CHAPTER 3: Complications of Obesity

Part 3: Other

References:

1. **Peter G. Kopelman, Ian D. Caterson, William H. Dietz - Clinical Obesity in Adults and Children 4e-Wiley-Blackwell (2022)**
2. **Sharon Akabas, Sally Ann Lederman, Barbara J. Moore - Textbook of obesity_ Biological, psychological and cultural influences-Wiley-Blackwell (2012)**

Outline

1. Metabolic Syndrome
2. Sleep Apnea
3. Fertility
4. Cancer

Part 1: Metabolic Syndrome

Introduction

- A cluster of conditions that increase the risk of heart disease, cerebrovascular attack, and T2DM.
- The prevalence of MS is increasing worldwide

Component	Clinical Cutoff Values
Waist Circumference	≥102 cm in men ≥88 cm in women
Triglycerides	≥150 mg/dL
HDL Cholesterol	<40 mg/dL in men <50 mg/dL in women
Blood Pressure (BP)	≥130 mmHg Systolic BP or ≥85 mmHg Diastolic BP
Fasting Glucose	≥100 mg/dL
Diagnosis	Any 3 of the 5 features above

IDF Definition

Table 1: The new International Diabetes Federation (IDF) definition

According to the new IDF definition, for a person to be defined as having the metabolic syndrome they must have:

Central obesity (defined as waist circumference* with ethnicity specific values)

plus any two of the following four factors:

Raised triglycerides	≥ 150 mg/dL (1.7 mmol/L) **or specific treatment for this lipid abnormality**
Reduced HDL cholesterol	< 40 mg/dL (1.03 mmol/L) in males < 50 mg/dL (1.29 mmol/L) in females **or specific treatment for this lipid abnormality**
Raised blood pressure	systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg **or treatment of previously diagnosed hypertension**
Raised fasting plasma glucose	(FPG) ≥ 100 mg/dL (5.6 mmol/L), **or previously diagnosed type 2 diabetes** If above 5.6 mmol/L or 100 mg/dL, OGTT is strongly recommended but is not necessary to define presence of the syndrome.

https://idf.org/media/uploads/2023/05/attachments-30.pdf

IDF Definition

Table 2: Ethnic specific values for waist circumference

Country/Ethnic group		Waist circumference
Europids* In the USA, the ATP III values (102 cm male; 88 cm female) are likely to continue to be used for clinical purposes	Male	≥ 94 cm
	Female	≥ 80 cm
South Asians Based on a Chinese, Malay and Asian-Indian population	Male	≥ 90 cm
	Female	≥ 80 cm
Chinese	Male	≥ 90 cm
	Female	≥ 80 cm
Japanese**	Male	≥ 90 cm
	Female	≥ 80 cm
Ethnic South and Central Americans	Use South Asian recommendations until more specific data are available	
Sub-Saharan Africans	Use European data until more specific data are available	
Eastern Mediterranean and Middle East (Arab) populations	Use European data until more specific data are available	

** In future epidemiological studies of populations of Europid origin, prevalence should be given using both European and North American cut-points to allow better comparisons.*

*** Originally different values were proposed for Japanese people but new data support the use of the values shown above.*

Han TS, Lean ME. A clinical perspective of obesity, metabolic syndrome and cardiovascular disease. JRSM Cardiovasc Dis. 2016 Feb 25;5:2048004016633371. doi: 10.1177/2048004016633371.

Pathophysiology

- **High plasma glucose and insulin resistance**

Some of the links between components of the metabolic syndrome relate to *insulin resistance*

A central feature is unresponsiveness to insulin at the cellular level.

Exposure to high FFA concentrations is a common mediator as a consequence of an *expanded intra-abdominal fat* mass.

Insulin resistance is closely related to impaired glucose tolerance, diabetes and risk of CHD

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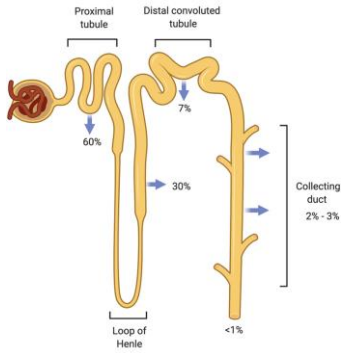
Pathophysiology



- **High blood pressure and insulin resistance**

Many hypertensive individuals have glucose intolerance and hyperinsulinaemia.

