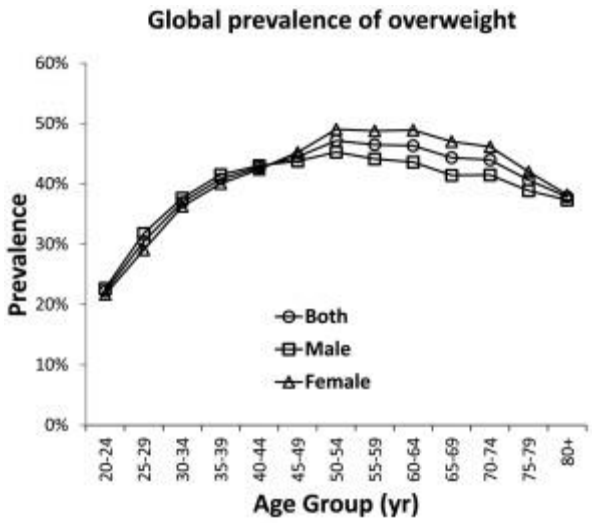
Sovrappeso-obesità e infertilità femminile

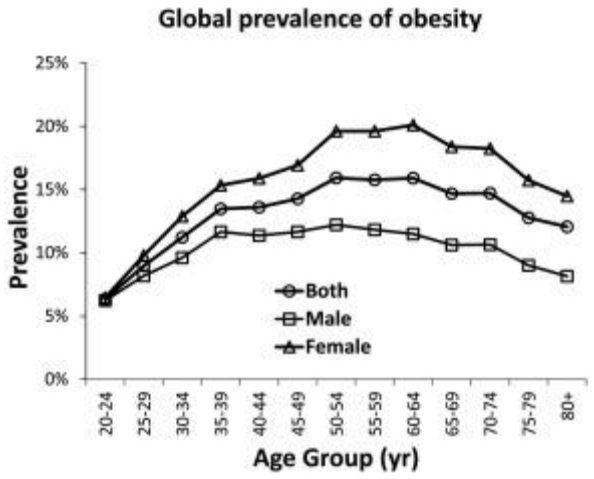
Approcci preventivi e terapeutici

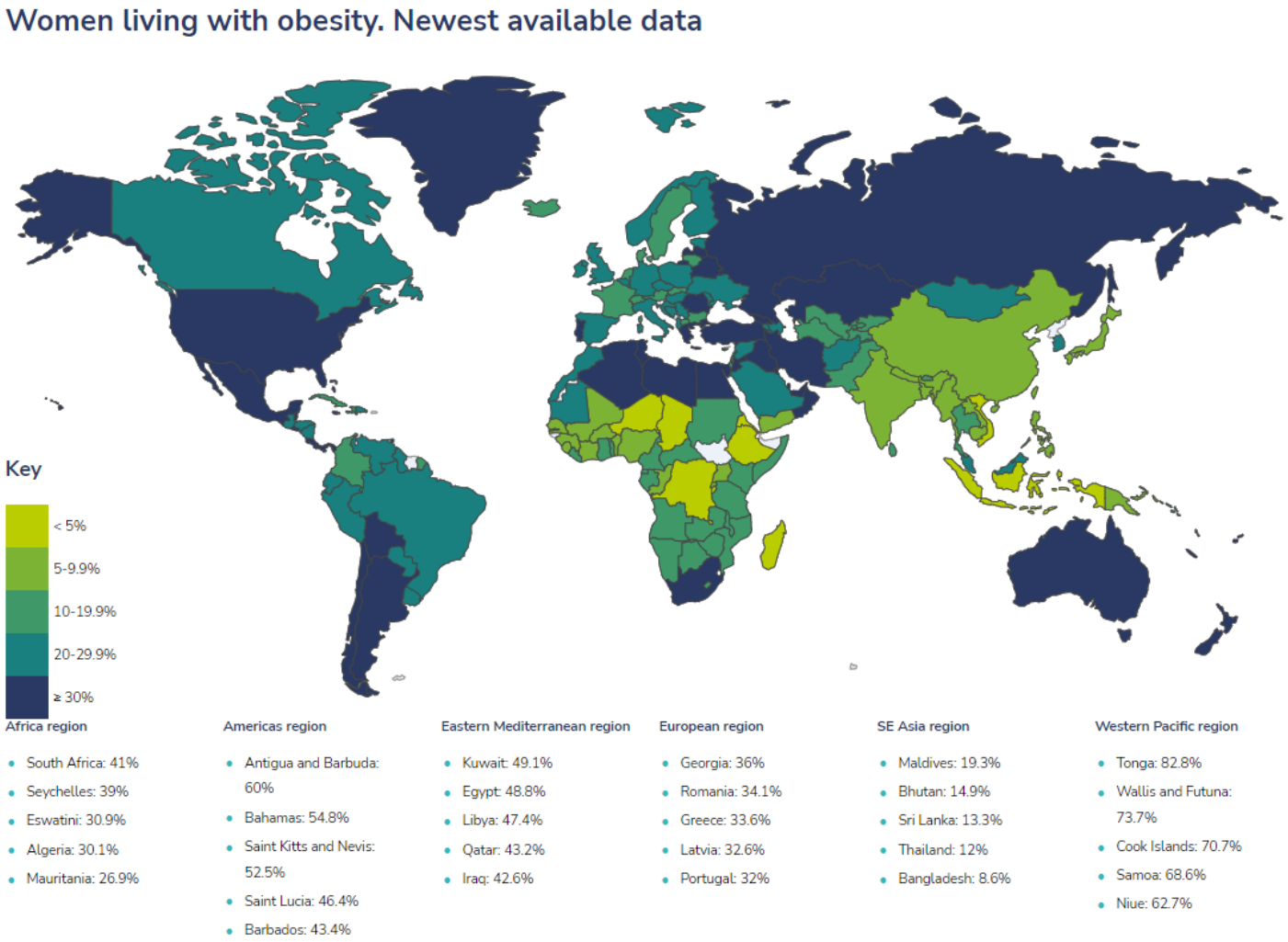
Dott.ssa Giulia Maria Pontesilli

Medicina Interna
Ospedale Santa Maria della Misericordia – Rovigo
Università di Padova

Epidemiologia







https://data.worldobesity.org/, 2023

In Italia più di **25 milioni** di persone sono affette da obesità o sovrappeso.
Il **46% degli adulti** (oltre 23 milioni) e il **26,3% dei bambini e adolescenti** tra i 3 e i 17 anni (2,2 milioni)

Chooi YC, Ding C, Magkos F. The epidemiology of obesity. Metabolism. 2019

Italian Barometer Obesity Report, riferito all'anno 2021, realizzato da IBDO Foundation in collaborazione con Istat, Coresearch e Bhave.

Una malattia cronica, recidivante, progressiva

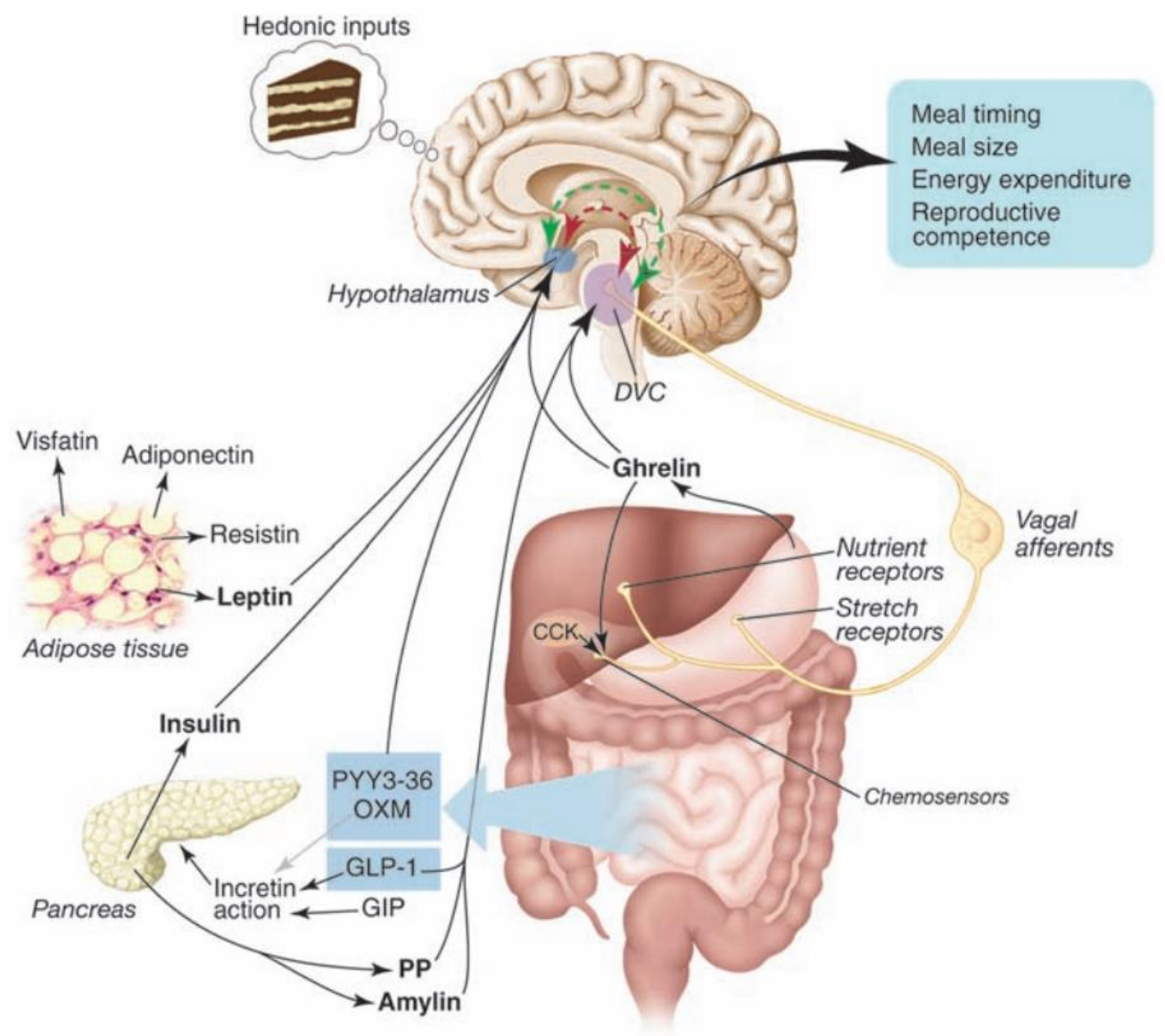
World Obesity Federation Position Statement

