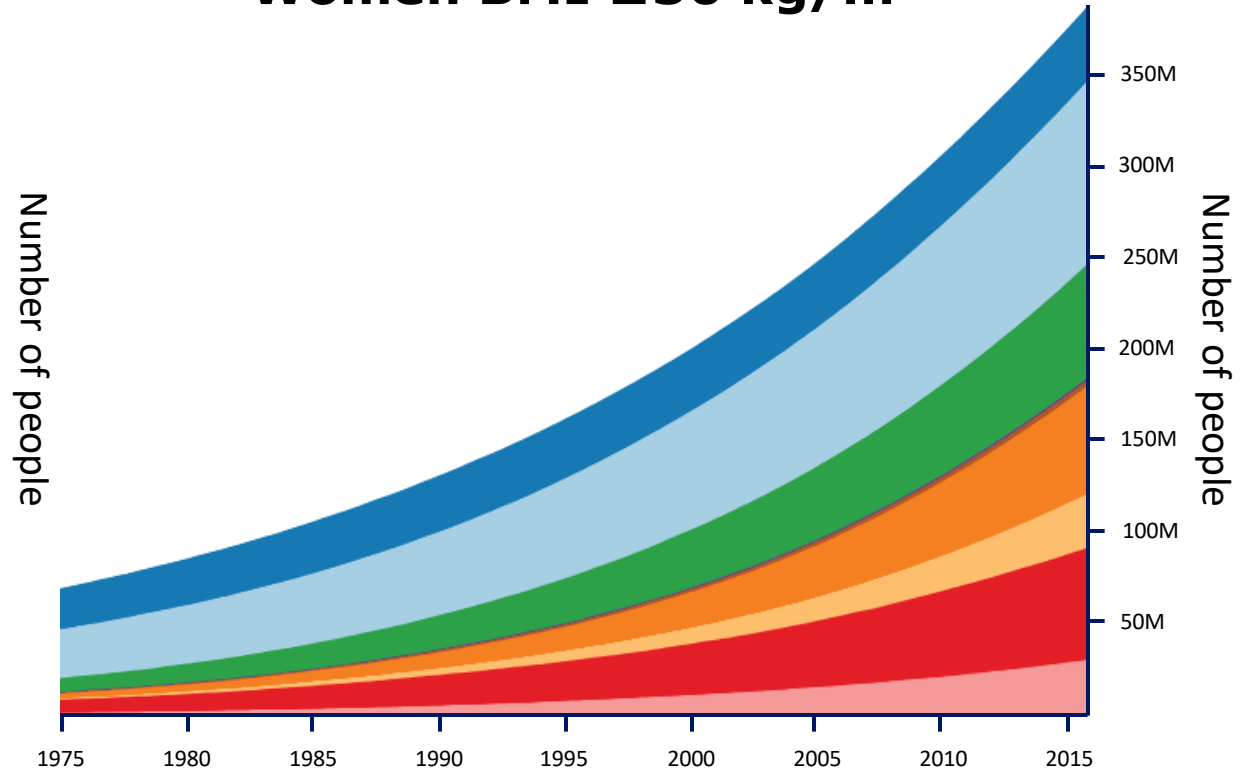
- Obesity is a **COMPLEX** and chronic disease of the subcortical areas of the brain.
- Treat the **PATIENT** and not only the disease
- There are no quick fixes - It's a **JOURNEY**
- Understand and communicate the desired **OUTCOMES**
- A **MULTI-DISCIPLINARY** approach is key
- Keep it **SIMPLE**
- The program should be supported by a *dynamic treatment schedule*
  
- Liraglutide 3.0 mg of once-daily subcutaneous liraglutide, as an adjunct to diet and exercise, was associated with clinically meaningful weight loss in individuals with obesity or overweight with comorbidities.
  
- Liraglutide 3.0 mg was also associated with improvements in glycaemia, cardiometabolic risk factors and health-related quality of life.

# Obesity rates worldwide are increasing

## Men BMI $\geq 30$ kg/m<sup>2</sup>



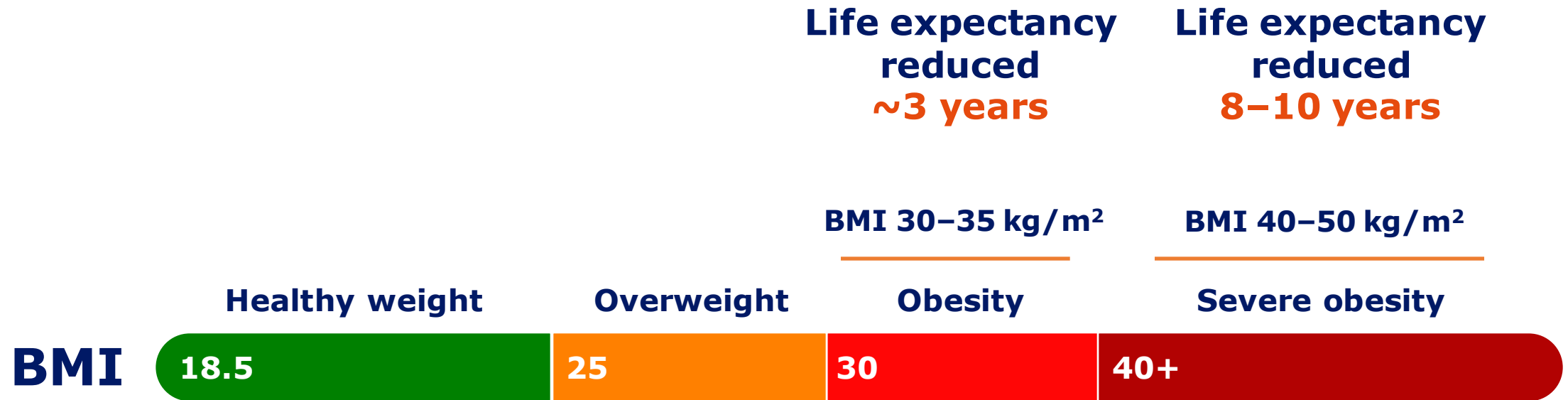
## Women BMI $\geq 30$ kg/m<sup>2</sup>



- Sub-Saharan Africa
- Central Asia, Middle East and North Africa
- South Asia
- East and South East Asia
- High-income Asia Pacific
- Oceania
- Latin America and Caribbean
- High-income English speaking countries and Western Europe
- Central and Eastern Europe

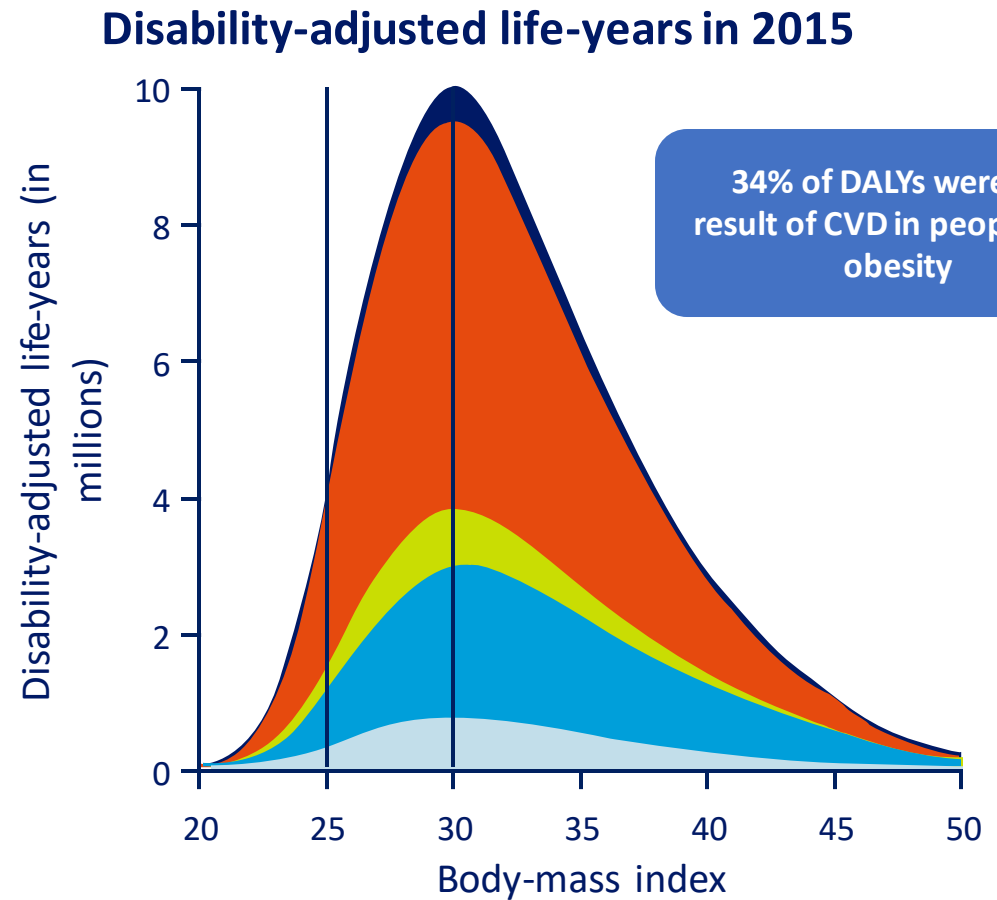
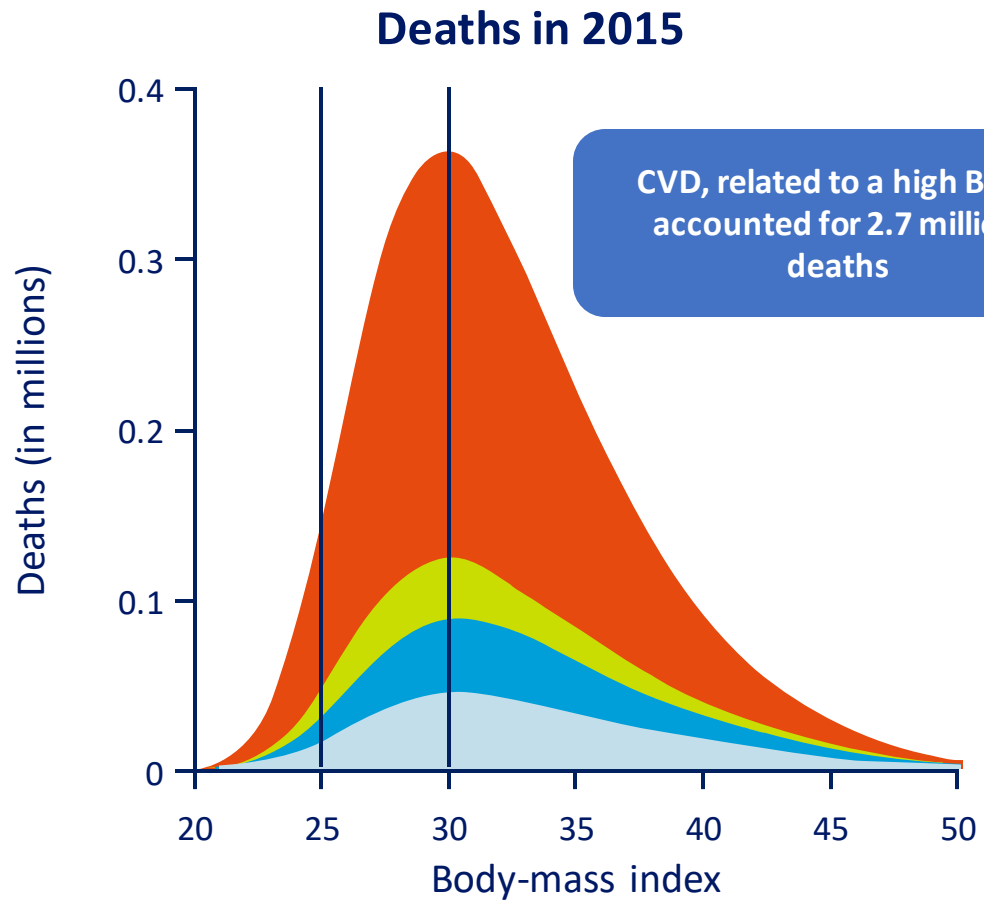
M, million

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



\*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

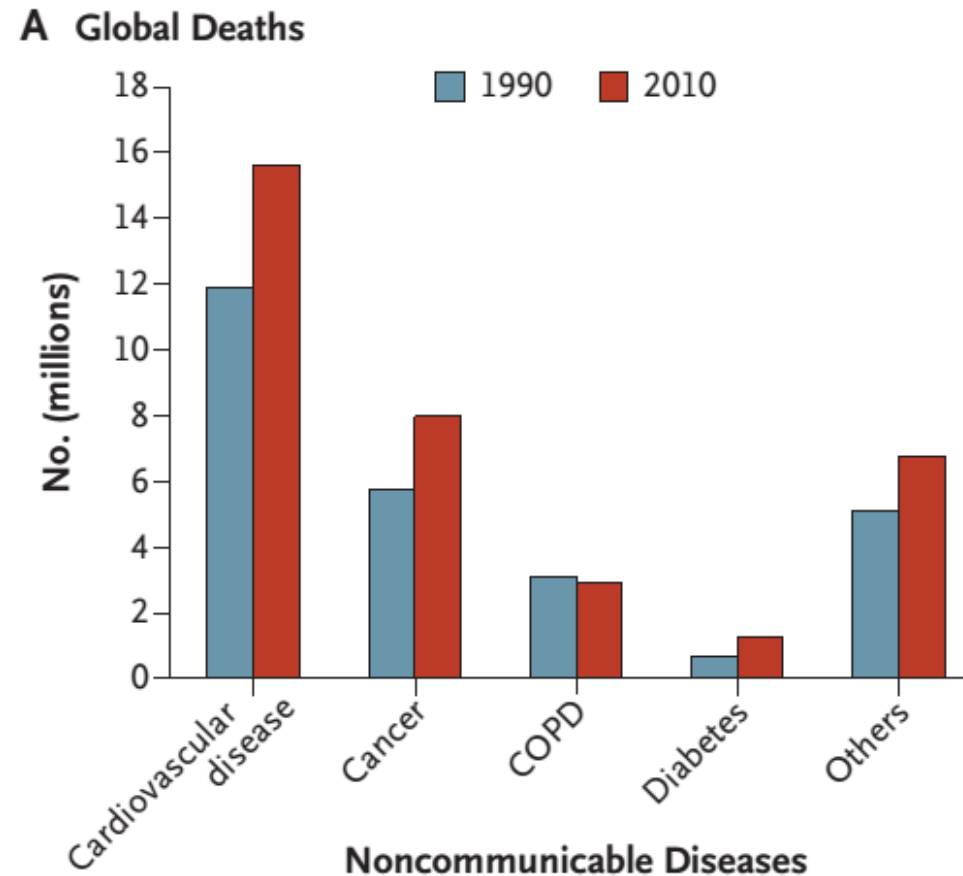
# Increasing BMI contributes to death and disability



■ Musculoskeletal disorders   ■ Cardiovascular diseases   ■ Cancers   ■ Chronic kidney disease   ■ Diabetes mellitus

CVD, cardiovascular disease, DALYs, disability-adjusted life-years

Largest fraction of deaths is due to cardiovascular diseases, especially atherosclerosis.