Obesity contributes to hypertension and hyperinsulinaemia, while weight reduction usually improves both.

Insulin resistance and hyperinsulinaemia could directly cause hypertension via **(1)** an increase in **catecholamine** activity, and **(2)** increased insulin concentration may also acutely raise blood pressure through insulin-mediated **renal tubular reabsorption** of sodium.

Han TS, Lean ME. A clinical perspective of obesity, metabolic syndrome and cardiovascular disease. JRSM Cardiovasc Dis. 2016 Feb 25;5:2048004016633371. doi: 10.1177/2048004016633371.

Pathophysiology

- **Dyslipidaemia**

High triglyceride and low HDL cholesterol levels are core components of the metabolic syndrome, which are associated with elevated levels of plasma **small dense low-density lipoprotein (LDL) cholesterol**, the most atherogenic subfraction of LDL, in individuals who are susceptible to gain weight.

Han TS, Lean ME. A clinical perspective of obesity, metabolic syndrome and cardiovascular disease. JRSM Cardiovasc Dis. 2016 Feb 25;5:2048004016633371. doi: 10.1177/2048004016633371.

Pathophysiology

- **Large waist circumference and intra-abdominal fat accumulation**

Increased intra-abdominal fat accumulation may have a direct intermediary role.

Intra-abdominal fat exhibits greater rates of *lipolysis* and glycolysis than the subcutaneous white adipose tissue → high-turnover distribution of FFAs to other body organs.

Large amounts of FFAs → Liver → may interfere with hepatic insulin clearance.

Intra-abdominal adipose tissue secretes a range of adipocytokines including *leptin, adiponectin, resistin, interleukins (IL) such as IL-1 and IL-6, and tumour necrosis factor alpha (TNF-α).* The imbalanced release of these factors by an expanded intra-abdominal fat mass is associated with increased metabolic disorders.

Han TS, Lean ME. A clinical perspective of obesity, metabolic syndrome and cardiovascular disease.
JRSM Cardiovasc Dis. 2016 Feb 25;5:2048004016633371. doi: 10.1177/2048004016633371.

Implications on CVD

- The prevalence of metabolic syndrome is estimated to be 10-30%
- It is likely that the prevalence of metabolic syndrome will continue to rise in the future given the persistently rising trends in obesity.
- To prevent or reduce long-term risk for CVD, preventative interventions should be initiated, with a focus on weight management to reduce excessive central fat accumulation.

Starting treatment *solely on the basis of large waist* is perfectly reasonable, without waiting for other components to develop.

Han TS, Lean ME. A clinical perspective of obesity, metabolic syndrome and cardiovascular disease.
JRSM Cardiovasc Dis. 2016 Feb 25;5:2048004016633371. doi: 10.1177/2048004016633371.

Muscle Mass is a key factor

- **Sarcopenia**:

