Lancet DE Commission on Clinical Obesity

Pathophysiology

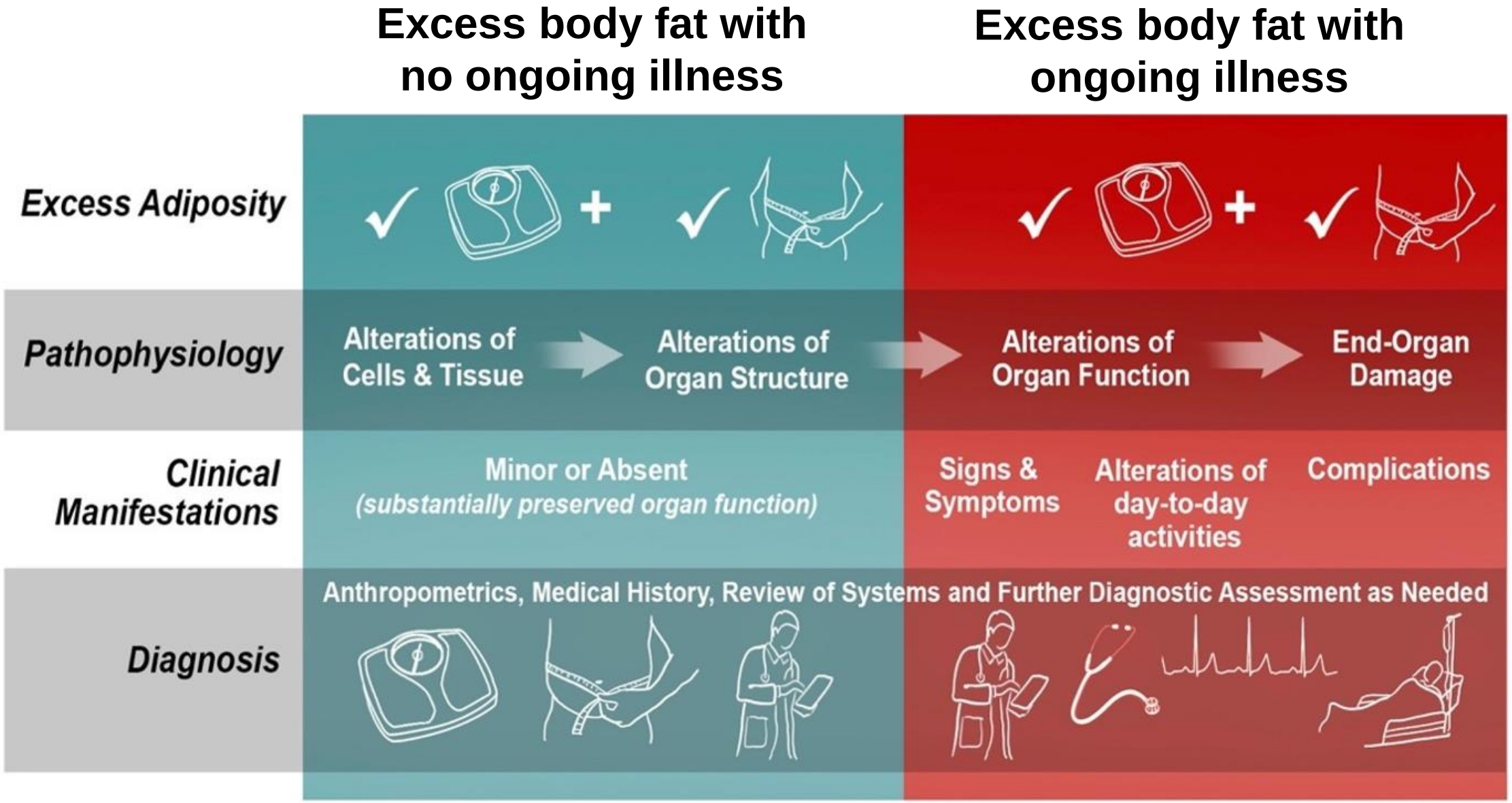
John B Dixon

Disclosures: Professor John B Dixon

I-Nova	Advisory board
Nestle Health Science	Consultant – Advisory board
Reshape Lifesciences	Consultant
Novo Nordisk	Advisory board and speaker fees
Lilly	Advisory board and speaker fees
Eurodrug	Advisory board and speaker fees
HealthED	Educational programs
NACOS	Vice President
Obesity collective	Leaders group