# Endothelial dysfunction drives atherosclerotic progression

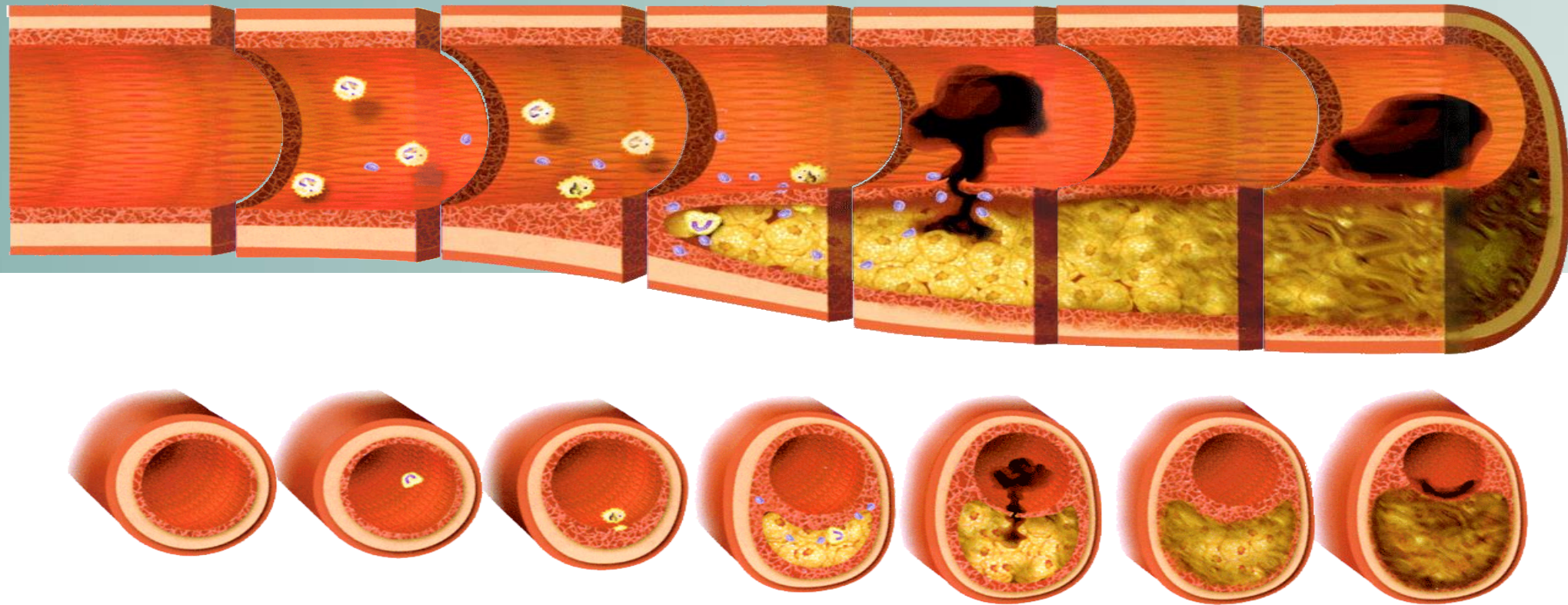
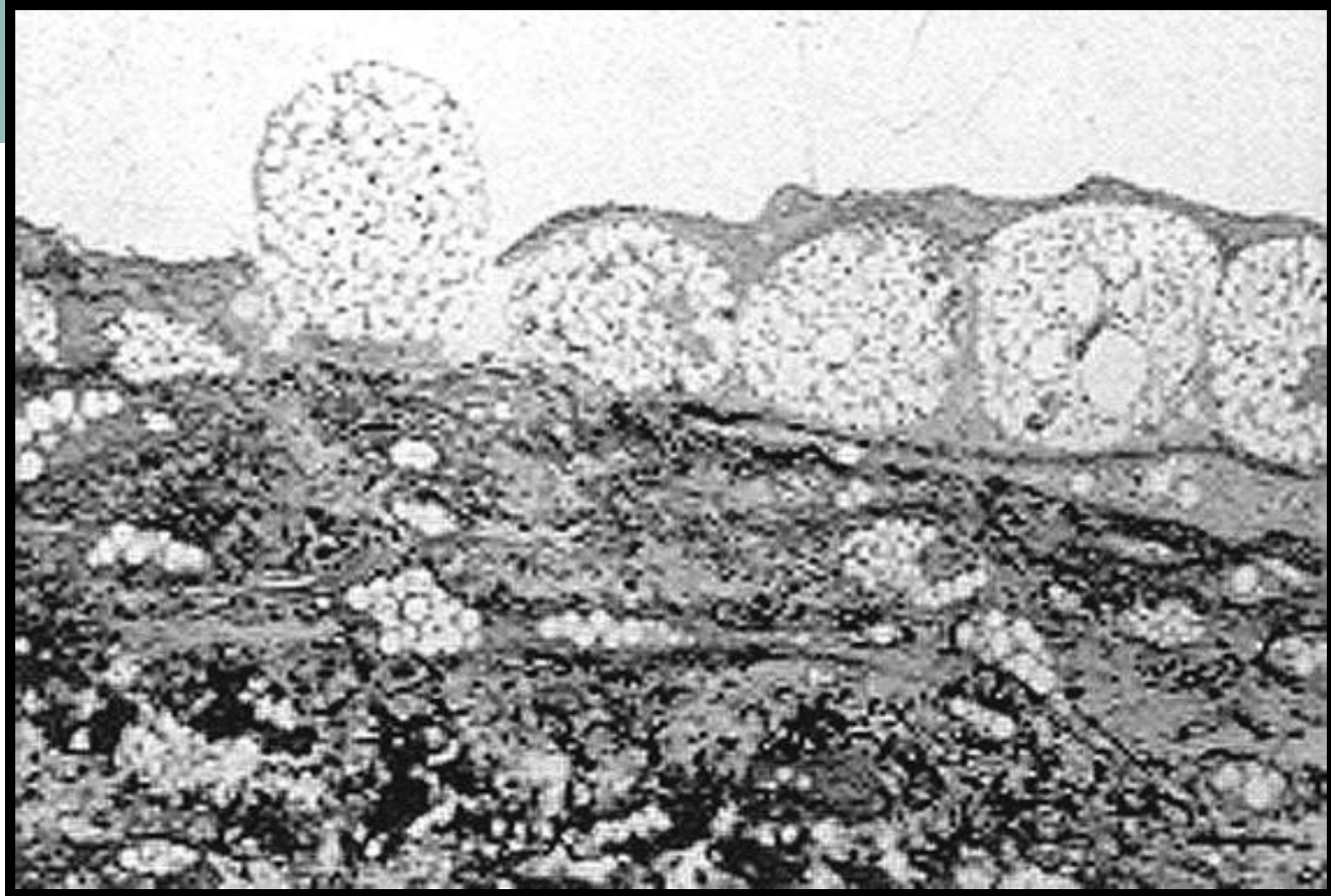


Figure adapted from Libby. *Circulation* 2001;104:365–72.  
Zeadin et al. *Can J Diabetes* 2013;37:345e350.





Cardiometabolic medicine: a new subspecialty?

# Cardiometabolic Medicine: A Call for a New Subspecialty Training Track in Internal Medicine

**Cardiometabolic medicine: time to recognize a new clinical specialty?**

Andrew J. Krentz<sup>a</sup> and Stephan Jacob<sup>b</sup>

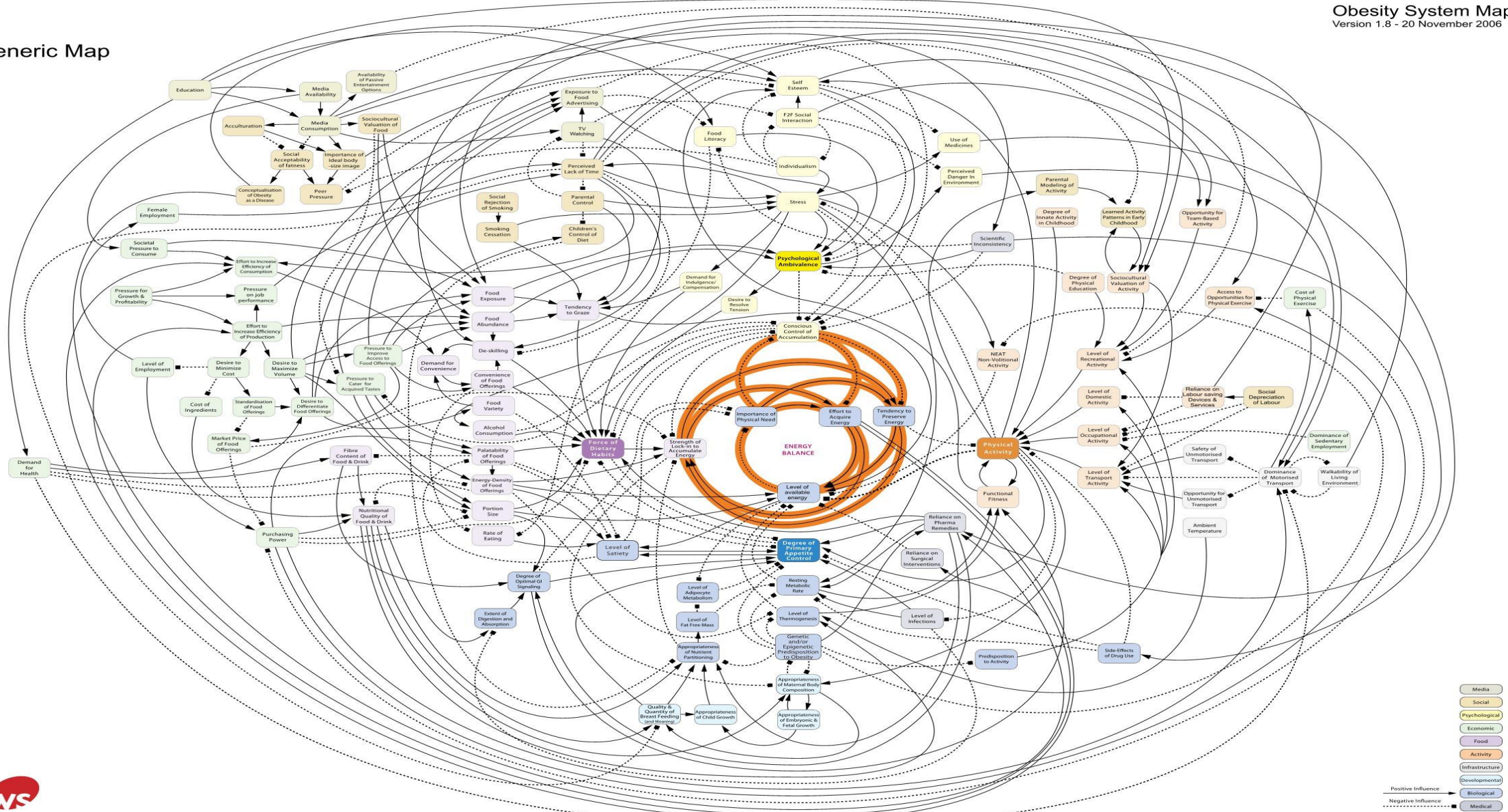


Cardiovascular  
Endocrinology  
& Metabolism



Map 0

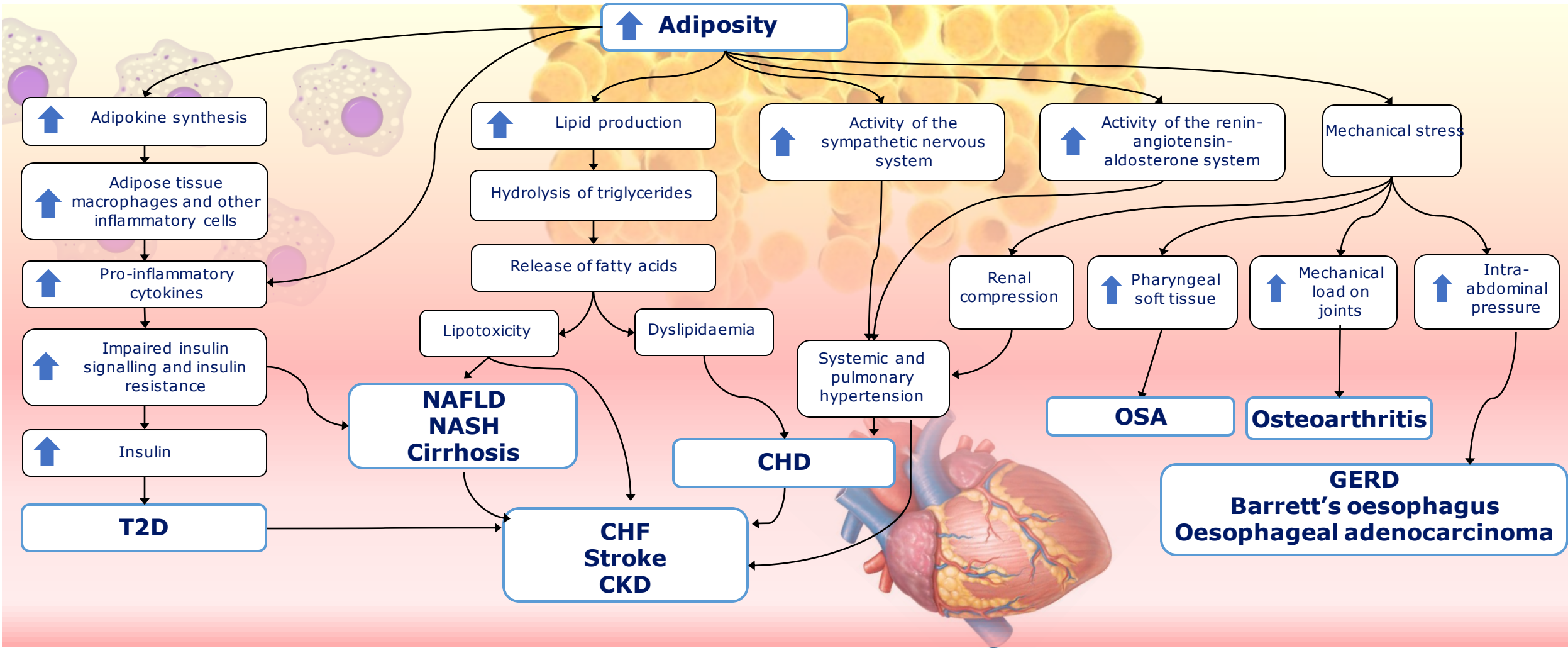
Full Generic Map



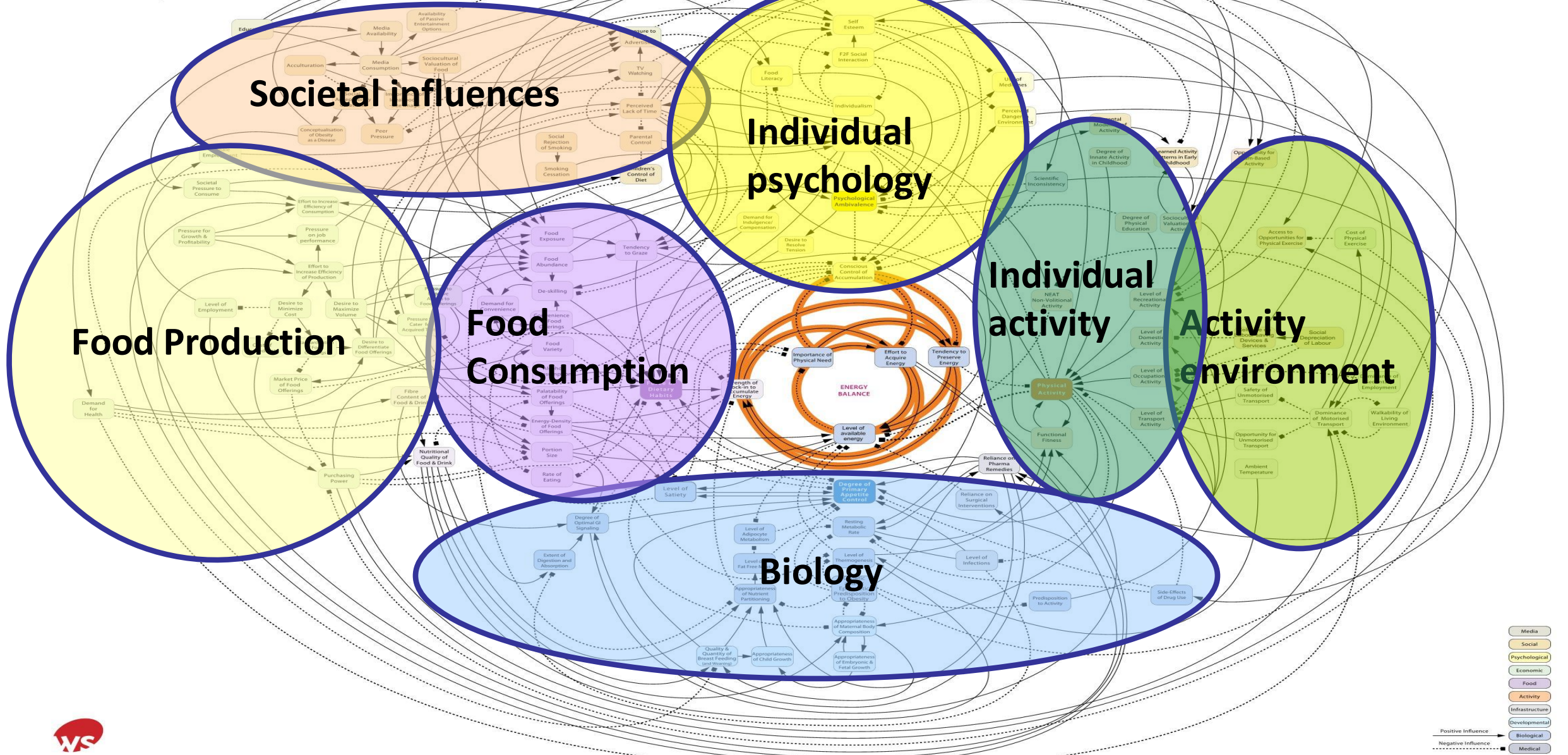
Positive Influence →  
Negative Influence - - - - -