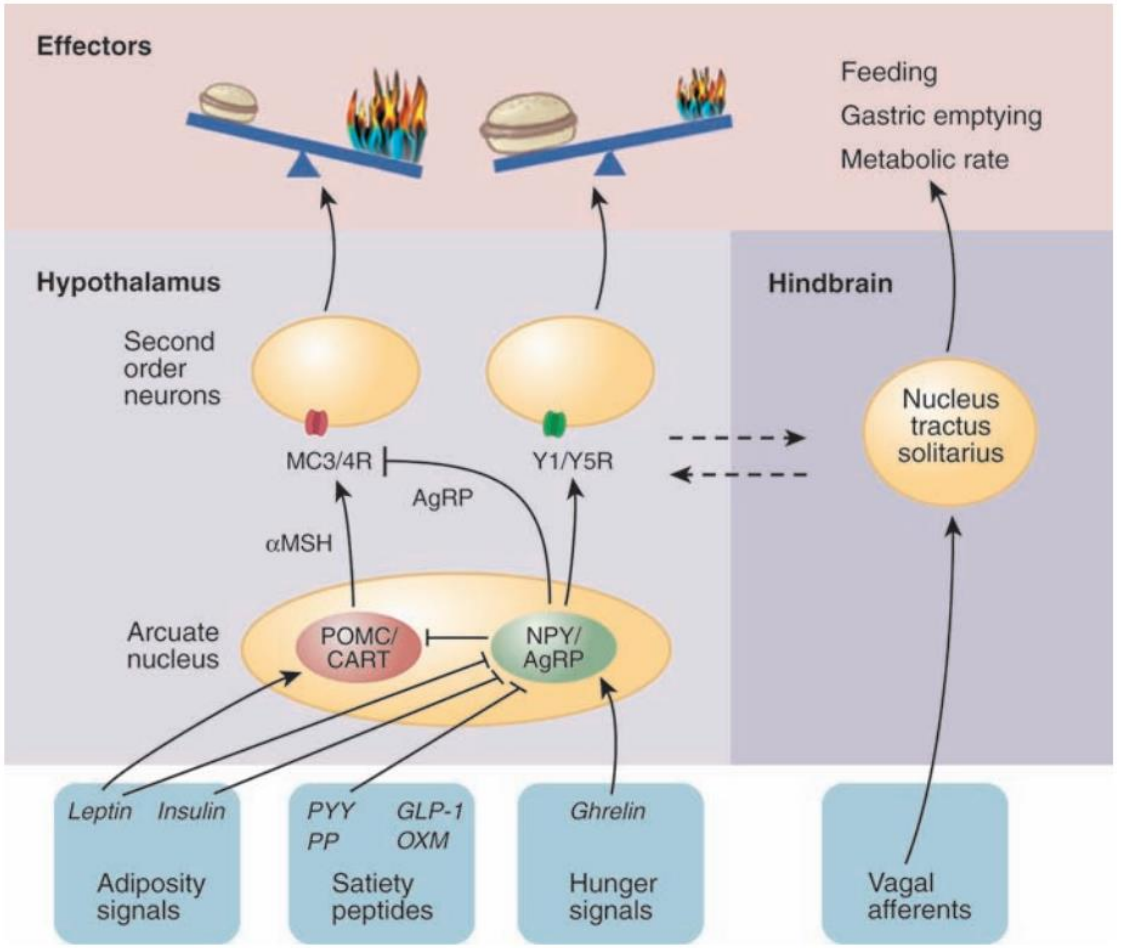
Obesity: a chronic relapsing progressive disease process. A position statement of the World Obesity Federation

Bray GA, Kim KK, Wilding JPH, on behalf of the World Obesity Federation. Obesity: a chronic relapsing progressive disease process. A position statement of the World Obesity Federation: Position Paper. Obes Rev. 2017

Fisiopatologia dell’obesità

La regolazione del peso corporeo





Badman MK, Flier JS. The Gut and Energy Balance: Visceral Allies in the Obesity Wars. Science. 2005

La regolazione del peso corporeo

Controllo volontario

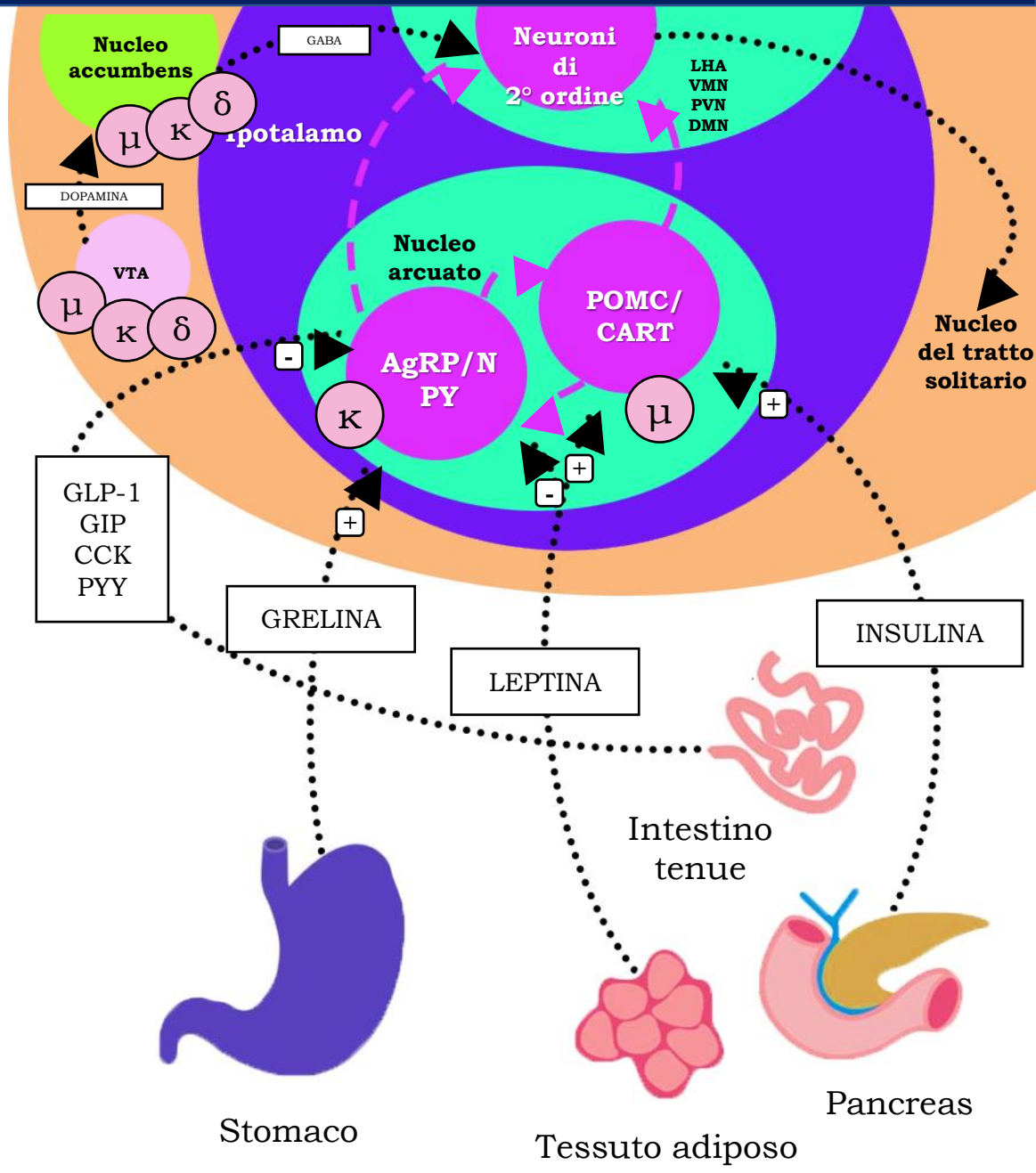
↓

Sistema omeostatico →

↑

Sistema edonico

μ	β-endorfina Endomorfine
κ	Dinorfina A Dinorfina B
δ	β-endorfina Metionina Encefalina Leucina



LHA = Area ipotalamica laterale
VMN = Nucleo Ventromediale
PVN = Nucleo Paraventricolare
DMN = Nucleo Dorsomediale
VTA = Area Tegmentale Ventrale (mesencefalo)

GLP-1 = Glucagon-like Peptide 1
GIP = Gastric Inhibitory Polieptide
CCK = Colecistochinina
PYY = Peptide YY

La regolazione del peso corporeo

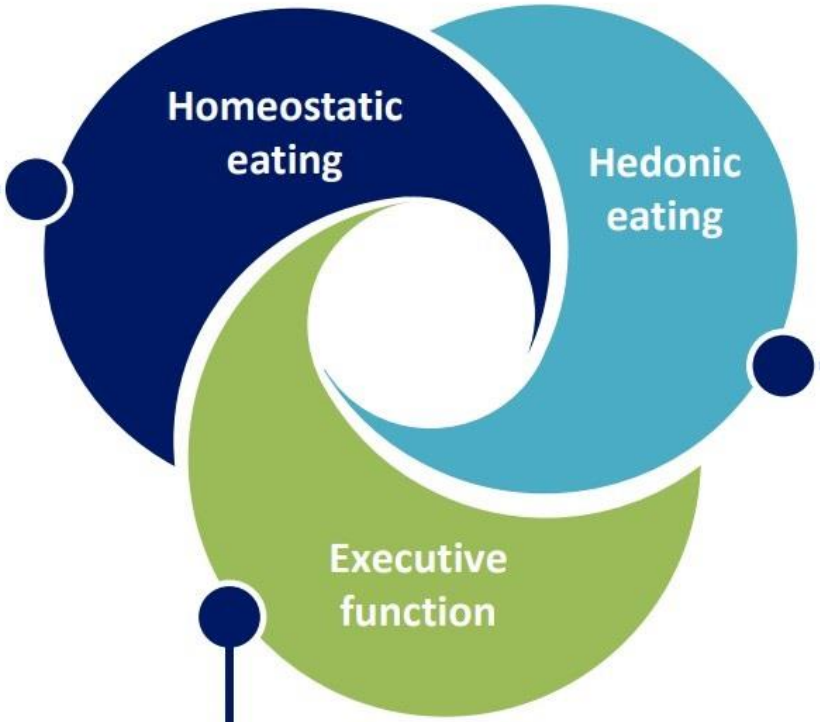
Satiety

- GLP-1
- Peptide YY
- Oxyntomodulin
- Pancreatic polypeptide
- Amylin

Eating in response to hunger

Hunger

- Ghrelin



Eating for pleasure

Dopamine
controls WANTING
the motivation to eat

Opioid and **cannabinoid** receptors control LIKING the pleasure associated with food

Deciding to eat

Behavioural interventions empower sustainable behaviours in controlling eating

Vallis M. Sustained behaviour change in healthy eating to improve obesity outcomes: It is time to abandon willpower to appreciate wanting. Clin Obes. 2019

EOSS – Edmonton Obesity Staging System

STAGE 0

- **NO** sign of obesity-related risk factors
- **NO** physical symptoms
- **NO** psychological symptoms
- **NO** functional limitations

Case Example:
Physically active female with a BMI of 32 kg/m², no risk factors, no physical symptoms, no self-esteem issues, and no functional limitations.

Class I, Stage 0 Obesity

EOSS Score

WHO Obesity Classfication

STAGE 1

- Patient has obesity-related **SUBCLINICAL** risk factors
(borderline hypertension, impaired fasting glucose, elevated liver enzymes, etc.)
- OR -
- **MILD** physical symptoms - patient currently not requiring medical treatment for comorbidities
(dyspnea on moderate exertion, occasional aches/pains, fatigue, etc.) *- OR -*
- **MILD** obesity-related psychological symptoms and/or mild impairment of well-being
(quality of life not impacted)

Case Example:
38 year old female with a BMI of 59.2 kg/m², borderline hypertension, mild lower back pain, and knee pain. Patient does not require any medical intervention.

Class III, Stage 1 Obesity

WHO CLASSIFICATION OF WEIGHT STATUS (**BMI kg/m²**)

Obese Class I ..... 30 - 34.9
Obese Class II ..... 35 - 39.9
Obese Class III ..... ≥40

Stage 0 / Stage 1 Obesity

Patient ***does not meet clinical criteria for admission*** at this time.
Please refer to primary care for further preventative treatment options.

STAGE 2

- Patient has **ESTABLISHED** obesity-related comorbidities requiring medical intervention
(HTN, Type 2 Diabetes, sleep apnea, PCOS, osteoarthritis, reflux disease) *- OR -*
- **MODERATE** obesity-related psychological symptoms
(depression, eating disorders, anxiety disorder) *- OR -*
- **MODERATE** functional limitations in daily activities
(quality of life is beginning to be impacted)

Case Example:
32 year old male with a BMI of 36 kg/m² who has primary hypertension and obstructive sleep apnea.

Class II, Stage 2 Obesity

STAGE 3

- Patient has **significant** obesity-related end-organ damage (myocardial infarction, heart failure, diabetic complications, incapacitating osteoarthritis) *- OR -*
- **SIGNIFICANT** obesity-related psychological symptoms
(major depression, suicide ideation) *- OR -*
- **SIGNIFICANT** functional limitations
(eg: unable to work or complete routine activities, reduced mobility)
- **SIGNIFICANT** impairment of well-being
(quality of life is significantly impacted)

Case Example:
49 year old female with a BMI of 67 kg/m² diagnosed with sleep apnea, CV disease, GERD, and suffered from stroke. Patient's mobility is significantly limited due to osteoarthritis and gout.

Class III, Stage 3 Obesity

STAGE 4

- **SEVERE** (potential end stage) from obesity-related comorbidities *- OR -*
- **SEVERELY** disabling psychological symptoms *- OR -*
- **SEVERE** functional limitations

Case Example:
45 year old female with a BMI of 54 kg/m² who is in a wheel chair because of disabling arthritis, severe hyperpnea, and anxiety disorder.