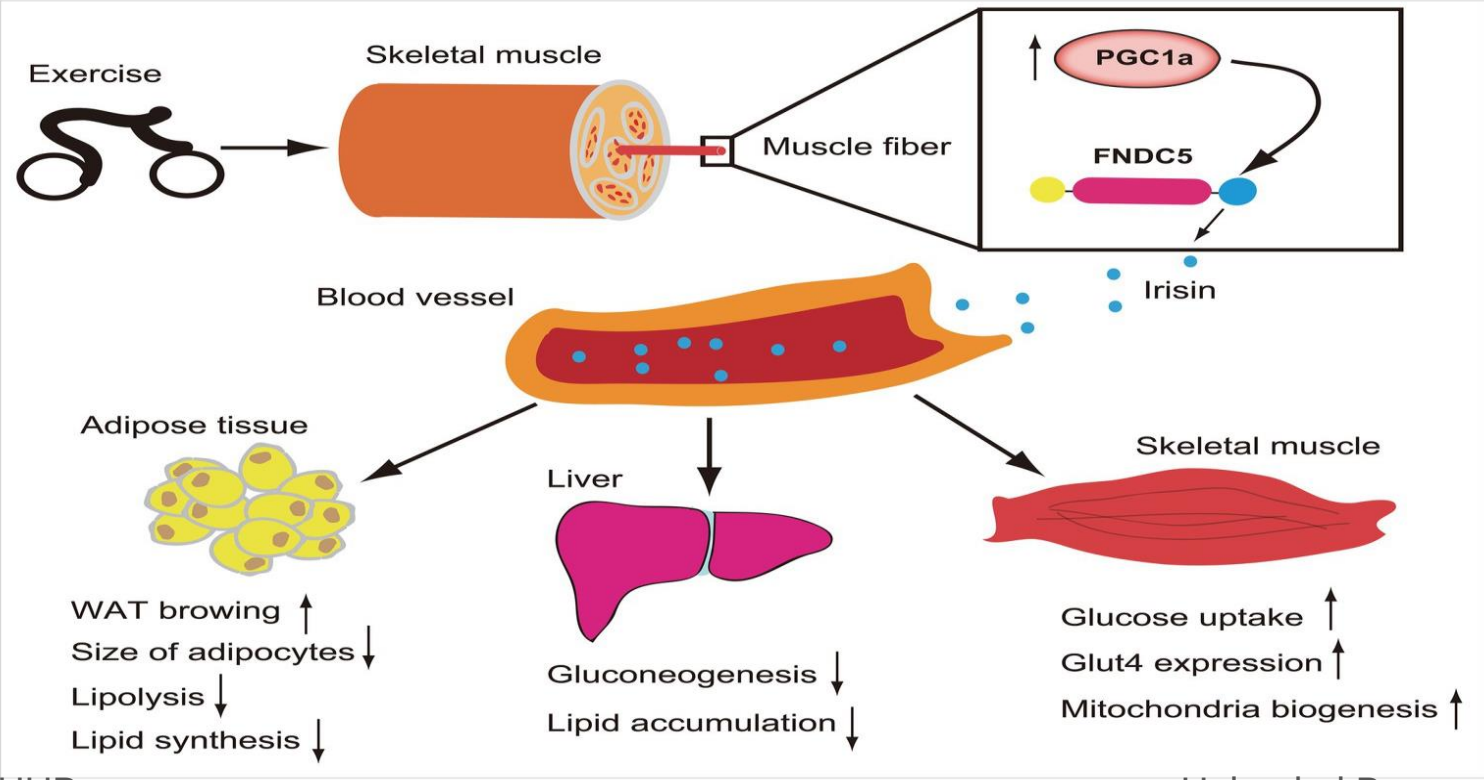
Individuals with sarcopenia had a 2-3X increased risk of Metabolic Dysfunction-Associated Fatty Liver Disease

Skeletal muscle secretes myokines, such as **Irisin**, that can affect other metabolic tissues.

- Irisin alleviates insulin resistance by increasing total body energy expenditure.
- Irisin levels were inversely associated with the degree of fat accumulation in the liver and fatty acid β-oxidation in the liver

Front. Physiol., 01 February 2021. Volume 12 - 2021
| https://doi.org/10.3389/fphys.2021.620608

Irisin: A New Code Uncover the Relationship of Skeletal Muscle and Cardiovascular Health



Part 2: Sleep Apnea

Introduction

- Obesity is a key factor in the development of **sleep disordered breathing** (SDB) and its clinical consequences.
- SDB is also associated with exacerbation of many of the health consequences of obesity so that a close pathophysiological **interplay** exists between both conditions.

