



Body Weight, Novel Therapies and Longevity

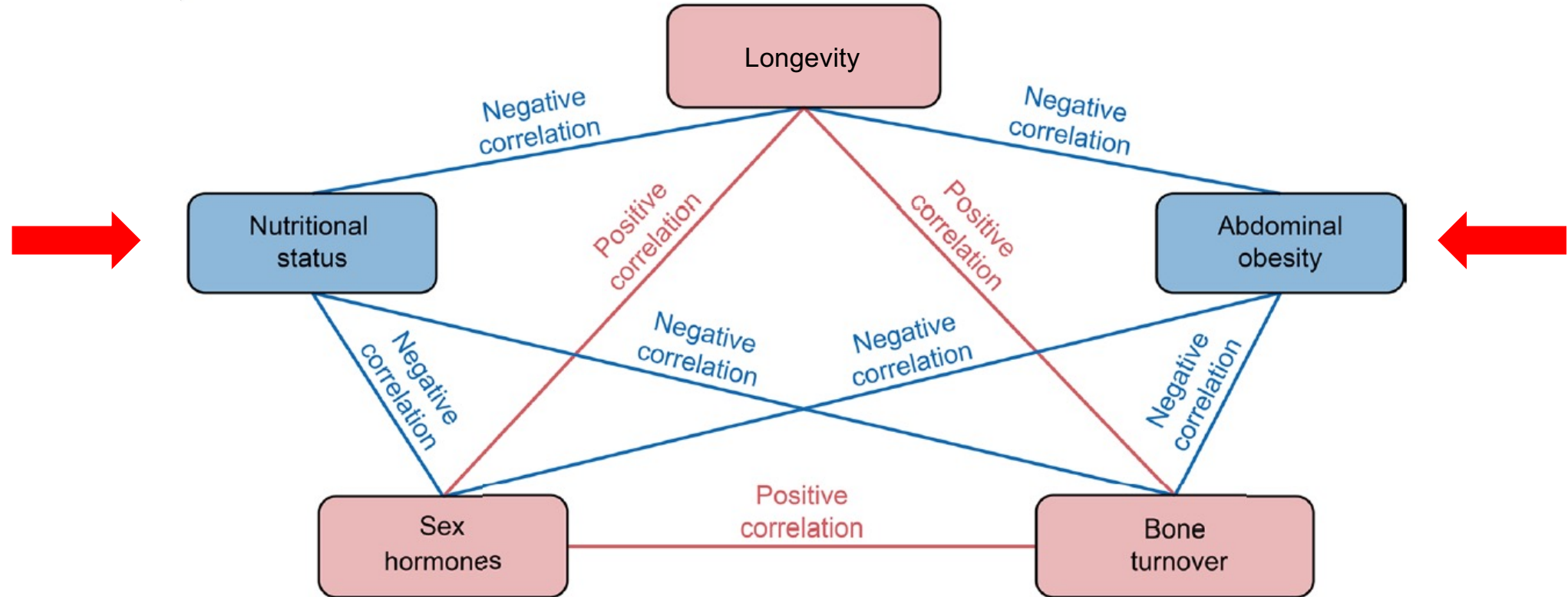
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Educazione alla Salute e
allo Sviluppo Sostenibile



Body weight, hormones and longevity



Body weight and life expectancy

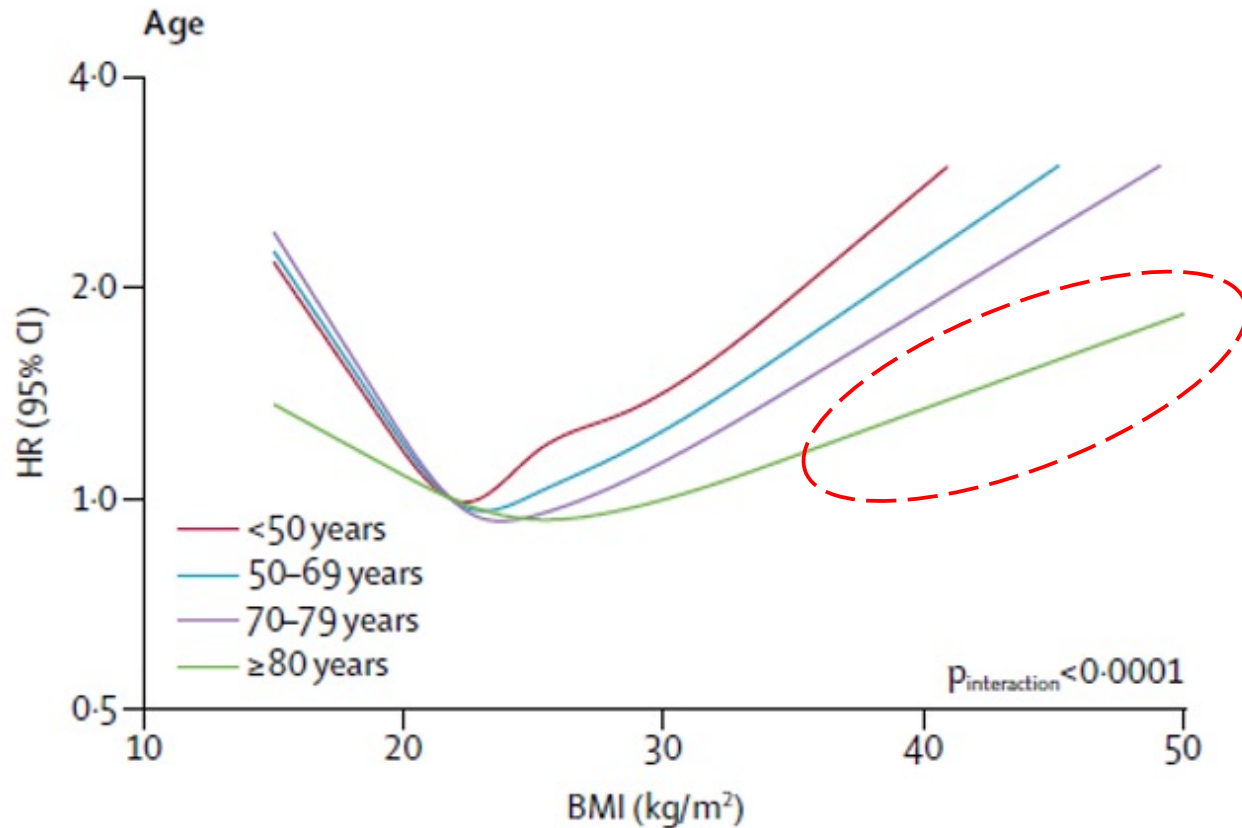
	Men		Women	
	Expected age of death at age 40 years (years)	Reduction in life expectancy (years)	Expected age of death at age 40 years (years)	Reduction in life expectancy (years)
Underweight (<18.5 kg/m ²)	77.9	4.3	79.8	4.5
Healthy weight (18.5–24.9 kg/m ²)	82.2	..	84.3	..
Overweight (25.0–29.9 kg/m ²)	81.2	1.0	83.5	0.8
Obese (all, ≥30.0 kg/m ²)	78.0	4.2	80.9	3.5
Obese class 1 (30.0–34.9 kg/m ²)	78.7	3.4	81.9	2.4
Obese class 2 (35.0–39.9 kg/m ²)	76.2	5.9	79.6	4.7
Obese class 3 (≥40.0 kg/m ²)	73.1	9.1	76.6	7.7