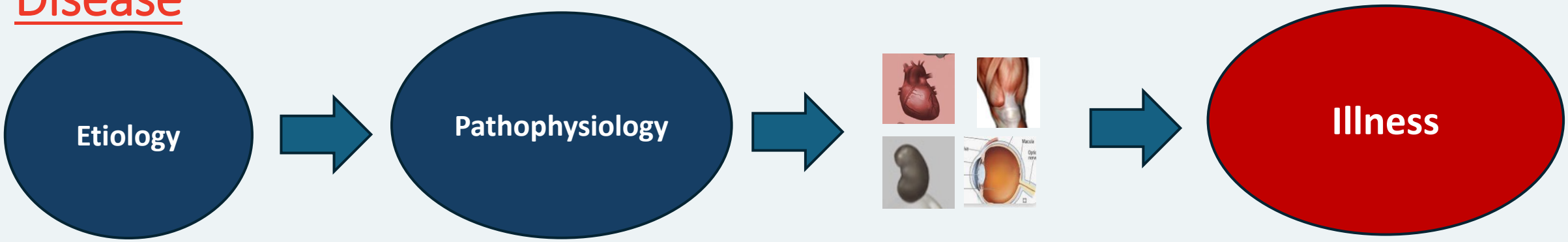
Disclosure

- No industry funding
- Logistic support from King’s Health Partners (Academic Partnership across hospitals affiliated with King’s College London)


Excess body fat with no ongoing illness
Excess body fat with ongoing illness
Excess Adiposity
Pathophysiology
Alterations of Cells & Tissue
Alterations of Organ Structure
Alterations of Organ Function
End-Organ Damage
Clinical Manifestations
Minor or Absent
(substantially preserved organ function)
Signs & Symptoms
Alterations of day-to-day activities
Complications
Diagnosis
Anthropometrics, Medical History, Review of Systems and Further Diagnostic Assessment as Needed

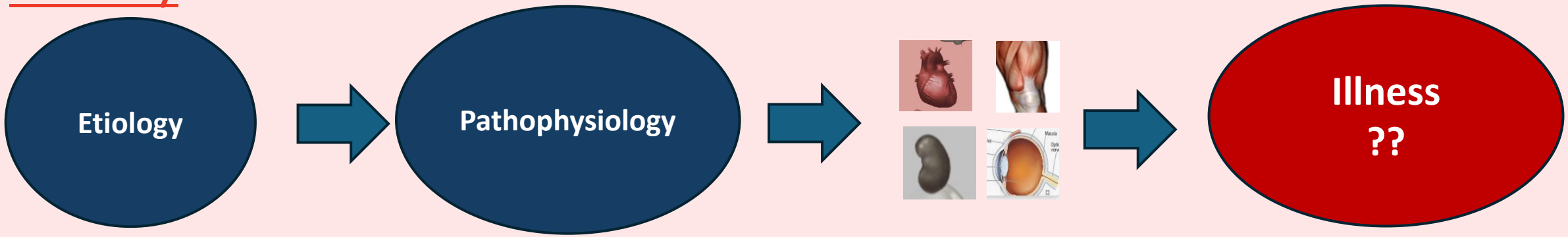
The “Missing Piece” in the Current Framing of Obesity

Disease



Causes of disease | **Specific disease mechanisms** | **Compromised organ function** | **Clinical Manifestations**

