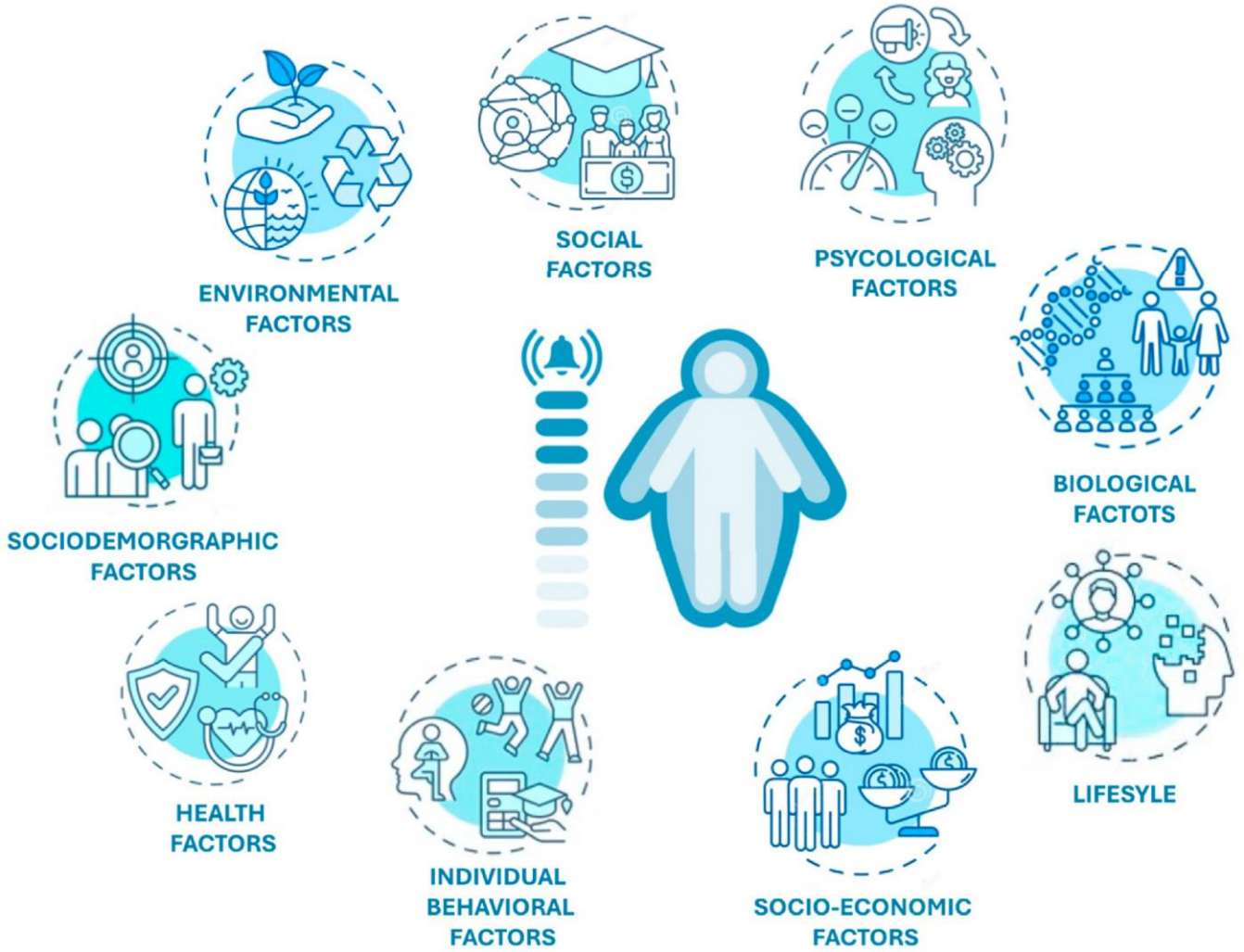
Principal biological determinants of obesity

Obesity is determined by an enormous complexity of the causal factors and their interrelationships, clearly indicating that individual physiology and behaviour are shaped by strong social and local environment factors.