Expected age of death at age 40 years estimated from a Poisson model for overall survival with six-category BMI variable, 5-year age bands, sex, and interaction terms for BMI with age at BMI, and BMI with sex (see appendix for details); estimates assume mortality observed in the study remains constant. Reduction in life expectancy is calculated as expected age of death minus expected age at death in the healthy weight category.

N= 3 632 674 individuals

Bhaskaran et al. - Lancet Diabetes Endocrinol, 2018

Body weight, age and mortality risk

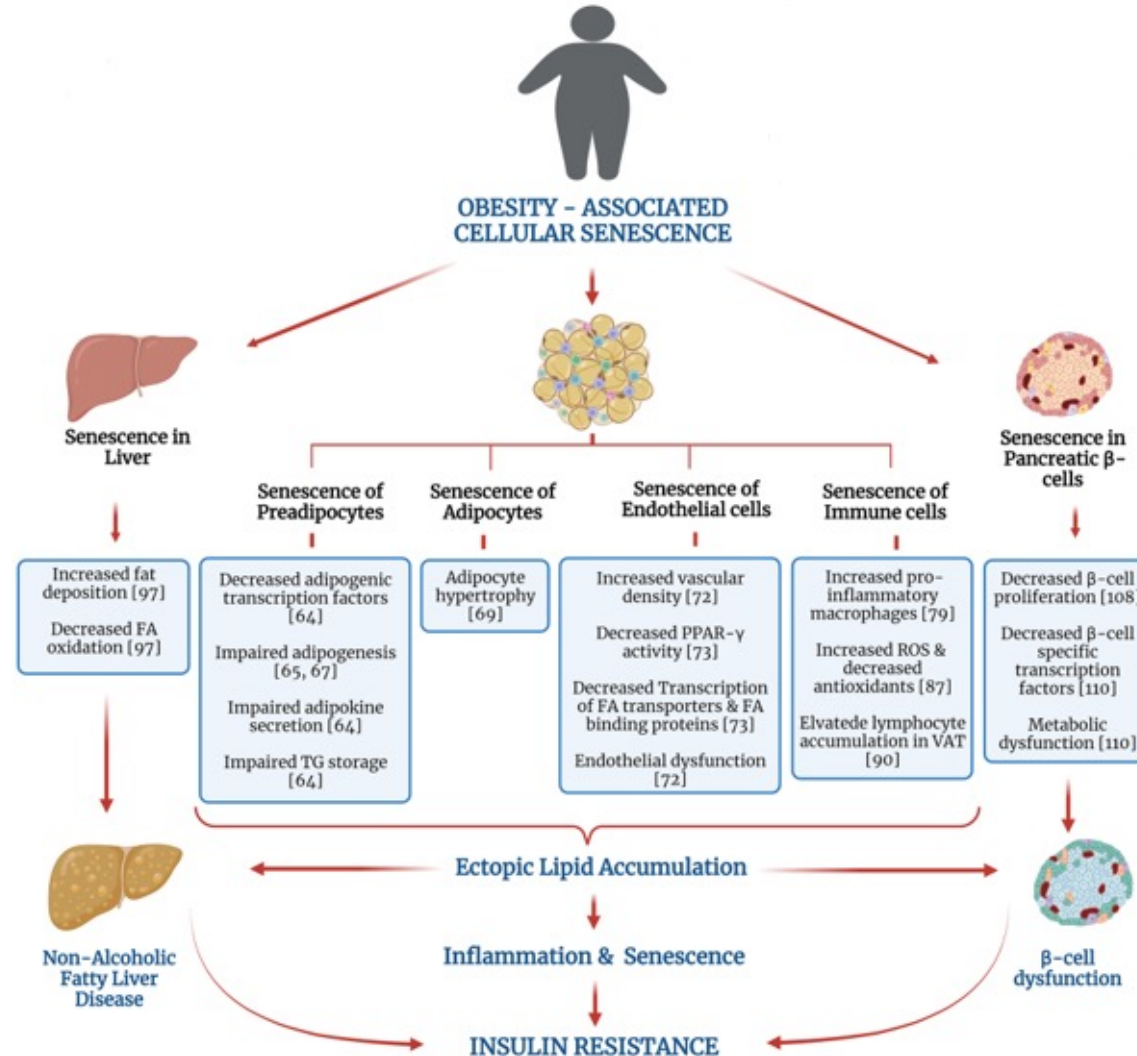


estimates adjusted for age, deprivation, calendar year, diabetes, and alcohol status (all as defined at date of BMI measure) and stratified by sex.