Class III, Stage 4 Obesity

Alberta Health Services

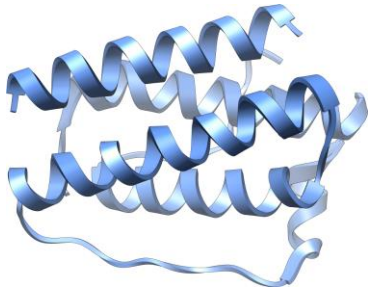
UNIVERSITY OF ALBERTA

Sharma AM & Kushner RF, *Int J Obes* 2009

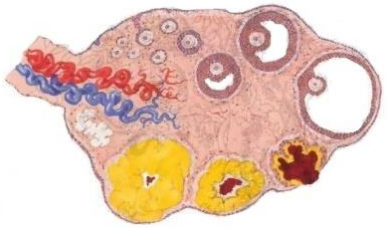
Obesità
e
infertilità femminile

Obesità e asse ipotalamo-ipofisi-ovaio

Leptina

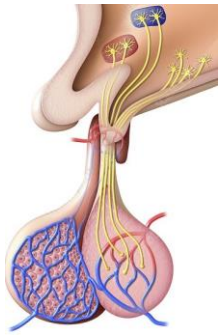


Inibisce la steroidogenesi a livello di cellule di teca e granulosa



OVAIO
Leptino-sensibile

Influenza il rilascio pulsatile di GnRH dall'ipotalamo



IPOTALAMO-IPOFISI
Leptino-resistenti
(↓espressione di recettori per la leptina a livello centrale)

Obesità e steroidi sessuali

TESSUTO ADIPOSO

produce

ANDROGENI
Testosterone
Androstenedione
Diidrotestosterone
Deidroepiandrosterone

converte

ESTROGENI
17-β-estradiolo
Estrone

Obesità e steroidi sessuali

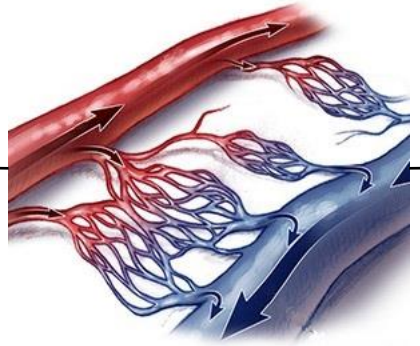
TESSUTO ADIPOSO

immagazzina

↑ ESTROGENI
17-β-estradiolo
Estrone

immagazzina

↑ ANDROGENI
Testosterone
Androstenedione
Diidrotestosterone
Deidroepiandrosterone

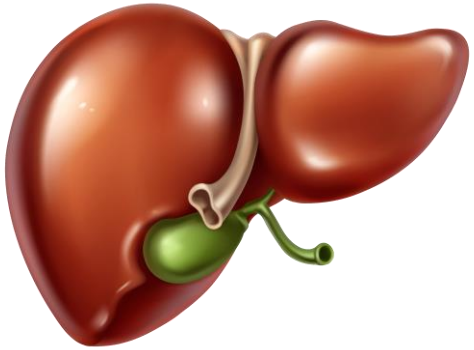


↓ SHBG

Il ruolo dell'insulina

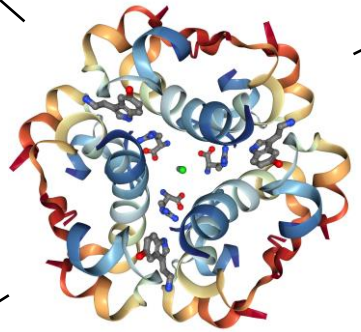
TESSUTO ADIPOSO

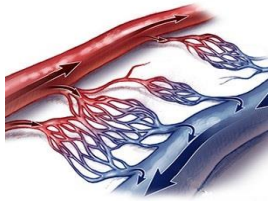
TESSUTO MUSCOLARE



FEGATO

Insulina

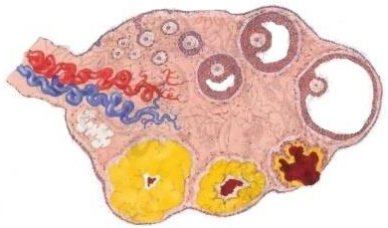




↓ produzione epatica di SHBG

↑ ANDROGENI in circolo

↑ produzione di LH



OVAIO

↑ produzione ANDROGENI (teca)

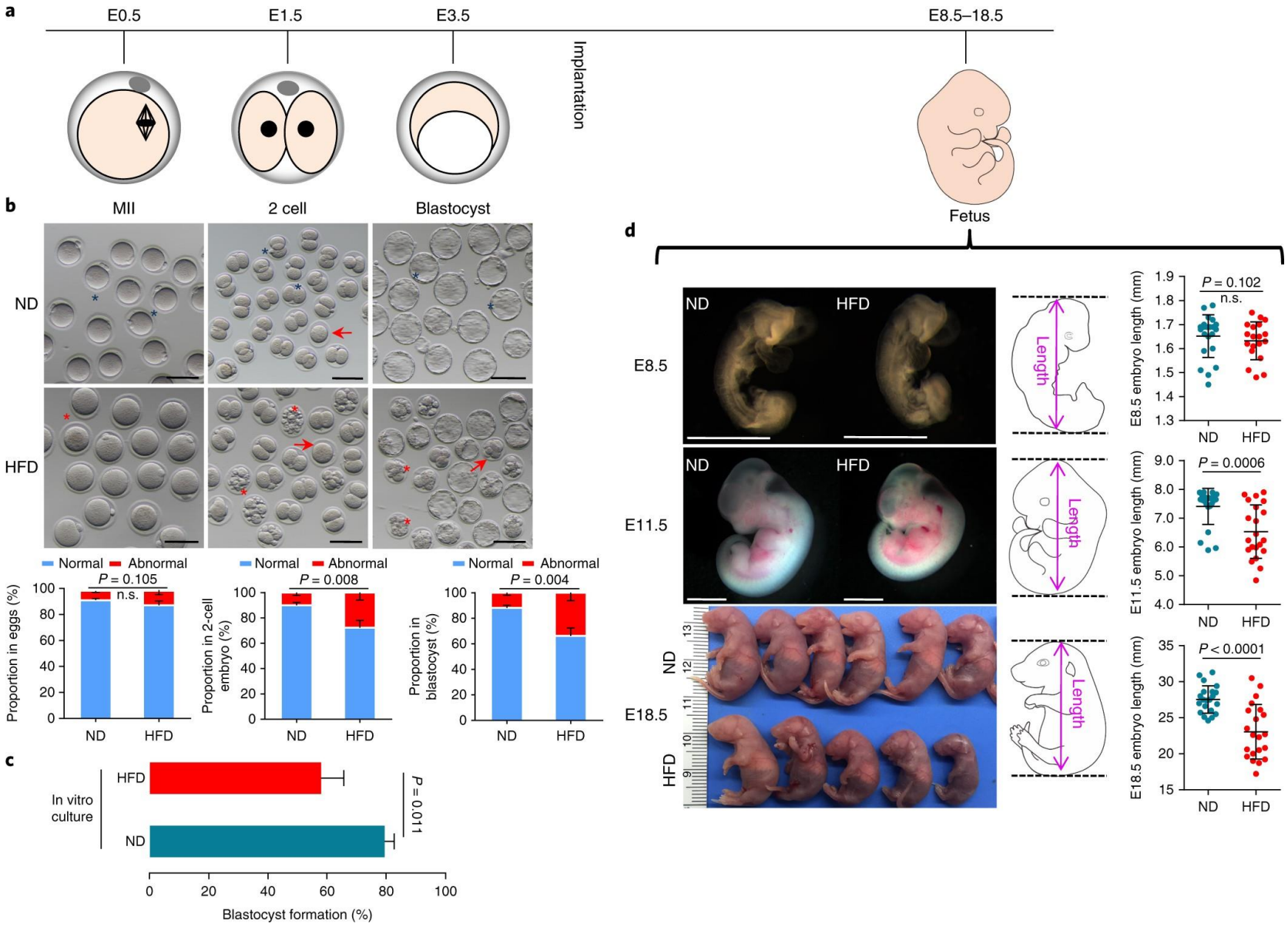
↑ sensibilità a LH

Atresia follicolare prematura

Luteinizzazione precoce delle cellule della granulosa

↓ qualità ovociti

Obesità e ovociti



Ovociti del modello animale obeso:

- Piccoli
- Ritardo nella maturazione meiotica
- Aumento dell'apoptosi follicolare
- Difetti di allineamento dei cromosomi

↓

Embrioni con aneuploidia massiva

↓

Aborti spontanei

Danno mitocondriale (mitocondri responsabili delle fasi di maturazione dell'ovocita, impianto, sviluppo dell'embrione)

Stress ossidativo

↑

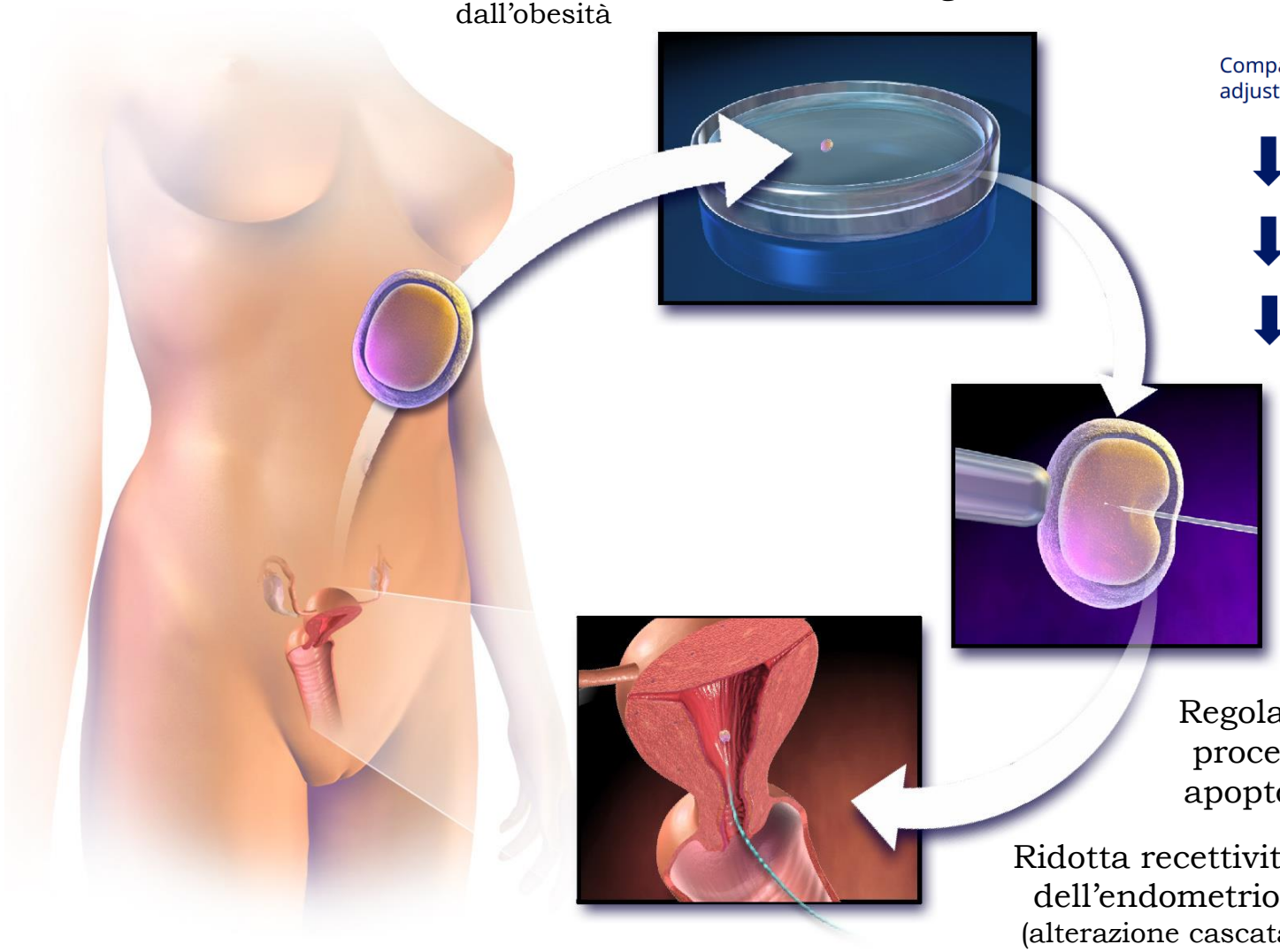
Lipotossicità

Han L, Ren C, Li L, Li X, Ge J, Wang H, et al. Embryonic defects induced by maternal obesity in mice derive from Stella insufficiency in oocytes. Nat Genet 2018