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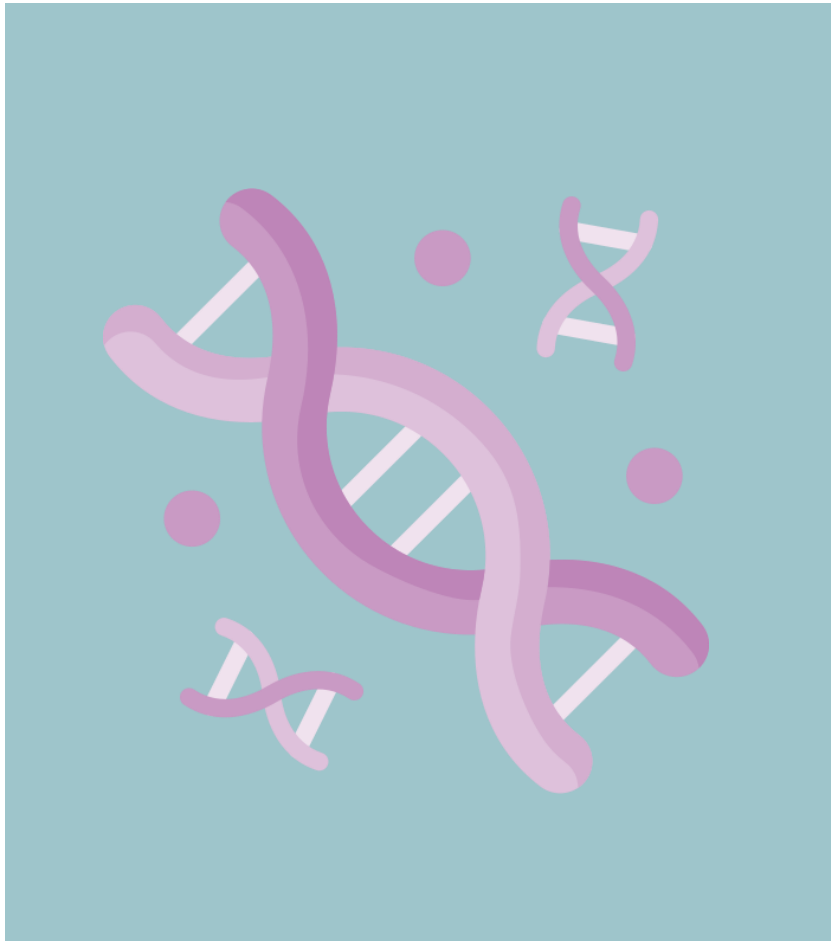
Biological determinants - genetics



- **Genetics variables** are known to set an individual's susceptibility to obesity. Monogenic (one gene) and polygenic (multiple genes) mutations may contribute like genes related to appetite and weight regulation systems (hypothalamus) or the reward systems (meso-limbic region of the brain).

- **Epigenetic** alterations, driven by pathological conditions (for example maternal obesity during pregnancy) may also shape obesity susceptibility by altering DNA regulation (mainly via changes in methylation patterns).

Based on Kong Y, et al. *Molecular biomedicine*, *6*(1), 25 (2025) - https://doi.org/10.1186/s43556-025-00264-9