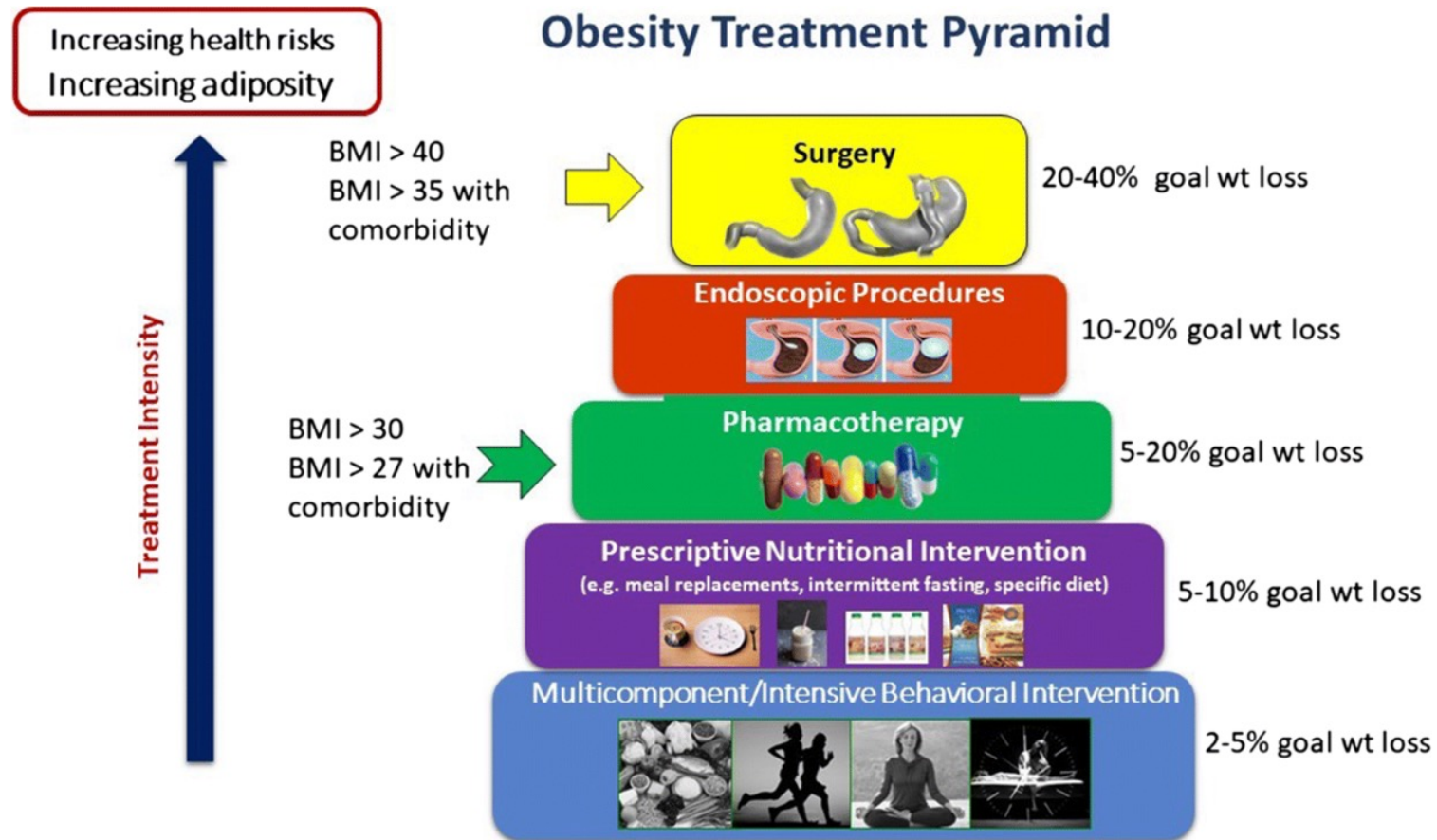
HR=hazard ratio.

- BMI had a **J-shaped association** with overall mortality
- However, the analyses stratified by age suggested that mortality was minimised in older individuals at higher BMI, perhaps indicating increased **importance of nutritional reserves in older age**
- There is increased risk of reverse causation in older people because of the increased prevalence of most diseases, and BMI might be compromised as a measure of **loss of muscle mass**

Obesity-associated cellular senescence



Treating obesity and its metabolic complications





The Impact of Different Nutritional Approaches on Body Composition in People Living with Obesity