- Media
- Social
- Psychological
- Economic
- Food
- Activity
- Infrastructure
- Developmental
- Biological
- Medical

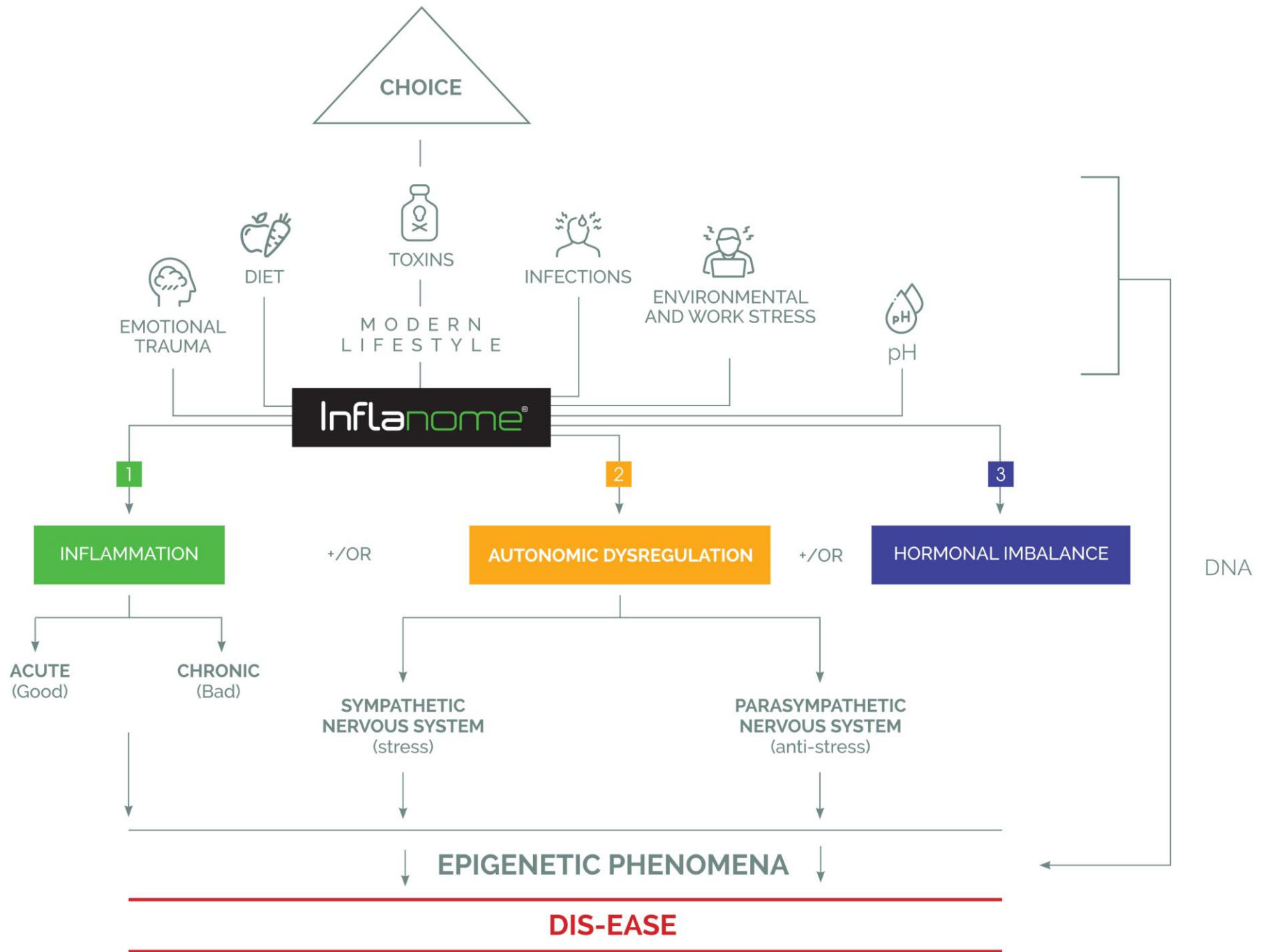
# Excess adiposity leads to major risk factors and common chronic diseases



Full Generic Map

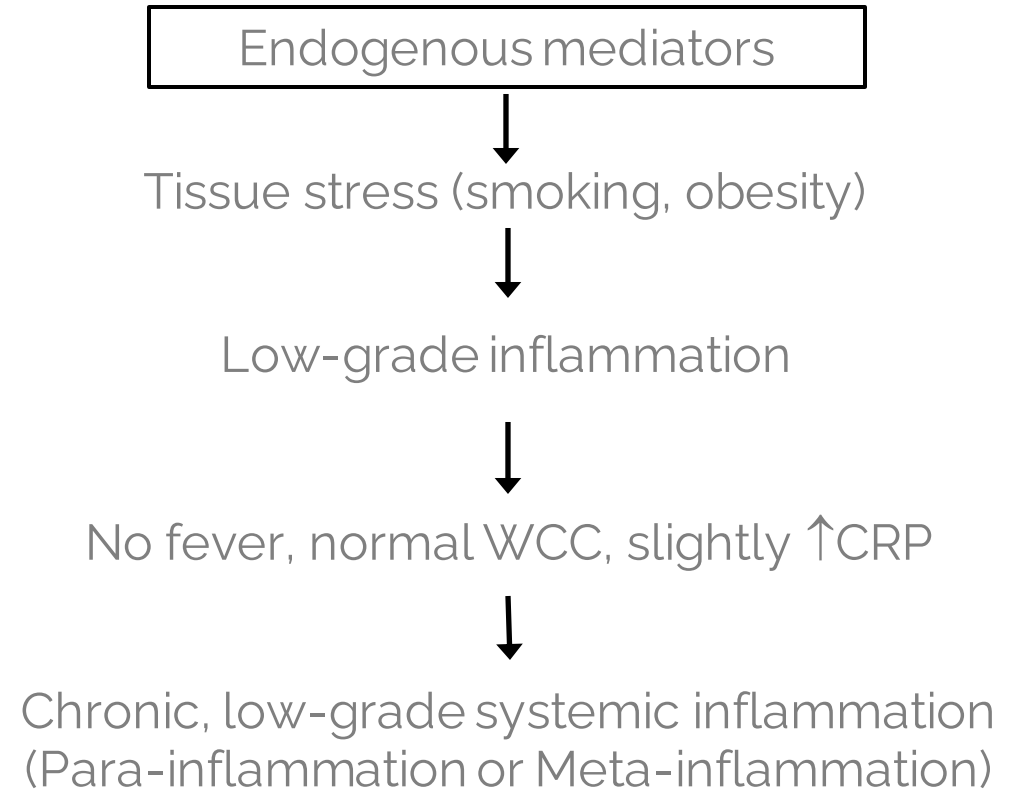
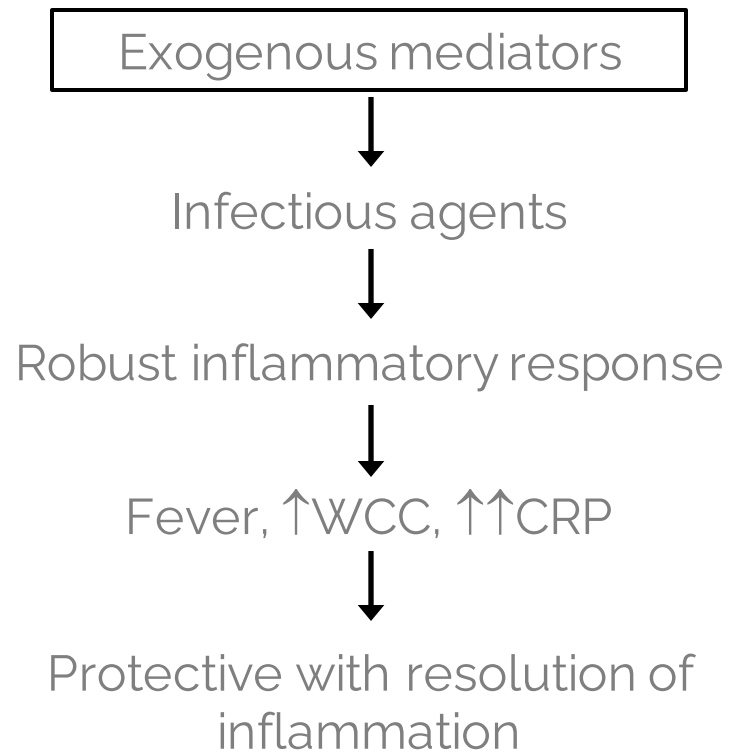


Inflanome<sup>®</sup>





# To put inflammation in perspective: Systemic inflammation has 2 forms



## Causes

- High Homocysteine. ( Low B12/Folate/B6)
- Low Cortisol
- High Omega 6 and Low Omega 3 rich diets
- Micronutrient Deficiencies
- Toxins
- Insulin Resistance / Diabetes
- Gum Disease
- Abnormal gut Microbiome
- Autonomic Dysfunction
- Chronic Infections
- Auto-immune Diseases

## 3 - Detection and monitoring of inflammation

### 2 Components

- Systemic inflammation
- Localized inflammation (atherosclerotic plaques)

#### 1. Systemic Inflammation

- Numerous potential biomarkers of systemic inflammation.

#### 2. Localized Inflammation

- PET CT and MRI
- Intravascular ultrasound

# Biomarkers of Inflammation

- hsCRP
- Serum amyloid A
- Cytokines
  - IL-6
  - IL-18
  - MCP-1
  - TNF $\alpha$
- Adhesion molecules
  - Vascular cell adhesion molecule-1 (VCAM-1)
  - Intercellular adhesion molecule-1 (ICAM-1)
  - E-selection
  - P-selection

## Biomarkers (cont.)

- Pentraxin-3 (acute phase reactant)
- Fibrinogen
- Apolipoprotein-associated phospholipase A2
- Soluble CD40 ligand

Heart, Lung and Circulation 2019;28:667

Most promising to date: **high sensitivity CRP (hsCRP)**

## High sensitivity CRP

- Assay measures CRP in the range 0.3 – 3 mg/L very accurately.
- Measure 2 weeks apart. Take average.
- $\geq 2 - 3$  mg/L increases risk.
- May be useful to monitor systemic inflammation and can be used to detect ongoing low-grade systemic inflammation.
- If hsCRP  $> 10$  mg/L suggests infection.

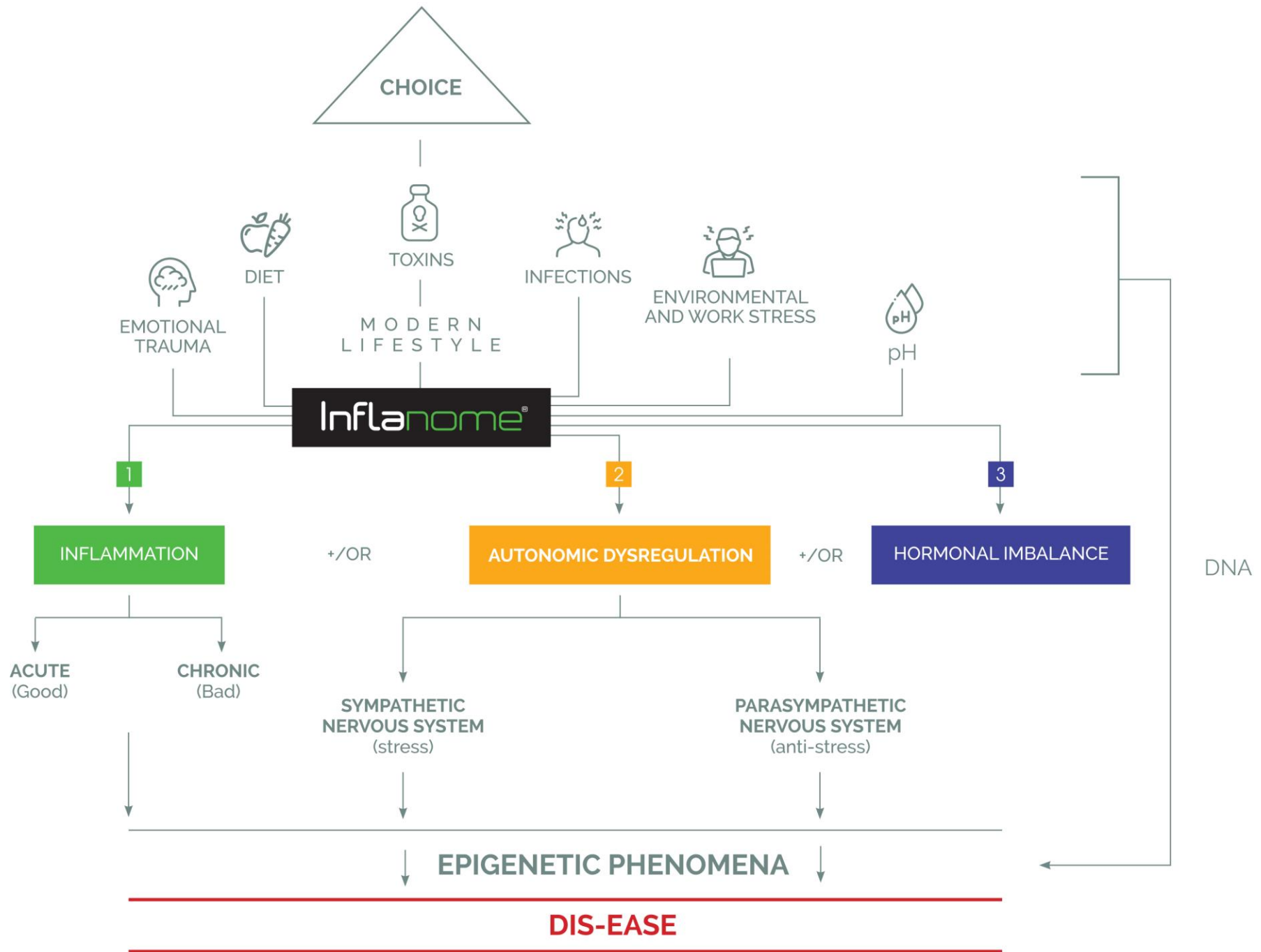
## Neutrophil:Lymphocyte ratio (NLR)