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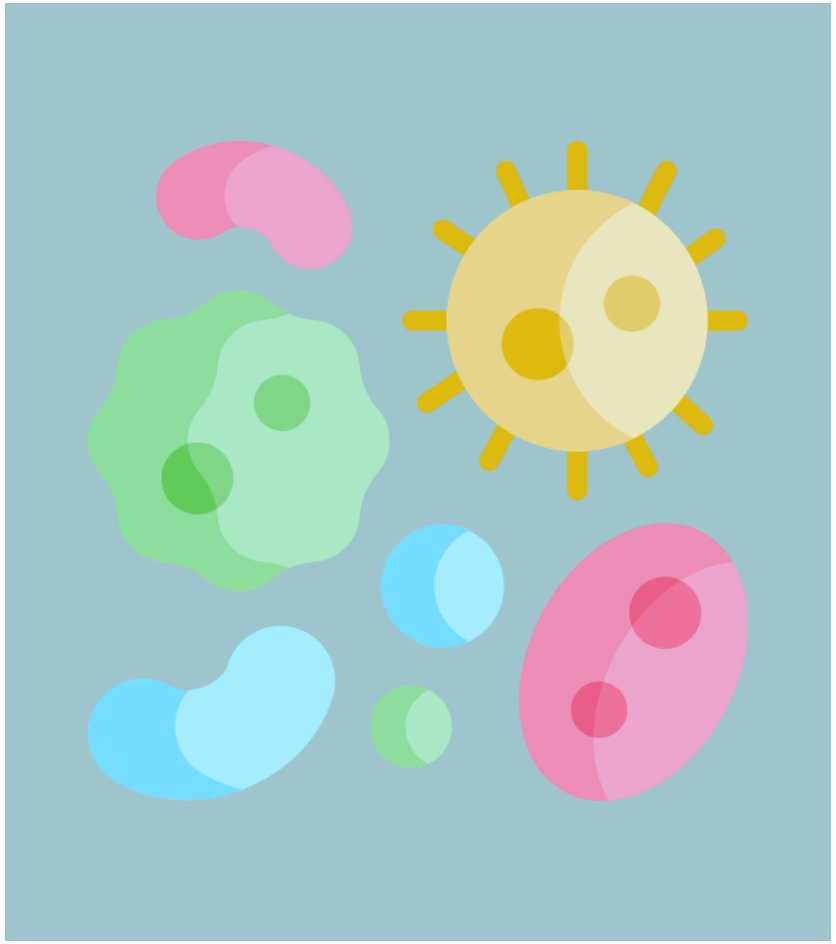
Biological determinants – gut microbiome



- The **gut microbiome** is a key regulator of host energy and substrate metabolism. Reduced microbial diversity and a decrease in bacteria-producing metabolites like short-chain fatty acids (acetate, propionate and butyrate) became known in the past decades to contribute to disrupted energy and substrate metabolism, affecting tissues such as adipose tissue, skeletal muscle, and the liver.
- **Gut microbiota dysbiosis** leads to a weakened intestinal barrier, circadian disruption, activation of inflammation and insulin resistance. As such, gut microbiota alterations have been linked to the development of obesity-related chronic low-grade inflammation.

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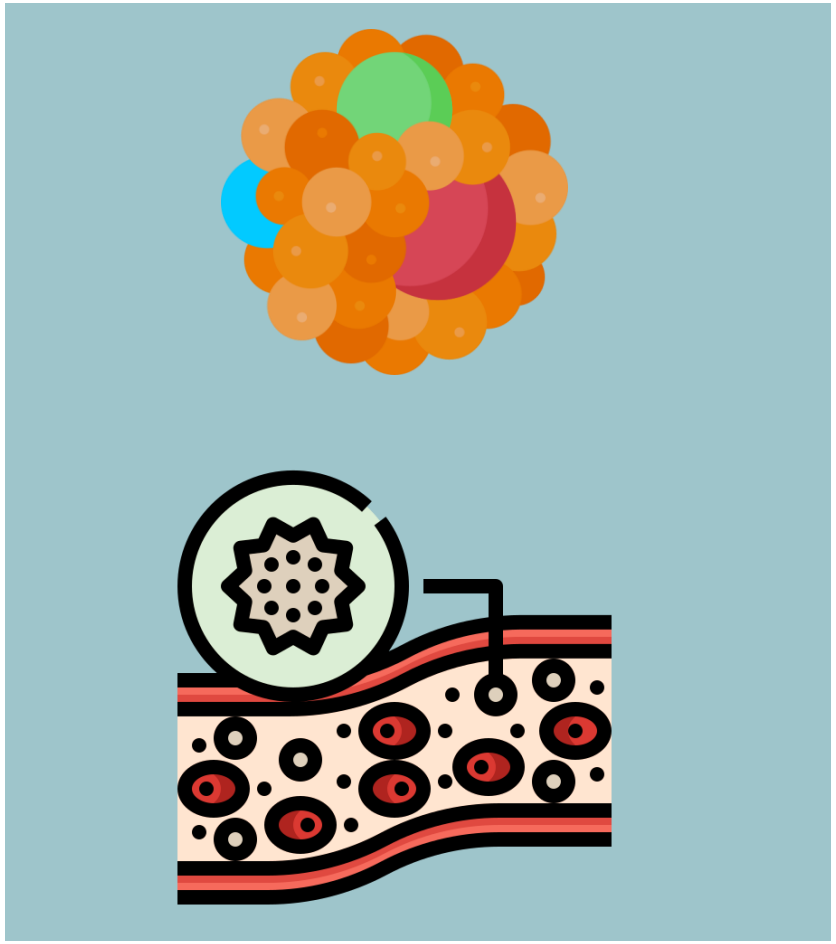
Biological determinants – inflammation