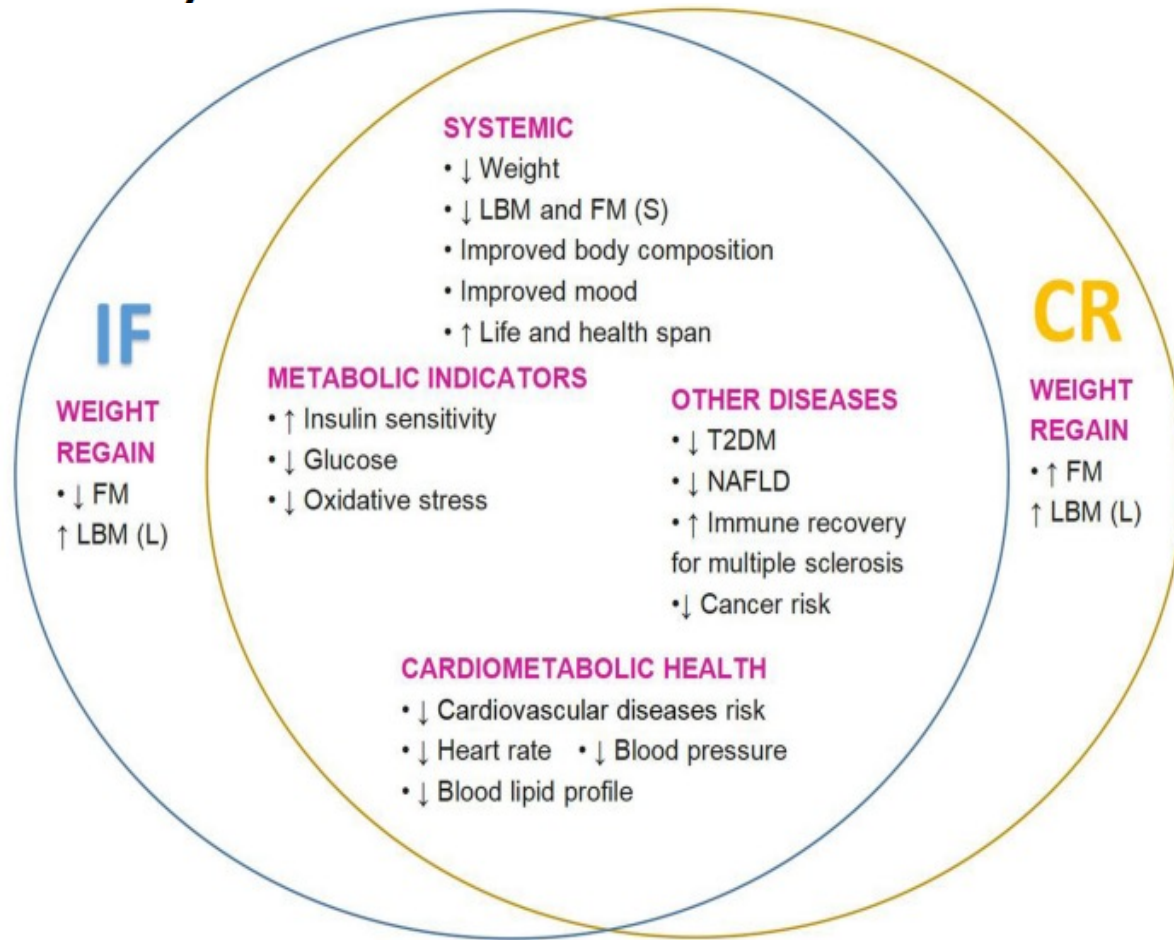
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- **High-protein** diet is associated with greater **preservation of lean body mass** (FFM)
- **Ketogenic diet** is associated with a significant **reduction in visceral adipose tissue** (VAT)
- **Mediterranean diet** has less dramatic results but allows for **long-term adherence** and improvements in **metabolic changes**
- The nutritional approach must be **personalized** based on the **necessary changes** in **body composition**, beyond simple weight loss.

Diets*	Composition of diet	FM	FFM	VAT	SAT
Low energy diet (LED) [22]	800–1200 kcal/die, P 15–25%, C 45–55%, F 20–30%	↓	↔	↓	↓
Very low energy diet (VLED) [23]	400–800 kcal/die, P 20%, C 60%, F 20%	↓↓	↓	↓↓	↓
Low fat diet (LFD) and very low fat diet (VLFD) [24]	P 10–35%, C 45–70%, F 10–25%	↓	↔	↓	↓
Low carbohydrate diet (LCD) [25]	P 20–30%, C 20–45%, F 30–50%	↓	↔	↔	↓
Ketogenic diet (KD) [26]	650–800 kcal/die, P 40–45%, C < 10%, F 30–40%	↓↓	↔	↓	↓↓
High protein diet (HPD) [27]	P > 25–35%, C 30–40%, F 25–35%	↓	↑	↔	↔
Mediterranean diet (MD) [28]	P 10–20%, F < 30%, C 45–55%	↓	↔	↓	↓

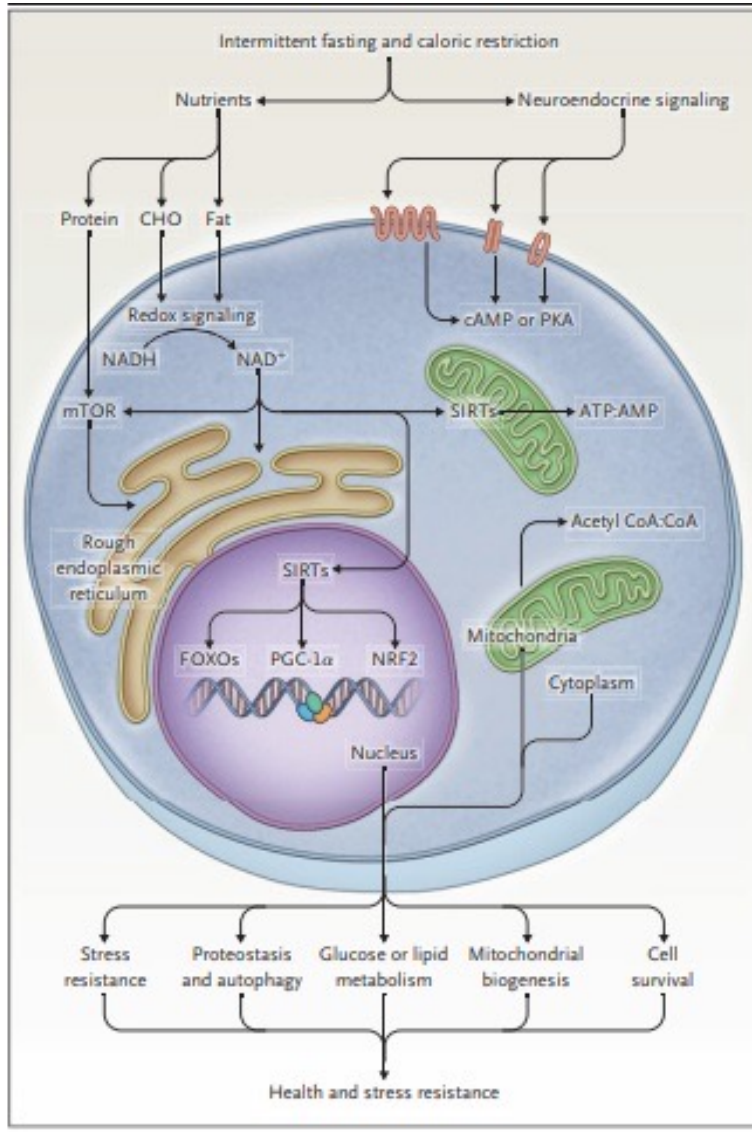
*with energy deficit. P, protein; F, fat; C, carbohydrate; FM, fat mass; FFM, fat free mass; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; ↓ decrease; ↑ increase; ↔ non significant

Is Intermittent Fasting Better Than Continuous Energy Restriction for Adults with Overweight and Obesity?