Symptoms

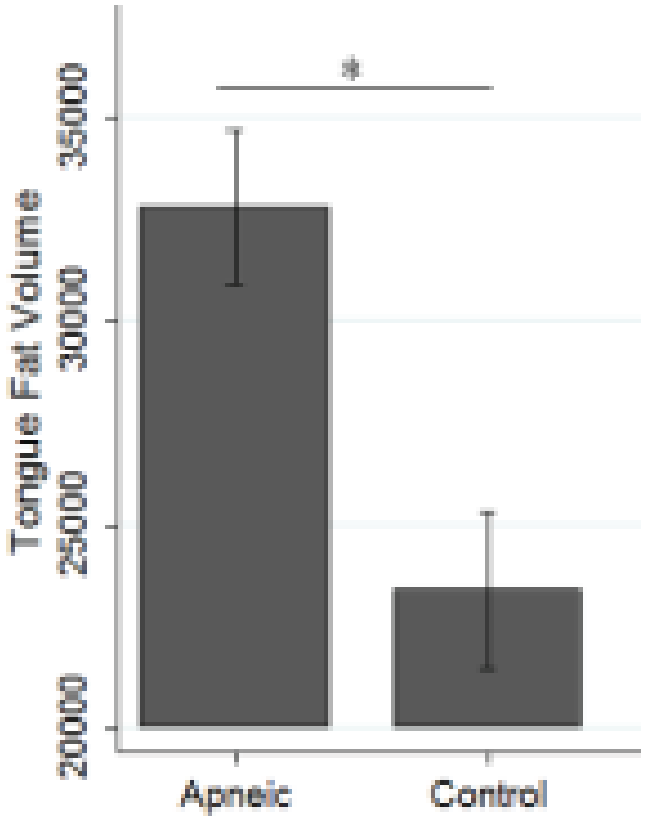
- Snoring
- Daytime sleepiness
- Disrupted sleep
- Choking or gasping during sleep
- Dry throat/mouth in morning
- Morning headaches
- Nocturia
- Heartburn
- Poor memory/concentration
- Fatigue
- Altered mood/irritability

Consequences of sleep-disordered breathing

- Excessive daytime sleepiness: Repetitive arousal and sleep fragmentation → impaired work performance and driving, defects in executive function and working memory
- Associations with depression
- Endocrine abnormalities:
  - Impaired growth hormone secretion in adults (→ can lead to central obesity and reduced bone and muscle mass)
  - Men with OSA have a defect in both GH and testosterone secretion

Pathogenesis of OSA: the role of obesity

1. Obesity is associated with an increased size of upper airway structures (particularly, the tongue) . Excess fat deposition within the tongue and upper airway soft tissues results in upper airway narrowing.
2. Fat deposition in the chest and abdomen. Waist measurement is well-correlated with Obstructive Sleep Apnea (OSA). Abdominal obesity can reduce lung volumes particularly in the supine posture and so reduce upper airway size.



Tongue volume and tongue fat were significantly enlarged in patients with OSA when compared to obese controls.

Kim, A. M., Keenan, B. T., Jackson, N., Chan, E. L., Staley, B., Poptani, H., … Schwab, R. J. (2014). *Tongue Fat and its Relationship to Obstructive Sleep Apnea. Sleep, 37(10), 1639–1648.* doi:10.5665/sleep.4072

Pathogenesis of OSA: the role of obesity

- Increased abdominal girth from excess fat can compress a person's chest wall → decreasing lung volume.
- Reduced lung capacity → diminishes airflow → Upper airway more likely to collapse during sleep.
- OSA risk continues to increase with a rising body mass BMI
- 10% weight gain is associated with a six-fold increase in OSA risk.

https://www.sleepfoundation.org/sleep-apnea/weight-loss-and-sleep-apnea

Pathogenesis of OSA: the role of obesity

- Subcutaneous neck or peripharyngeal fat may be the critical “load” that tips the balance in favor of upper airway closure in sleep.
- The prevalence of OSA increases with age (increased central fat deposition with age)
- Males have a 3-4X increased risk of OSA in the middle aged population, though the prevalence in women increases following menopause.

A neck circumference of more than **35.5 cm** in men and more than **32 cm** in women should be termed obesity.

https://www.sleepfoundation.org/sleep-apnea/weight-loss-and-sleep-apnea

Can Sleep Apnea Cause Weight Gain?

- Excess weight is a known to be a risk factor for OSA, but the **relationship is reciprocal**.
- Sleep deprivation is associated with decreased leptin and increased ghrelin
- Insufficient sleep can lead to overeating.
- Effect of daytime sleepiness on PA.

https://www.sleepfoundation.org/sleep-apnea/weight-loss-and-sleep-apnea

Part 3: Fertility

Introduction

- Obesity reduces fertility in both women and men and is a major factor underlying the prevalence of infertility.
- Maternal obesity also increases the risk of miscarriage and poor pregnancy outcomes significantly, and its transgenerational impact is a key driver of the global epidemic of obesity.