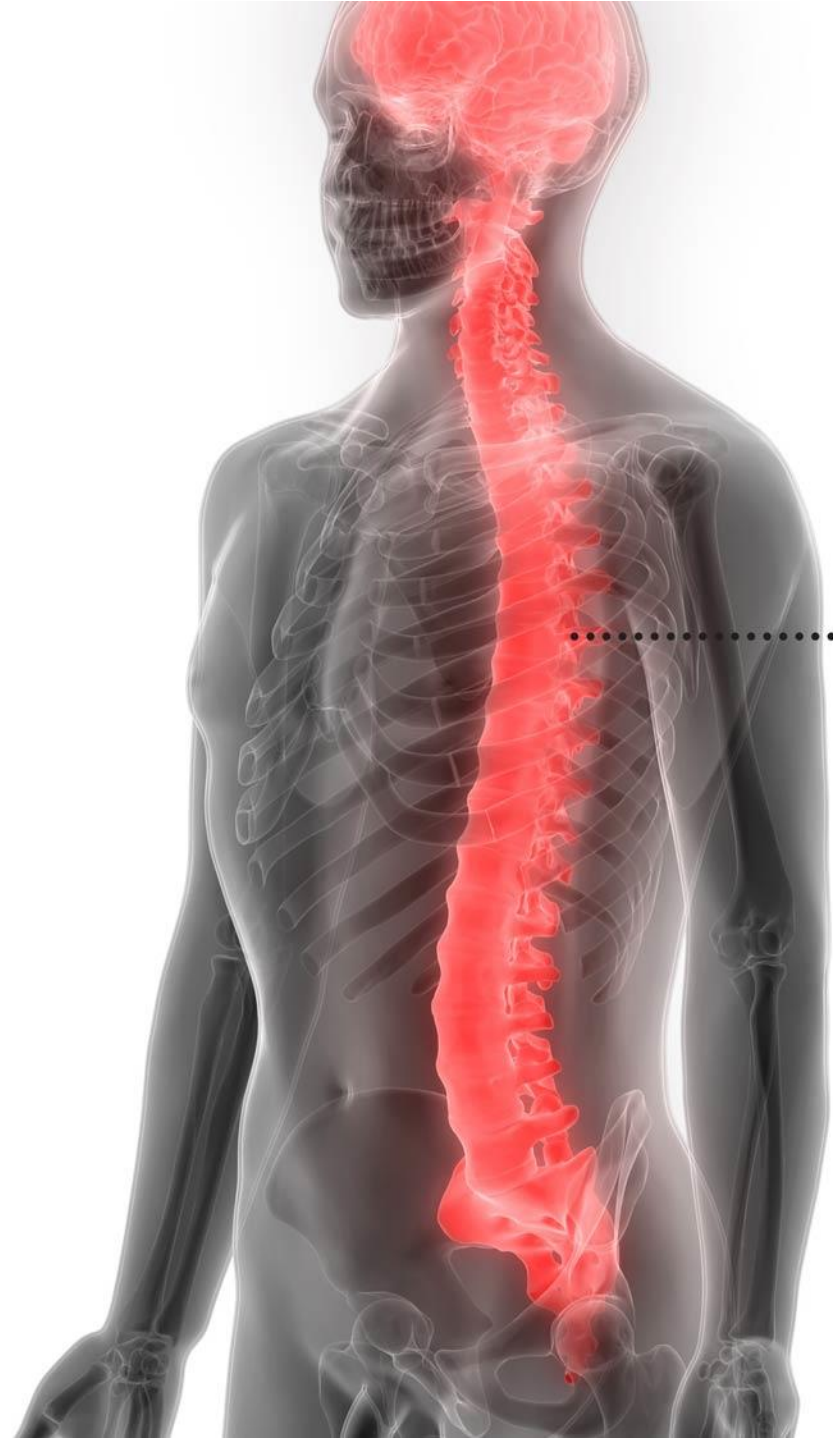
- The NLR may be a useful indicator of risk.
- Widely available.
- Normal NLR = 1.76 (0.83 – 3.92). Sci Rep 2018;12:10566
- Primary prevention: NLR > 4.5 predicts future cardiovascular events. Int J Cardiol 2014;171:390
  
- Secondary prevention
  - NLR increases in patients with acute MI. Med Arch 2017;71:312
  - NLR predicts all-cause mortality in patients with heart failure. Clin Chim Acta 2018;485:44

# Concept of “Residual Cholesterol Risk” and “Residual Inflammatory Risk”

- “Residual cholesterol risk” is present if the target LDL not reached
- “Residual inflammatory risk” is the risk of cardiovascular events or death due primarily to systemic inflammation (hsCRP  $\geq$  2mg/L).
- About 60% of the general population may have a hsCRP concentration 2mg/L and 48%  $\geq$  3mg/L. The FASEB J 2017; 31: 1787
- 30% of the US population have a hsCRP concentration  $\geq$  3 mg/L.
- Some patients may have both cholesterol and inflammatory risk.
- Therefore, dual targets, namely LDL cholesterol and inflammation.







# THE CENTRAL NERVOUS SYSTEM

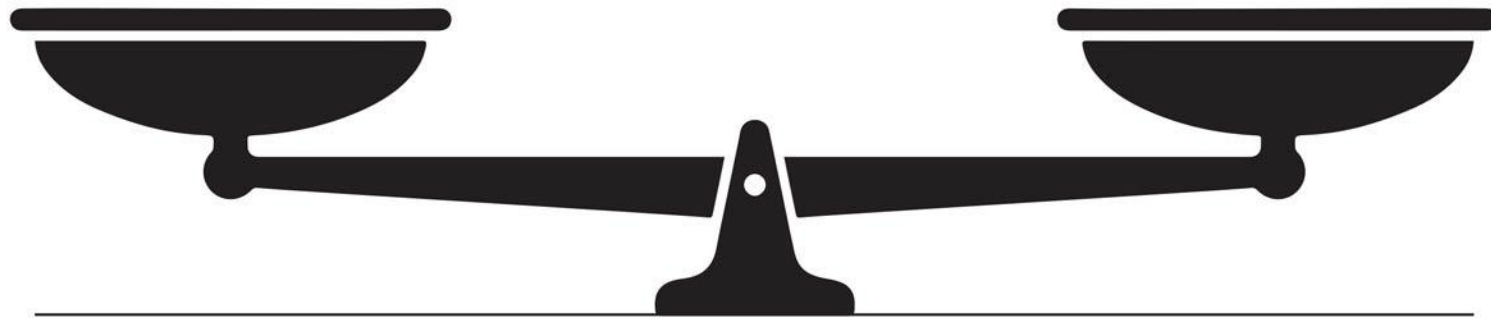
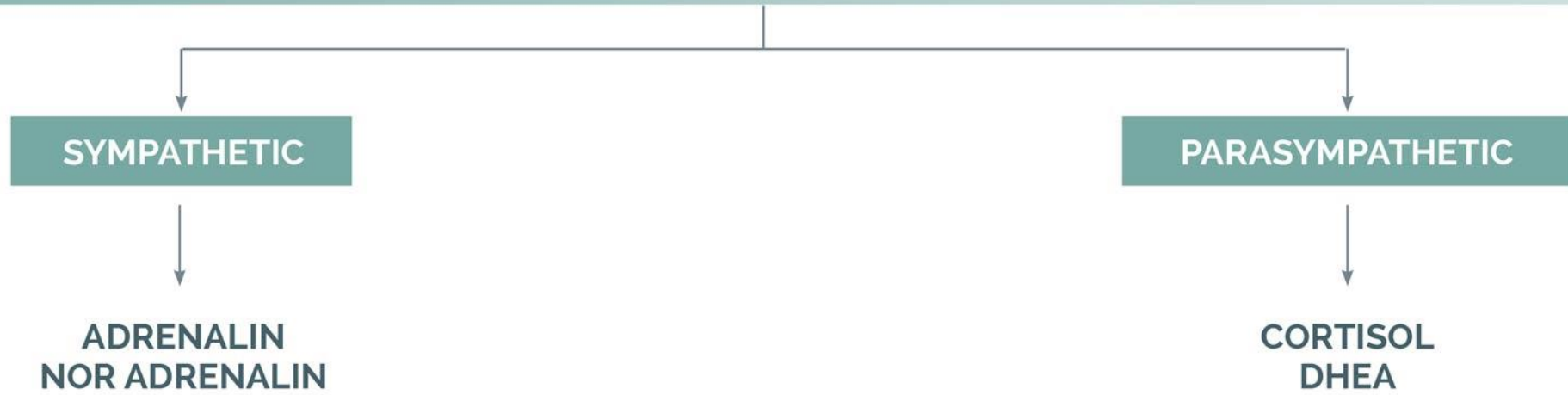


## PERIPHERAL NERVOUS SYSTEM

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- PERIPHERAL NERVOUS SYSTEM
- AUTONOMIC NERVOUS SYSTEM

# AUTONOMIC NERVOUS SYSTEM



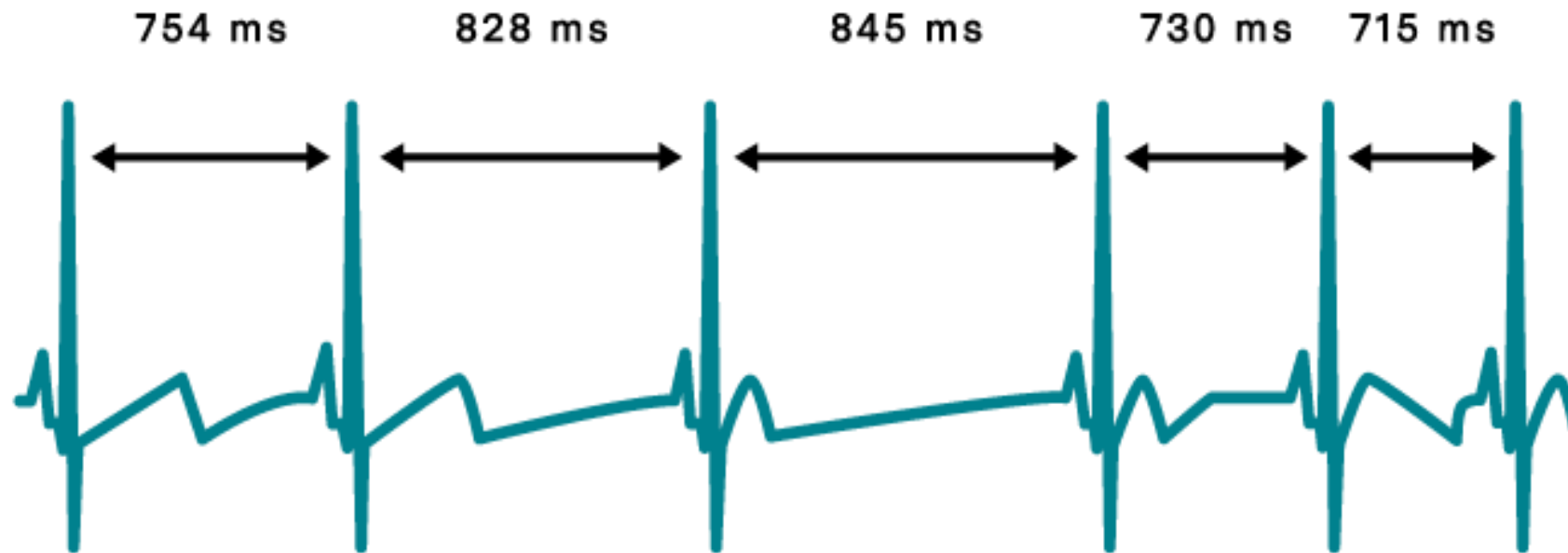
## DIAGNOSING SYMPATHETIC OVERDRIVE

**TRADITIONALLY = ↑ HEART RATE + CLASSIC SYMPTOMS**

**HEART RATE VARIABILITY**

- Baevsky Theory
- 5 Minute Test
- Non Invasive

# Heart Rate Variability



- High HRV is associated with rest-and-digest, general fitness, and good recovery
- Low HRV is associated with fight-or-flight, stress, illness, or overtraining

Profile

Measure

Analysis

2

7

3

5

6

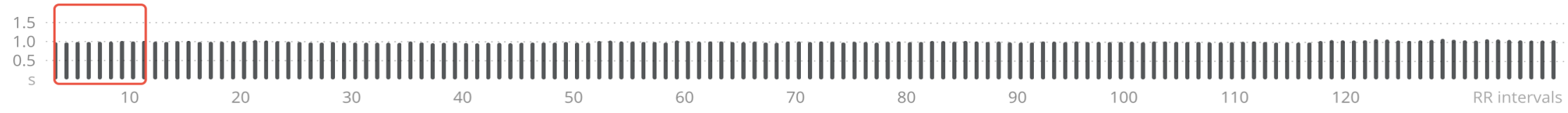
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7

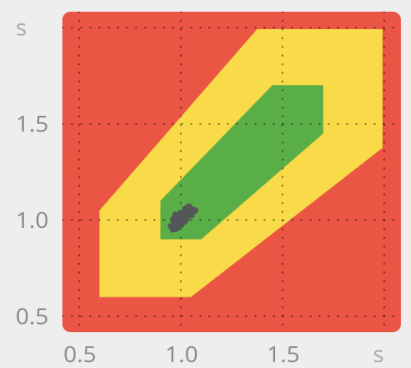
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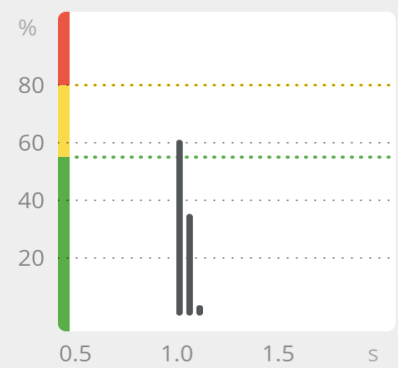
### Rhythmogram