- Both intermittent fasting and continuous energy restriction achieved a **comparable effect in promoting weight-loss** and **metabolic improvements**.
- During weight regain, continuous energy restriction increased fat mass and lean body mass, whereas **intermittent fasting decreased fat mass while increasing lean body mass**

Fasting and longevity

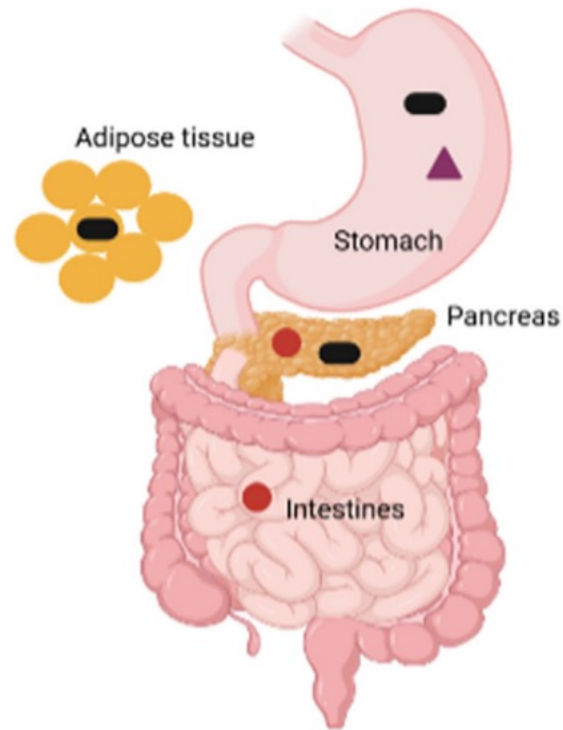
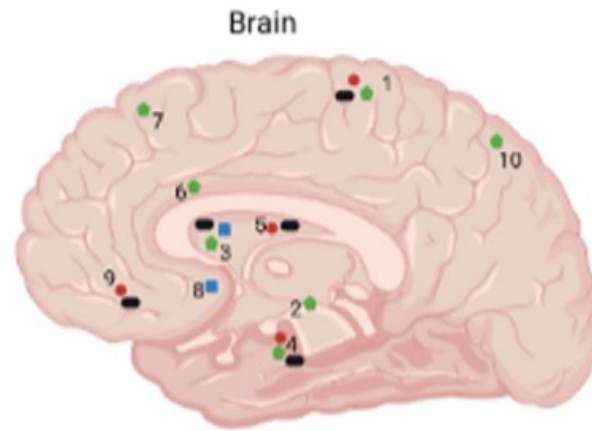


- Fasting (especially **time-restricted eating**) induces neuroendocrine signals and a reduction in amino acid, glucose, and insulin concentrations.
- Downregulation of the IGF-1 signaling pathway and a reduction in circulating amino acids repress mTOR activity, resulting in **inhibition of protein synthesis** and **stimulation of autophagy**.
- The AMP-to-ATP ratio increases, and AMPK is activated, triggering the **inhibition of anabolic processes** (synthesis, growth, and reproduction).
- Epigenetic modifications (SIRT's that deacetylate FOXO and PGC-1) occur, increasing the expression of genes involved in **stress resistance** and **mitochondrial biogenesis**.



PROMOTING CELLULAR SURVIVAL

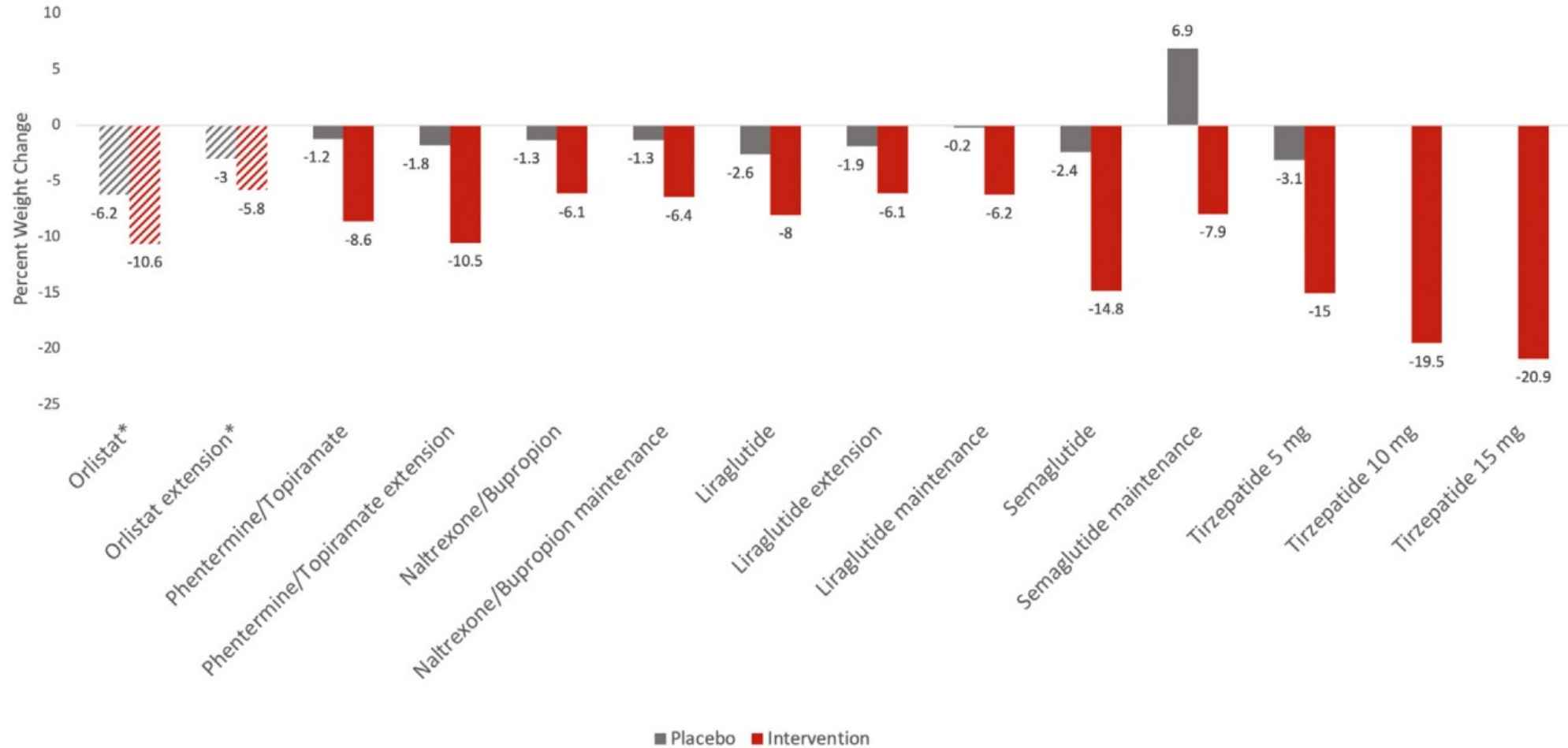
Mechanism of action of anti-obesity drugs