Obesity

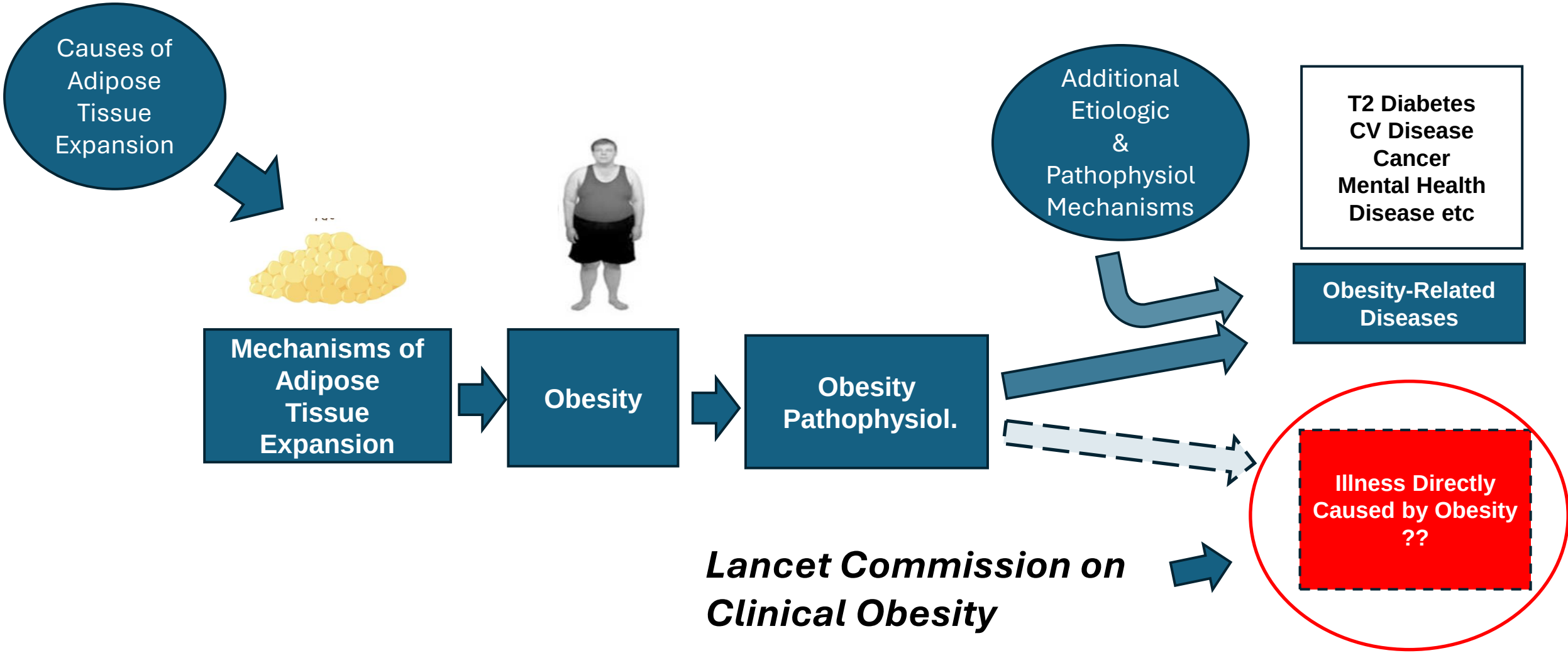


Genetic
Environmental
Unknown

Mechanical
Endocrine/metabolic
Inflammation

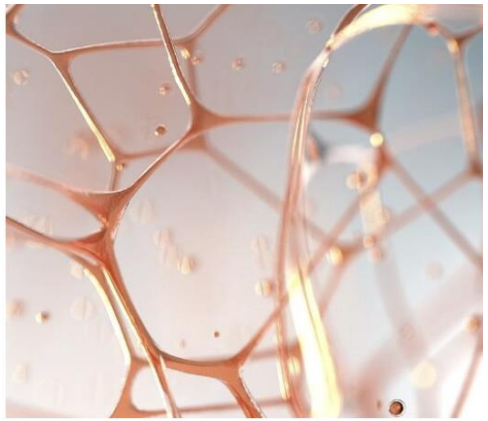
“Obesity-related <u>diseases</u>”
(e.g. diabetes/cancer, etc.) are diseases in their own right, <u>not</u> clinical manifestations of a distinct disease entity

Definition of Illness due to Obesity

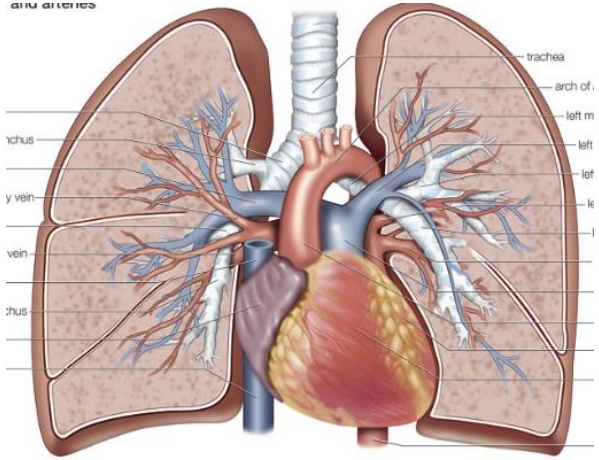


A Pragmatic, Objective Approach to Define Illness due to Obesity

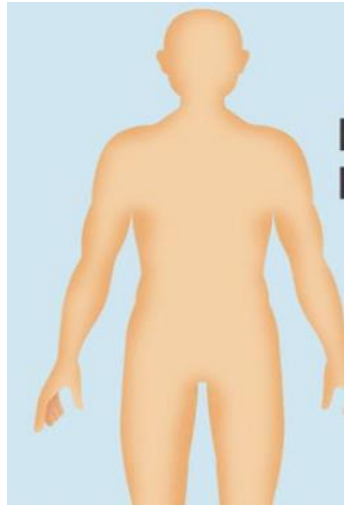
Illness due to obesity is a condition in which the risk to health associated with excess adiposity has already materialised and can be objectively documented by specific signs and symptoms reflecting ***abnormal function of tissues and organs or of the whole organism****, causing sickness.*



Tissue



Organ



Organism

Clinical Obesity

What is it?

A chronic, systemic illness characterised by alterations in the function of tissues, organs and/or the entire individual, due to excessive and/or abnormal adiposity, (independent on the presence of other adiposity-related diseases)

What characterises clinical obesity?