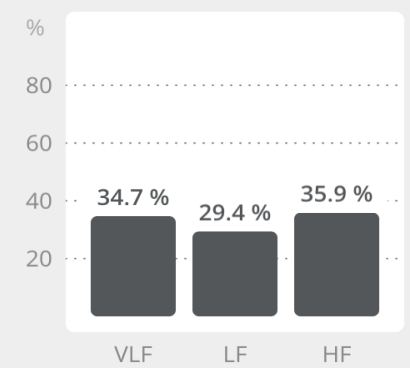
### Scattergram



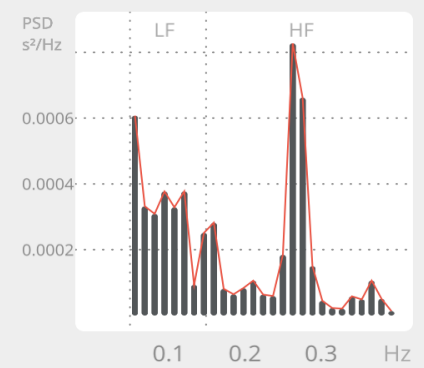
### Histogram



### Spectrum bars



### Spectrogram

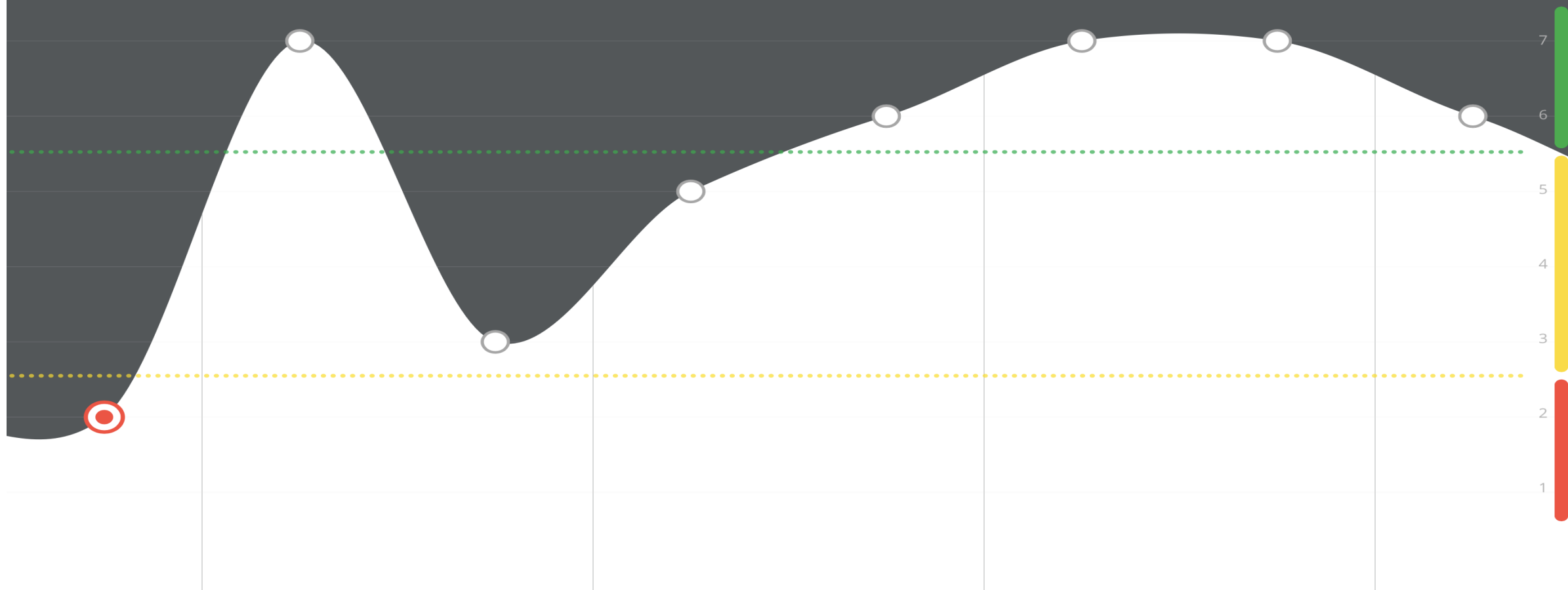




Profile

Measure

Analysis



System Readiness 2

Recovery pattern 0.09

Adaptation reserves 3

Resting heart rate 61

Stress 2

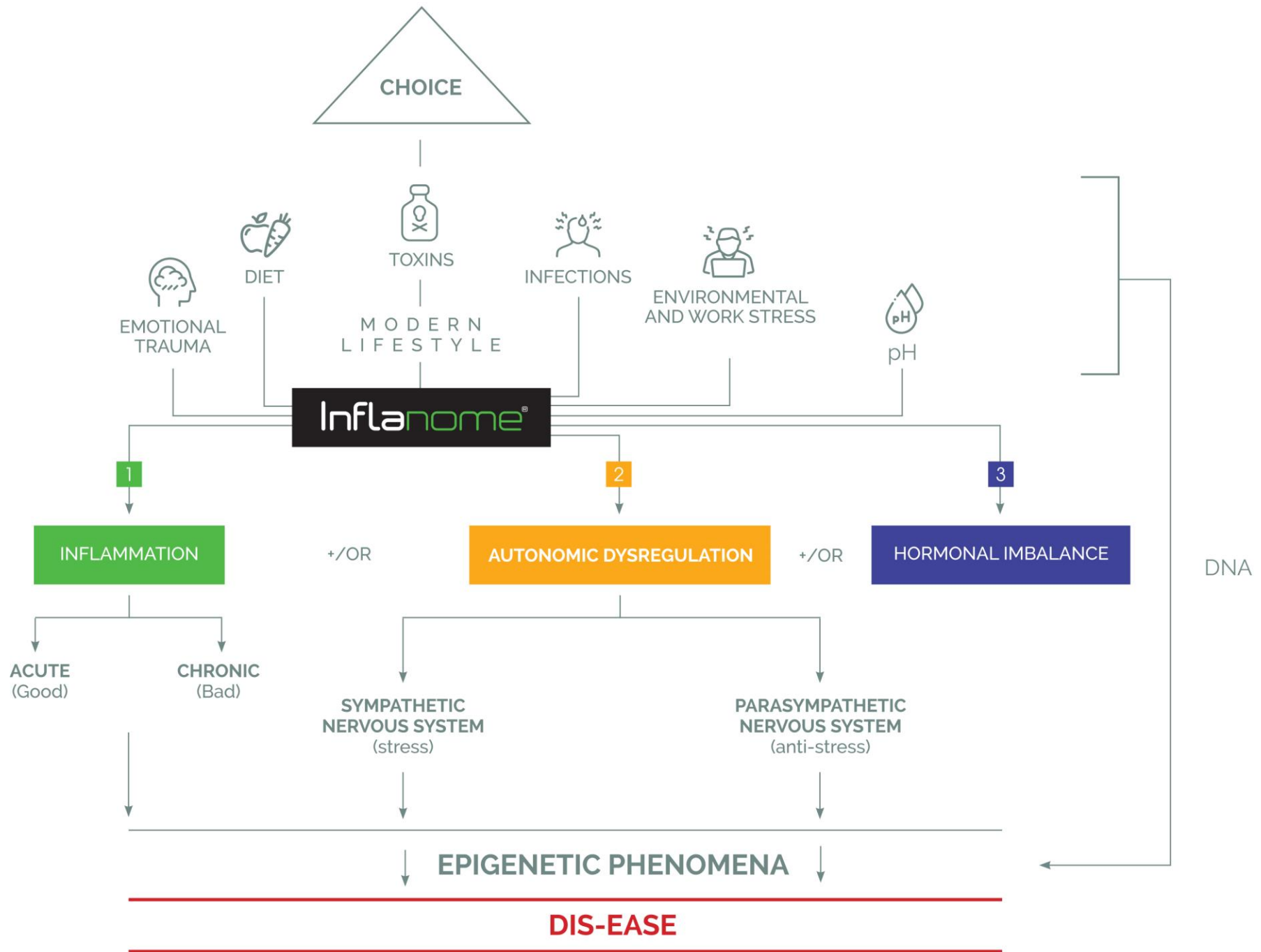
Autonomic balance

PSNS

SNS







# Globesity

# Obesity is recognised as a disease and a health issue

**WOF**

“WOF takes the position that obesity is a chronic, relapsing, progressive disease process and emphasizes the need for immediate action for prevention and control of this global epidemic”

World Obesity Federation<sup>1</sup>

**AMA**

“AMA recognizes obesity and overweight as a chronic medical condition (de facto disease state) and urgent public health problem...and work towards the recognition of obesity intervention as an essential medical service...”

American Medical Association<sup>2</sup>

**RCP UK**

“It is important to the health of the nation that we remove the stigma associated with obesity. It is not a lifestyle choice caused by individual greed but a disease caused by health inequalities, genetic influences and social factors..”

Royal College of Physicians UK<sup>5</sup>

**OC**

“Obesity is a progressive chronic disease, similar to diabetes or high blood pressure, which is characterized by abnormal or excessive fat accumulation that may impair health”

Obesity Canada<sup>3</sup>

**EASO**

“A progressive disease, impacting severely on individuals and society alike, it is widely acknowledged that obesity is the gateway to many other disease areas...”

European Association for the Study of Obesity<sup>4</sup>

**AOASO**

“We hereby propose a concept for international recognition of a pathological state (obesity disease) in which a person suffers health problems caused by or related to obesity thus making weight loss clinically desirable and requiring treatment as a disease entity”

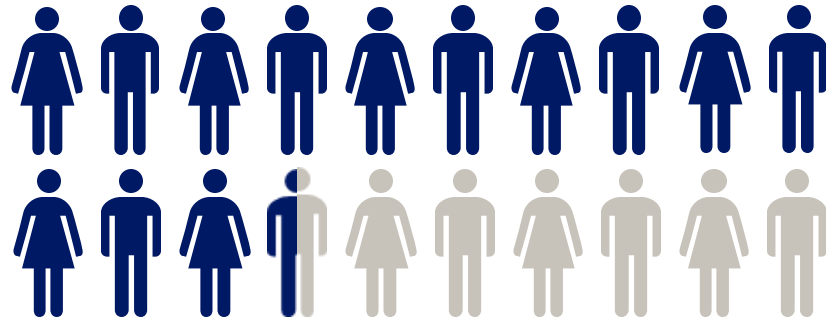
Asia Oceania Association for the Study of Obesity<sup>6</sup>

# Obesity disease recognition

Results from the ACTION IO study

**68%** of PwO

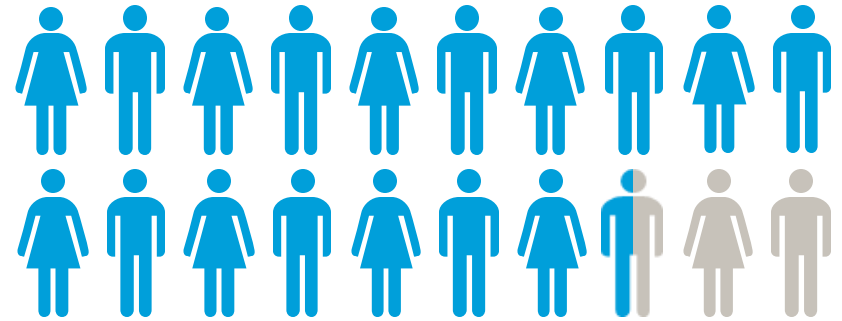
recognise obesity as a disease



 All Global PwO (n=14,480)\*

**88%** of HCPs

recognise obesity as a disease

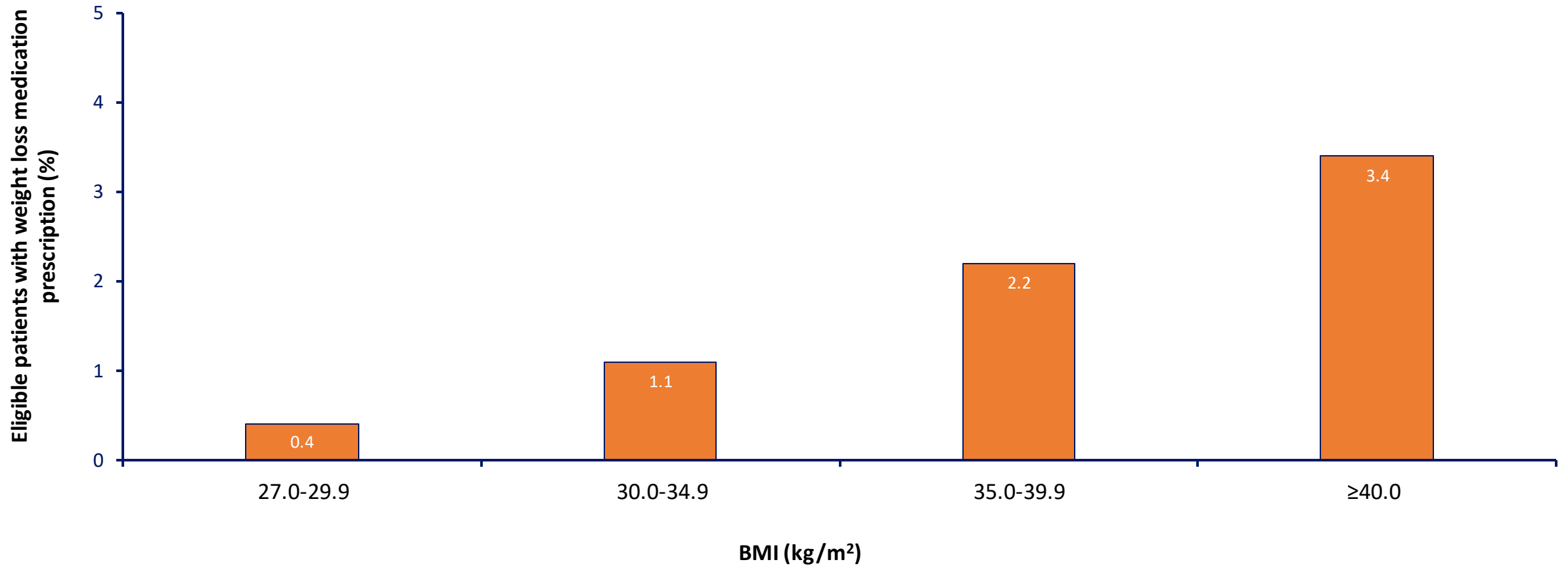


 All Global HCPs (n=2,785)

\*N-size is less than total due to respondents selecting 'not sure' for attributes.  
HCP, healthcare professional; PwO, people with obesity.

# Weight loss medications are rarely prescribed for eligible adults with obesity

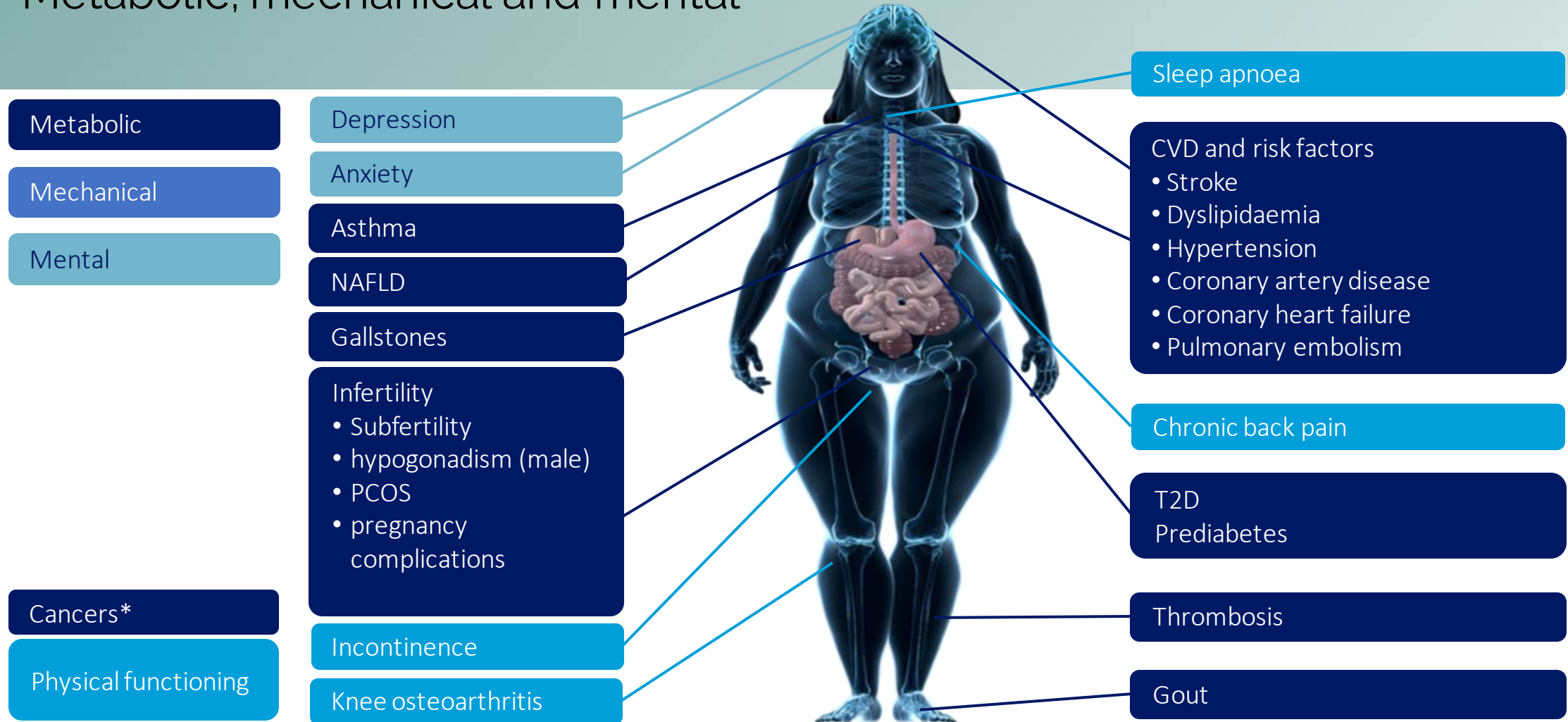
Data collected from adults across eight health care organizations (N=2,248,407)