Obesità e PMA

Necessarie maggiori dosi di gonadotropine per compensare la resistenza alle stesse indotta dall'obesità

Peggiore qualità degli ovociti



Regolazione alterata dei processi proliferativi e apoptotici endometriali

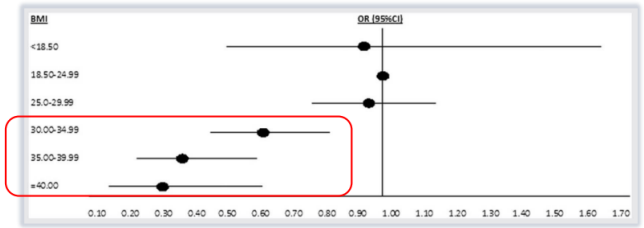
Ridotta recettività dell'endometrio (alterazione cascata MAP/ERK)

Live birth rate according to body mass index

Effect of BMI on live birth rates in 4,609 patients undergoing their first IVF cycle

Compared with normal BMI, the adjusted odds of live birth are:

- **37%** in class I obesity
- **61%** in class II obesity
- **68%** in class III obesity



Moragianna VA, et al. Fertil Steril 2012

Elevato tasso di abortività

Basso tasso di nati vivi

Each BMI unit > 29 reduces the chance of achieving a pregnancy within 12 months by about 4%

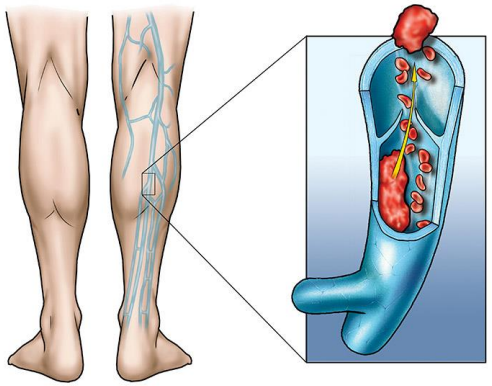
Luke B, Brown MB, Stern JE, Missmer SA, Fujimoto VY, Leach R, et al. Female obesity adversely affects assisted reproductive technology (ART) pregnancy and live birth rates. Hum Reprod 2011

Gambineri A et al. Int J Obes Suppl 2019;
Jan Willem et al Human Reproduction 2008.

Obesità e gravidanza

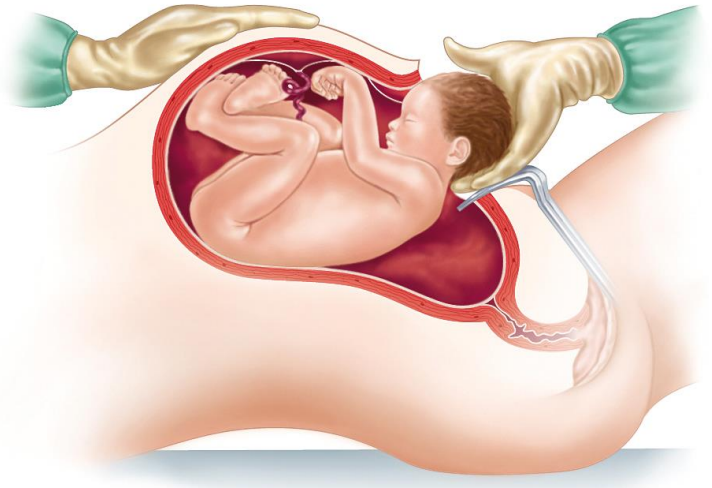
Ipertensione

Diabete gestazionale



Tromboembolismo venoso

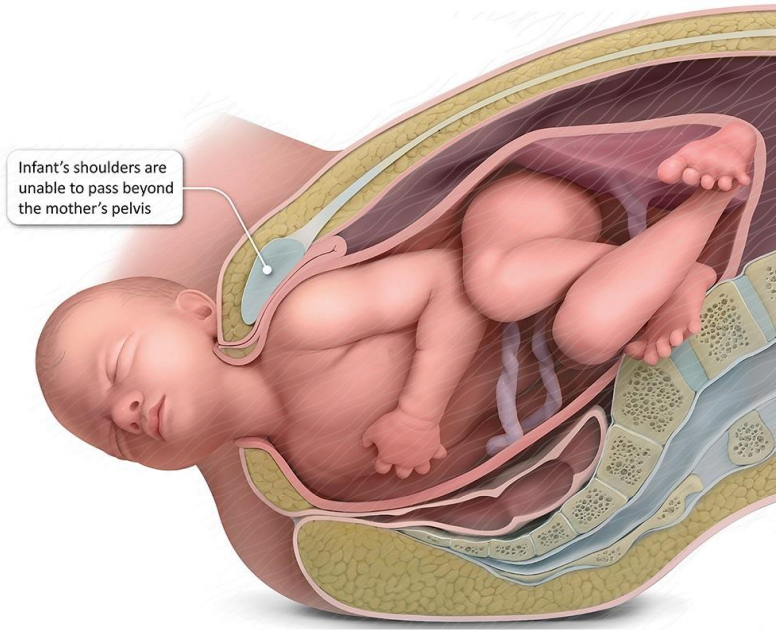
Parto cesareo



Infezione della ferita

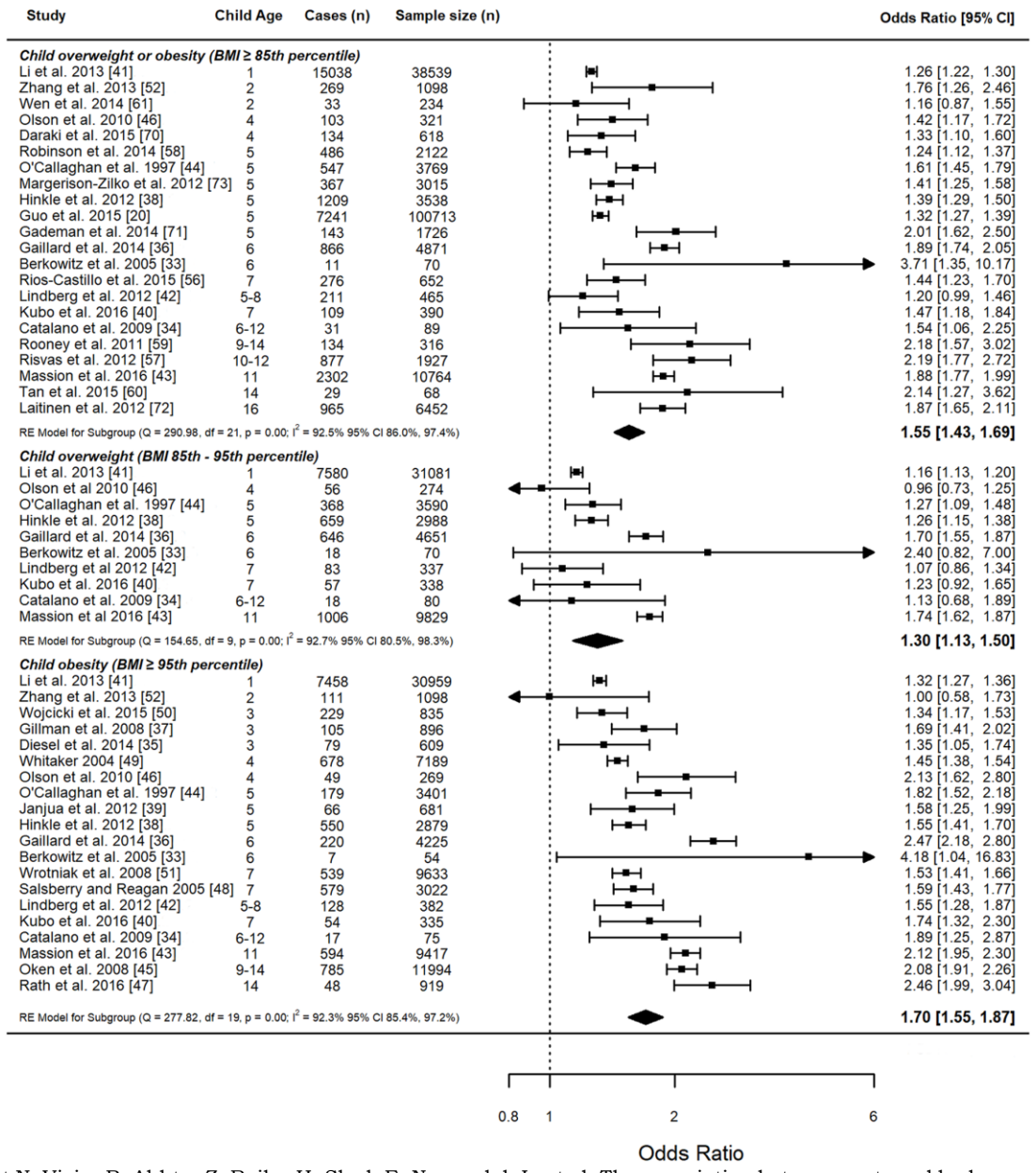
Macrosomia

Distocia di spalla



Satpathy H. Maternal Obesity and Pregnancy. Postgrad Med 2008

Correlazione fra BMI materno e obesità infantile



Heslehurst N, Vieira R, Akhter Z, Bailey H, Slack E, Ngongalah L, et al. The association between maternal body mass index and child obesity: A systematic review and meta-analysis. 2019

Rischio di obesità del nascituro aumentato del 264% per le madri affetti da obesità prima del concepimento.

È necessario sviluppare strategie che abbiano inizio prima del concepimento per interrompere il circuito dell'obesità intergenerazionale.