The definition of clinical obesity implies the combination of a physical obesity phenotype with objective evidence of ongoing illness due to obesity alone (this includes signs, symptoms and/or limitations of day-to-day activities)

Co-morbidities: The term “co-morbidities” should only be used to refer to diseases and other conditions that incidentally co-exist with obesity, without cause-effect relationship or pathophysiologic overlap.

“**Obesity-related diseases/disorders”** (or “associated/overlapping diseases/disorders”) should be used for non-communicable diseases (NCDs) and disorders (e.g. type 2 diabetes, certain types of cancer, OSA, NASH, mental illness etc) that typically co-occur with obesity because of overlapping etiology and/or pathophysiology.

“Complications": Clinical obesity may lead to severe organ dysfunction and end-organ damage, causing life-altering and/or potentially life-threatening complications (e.g. heart attack, stroke, renal failure).

The diagnosis of Clinical Obesity requires:

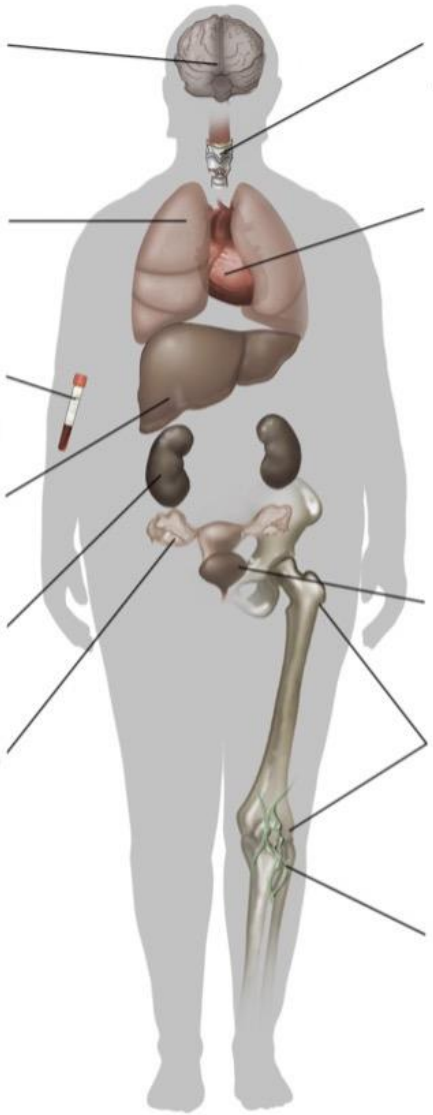
A. **Clinical confirmation of obesity status**
by anthropometric criteria (e.g. WC, WHR) or by direct body fat measurement

Plus one or both of the following criteria:

B. **Evidence of reduced organ/tissue function due to obesity**
(i.e. signs, symptoms and/or diagnostic tests showing abnormalities in the function of one or more tissue/organ system)

C. **Significant, age-adjusted limitations of day-to-day activities**
reflecting the specific impact of obesity on mobility and/or other basic Activities of Daily Living (ADL = bathing, dressing, toileting, continence, eating).

Diagnostic Criteria of Clinical Obesity
(adults)



CNS
Vision loss and/or recurrent headaches
due to raised intracranial pressure

Respiratory System
Hypoventilation and/or breathlessness and/or wheezing
due to reduced lung and/or diaphragmatic compliance

Metabolism
The cluster of hyperglycaemia, high triglycerides levels & low HDL cholesterol

Liver
MASLD with fibrosis

Renal
Microalbuminuria with reduced eGFR

Reproductive
Anovulation, oligo-menorrhea and PCOS, male hypogonadism

Limitations of day-to-day activities
Significant, age-adjusted limitations of daily living
(ADL = bathing, dressing, toileting, continence, eating)

Upper-Airways
Apnoeas/Hypopnoeas during sleep
due to increased upper airways resistance

Cardiovascular system
- Heart Failure with reduced ejection fraction
  due to reduced LV systolic function
- Chronic Fatigue, Lower Limb Edema
  due to impaired diastolic dysfunction– Heart Failure with Preserved Ejection Fraction - HFpEF -
- Chronic/recurrent AF
- Pulmonary Artery Hypertension
- Recurrent DVT/PE
- Raised Arterial Blood Pressure

Urinary System
Recurrent/Chronic Urinary Incontinence

Musculoskeletal System
Chronic, severe knee or hip pain
associated with joint stiffness & reduced range of motion

Lymphatic system
Lower Limbs lymphederma
causing chronic pain and/or reduced range of motion

