

Lesson on obesity

Costanzo Moretti

Dipartimento di Medicina dei Sistemi Università di Roma TorVergata

OBESITA' : UNA NUOVA EPIDEMIA

Obesity has become one of the most important public health problem in the world

Definition of obesity

$$BMI = \frac{\text{weight (kg)}}{\text{height (m}^2\text{)}}$$

- Obesity is defined as abnormal or excessive fat accumulation that may impair health
- Body mass index (BMI) provides the most convenient population-level measure of overweight and obesity currently available

Classification	BMI (kg/m ²)
Underweight	<18.5
Normal range	≥18.5 and <25
Overweight	≥25 and <30
Obesity	≥30
Obesity class I	≥30 and <35
Obesity class II	≥35 and <40
Obesity class III	≥40

Children/Adolescents

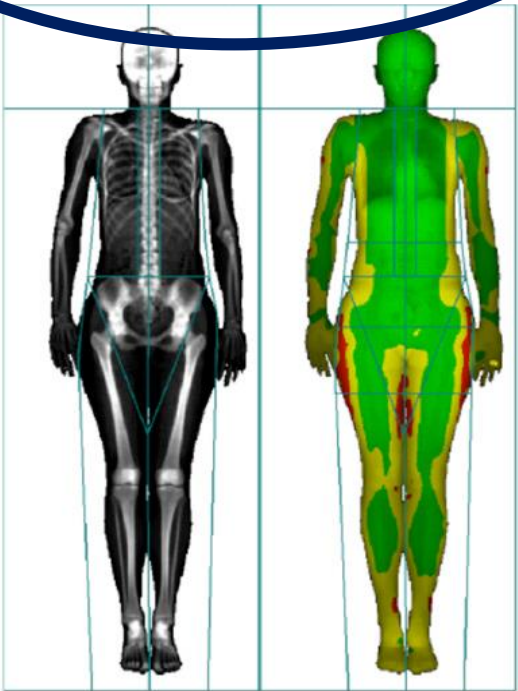
- Sex/age-specific BMI
- BMI ≥ 95th percentile is obese
- 85th to less than 95th percentile is overweight

Fat/Lean weight by DXA

ROI Visceral fat

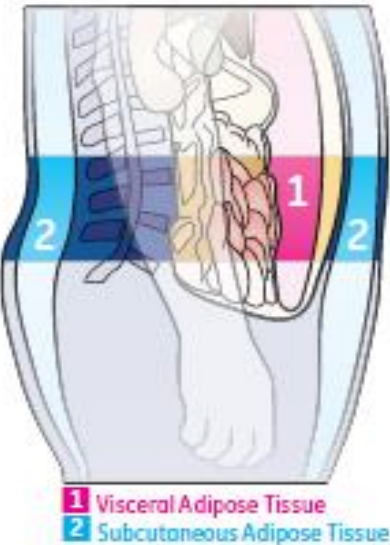
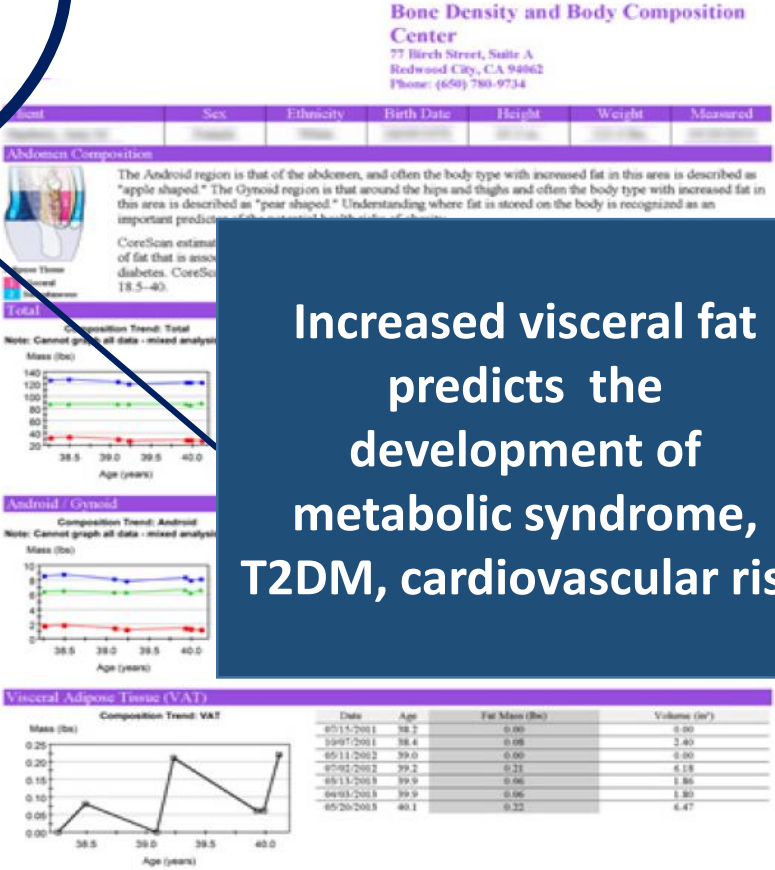
Volume 250.3±194.5 cm³
Mass 235.9±183.1 gr
Cutoff mass 350 gr