Obesità intergenerazionale

Stato socio-economico
Ambiente obesogenico
Marketing alimentare

→ Stili di vita malsani a cui alcuni individui sono geneticamente più suscettibili

→ Stigma
→ DCA

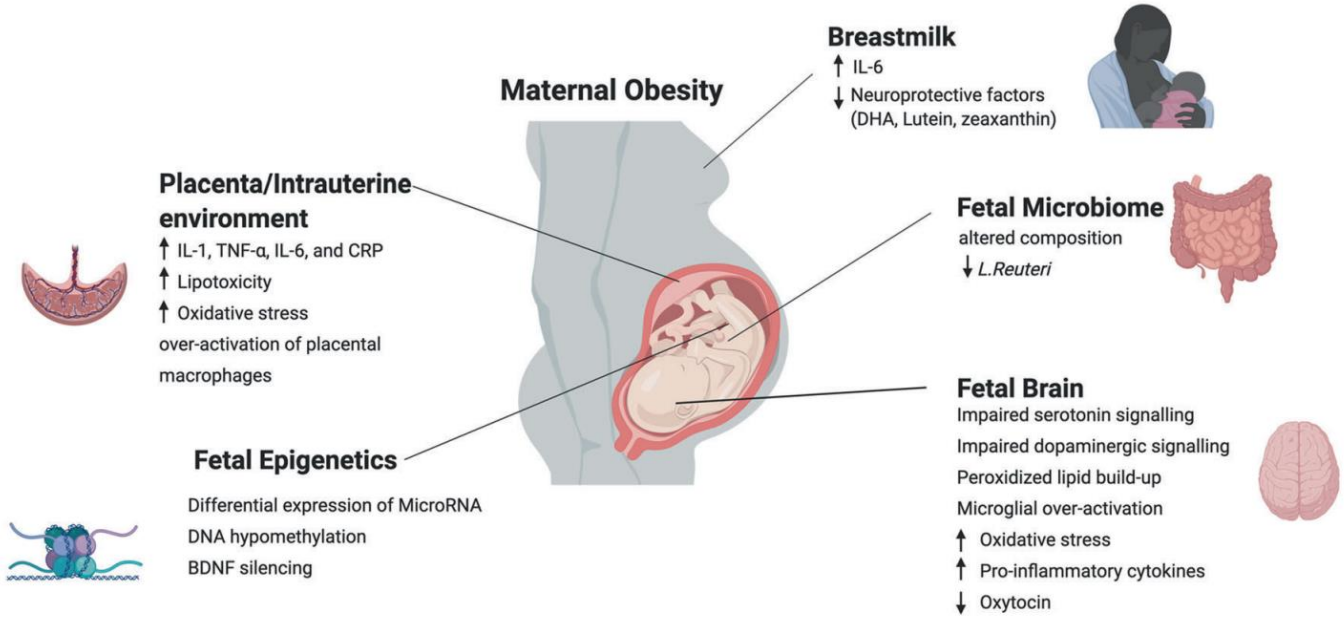
Food Insecurity. Il cibo sano inaccessibile

Denutrizione e obesità vengono solitamente visti come problemi separati. La FAO però suggerisce un approccio integrato a queste due forme di malnutrizione. Infatti, se è vero che nella maggior parte dei paesi con alta prevalenza di denutrizione la prevalenza di obesità è più bassa e viceversa, alcuni paesi registrano un'elevata prevalenza delle due contemporaneamente. La malnutrizione non è semplicemente il risultato di un ridotto accesso ad un'alimentazione sufficiente e sana, ma deriva più in generale da un ridotto accesso a risorse e servizi, primi fra questi l'assistenza sanitaria, l'istruzione, l'acqua potabile e l'igiene.

https://www.saluteinternazionale.info/2017/11/food-insecurity-il-cibo-sano-inaccessibile/

World Obesity Federation Position Statement

Obesity: a chronic relapsing progressive disease process. A position statement of the World Obesity Federation

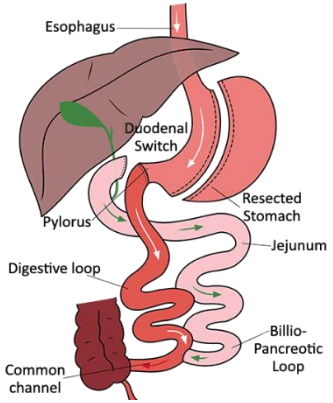


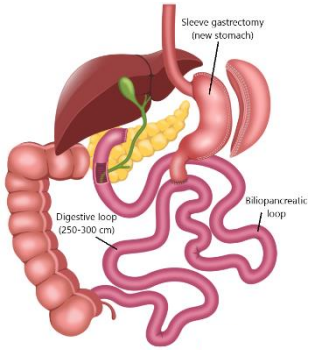
Tong L, Kalish BT. The impact of maternal obesity on childhood neurodevelopment. J Perinatol, 2021

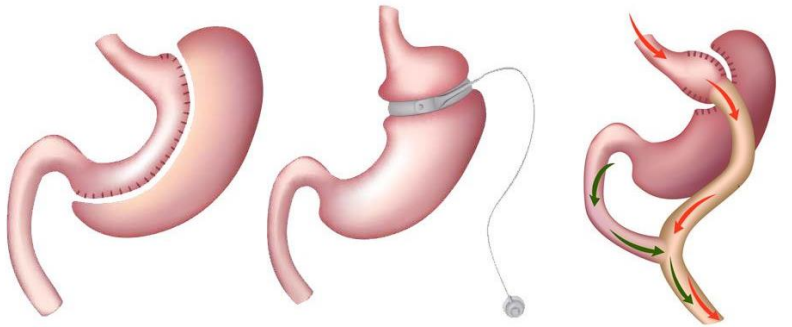

UNCLE TOBYS OATS
QUICK 2 MINUTES
Natural Oat Energy
Berry Berry Kix
Kid Tested Mother Approved
FAMILY SIZE
Dora the Explorer
Kellogg's Frosted Flakes
Reese's Puffs
Real Reese's Peanut Butter
Cinnamon Toast Crunch
Lucky Charms
3 New Rainbow Magic
Herr's Cheese Curls
Herr's Deep Dish Pizza Flavored Cheese Curls
Herr's Crunchy Cheestix
Chester's Fries
Cheetos Crunchy Jalapeño Cheese Flavored Snacks
Cheetos Flamin' Hot
Cheetos Puffs
Cocoa Puffs
Made with Real Cocoa
Cookie Crisp
Honey Nut Cheerios Oats
Kellogg's Apple Jacks
Sunbites Grain Waves Sour Cream & Chives
Kettle Rosemary & Sea Salt
Kettle Parmesan & Sweet Roasted Garlic
Kettle Honey Soy Chicken
Kettle Chilli
Kettle Sea Salt & Vinegar
Kettle Sweet Chilli & Sour Cream
Kettle Original Sea Salt
Doritos Colossal Chargrilled Steak
Doritos Original Salted
Doritos Mexicana
Doritos Cheese Supreme
Cobs Natural Popcorn Cheddar Cheese
Cobs Natural Popcorn Butter
Cobs Natural Popcorn Sea Salt & Cider Vinegar
Cobs Natural Popcorn Lightly Salted Slightly Sweet
Cobs Natural Popcorn Sea Salt
Tim Tam
Pringles
Coca-Cola
Raisin Bran Crunch
Kellogg's Crispix
Kellogg's Froot Loops
Lucky Charms
Cinnamon Toast Crunch
Nutri-Grain

Strategie terapeutiche

Strategie terapeutiche







Strategie terapeutiche

Trattamento dietetico-comportamentale

BMI ≥ 25 kg/m²

Terapia farmacologica

- (Orlistat)
- Liraglutide
- Naltrexone/bupropione
- …Semaglutide

BMI ≥ 27 kg/m² con comorbidità

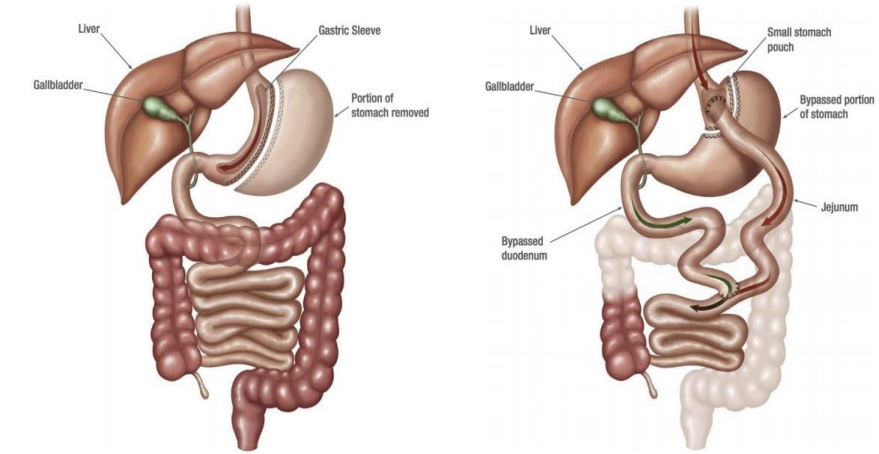
BMI ≥ 30 kg/m²

Chirurgia bariatrica

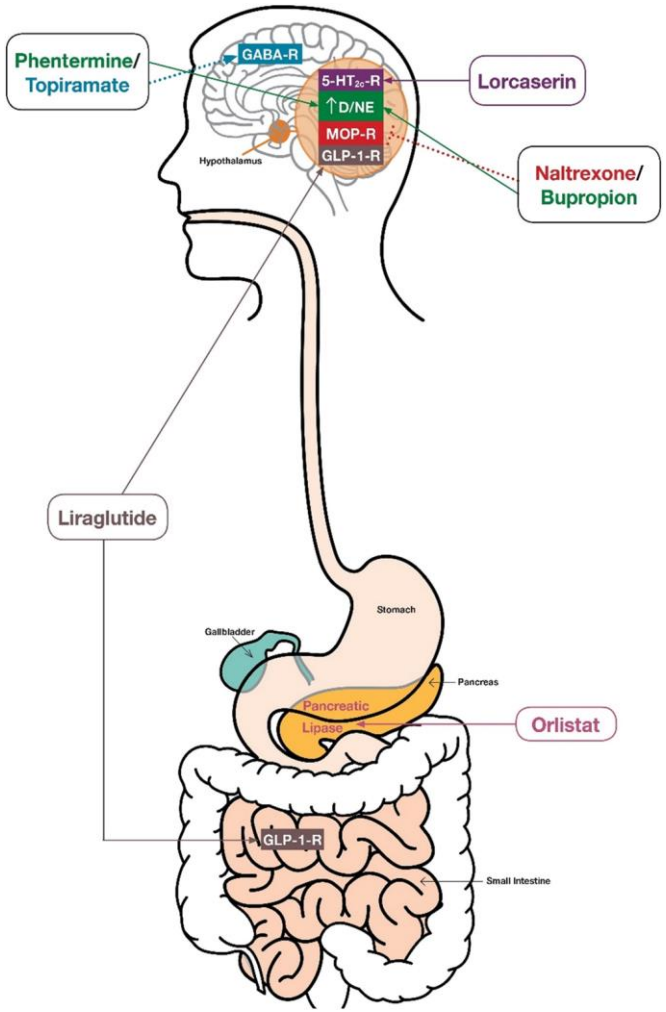
- Sleeve gastrectomy
- Bypass gastrico Roux-en-Y