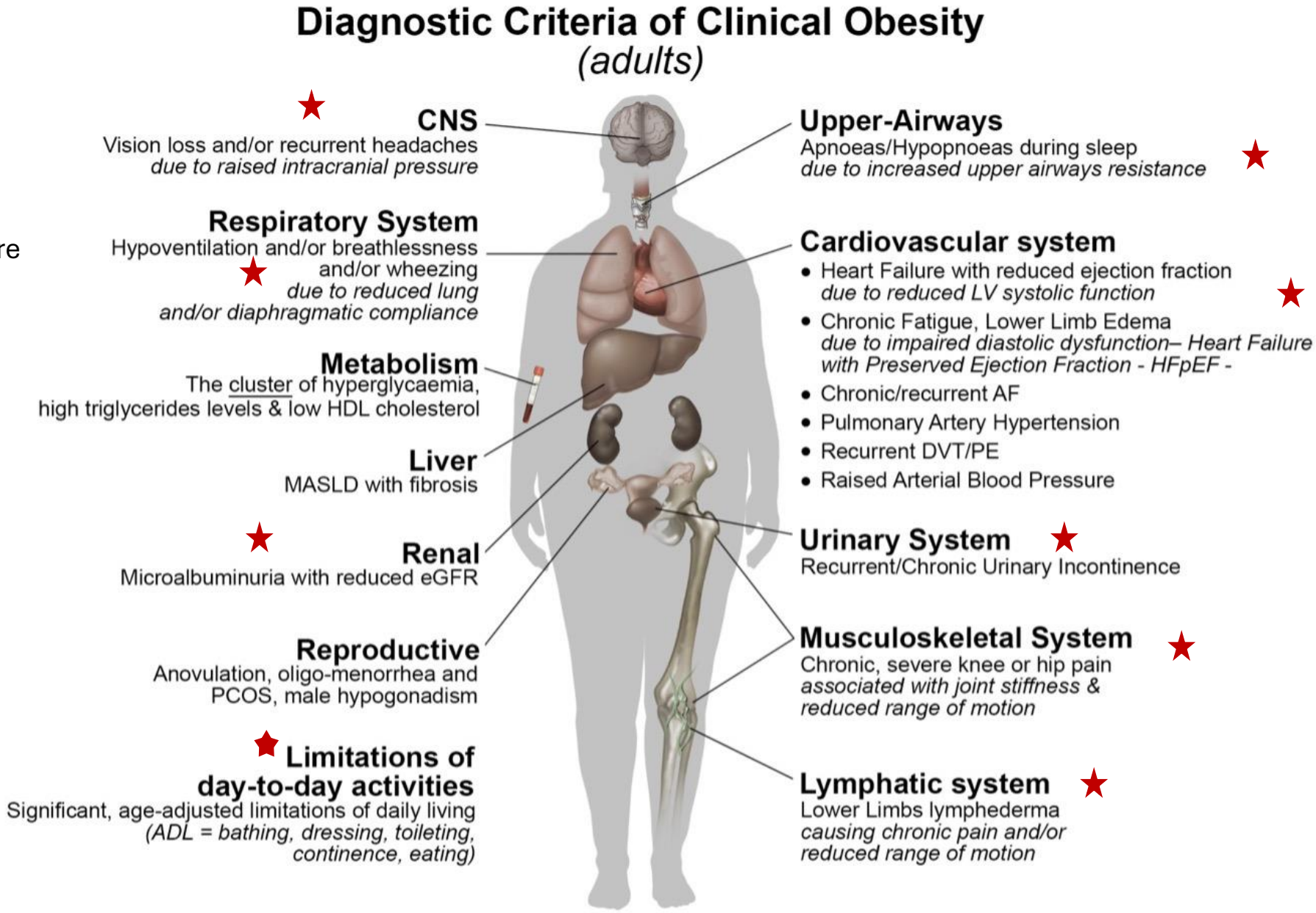
Mechanical Pressure & Obstruction

Intra-abdominal pressure ++

- Raised Intracranial pressure
- Lung Reduced functional residual Capacity
- Bronchial obstruction of medium sized airways
- Impaired venous return
  - Reduced compliance of intra-abdominal veins
  - Lymphedema
  - Lipedema
  - Ulceration

Direct Pressure effects ++

- GERD
- Weight bearing joints
- Skin on skin pressure
- Reduces joint mobility
- Physical Function
- Neuropathy