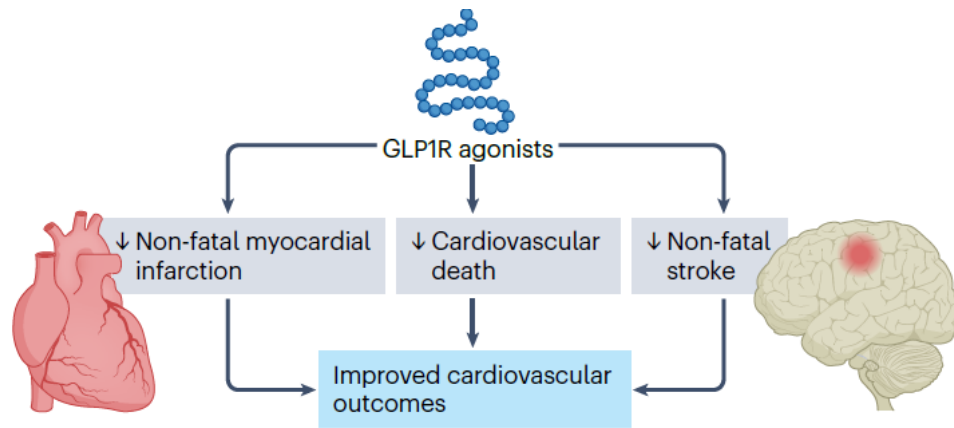


- (1) parietal cortex
- (2) Hippocampus
- (3) Hypothalamus
- (4) Insula
- (5) putamen
- (6) dorsal anterior cingulate
- (7) superior frontal cortex
- (8) nucleus accumbens
- (9) orbitofrontal cortex
- (10) superior parietal cortex

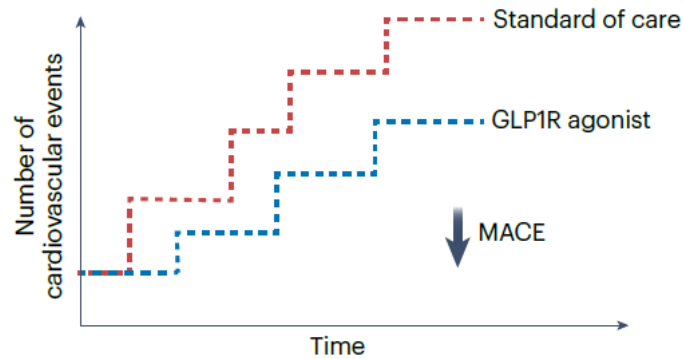
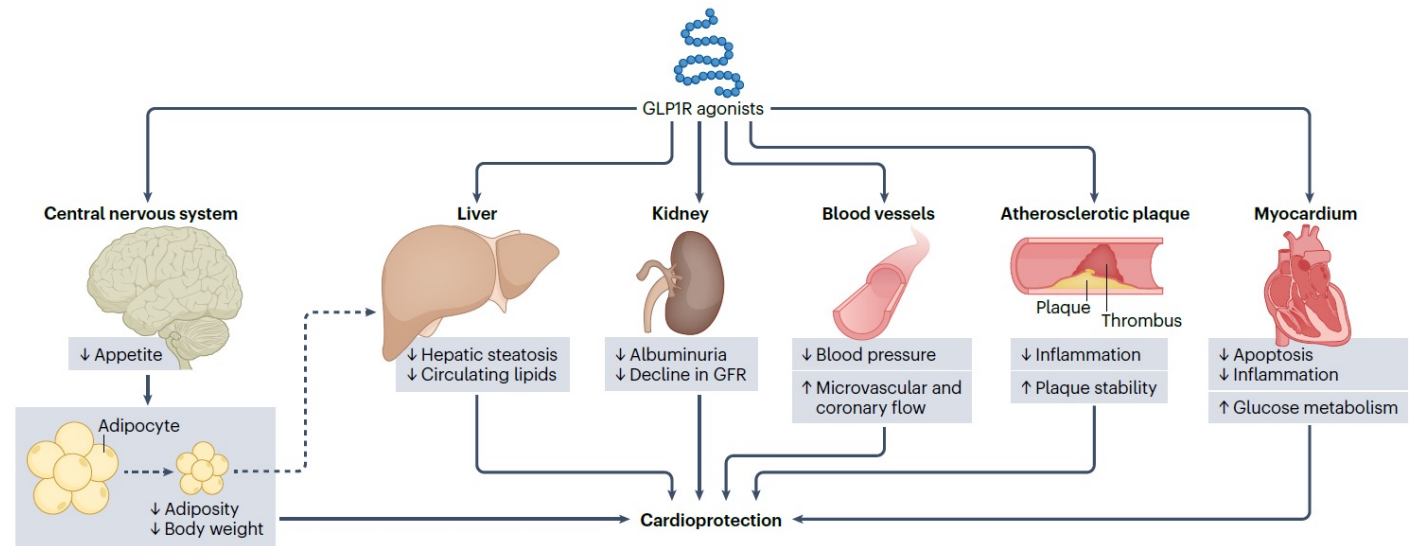
Medication	Central site of action	Peripheral site of action
● GLP-1 Receptor Agonists	1,3,4,5,9	Gastrointestinal tract
◆ Naltrexone/Bupropion	1,2,3,4,6,7,10	None
■ Phentermine/Topiramate	2,3,8	None
▲ Orlistat	None	Gastrointestinal tract
● GIP/GLP-1 dual agonists	1,3,4,5,9	Adipose tissue, gastrointestinal tract