- In obesity, the release of **pro-inflammatory cytokines** from dysfunctional adipocytes and activated immune cells in the adipose tissue can cause insulin resistance and **systemic low-grade inflammation.**
- As obesity triggers a self-perpetuating cycle of **monocyte/macrophage infiltration** in the (dysfunctional) adipose tissue, it perpetuates low-grade chronic inflammation.
- **Other immune cell alterations** may contribute to the sustained inflammatory status, including neutrophils, regulatory T-cells, and increased B-cell, mast cell, dendritic cell, and eosinophil activity.

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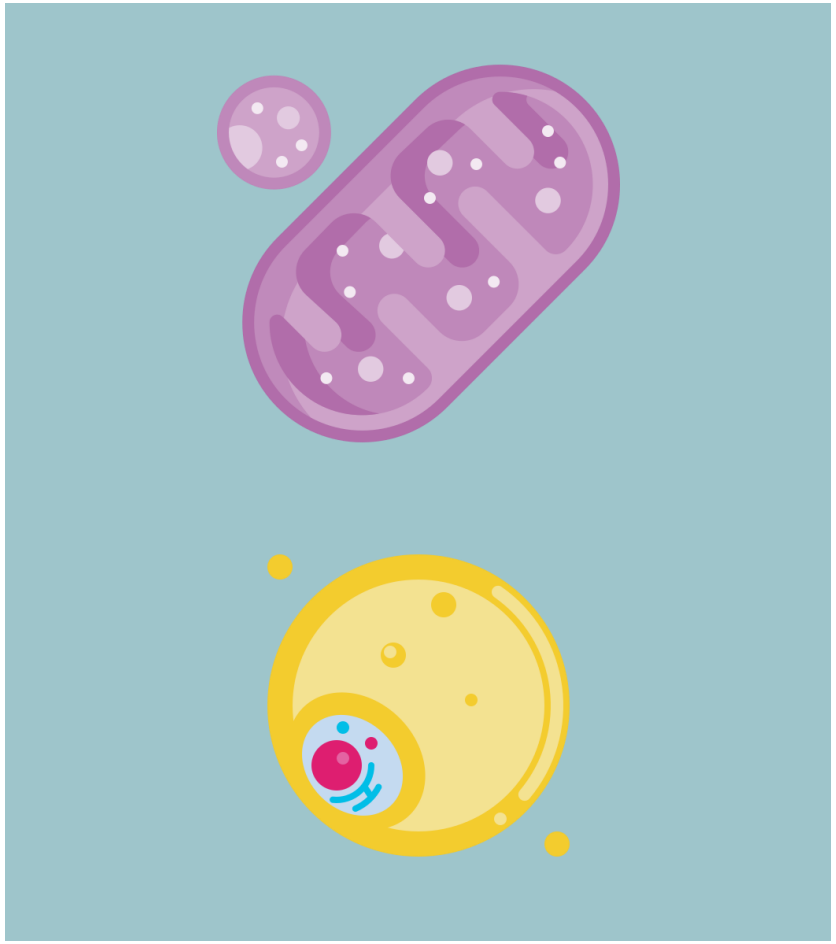
Biological determinants – metabolic imbalance



- **Mitochondrial malfunctioning** drives (partly) metabolic inflexibility of adipocytes in obesity, contributing to metabolic dysfunction.
- **Metabolic dysfunction**(s): low metabolic rate or insulin resistance promote disrupted energy balance, where excess energy is retained in adipocytes.
- **Dysfunctional adipocytes** impair metabolic homeostasis, initiating and sustaining a vicious cycle.