BMI, body mass index

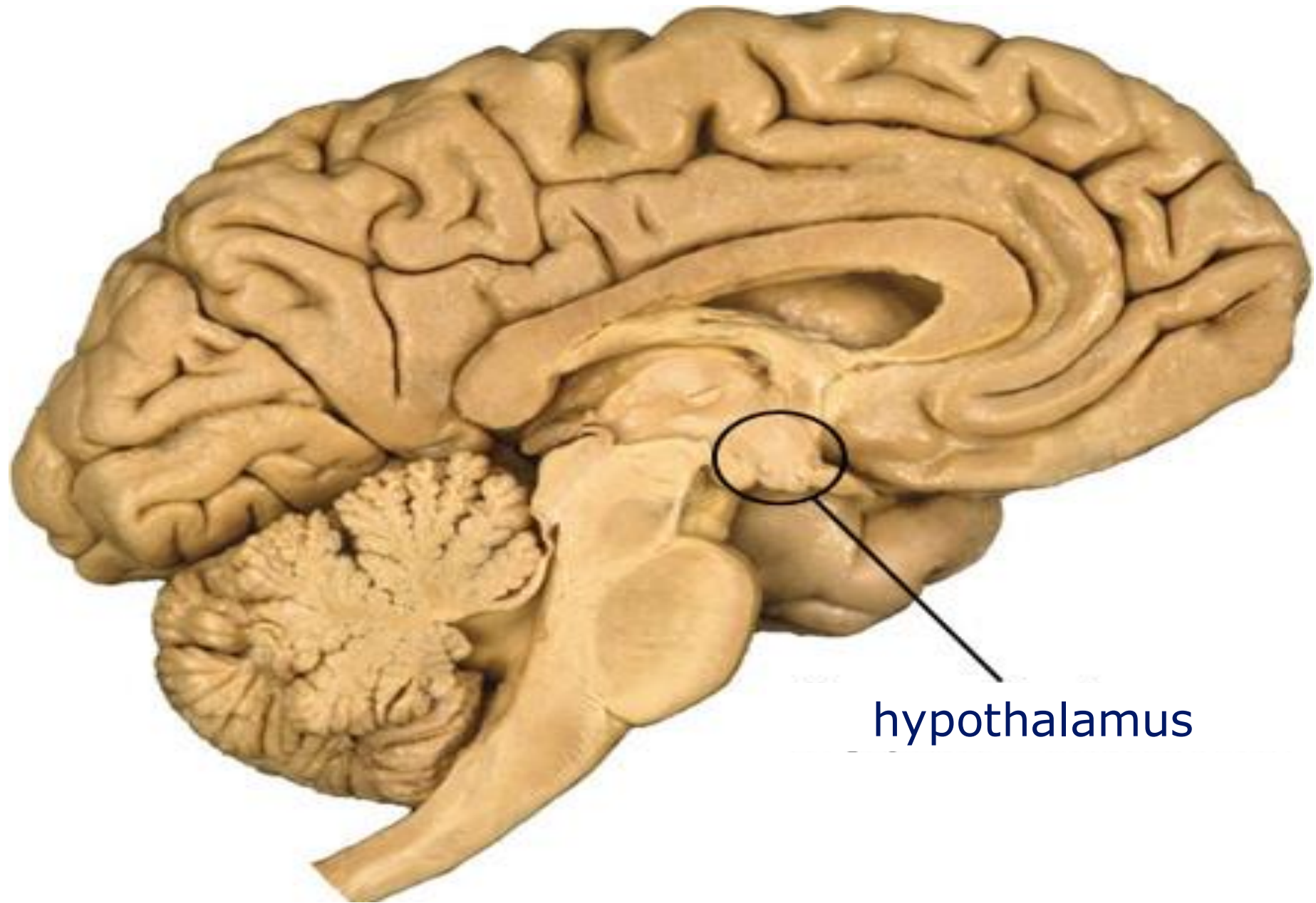
# Obesity is associated with multiple comorbidities and complications

## Metabolic, mechanical and mental



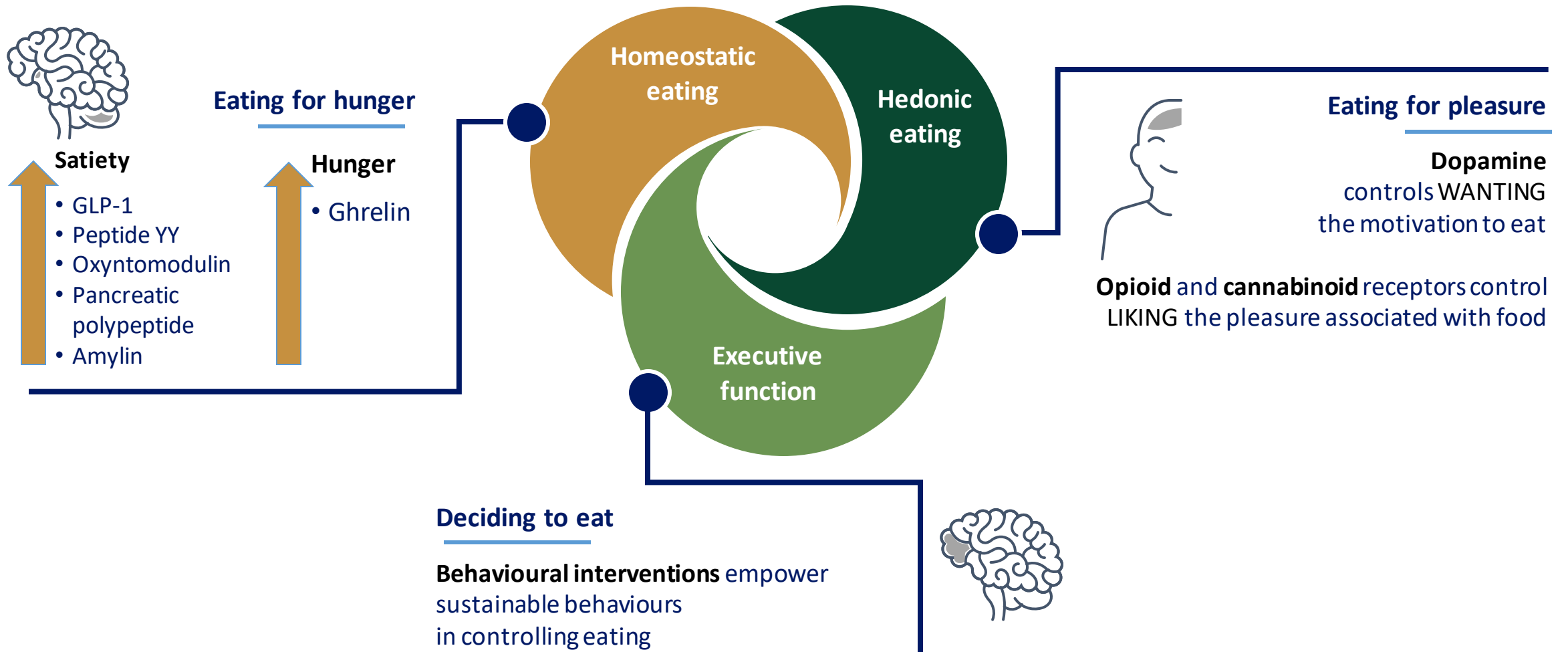
CVD, cardiovascular disease; NAFLD, non-alcoholic fatty liver disease \*Including breast, colorectal, endometrial, oesophageal, kidney, ovarian, pancreatic and prostate; T2D, type 2 diabetes

Adapted from Sharma AM. *Obes Rev.* 2010;11:808-9; Guh et al. *BMC Public Health* 2009;9:88; Luppino et al. *Arch Gen Psychiatry* 2010;67:220-9; Simon et al. *Arch Gen Psychiatry* 2006;63:824-30; Church et al. *Gastroenterology* 2006;130:2023-30; Li et al. *Prev Med* 2010;51:18-23; Hosler. *Prev Chronic Dis* 2009;6:A48



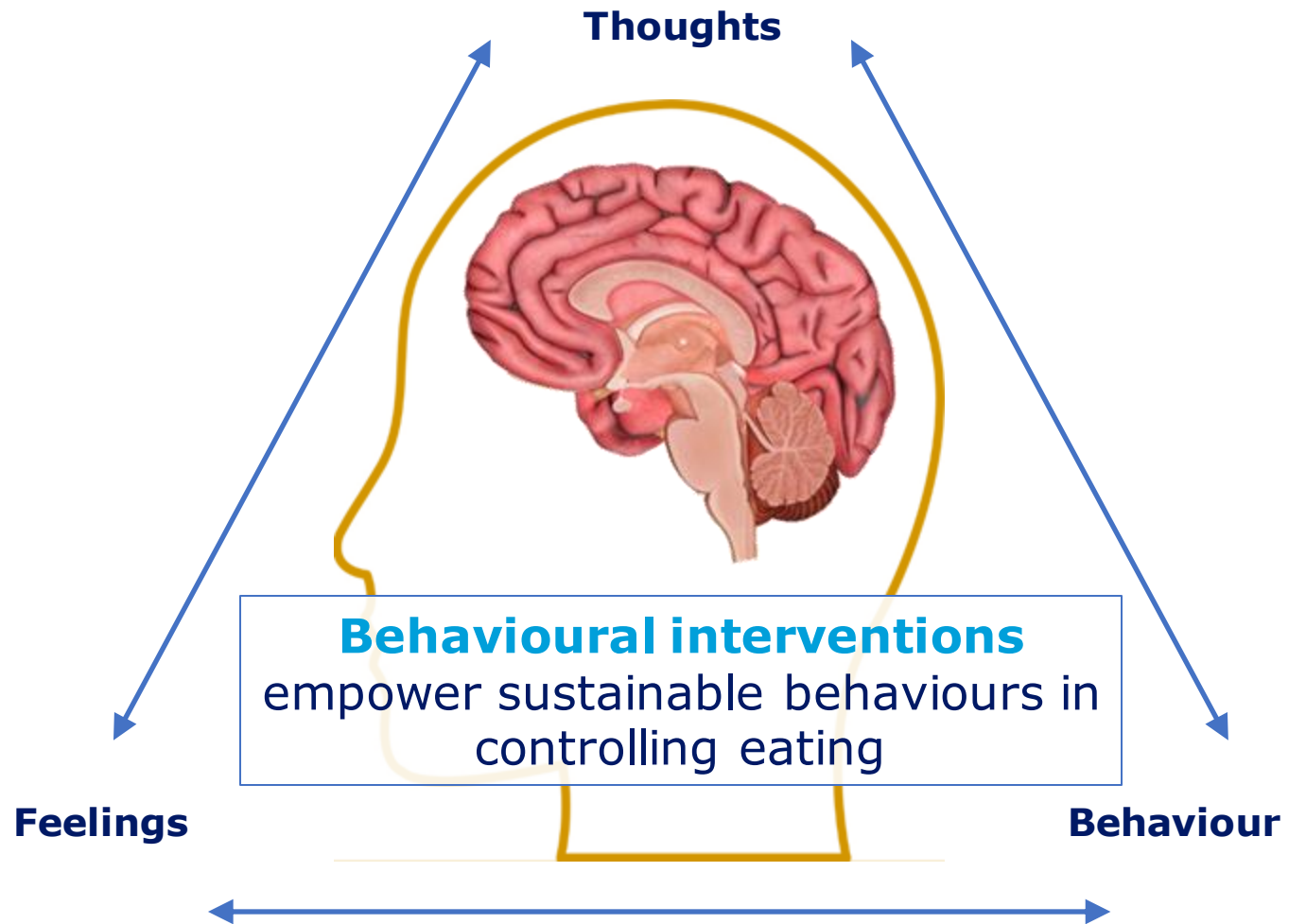
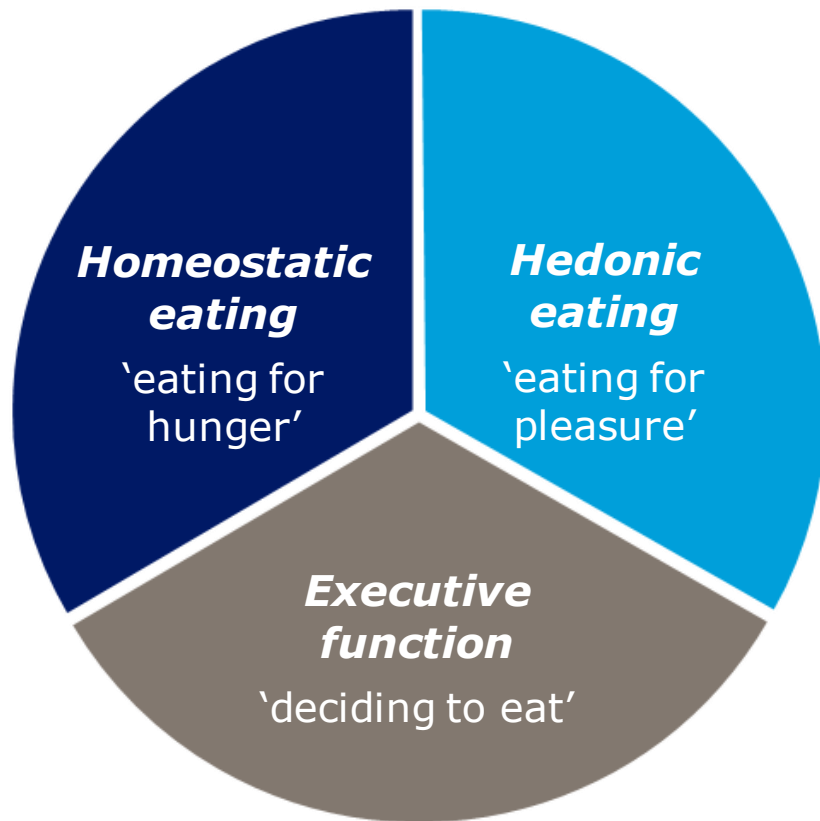
hypothalamus

# The Role of the Brain in Regulating Eating Behaviour





# The role of the brain in controlling eating



HOW IS OBESITY DIAGNOSED?

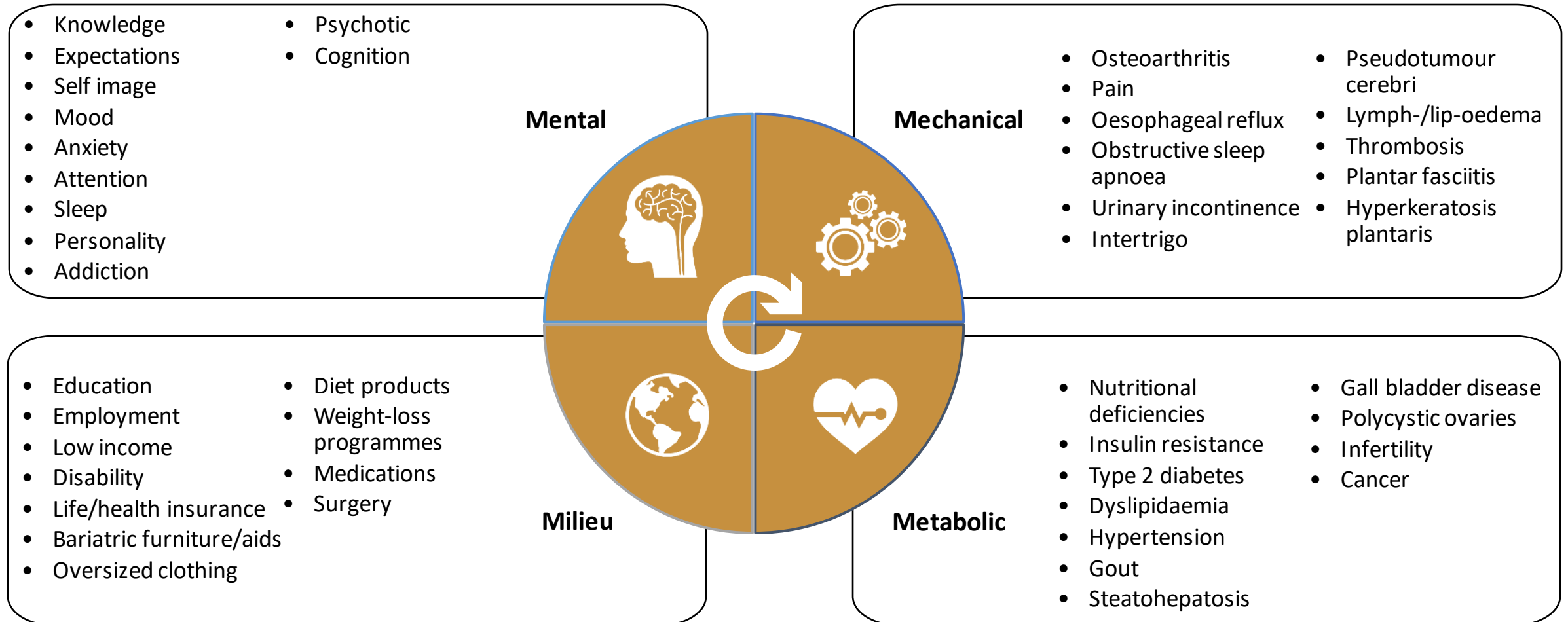


## Key Goals of Obesity Assessment

- Why does this patient have obesity?
- How does obesity affect this patient?
- What are the potential barriers to obesity management?