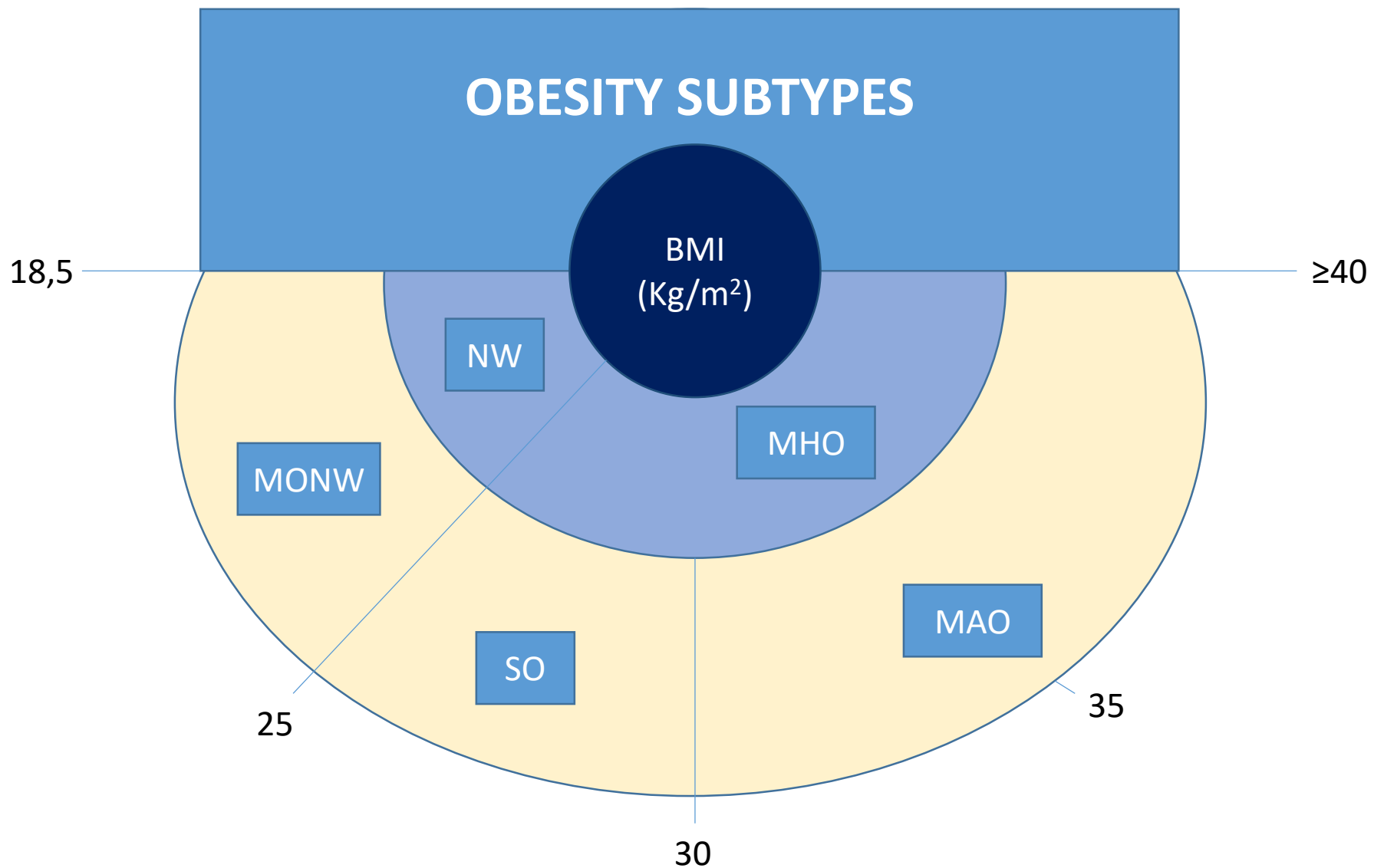
Endocrine 2014 (47)