BMI ≥ 35 kg/m² con comorbidità

BMI ≥ 40 kg/m²

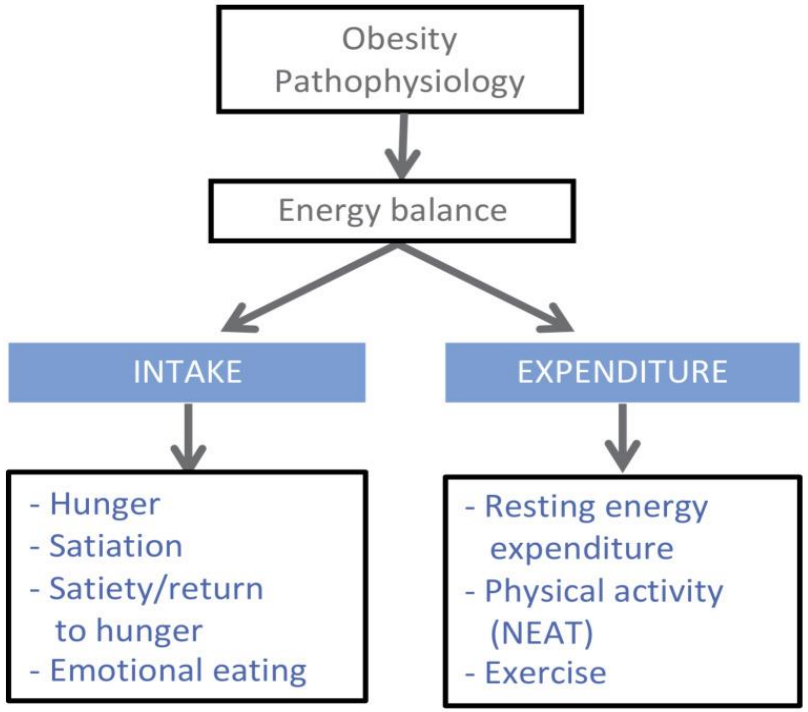


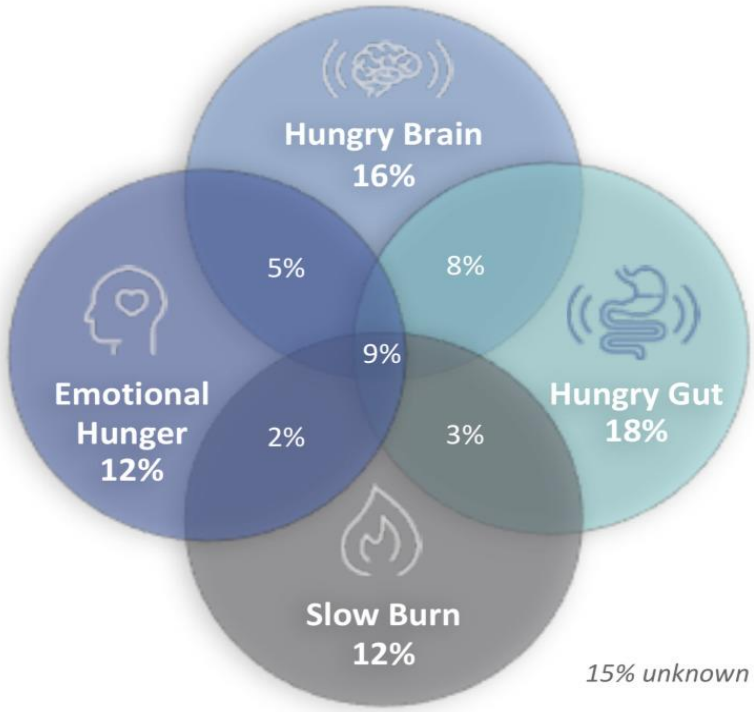
Strategie terapeutiche



			Mode of action	Indications
Orlistat (Xenical®, Alli®)	✓	✓	Energy wastage	Adjunct to diet and physical activity for chronic weight management in a) obesity BMI ≥30 kg/m² b) overweight BMI ≥27 kg/m² with comorbidity
Phentermine* (Adipex-P®, Suprenza®)	✗	✓	Appetite suppression	
Phentermine/topiramate (Qsymia®)	✗	✓	Appetite suppression	
Lorcaserin (Belviq®, Belviq XR®)	✗	✓	Appetite suppression	
Naltrexone/bupropion (Mysimba®, Contrave®)	✓	✓	Appetite suppression	
Liraglutide 3.0 mg (Saxenda®)	✓	✓	Appetite suppression	
Sibutramine (Merida®)	✗	✗	Appetite suppression	n/a

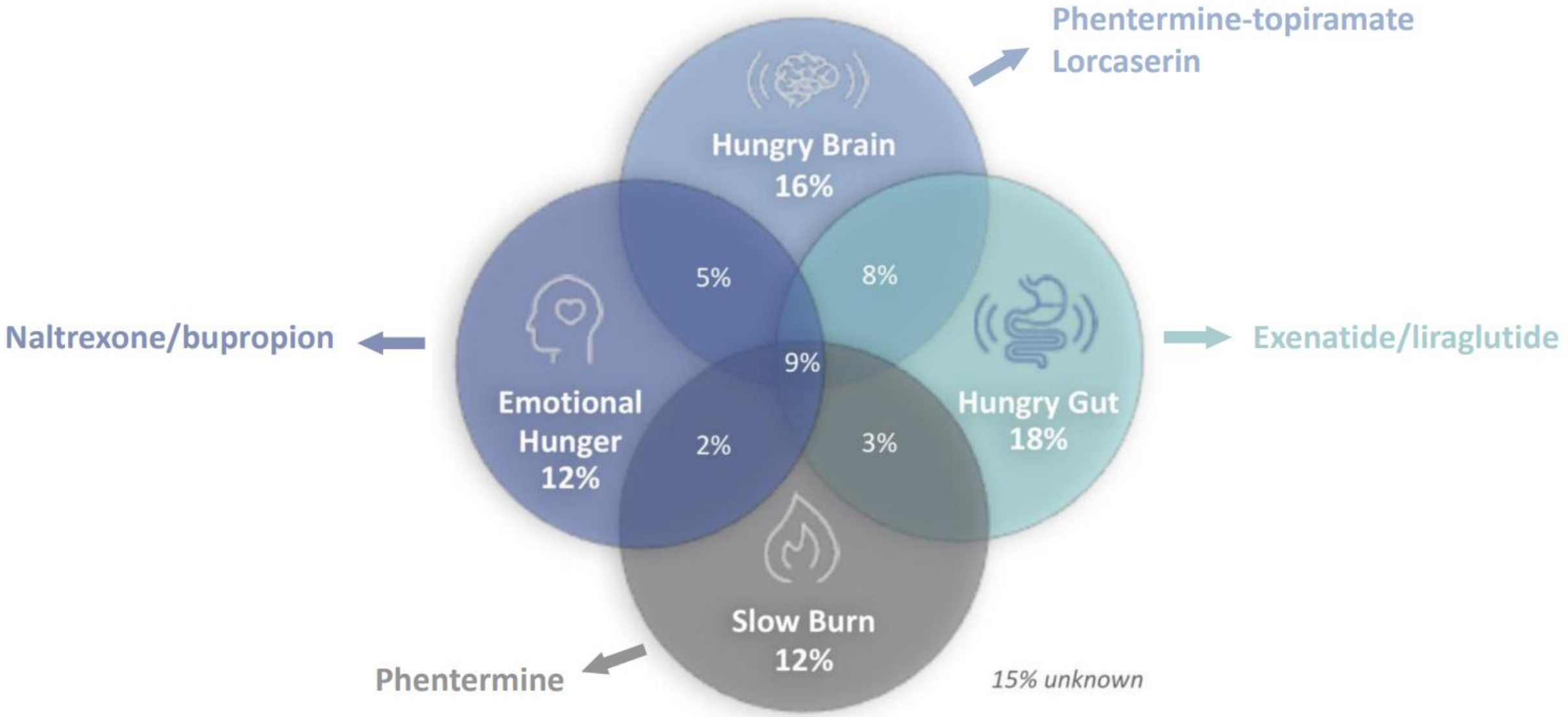
Tailored therapy





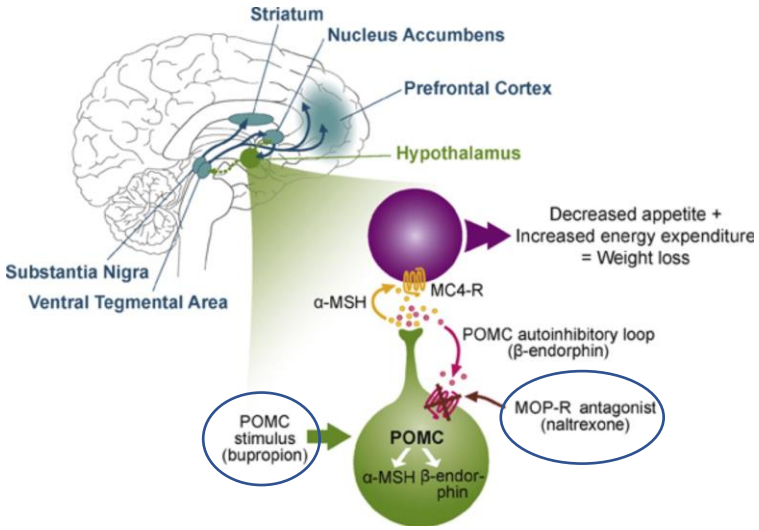
Acosta A, Camilleri M, Abu Dayyeh B, Calderon G, Gonzalez D, McRae A, et al. Selection of Antiobesity Medications Based on Phenotypes Enhances Weight Loss: A Pragmatic Trial in an Obesity Clinic. Obesity 2021

Tailored therapy

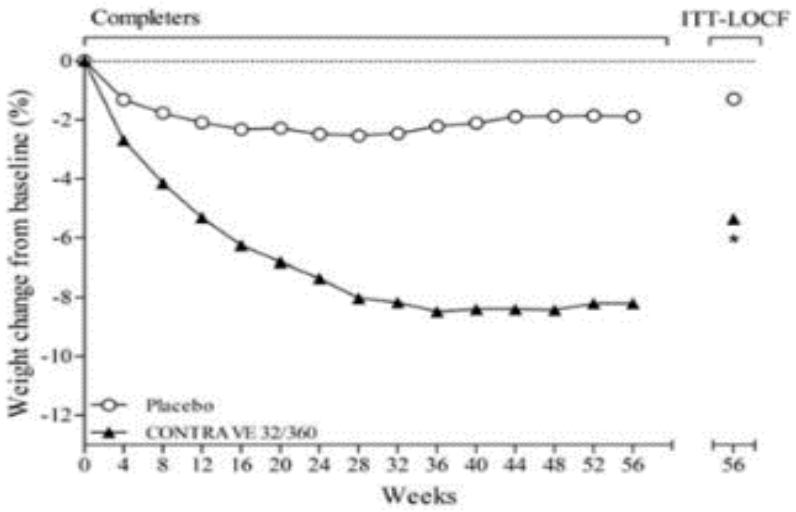


Acosta A, Camilleri M, Abu Dayyeh B, Calderon G, Gonzalez D, McRae A, et al. Selection of Antiobesity Medications Based on Phenotypes Enhances Weight Loss: A Pragmatic Trial in an Obesity Clinic. Obesity 2021

Naltrexone/Bupropione 8/90 mg, 2 cp BID

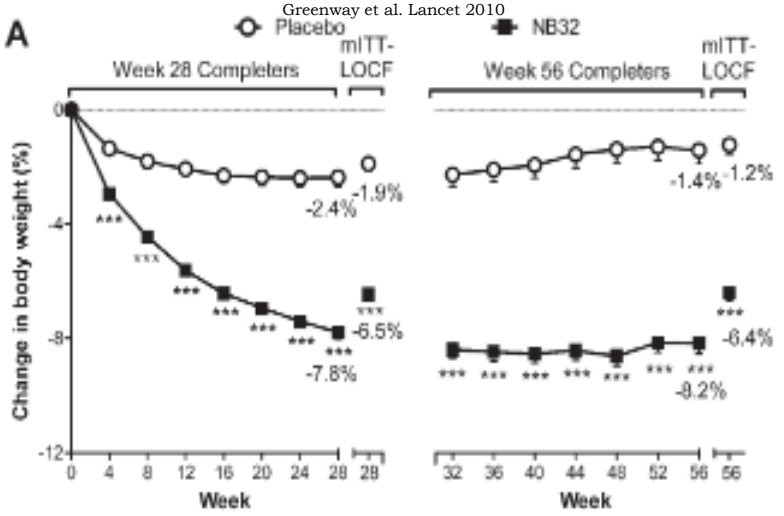


Vallis M. Sustained behaviour change in healthy eating to improve obesity outcomes: It is time to abandon willpower to appreciate wanting. Clin Obes. 2019