Weight loss with anti-obesity drugs





GLP-1 Agonists and Cardiovascular Diseases



MACE: major adverse cardiovascular events

Ussher & Drucker -. Nat Rev Cardiol, 2023

Wednesday, September 2, 2026

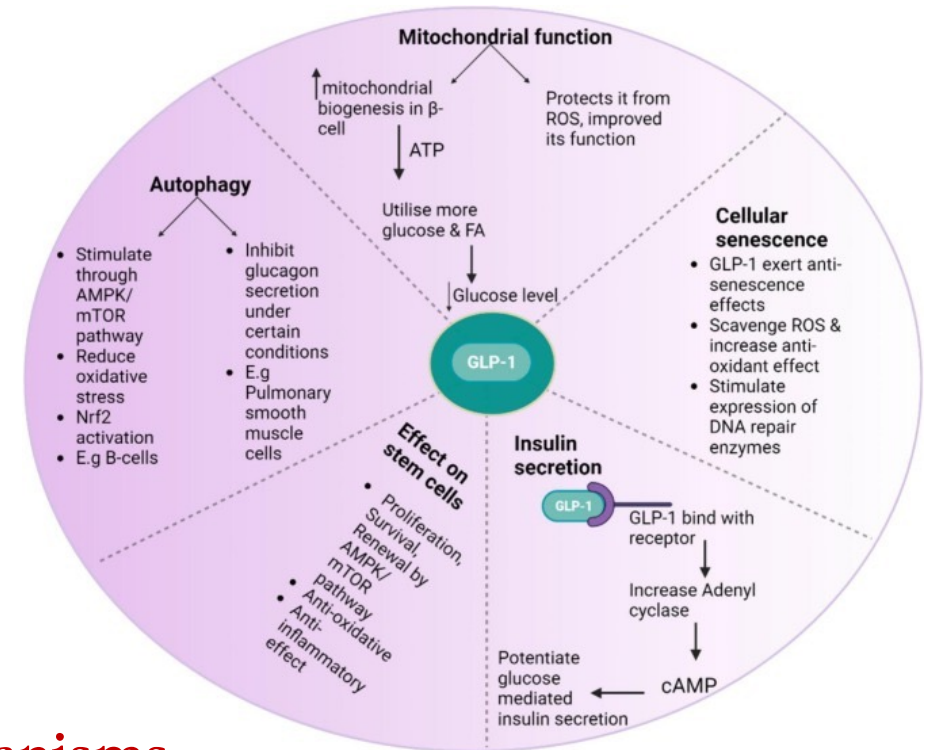
GLP-1 treatment late in life extends lifespan in animal model

Medication produced benefits beyond what was achieved by calorie restriction alone.

The New York Times

Are Weight-Loss Drugs Also Longevity Drugs?

Experts are intrigued by the theory. Here's what early research suggests.



... proposed mechanisms...