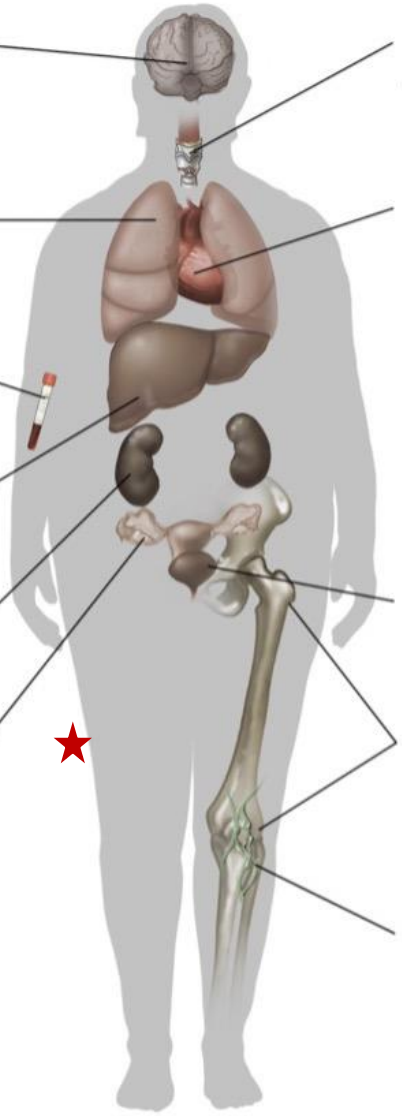


Visceral & Ectopic Cardio-metabolic-inflammatory

Brain ★

- Disordered eating
  - Hunger
  - Always ready to eat
  - Never satisfied
  - Out of control eating
  - Pervasive food noise
- Daytime sleepiness
  - EES in clinical obesity not associated with AHI
- Sleep
  - OSA OHS
  - Insomnia
  - Restless leg syndrome
  - Periodic limb movement disorder
  - Shift work –Disturbed – biological clock
- Cognitive domains
- Depression – Bidirectional associations
- Weight Stigma

Diagnostic Criteria of Clinical Obesity
(adults)



★ **CNS**
Vision loss and/or recurrent headaches
due to raised intracranial pressure

Respiratory System
Hypoventilation and/or breathlessness and/or wheezing
due to reduced lung and/or diaphragmatic compliance

★ **Metabolism**
The cluster of hyperglycaemia, high triglycerides levels & low HDL cholesterol

★ **Liver**
MASLD with fibrosis

★ **Renal**
Microalbuminuria with reduced eGFR

★ **Reproductive**
Anovulation, oligo-menorrhea and PCOS, male hypogonadism

Limitations of day-to-day activities
Significant, age-adjusted limitations of daily living
(ADL = bathing, dressing, toileting, continence, eating)

Upper-Airways ★
Apnoeas/Hypopnoeas during sleep
due to increased upper airways resistance

Cardiovascular system ★
- Heart Failure with reduced ejection fraction *due to reduced LV systolic function*
- Chronic Fatigue, Lower Limb Edema *due to impaired diastolic dysfunction– Heart Failure with Preserved Ejection Fraction - HFpEF -*
- Chronic/recurrent AF
- Pulmonary Artery Hypertension
- Recurrent DVT/PE
- Raised Arterial Blood Pressure

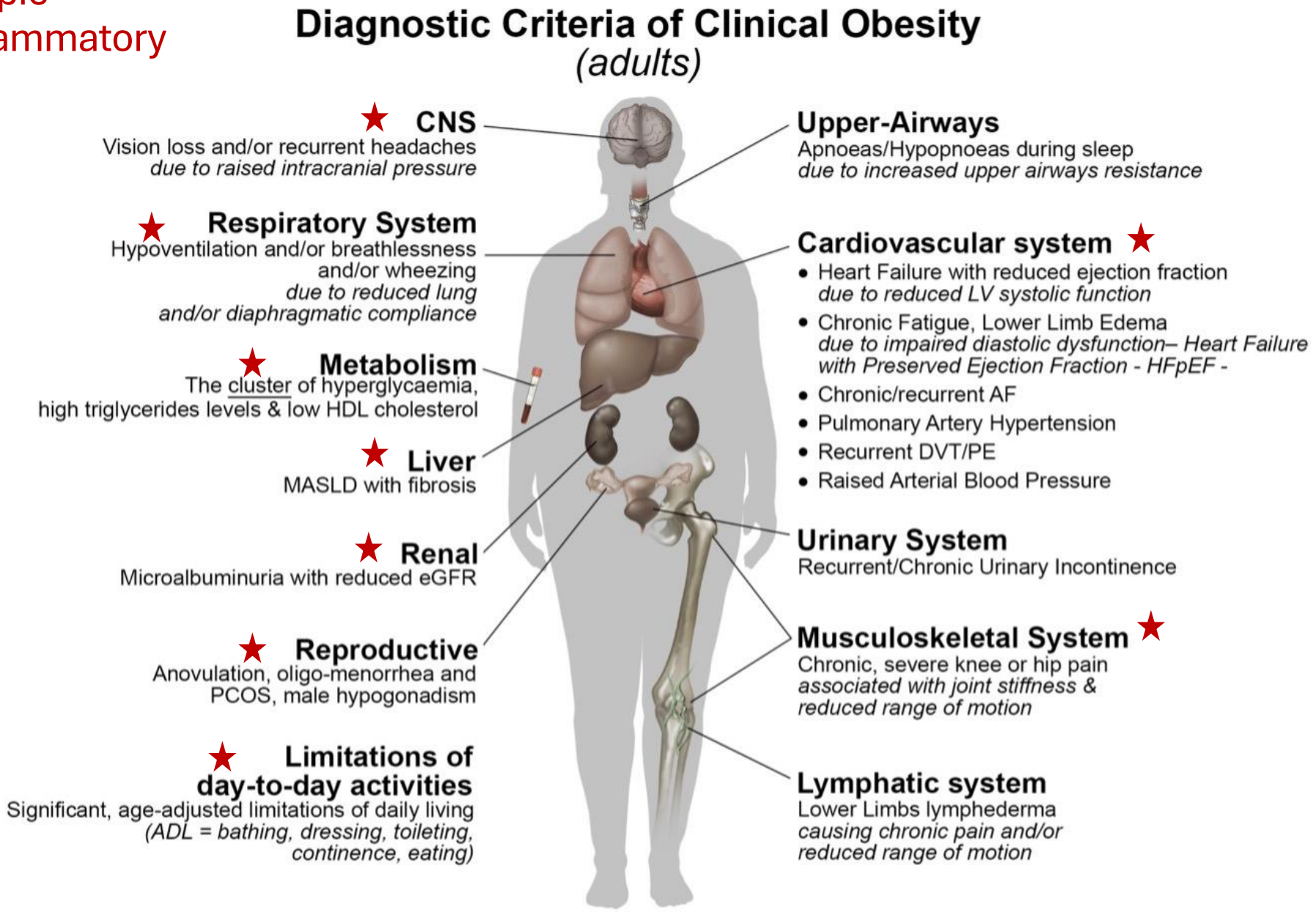
Urinary System
Recurrent/Chronic Urinary Incontinence