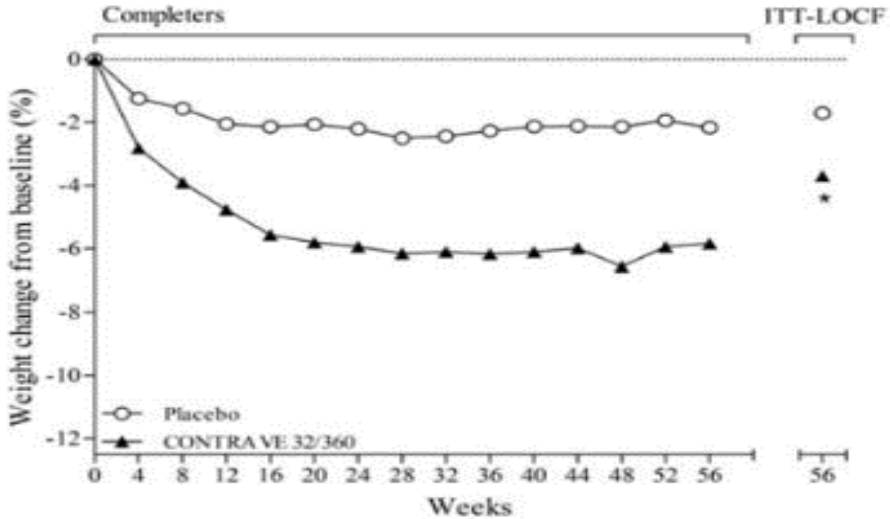
COR-I Trial

Greenway et al. Lancet 2010



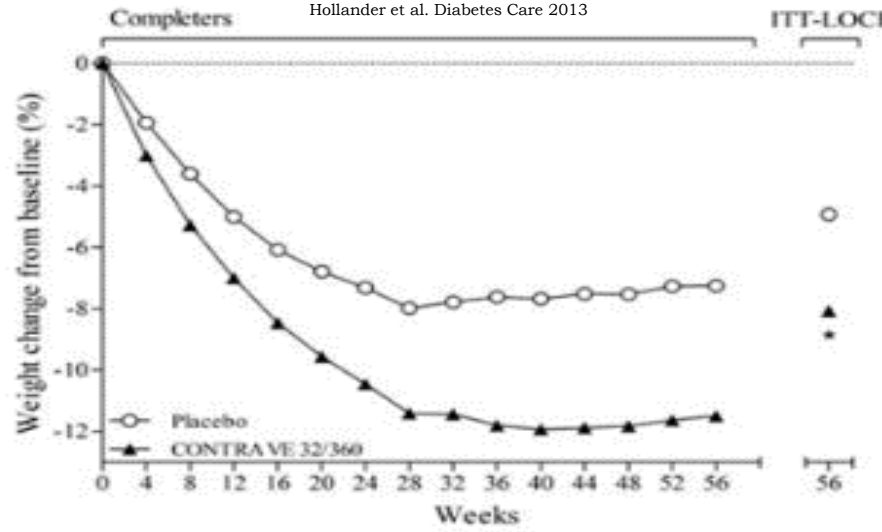
COR-II Trial

Apovian et al. Obesity 2013



COR-Diabetes Trial

Hollander et al. Diabetes Care 2013

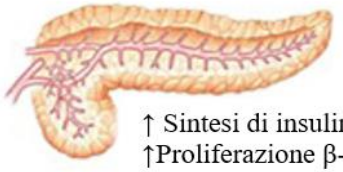


COR-BMOD Trial

Wadden et al. Obesity 2011

Liraglutide 3 mg, 1 iniezione SC/die

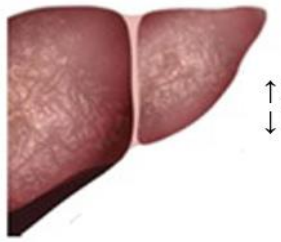
FARMACODINAMICA



↑ Sintesi di insulina
↑Proliferazione β-cellule
↓ Apoptosi β-cellule
↓ Produzione di glucagone

↓ Senso di fame

Rallentamento dello
svuotamento gastrico



↑ Sensibilità all'insulina
↓ Produzione di glucosio

LIRAGLUTIDE

EFFETTI AVVERSI

Nausea, vomito, diarrea, stipsi ecc.

↑ frequenza cardiaca

↑ lipasi e amilasi pancreatiche

Liraglutide 3 mg, 1 iniezione SC/die

GLP-1 endogeno umano

$T_{½}$= ~2 mins

C-16 fatty acid (palmitoyl)

Liraglutide

Omologia del 97% rispetto a GLP-1 umano;
Migliore farmacocinetica: si lega ad albumina e forma eptameri

Si assorbe lentamente dal sottocute
Resistente a DPP-4
Lunga emivita

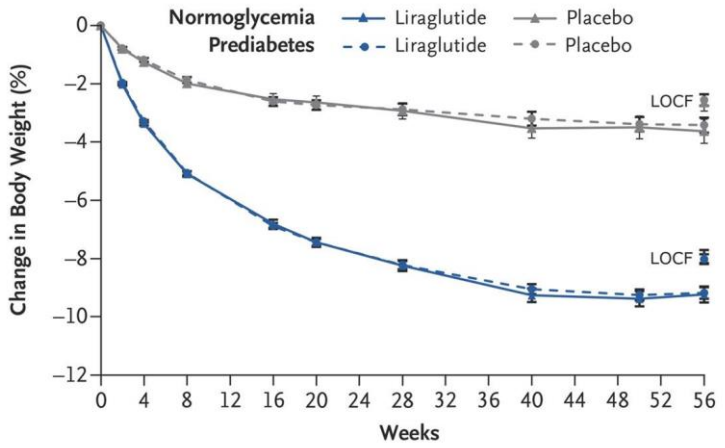
($T_{½}$=13 h)

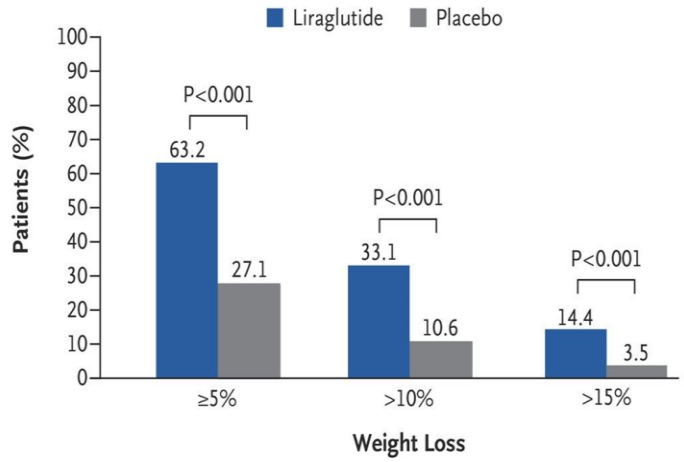
GLP-1: glucagon-like peptide-1, DPP-4: dipeptidyl peptidase-4