Based on Kong Y, et al. *Molecular biomedicine*, *6*(1), 25 (2025) - https://doi.org/10.1186/s43556-025-00264-9

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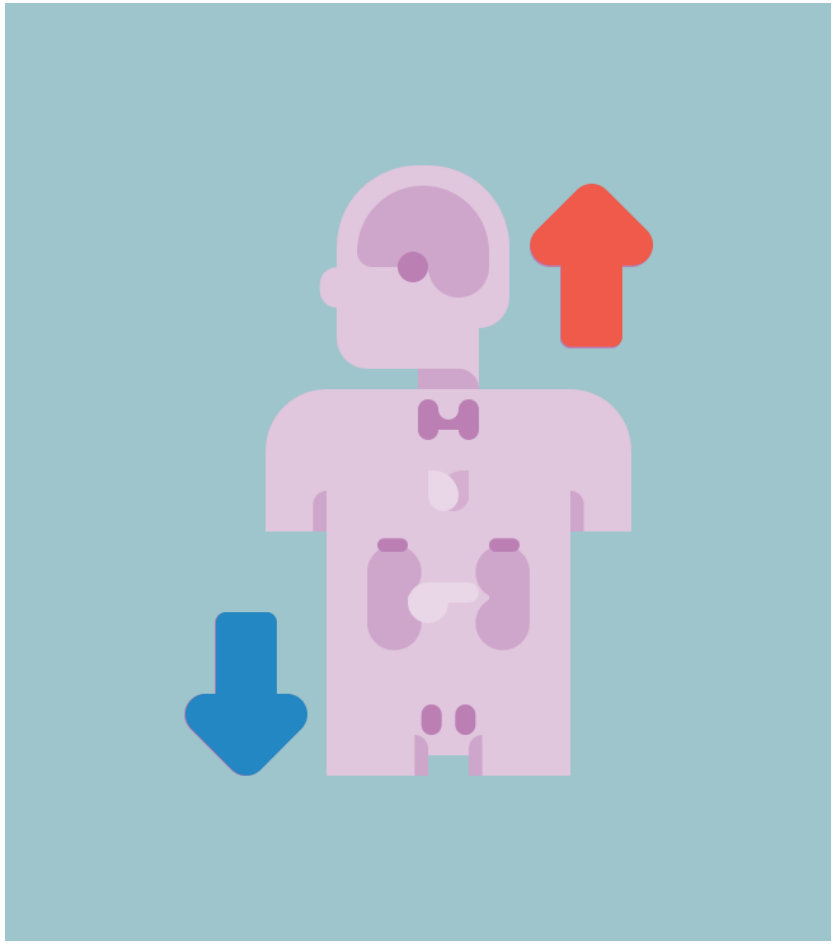
Biological determinants – hormonal regulation



- **Hormonal dysregulation**: mainly related to appetite control, satiety in the brain.
- **Leptin resistance** of the hypothalamic region (arcuate nucleus) in the brain diminishes satiety signaling, hyperphagia, and progressive body mass accumulation (partly due to lower fat oxidation, as adiponectin levels are lower in obesity).
- **Lipotoxicity** (e.g. increase release of free fatty acids from adipose tissue) causes ectopic lipid deposition (e.g. in muscle, liver, pancreas), thereby **impairing insulin sensitivity** of these tissues.
- **Reduced ghrelin signaling and sensitivity** contribute to hypothalamic ghrelin resistance

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