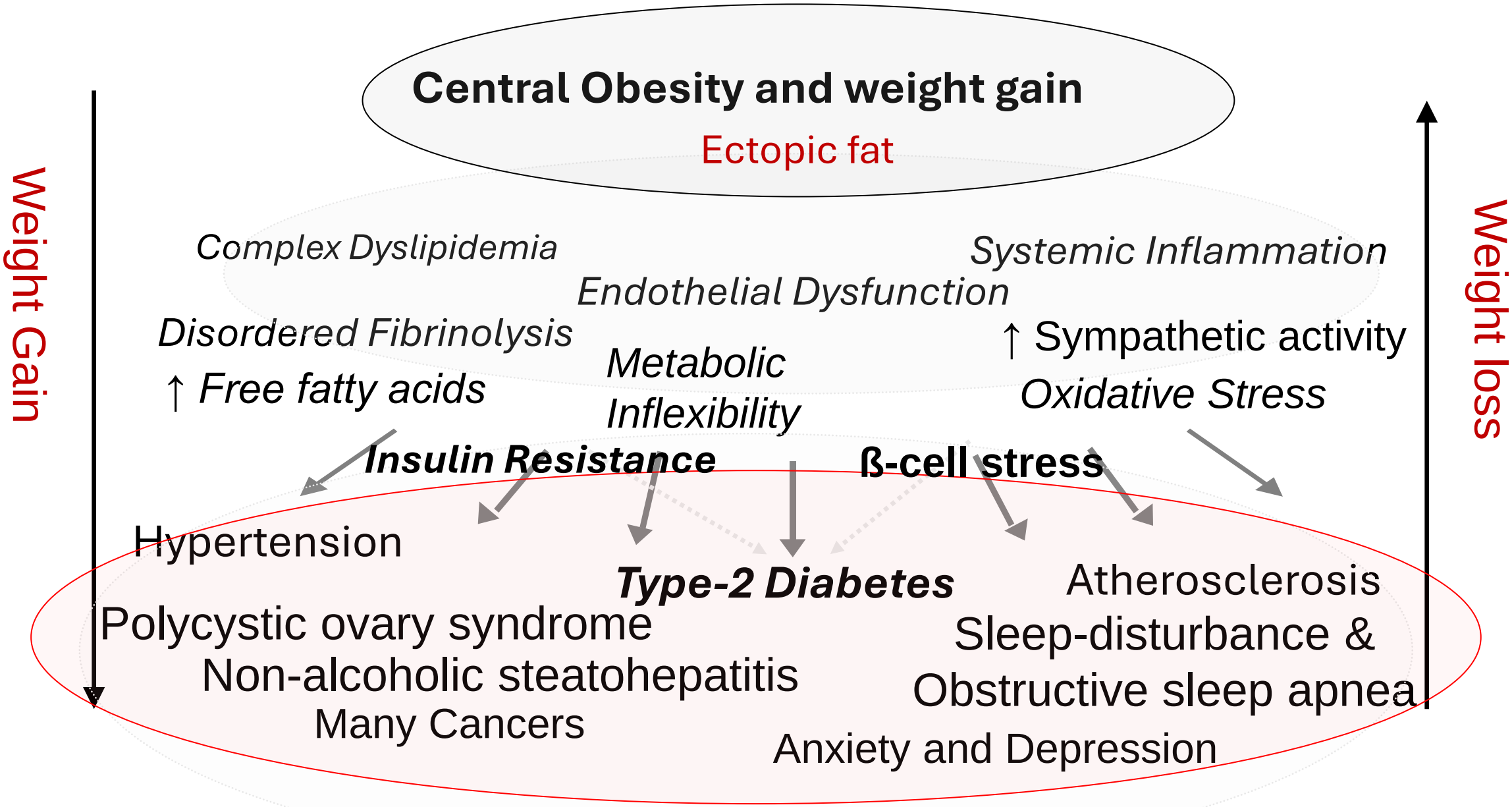
Musculoskeletal System ★
Chronic, severe knee or hip pain *associated with joint stiffness & reduced range of motion*