Female Fertility

- Obesity is associated with reproductive disorders.
- For example, women with BMI ≥40 kg/m2 are almost 7X more likely to take more than 12 months to conceive compared with women with a normal BMI
- Obesity decreases also has a pathophysiological role in the development of polycystic ovary syndrome (PCOS).

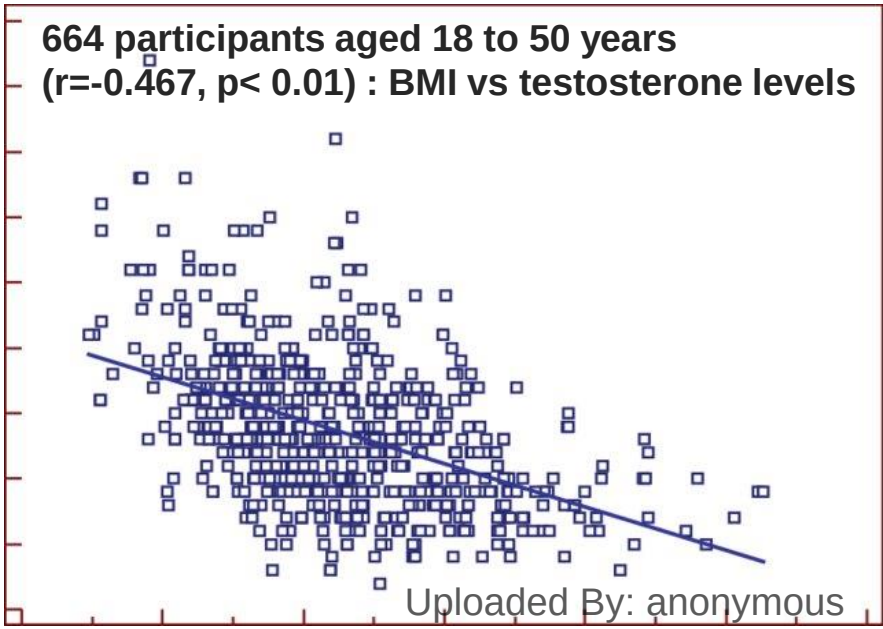
PCOS

- Refer to the hand-out

Male Fertility

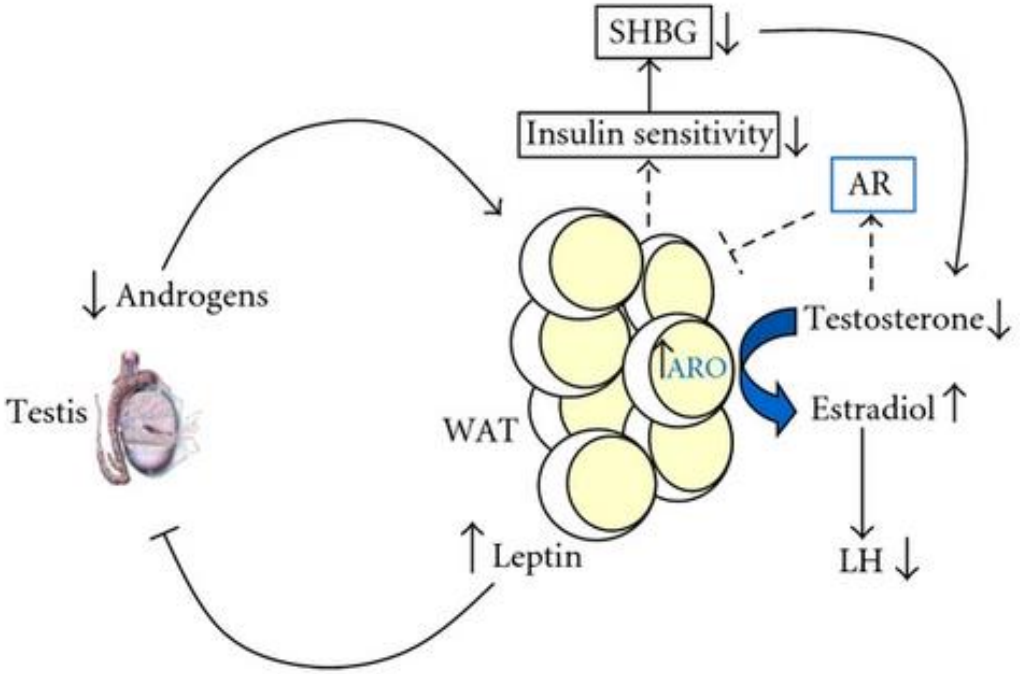
- Obesity in men is associated with various factors that contribute to decreased fertility, including:
  - Reduced plasma testosterone levels
  - Impaired spermatogenesis
- The level of both total and free testosterone is inversely correlated to increasing BMI.