A/G Fat

Increased visceral fat predicts the development of metabolic syndrome, T2DM, cardiovascular risk





NW : normal weight metabolically healthy and normal visceral adipose tissue (VAT)
MHO : metabolically healthy obese : high BMI and healthy metabolic profile+low VAT
MAO : metabolically abnormal obese : high BMI, abnormal metabolic profile, high VAT
SO : sarcopenically obese, loss of muscle mass, high VAT, high risk of metabolic alteration
MONW : metabolically obese normal weight : high VAT and normal BMI

Prevalence of obesity globally

Adults (18+)

- 13% obese
 - 600 million
- 39% overweight
 - 1.9 billion

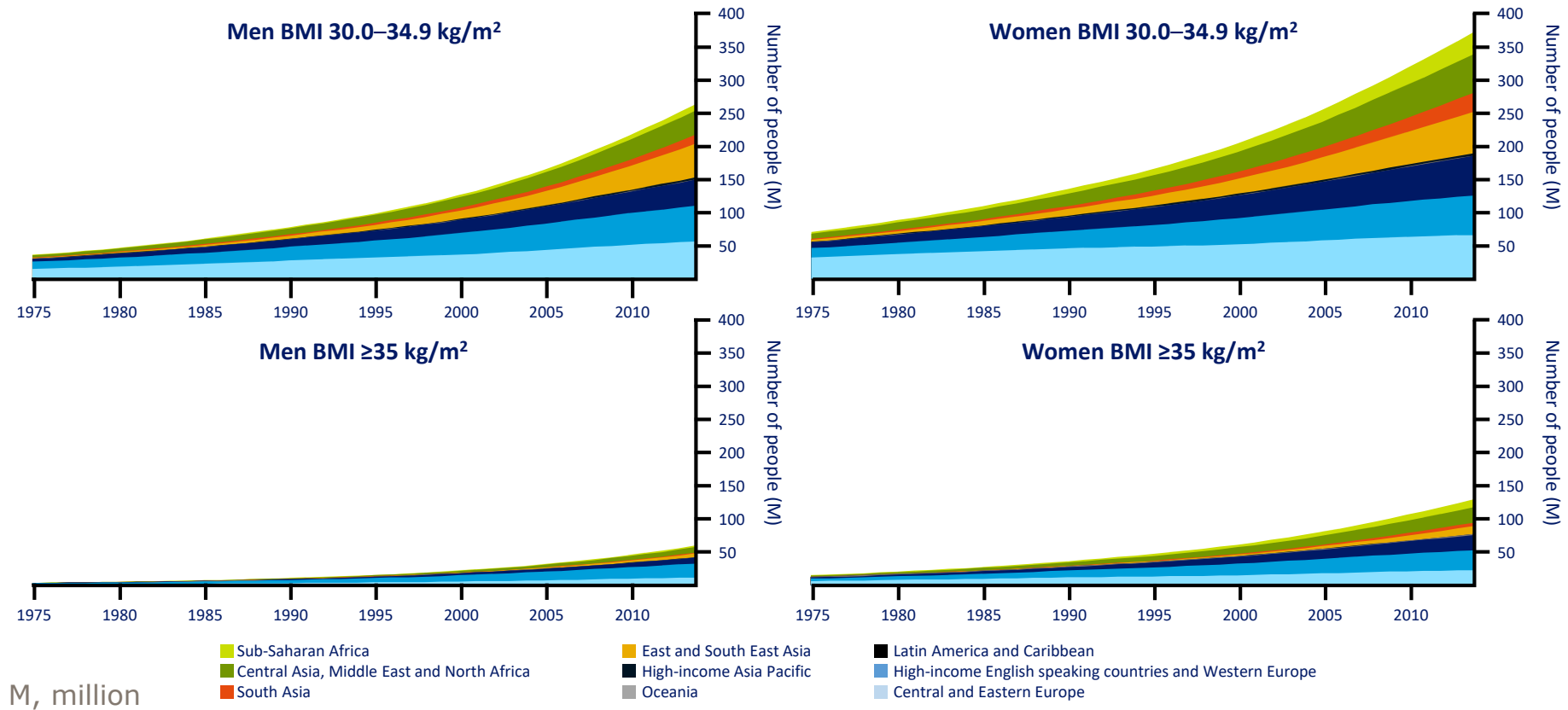
Children (under 5)