Lymphatic system
Lower Limbs lymphederma *causing chronic pain and/or reduced range of motion*

Visceral & Ectopic Cardio-metabolic-inflammatory

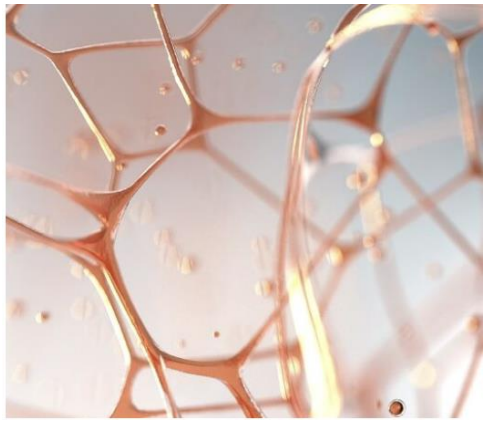
- Ectopic fat
  - Liver
  - Skeletal Muscle
  - Pancreas
  - Epicardial & cardiac
- Insulin resistance
  - Liver, muscle, pancreas,
  - Systemic hyperinsulinemia,
- Inflammatory
  - Local
  - Systemic

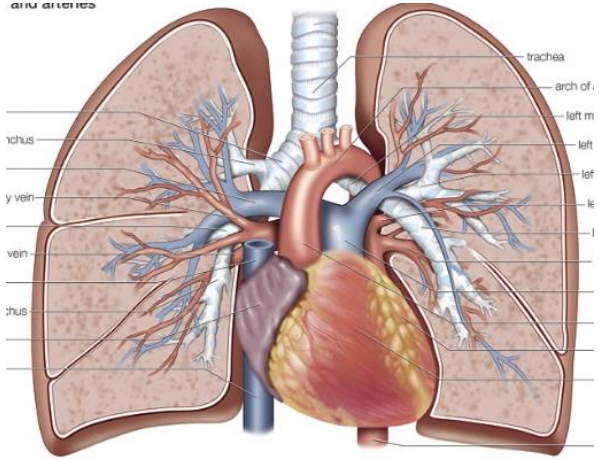


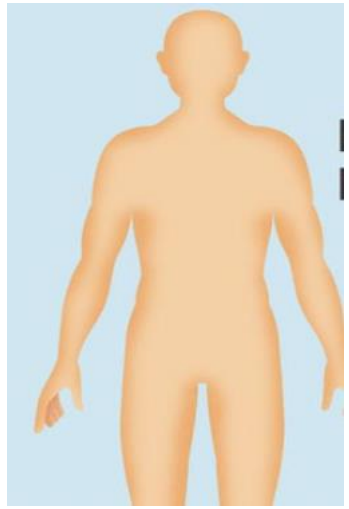

Obesity related illness
Result of Metabolic and inflammatory cascade driven by
Central Obesity and weight gain
Ectopic fat
Weight Gain
Weight loss
Complex Dyslipidemia
Systemic Inflammation
Endothelial Dysfunction
Disordered Fibrinolysis
↑ Sympathetic activity
↑ Free fatty acids
Metabolic Inflexibility
Oxidative Stress
Insulin Resistance
ß-cell stress
Hypertension
Type-2 Diabetes
Atherosclerosis
Polycystic ovary syndrome
Sleep-disturbance &
Non-alcoholic steatohepatitis
Obstructive sleep apnea
Many Cancers
Anxiety and Depression

A Pragmatic, Objective Approach to Define Illness due to Obesity

Illness due to obesity is a condition in which the risk to health associated with excess adiposity has already materialised and can be objectively documented by specific signs and symptoms reflecting ***abnormal function of tissues and organs or of the whole organism****, causing sickness.*







Waist Circumference

BMI

Systolic BP

Tissue **Organ** **Organism**

Risk factors driving health costs in Finland, UK, and The Netherlands

1. Lee J, Jukarainen S, Karvanen et al,*Nat Commun*. 2023;14:5672. doi: 10.1038/s41467-023-41394-4