https://www.researchgate.net/publication/303570347_Obesity_is_an_independent_risk_factor_for_low_serum_testosterone_in_adult_males



Male Fertility

- Increased peripheral conversion of testosterone into estradiol in adipose tissue leads to a rise in serum estradiol levels.



Androgens and Adipose Tissue in Males: A Complex and Reciprocal Interplay. Caterina Mammi, Matilde Calanchini, Antonella Antelmi, Francesca Cinti, Giuseppe M. C. Rosano, Andrea Lenzi, Massimiliano Caprio, Andrea Fabbri. First published: 22 December 2011. https://doi.org/10.1155/2012/789653

Assisted reproductive technology

- Men and women with obesity have less success with ART, including IVF, with significantly decreased **implantation**, clinical **pregnancy**, and **live birth** rates.
- Compared to women with a BMI <30, reduction in live birth rate following the initial ART cycle is:
  - 37% for BMI 30.00–34.99
  - 61% for BMI 35.00–39.99
  - 68% for BMI ≥40.0

BMI Threshold?

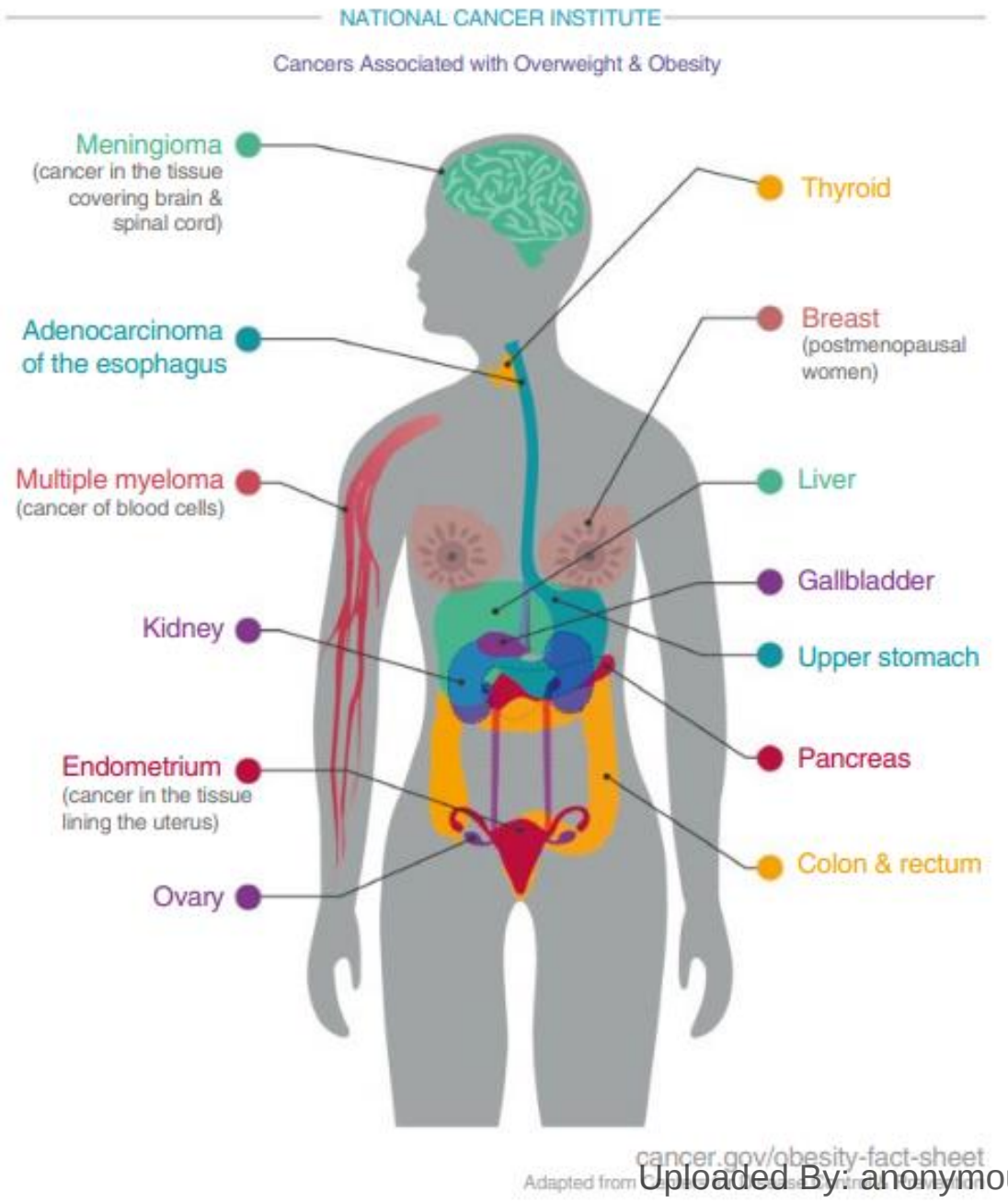
Obesity and pregnancy outcomes

	Maternal	Offspring
Preconception	Reduced fertility	
	Preexisting complications (hypertension, diabetes)	
Antenatal	Miscarriage	Congenital abnormalities (e.g. neural tube defects)
	Gestational diabetes	Small-for-gestational-age
	Preeclampsia	Large-for-gestational-age and macrosomia
	Gestational hypertension	Preterm delivery