Late-life semaglutide treatment slows ageing and extends lifespan in female mice

<https://doi.org/10.1038/s41586-026-10940-7>

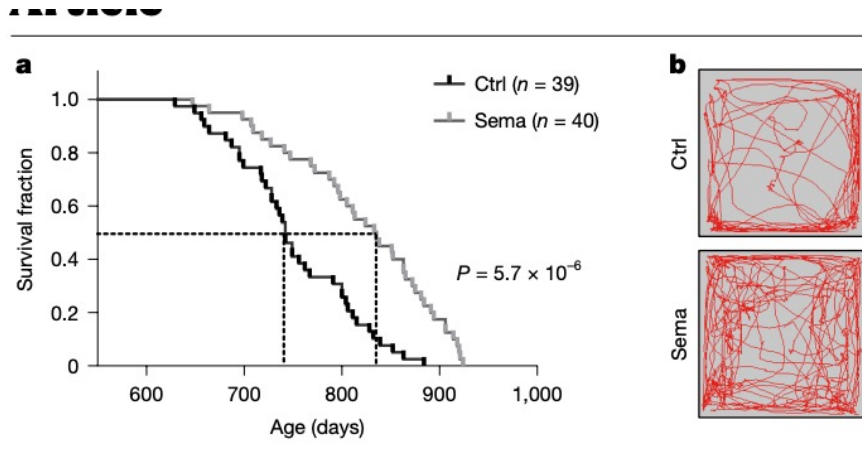
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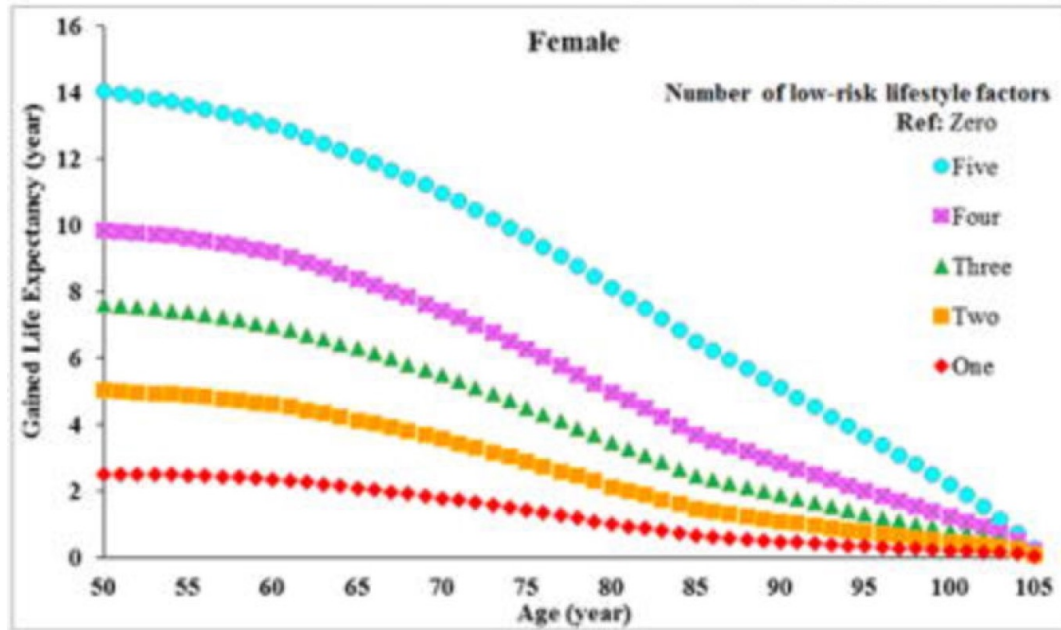
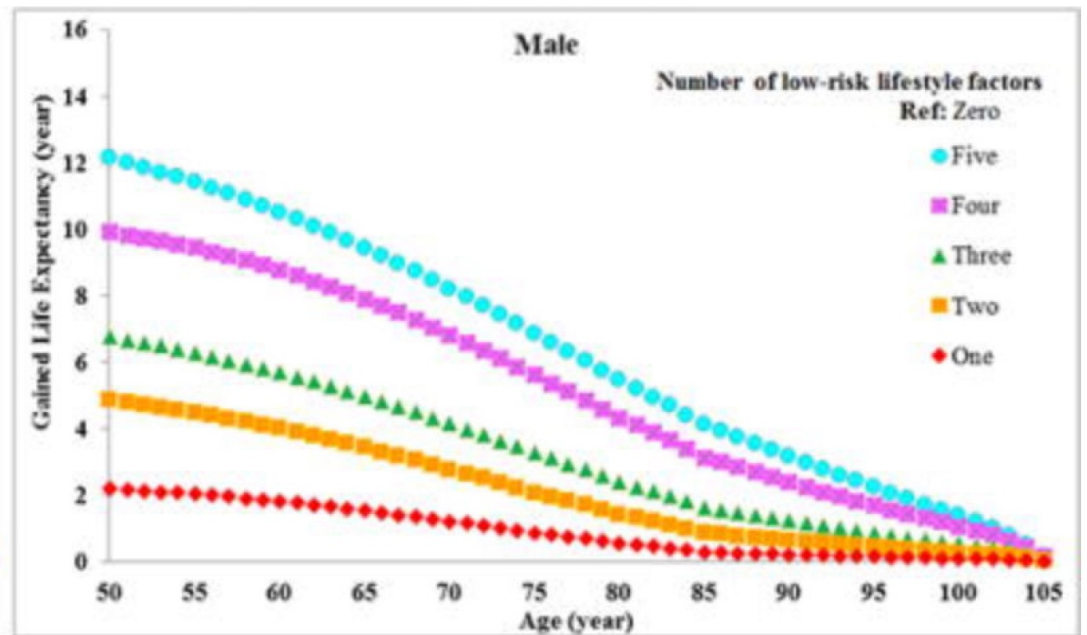
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Pharmacological glucagon-like peptide-1 receptor (GLP-1R) activation reduces food



Pharmacological glucagon-like peptide-1 receptor (GLP-1R) activation reduces food intake and is an effective therapy for type 2 diabetes and obesity¹. The use of GLP-1 medicines has revealed pleiotropic beneficial effects beyond glucose and weight control^{2–5}, but little is known about the underlying basis of the pleiotropic effects. Here, treatment of 20-month-old female C57BL/6 mice with the GLP-1R agonist semaglutide for 3 months improved physiological function, attenuated hallmarks of ageing and modulated nutrient sensors and conserved genetic regulators of ageing. Continued treatment extended mouse lifespan. These effects parallel key features of calorie restriction, a dietary intervention that slows ageing, extends lifespan and alleviates a wide spectrum of ageing-associated diseases⁶. In a longitudinal study in direct comparison to matched calorie restriction, semaglutide treatment preserved baseline function and recapitulated many functional benefits of calorie restriction by attenuating age-associated decline, while also producing improvements above baseline and more favourable trajectories than calorie restriction in exploratory drive, spatial memory and glucose control. Together, these findings demonstrate that GLP-1R activation initiated late in life slows ageing and extends lifespan in female mice, supporting its function as a calorie restriction mimetic and providing a mechanistic framework that may help to explain its broad beneficial effects while revealing effects beyond those attributable to reduced calorie intake.

Lifestyle and longevity (over BMI)



Low-risk lifestyle factors included:

- normal weight (body mass index <25 kg/m²)
- cigarette smoking (never smoking)
- physically active (≥ 3.5 hours/week moderate to vigorous intensity activity)
- high diet quality (upper 40% of alternative healthy eating index (AHEI))
- moderate alcohol intake of 5–15 g/day (female) or 5–30 g/day (male)

Take-home message



Beyond simple weight loss: Body composition and overall lifestyle quality matter more than body weight only for ensuring longevity

The BMI paradox in older age: In elderly individuals, a higher BMI can be protective by providing essential nutritional reserves

Body composition: Dietary approaches must be tailored to specific goals (i.e., reducing visceral fat, preserve lean muscle mass)

Diet promoting longevity: Fasting triggers autophagy, optimizes body composition, and actively promotes cellular survival

The new therapy revolution: Modern anti-obesity achieve weight reductions exceeding 20%, provide crucial cardioprotection, and emerge as potential longevity therapies



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