**Mental health status can play an important role in all of these aspects!**

# The Four Ms of Obesity Assessment



# Definition and Classification of Obesity

- 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

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

Classification	BMI (kg/m <sup>2</sup> )		
	International classification <sup>1</sup>	Asian population <sup>2,3</sup>	Japanese guidelines <sup>4</sup>
Underweight	<18.5		<18.5
Normal range	≥18.5 - <25	≥18 - <23	≥18.5 - <25
Pre-obesity*	≥25 - <30	≥23 - <25	
Obesity	≥30	>25	
Obesity class I	≥30 - <35		≥25 - <30
Obesity class II	≥35 - <40		≥30 - <35
Obesity class III	≥40		≥35 - <40
Obesity class IV			≥40

\*Previously described as overweight  
BMI, body mass index

# Waist Circumference as a Measure of Obesity

- Waist circumference helps to screen health risks of obesity and overweight
- This risk goes up with a waist size that is greater than 35 inches for women or greater than 40 inches for men

Classification	BMI (kg/m <sup>2</sup> )	Disease risk relative to normal weight	
		Men ≤40 in (102 cm) Women ≤35 in (88 cm)	Men >40 in (102 cm) Women > 5 in (88 cm)
Pre-obesity*	≥25 and <30	Increased	High
Obesity			
Obesity class I	≥30 and <35	High	Very high
Obesity class II	≥35 and <40	Very high	Very high
Obesity class III	≥40	Extremely high	Extremely high

\* previously described as overweight according to WHO nomenclature  
BMI, body mass index

## SIMPLIFIED OBESITY PROFILE

Insulin

Body % Fat

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Testosterone : Oestrogen (M)

Oestrogen : Progesterone (F)

Testosterone

Body % Muscle

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Thyroid

Metabolic Rate

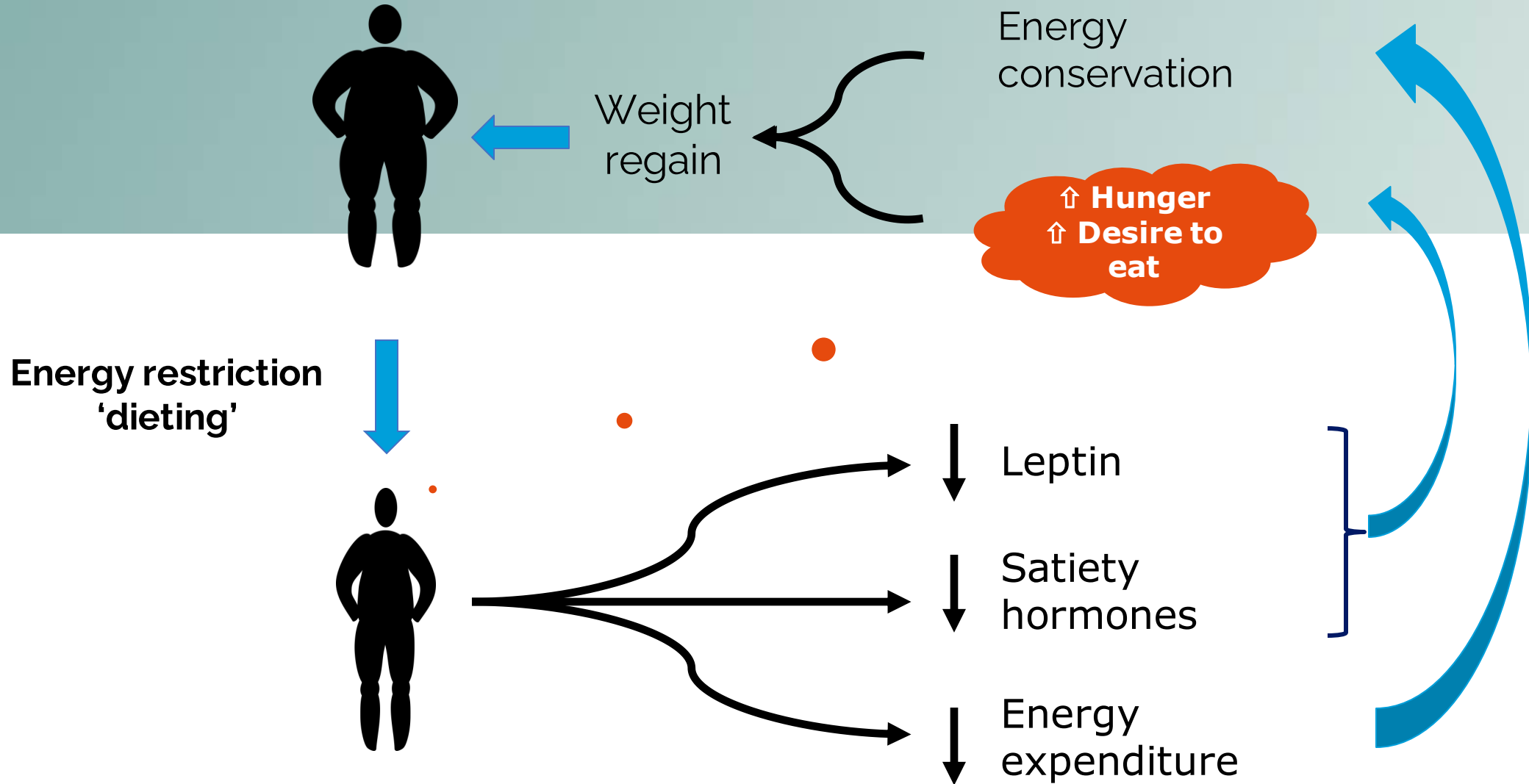
# TREATMENT STRATEGIES

## REGULATION OF APPETITE AND ENERGY INTAKE



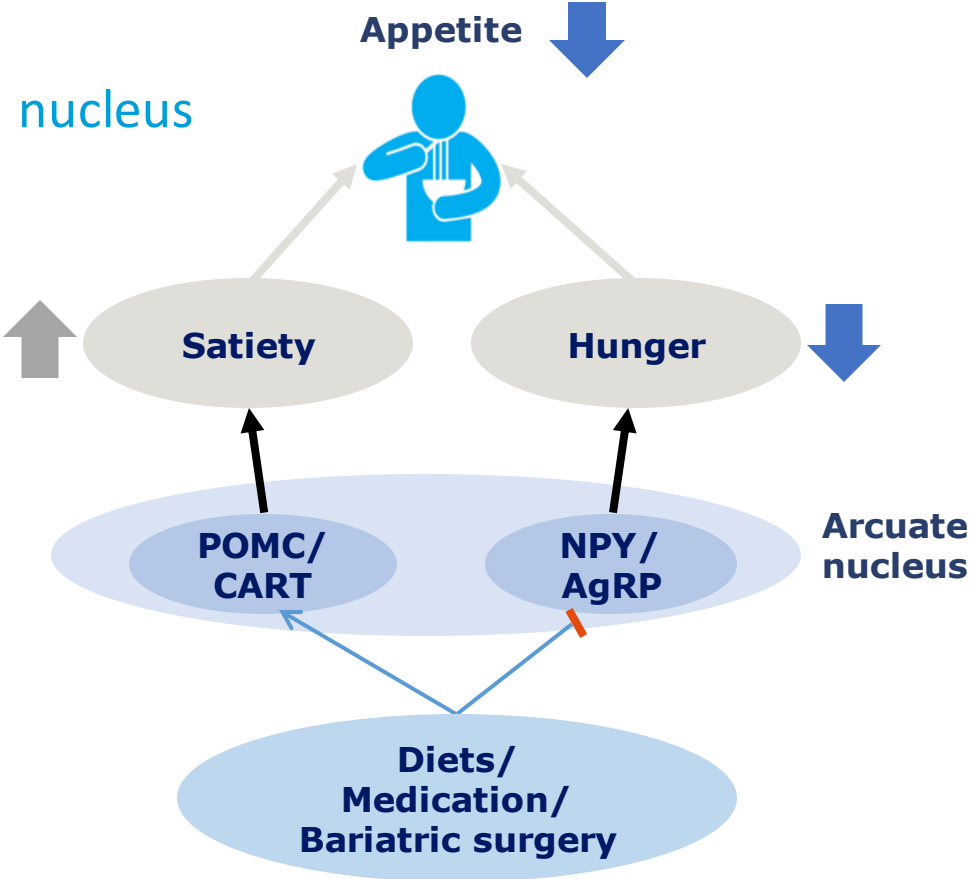


# Effects of Energy Restriction



# Successful Weight Loss Treatments Increase Satiety and Reduce Hunger

Via neurons in the arcuate nucleus



AgRP, Agouti-related peptide; CART, cocaine- and amphetamine-regulated transcript; NPY, neuropeptide Y; POMC, pro-opiomelanocortin  
Secher et al. *J Clin Invest* 2014;124:4473-88; van Can et al. *Int J Obes (Lond)* 2014;38:784-93

# Liraglutide is a once-daily, human GLP-1 analogue



Human endogenous GLP-1

$T_{1/2} = \sim 2 \text{ mins}$

**C-16 fatty acid (palmitoyl)**



Liraglutide

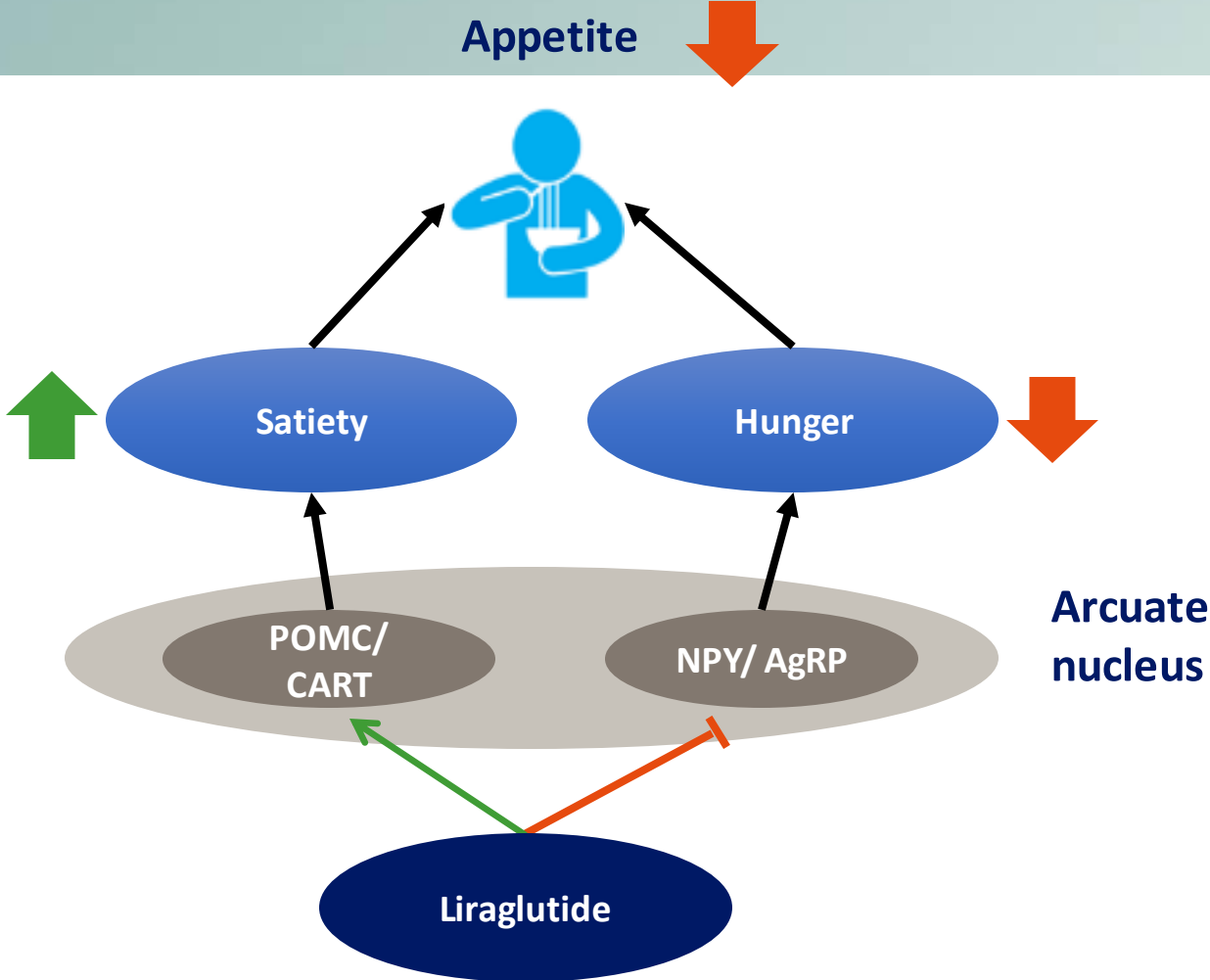
97% amino acid homology to human GLP-1; improved PK: albumin binding through acylation; heptamer formation



Slow absorption from subcutis  
Resistant to DPP-4  
Long plasma half-life  
 $(T_{1/2} = 13 \text{ h})$

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; PK, pharmacokinetics;  $T_{1/2}$ , plasma half-life  
Knudsen et al. *J Med Chem* 2000;43:1664-9; Degn et al. *Diabetes* 2004;53:1187-94

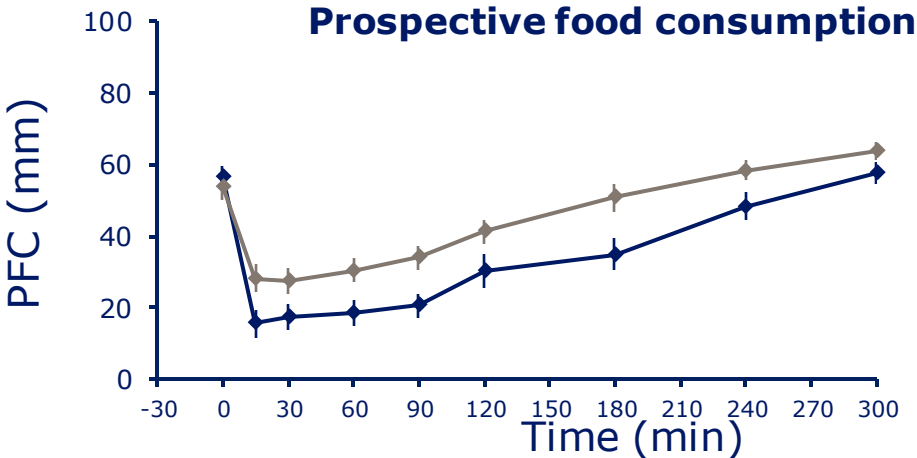
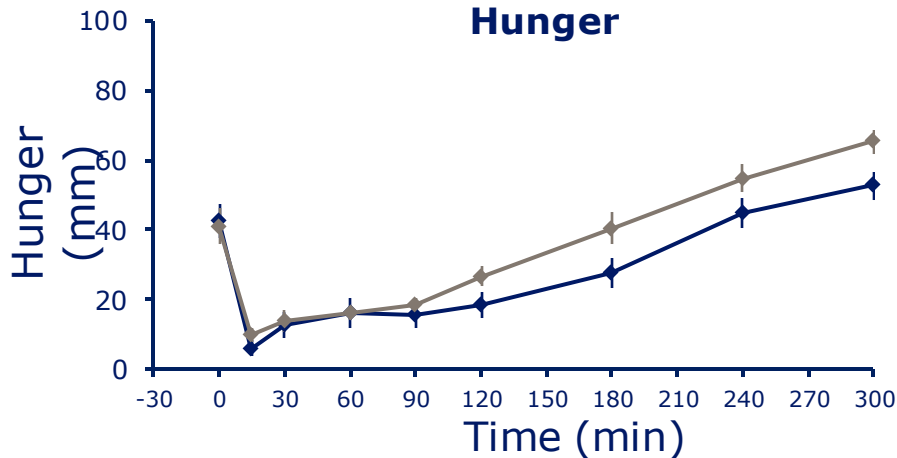
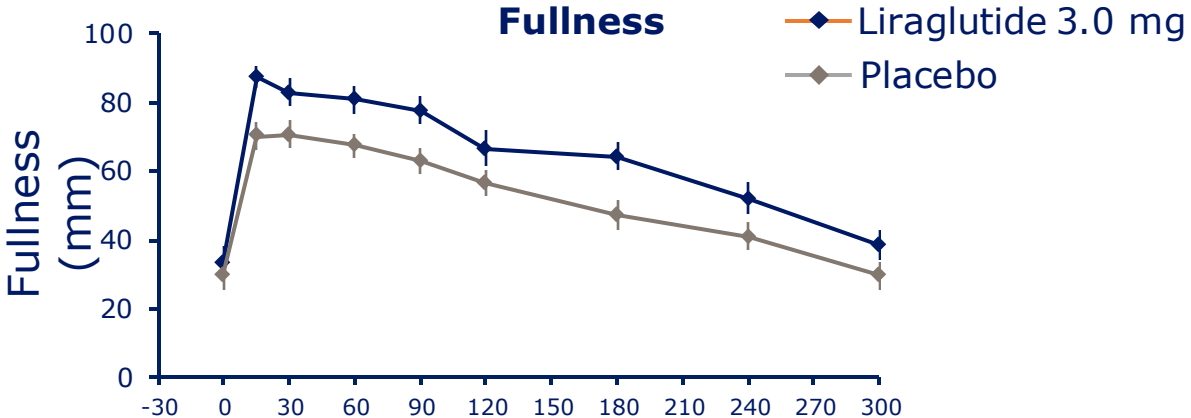
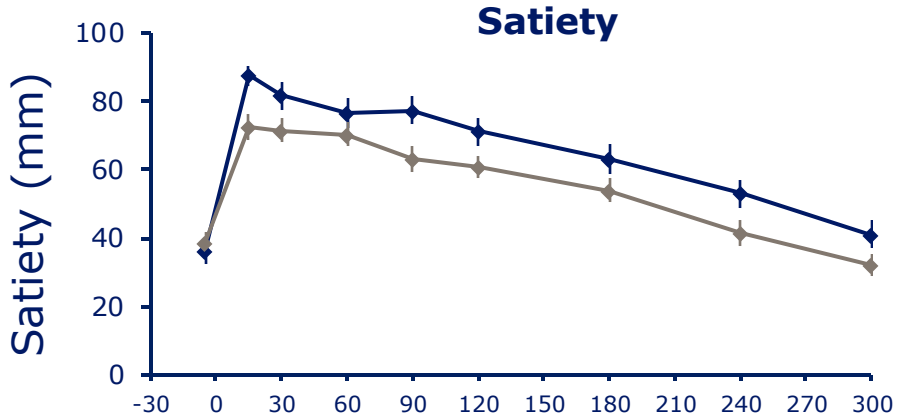
# Liraglutide increases satiety and reduces hunger via neurons in the arcuate nucleus