	Gastro-esophageal reflux disease	Stillbirth
	Obstructive sleep apnea	
Intrapartum	Induction of labor	Fetal distress
	Prolonged labor and failure to progress instrumental delivery	Neonatal birth injuries (e.g. shoulder dystocia, brachial nerve injury)
	Cesarean section	Neonatal intensive care admission
	Difficulties with fetal heart rate monitoring anaesthetic risks	
	Peripartum death	
Postpartum	Hemorrhage	
	Delayed wound healing and infection	
	Venous thromboembolism	
	Support with breastfeeding	
	Depression	
Long-term	Type 2 diabetes	Obesity
	Dyslipidemia	Impaired glucose tolerance
	Hypertension and cardiovascular disease	Hypertension
		Dyslipidemia

Part 4: Cancer

Introduction

The WHO International Agency for Research on Cancer (IARC) has identified **13 sites or types** of cancer that are prevented by an absence of excess body fatness



Introduction

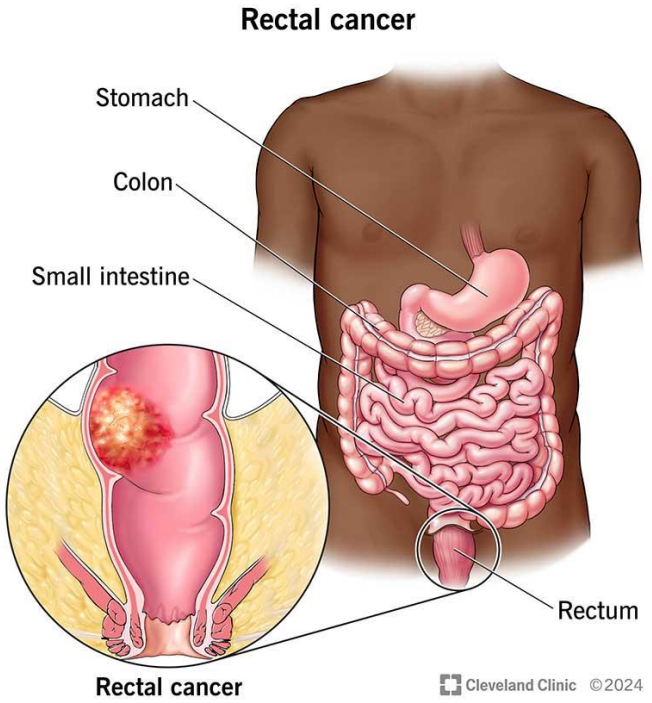
- The World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR) Expert Panel concludes that there is:
  - **Convincing evidence** of increased risk of cancers of the esophagus (adenocarcinoma), pancreas, liver, colorectum, breast (postmenopause), endometrium, and kidney
  - **Probable evidence** of increased risk of cancers of the mouth, pharynx and larynx, stomach cardia, gallbladder, ovary, and prostate (advanced)
  - **Limited evidence** of increased risk of cancer of the cervix