Knudsen et al. J Med Chem 2000; Degn et al. Diabetes 2004

A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management: SCALE study

Pi-Sunyer et al. NEJM 2015;373:11-22





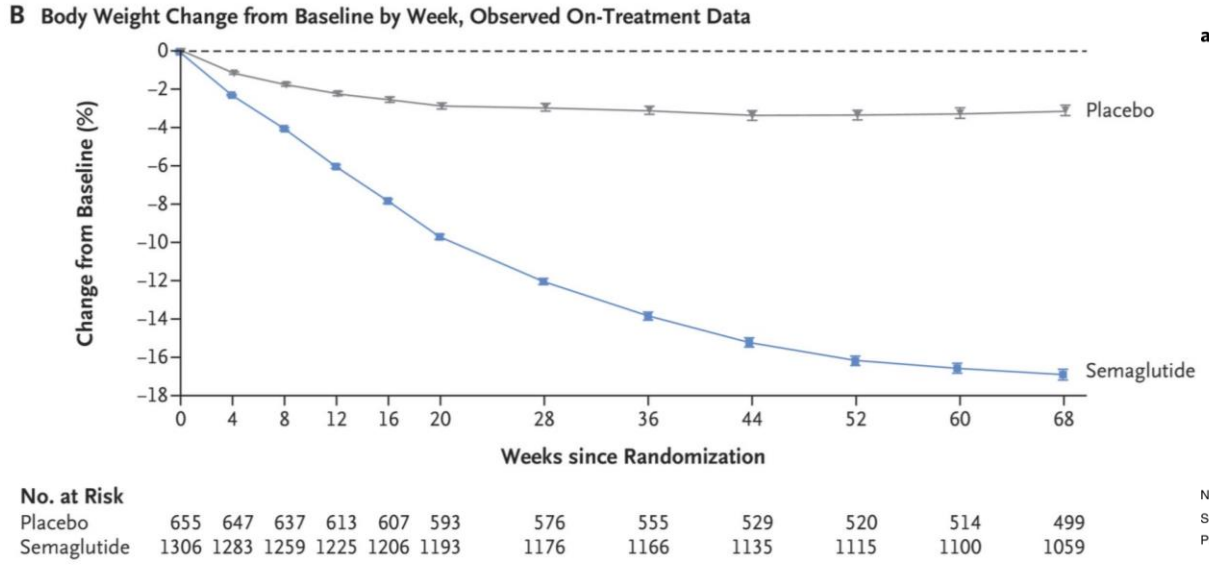
Novità terapeutiche

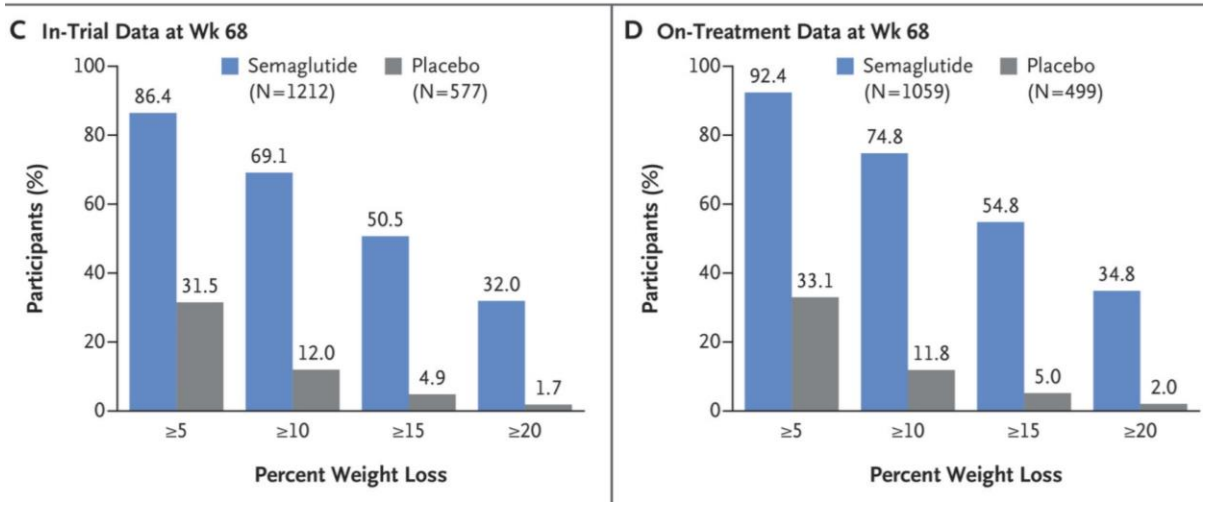
Stay tuned…

Semaglutide 2,4 mg, 1 iniezione SC/settimana

STEP-1: Once-Weekly Semaglutide in Adults with Overweight or Obesity

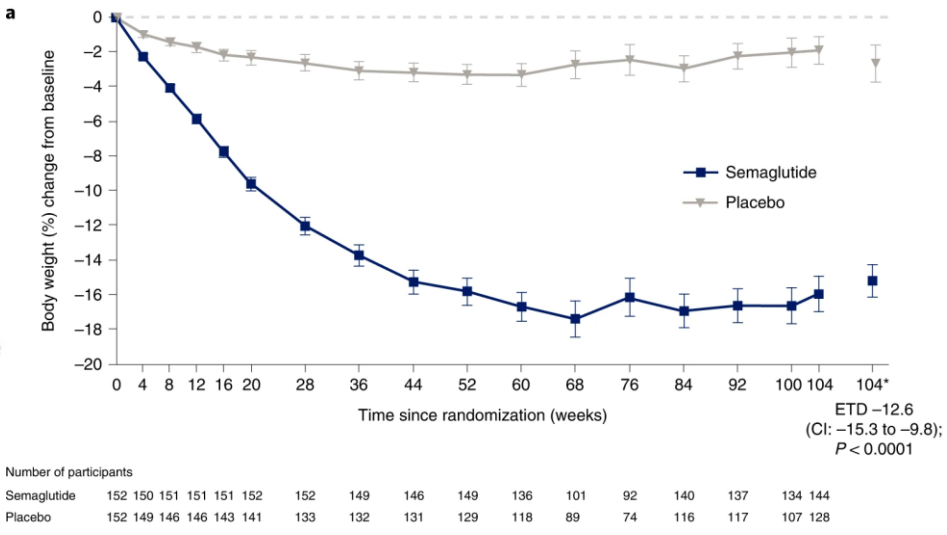
Wilding et al. N Engl J Med 2021

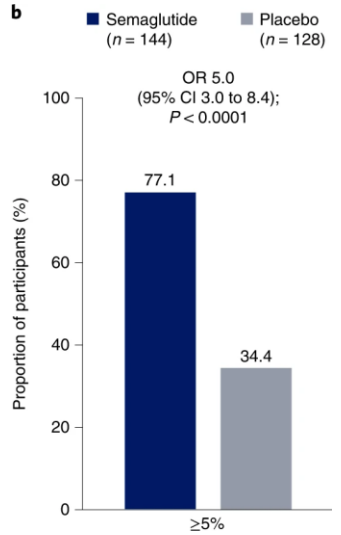




STEP-5: Two-year effects of semaglutide in adults with overweight or obesity

Garvey et al. Nature Medicine. 2022

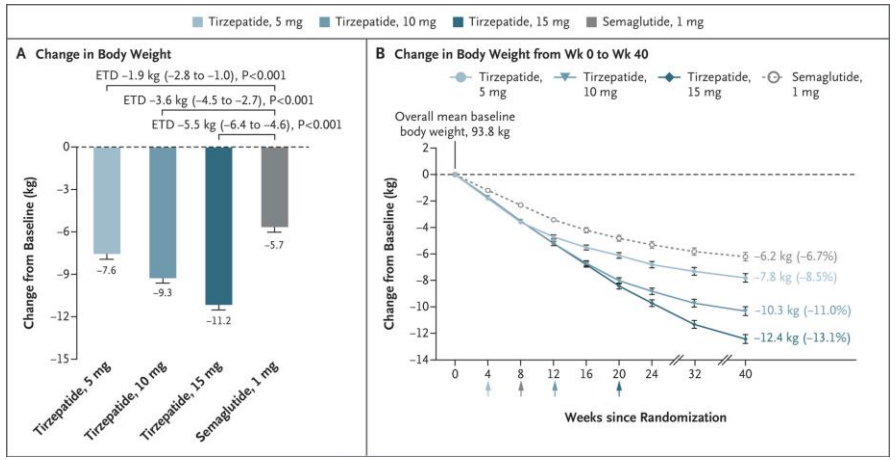




Tirzepatide 5 – 10 – 15 mg, 1 iniezione SC a settimana

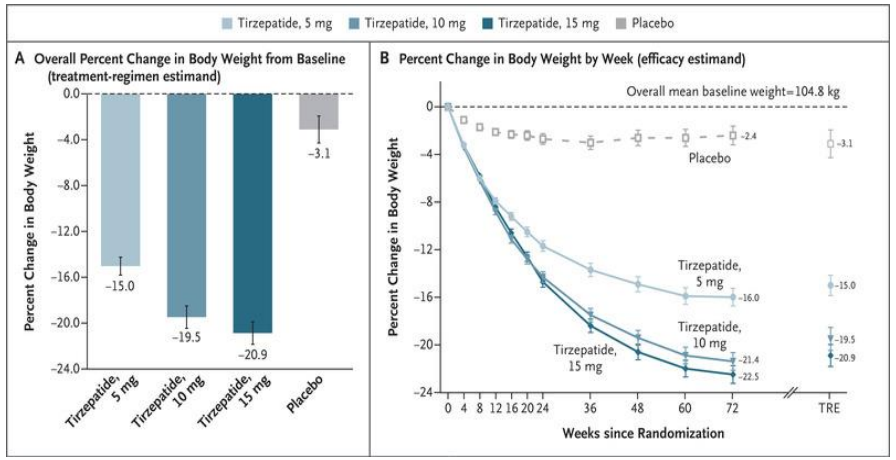
SURPASS-2: Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes

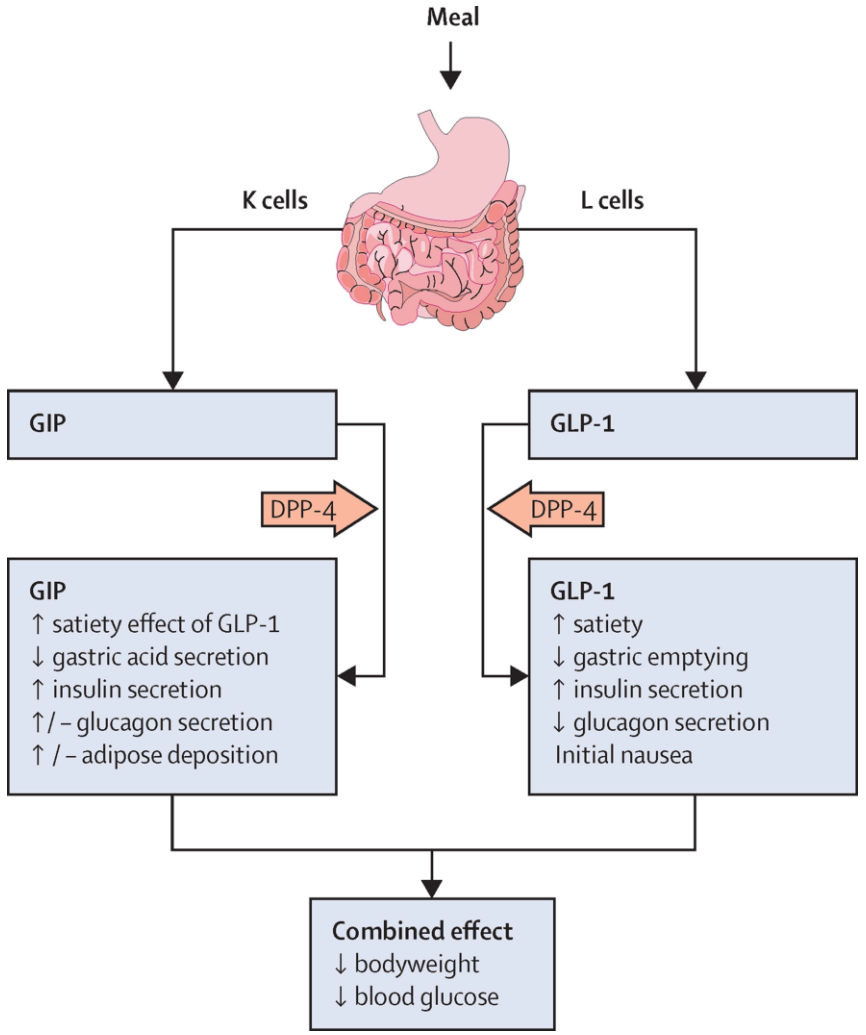
Frias JP et al. NEJM 2021



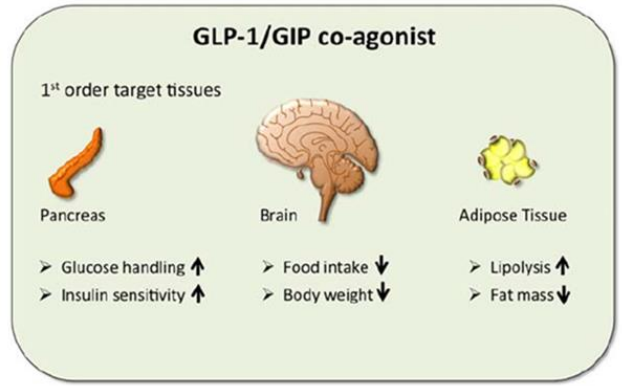
SURMOUNT-1: Tirzepatide Once Weekly for the Treatment of Obesity

Jastreboff AM et al. NEJM 2022





Bailey CJ. Tirzepatide: a new low for bodyweight and blood glucose. Lancet Diabetes Endocrinol 2021

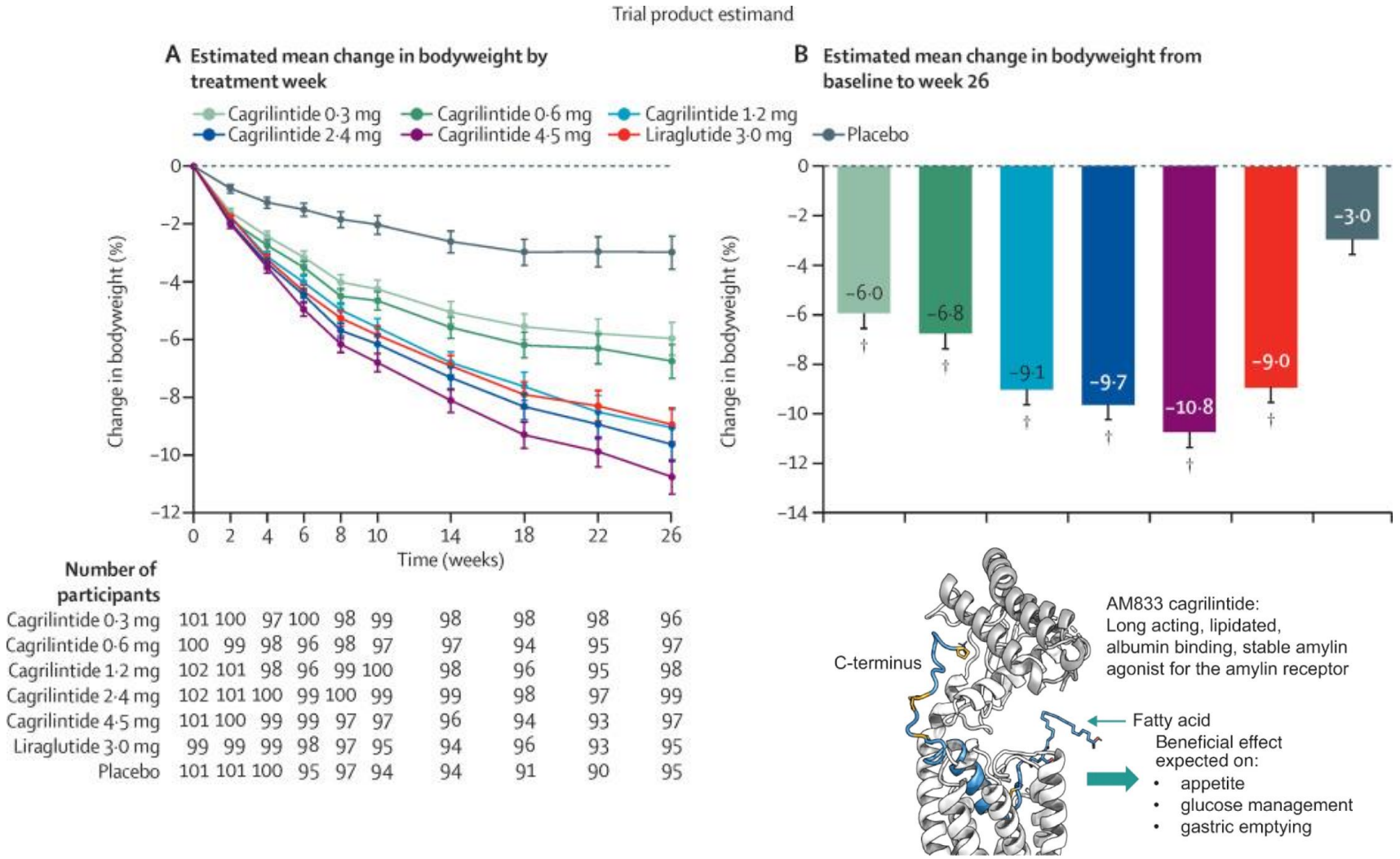


Kleinert M et al. Obesity 2017;25:1647

Cagrilintide, 1 iniezione SC a settimana

Once-weekly cagrilintide for weight management in people with overweight and obesity

Lau et al. Lancet. 2021



Amilina: peptide prodotto dalle cellule beta del pancreas e secreto insieme all'insulina.

- Ritarda lo svuotamento gastrico
- Sopprime la produzione post-prandiale di glucagone
- Induce sazietà post-prandiale

Cagrilintide: omologia dell'84%con l'amilina nativa, grazie a sostituzioni di aminoacidi è maggiormente stabile

$t_{1/2}$ di 180 ore.

Take home messages

- L’obesità è una patologia complessa, multifattoriale, cronica, recidivante e progressiva
- Ha un notevole impatto sulla fertilità femminile e su tutte le fasi dal concepimento al parto
- La predisposizione all’obesità si trasmette di generazione in generazione, tramite fattori genetici, epigenetici e socio-culturali
- Le pazienti affette da sovrappeso e obesità vanno trattate precocemente e indirizzate a Centri per lo studio e il trattamento dell’obesità
- La terapia va personalizzata sulla base di strumenti oggettivi come l’EOSS e della fenotipizzazione della malattia
- La perdita di peso migliora le probabilità di concepimento e di ottenere una gravidanza e un parto con decorso favorevole

Grazie per l'attenzione

Grazie per l'attenzione

giulia.pontesilli@aulss5.veneto.it

AULSS 5 Polesana – Ospedale Santa Maria della Misericordia di Rovigo