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

Secher A et al. *J Clin Invest.* 2014;124:4473–88; van Can J et al. *Int J Obes (Lond).* 2014;38:784–93

# Liraglutide 3.0 mg influences all dimensions of appetite



Appetite ratings were assessed by visual analog scale. Data are presented as mean ± standard error. PFC, prospective food consumption  
Adapted from: van Can et al. *Int J Obes* 2014;38:784-93

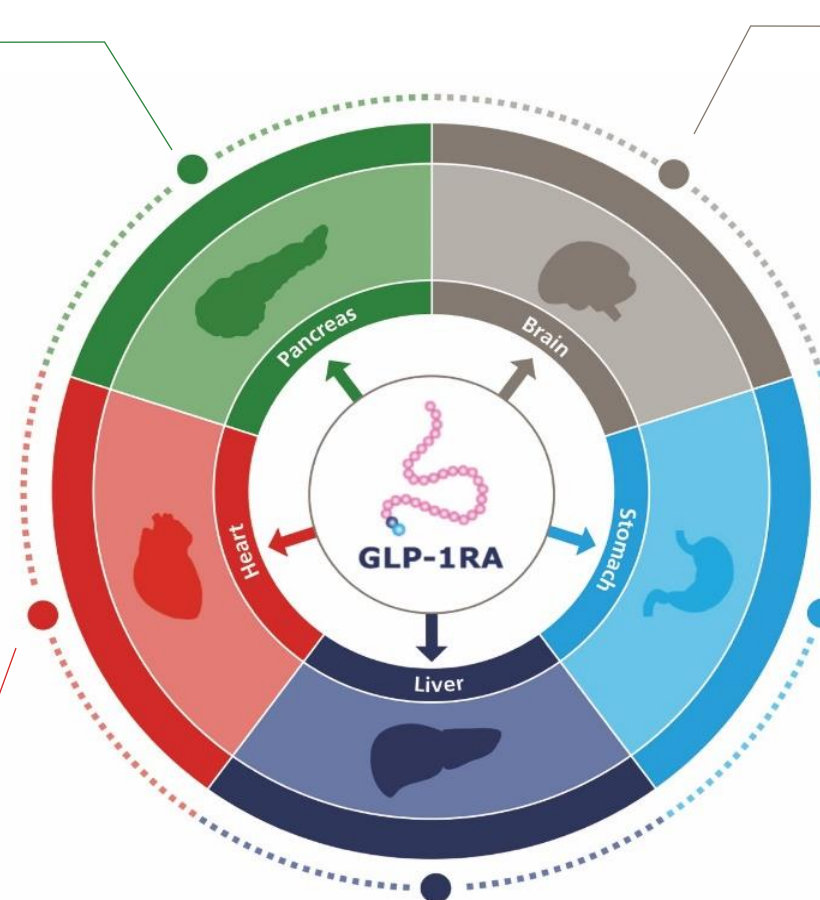
# GLP-1RAs have multifactorial effects

Pharmacological effects of GLP-1RAs

## Pancreas

- ↑ Beta-cell function<sup>1</sup>
- ↓ Beta-cell apoptosis<sup>1</sup>
- ↑ Insulin biosynthesis<sup>1</sup>
- ↑ Glucose-dependent insulin secretion<sup>1</sup>
- ↓ Glucose-dependent glucagon secretion<sup>1</sup>

- ↓ Cardiovascular risk<sup>2</sup>
- ↓ Fatty acid metabolism<sup>3</sup>
- ↑ Cardiac function<sup>3</sup>
- ↓ Systolic blood pressure<sup>3</sup>
- ↓ Inflammation<sup>4</sup>



## Brain

- ↓ Body weight<sup>5</sup>
- ↓ Food intake<sup>6</sup>
- ↑ Satiety

## Stomach

- ↓ Gastric emptying<sup>9</sup>
- ↓ Endogenous glucose production<sup>10</sup>
- ↑ Hepatic insulin sensitivity<sup>10</sup>
- ↓ *De novo* lipogenesis<sup>10</sup>
- ↓ Lipotoxicity<sup>10</sup>
- ↓ Steatosis<sup>11</sup>

GLP-1RA, glucagon-like peptide-1 receptor agonist

Adapted from Campbell & Drucker. *Cell Metab* 2013;17:819–37; Pratley & Gilbert. *Rev Diabet Stud* 2008;5:73–94. Full reference list in slide notes.

# The **SCALE** programme

Satiety and **Clinical Adiposity** –  
Liraglutide **Evidence**



# Efficacy summary across Phase 3a trials

Key efficacy outcomes with liraglutide 3.0 mg



SCALE Obesity and  
Prediabetes<sup>1,2</sup>

**-8.0%**

change in body weight  
after 1 year



SCALE  
Diabetes<sup>3</sup>

**-6.0%**

change in body weight  
after 56 weeks



SCALE Maintenance<sup>4</sup>

**81%**

maintained  $\geq 5\%$  weight  
loss after 1 year



SCALE Sleep  
Apnoea<sup>5</sup>

**-12.2**

events p/h  
vs. 6.1 with placebo

**80%**

reduction in the risk of  
T2D over 3 years

**-1.3%**

change in HbA<sub>1c</sub>  
from baseline

**6.2%**

additional weight loss  
with liraglutide 3.0 mg\*

**-5.7%**

change in body weight  
after 32 weeks

\*Following lifestyle intervention induced weight loss of  $\geq 5\%$  over a 12 week run in period



# CASE STUDY



## CASE STUDY - 02/02/21

### History

19 year old male AB  
Weight gain 40kg over 2 years  
Chronic Fatigue  
Cravings for sweet + starchy foods  
Poor Concentration  
Headaches

---

### Social

Parents divorced  
Mom diagnosed with Breast Cancer  
Dad unemployed and family had financial constraints  
Felt despondent and depressed

### Past Medical History

ITP 2010



## CASE STUDY - 02/02/21

### Examination

	Grossly Overweight
BP	143/95
Weight	131 kg
Height	1,89 m
BMI	36,7

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### Investigations

Inflammation:	hsCRP	5.1
ANS:	Reduced HRV	
	Severe Sympathetic Overdrive	

---

### Endocrine:



## CASE STUDY - ENDOCRINE 02/02/21

TSH	3,61	
HbA1c	7,3	
Fasting Insulin	33,5	(2,1 - 10,4)
C- Peptide	1,97	(0,37 - 1,47)
Vitamin D	16,9	
Free Testosterone	145,1	(170 - 660)
Vitamin B12	125	(107 - 418)
Uric Acid	0,44	(0,2 - 0,43)
LDL	3,3	



## INFLANOME

hsCRP 5.1

## ANS

HRV High  
Pulse 102  
BP 143/95

## ENDOCRINE

TSH 3,61  
HbA1c 7,3  
Fasting Insulin 33,5  
C- Peptide 1,97  
Vitamin D 16,9  
Free Testosterone 145,1  
Vitamin B12 125  
Uric Acid 0,44  
LDL 3,3



WHAT WOULD YOU DO

**Driving** | in  
**change** | obesity

## TREATMENT



<b>Allopurinol</b>	<b>100mg daily</b>
<b>Metformin</b>	<b>XR 500 mg bd</b>
<b>Liraglutide</b>	<b>3mg</b>
<b>Vitamin B12</b>	
<b>Vitamin D3</b>	

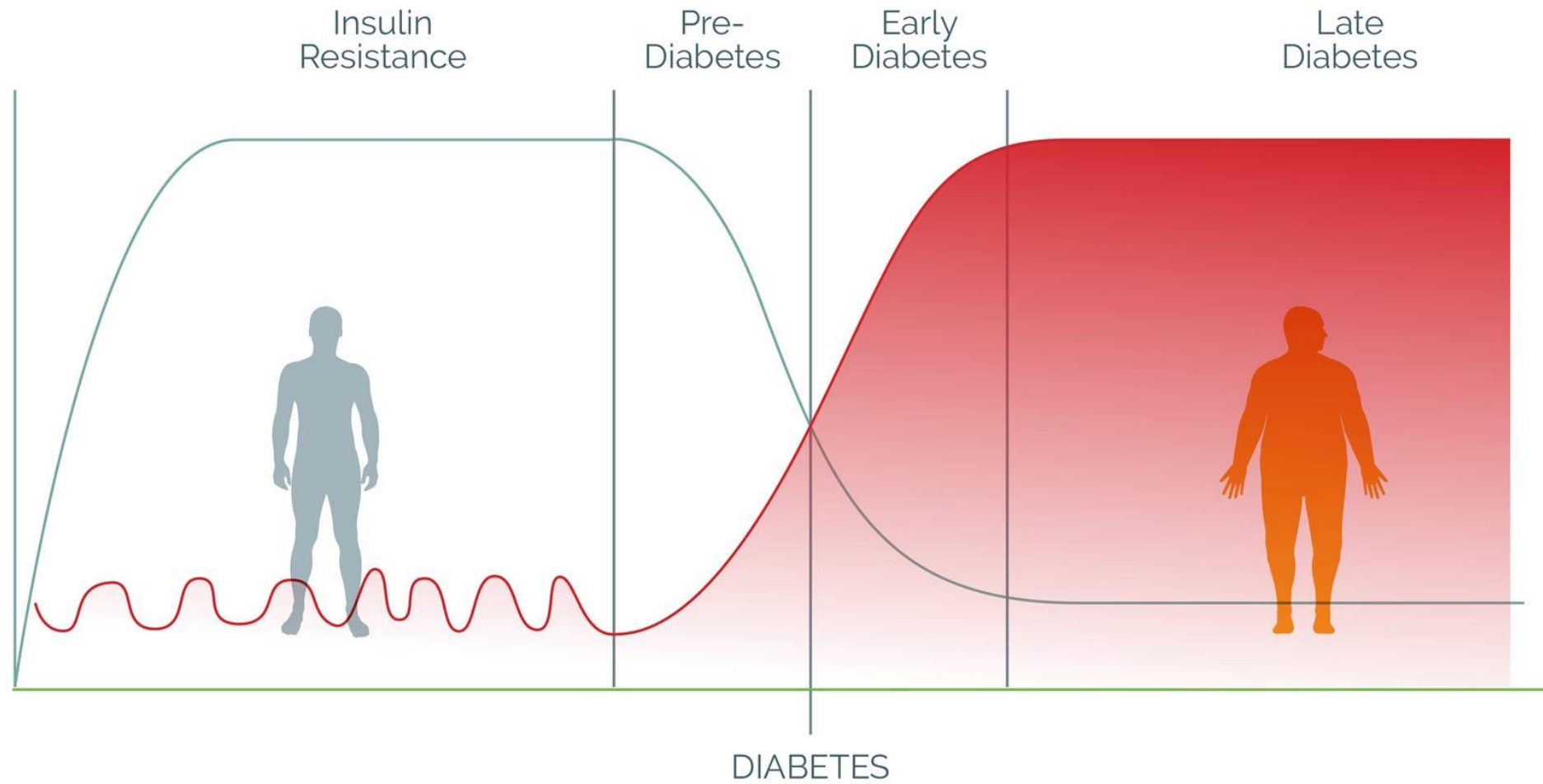
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<b>Diet</b>	<b>Anti-Inflammatory diet</b>
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<b>Mental</b>	<b>Family counselling</b>
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# DIABETES CONTINUUM





## CASE STUDY - 28/04/21

<b>Examination</b>	Grossly Overweight
BP	124/70
Weight	93 kg
Height	1,89 m
BMI	26

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### Investigations

Inflammation:	hsCRP	1,4
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ANS:	Normal HRV
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### Endocrine:

## INFLANOME

hsCRP 1.4

## ANS

HRV Normal

Pulse 78

BP 124/70

## ENDOCRINE

TSH 2.2

HbA1c 5.2

Fasting Insulin 8.1

Free Testosterone **187**

Vitamin B12 410

Uric Acid 0,41





## 4.2 Posology and method of administration

Dose escalation	Dose	Week
4 weeks	0.6 mg	1
	1.2 mg	1
	1.8 mg	1
	2.4 mg	1
Maintenance dose	3mg	

Treatment with Saxenda® should be discontinued after 12 weeks on the 3,0 mg/day dose if a patient has not lost **at least 5 %** of the **initial body weight**.

- The starting dose is 0,6 mg once daily.
- The dose should be increased to 3.0 mg once daily in increments of 0,6 mg with at least one week intervals to improve gastro-intestinal tolerability.
- If escalation to the next dose step is not tolerated for two consecutive weeks, consider discontinuing treatment.
- Daily doses higher than 3,0 mg are not recommended.

# Adolescents

- Saxenda<sup>®</sup> can be used as an adjunct to a healthy nutrition and physical activity counselling for weight management in adolescent patients from the age of 12 years and above with:
  - body weight above 60 kg and
  - obesity (BMI corresponding to  $\geq 30$  kg/m<sup>2</sup> for adults by international cut-off points)\*.
- \*IOTF BMI cut-off points for obesity by sex between 12–18 years

Age (years)	Body mass index 30 kg/m <sup>2</sup>	
	Males	Females
12	26.02	26.67
12.5	26.43	27.24
13	26.84	27.76
13.5	27.25	28.20
14	27.63	28.57
14.5	27.98	28.87
15	28.30	29.11
15.5	28.60	29.29
16	28.88	29.43
16.5	29.14	29.56
17	29.41	29.69
17.5	29.70	29.84
18	30.00	30.00

\*IOTF: International Obesity Task Force;

Key: **Green:** new section **Red text:** update

# Conclusion

- Obesity is a **COMPLEX** and chronic disease of the subcortical areas of the brain.
- Treat the **PATIENT** and not only the disease
- There are no quick fixes - It's a **JOURNEY**
- Understand and communicate the desired **OUTCOMES**
- A **MULTI-DISCIPLINARY** approach is key
- Keep it **SIMPLE**
- The program should be supported by a *dynamic treatment schedule*
  
- Liraglutide 3.0 mg of once-daily subcutaneous liraglutide, as an adjunct to diet and exercise, was associated with clinically meaningful weight loss in individuals with obesity or overweight with comorbidities.
  
- Liraglutide 3.0 mg was also associated with improvements in glycaemia, cardiometabolic risk factors and health-related quality of life.