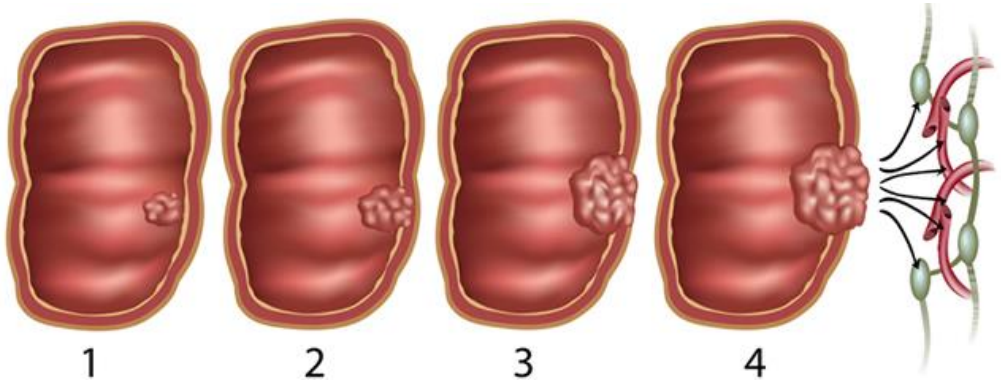
Mechanisms

- Suggested mechanisms include:
  - Insulin resistance (characterized by hyperinsulinemia) and hyperglycemia
  - Insulin-like growth factor 1 (IGF-1) effect
  - Certain cytokines and low-grade inflammation: Leptin and Adiponectin

Colorectal cancer

- Most colorectal cancers are adenocarcinomas located on the inner wall of the colon or rectum.
- There is strong evidence that being **overweight or obese** increases the risk of colorectal cancer.





Colorectal cancer

- Meta-analysis of prospective cohorts shows a 6% increase (95%CI 4–7) in risk of **colorectal cancer** for every 5 kg/m2 higher BMI (slightly stronger in men)
- The association of BMI with **colon cancer** is linear across the spectrum of BMI, whereas for **rectal cancer**, only those with a BMI >27 kg/m2 are at increased risk

Colorectal Cancer

- The weaker association with female obesity can be explained by:
  1. Different body fat distribution and difference in adipocytokines
  2. Higher insulin sensitivity
- The association between female gender, obesity, and colon cancer was stronger when **waist–hip ratio** and **waist circumference** were used as surrogate measures of obesity instead of BMI.

Colorectal cancer: Risk Factors

- **Insulin and IGF-1**

Insulin can stimulate production of insulin-like growth factor 1 (IGF-1)

IGF-1 receptors exist on both normal and colonic adenocarcinoma → binding of IGF-1 → cell cycle progression and inhibition of normal apoptosis.

IGF-1 is capable of promoting angiogenesis.

A significant link between insulin/IGF-1 and the activation of a pathway which induces the transformation from adenoma to invasive carcinoma.

Colorectal cancer: Risk Factors

- **Leptin**

Leptin has also been shown to stimulate oncogenic pathways in colonic adenocarcinoma cell lines. (inhibit apoptosis, induce angiogenesis, and promote cellular proliferation)

- **Adipocytokines**

Potent proinflammatory substances such as TNF-α, IL-6 may provide a link between a low-grade inflammatory state associated with obesity and colorectal cancer.

Colorectal cancer: Risk Factors

- The Crucial Effect of Exercise

Exercise has been shown to decrease the incidence of colorectal cancer **even in obese populations** (20% risk reduction for men and a 14% risk reduction for women for colon cancer), with a *linear dose–response* relationship.

Mechanisms? Shortening intestinal transit time, enhances immune function, maintains insulin sensitivity, lowers the activity of insulin-like growth factor, and decreases adiposity.