- 6.7% overweight or obese
 - 43 million

<http://www.who.int/mediacentre/factsheets/fs311/en/>

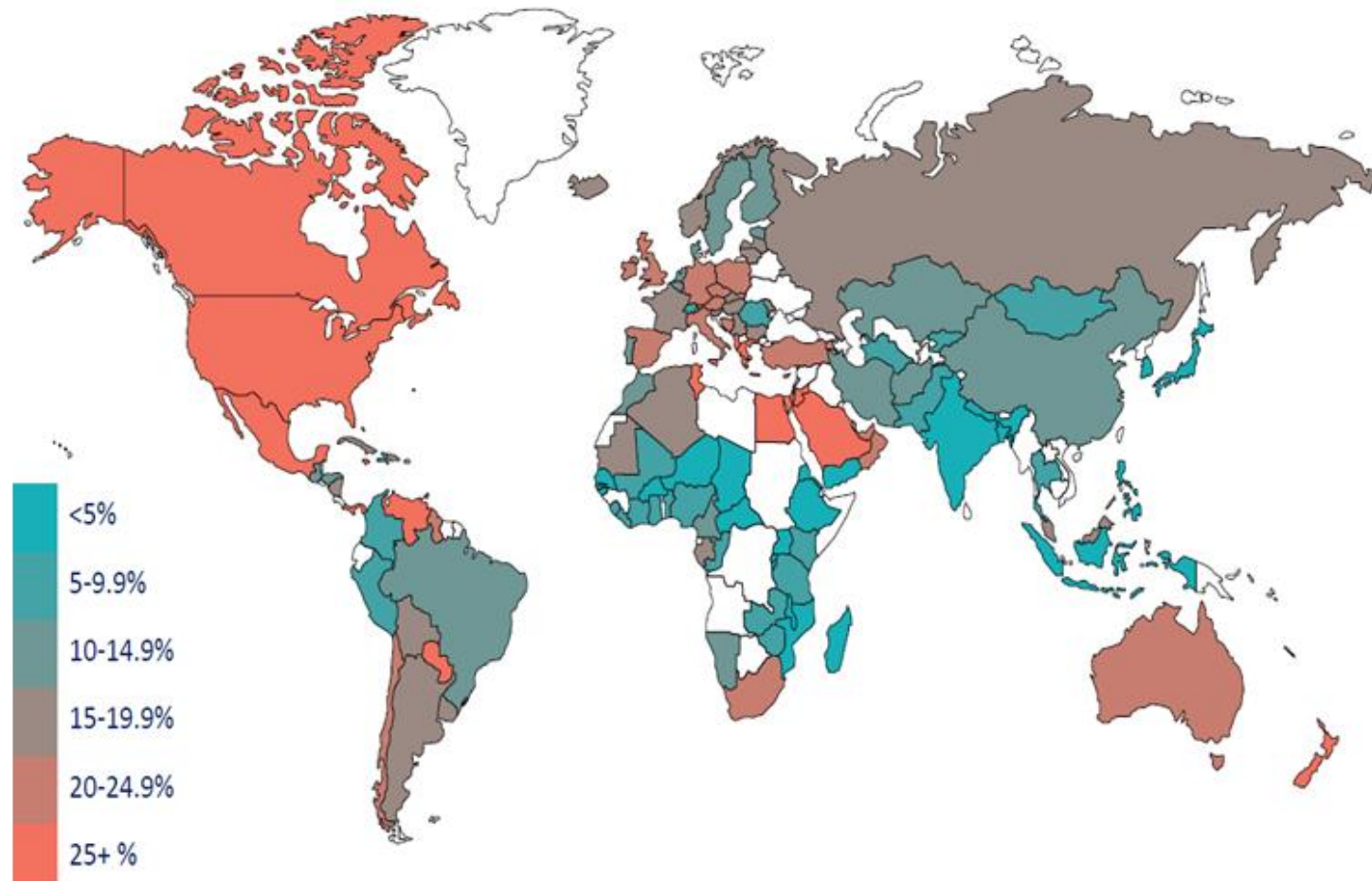
http://www.who.int/nutgrowthdb/publications/overweight_obesity/en/

Obesity rates worldwide are increasing



Adapted from NCD Risk Factor Collaboration (NCD-RisC). *Lancet* 2016;387;1377–96

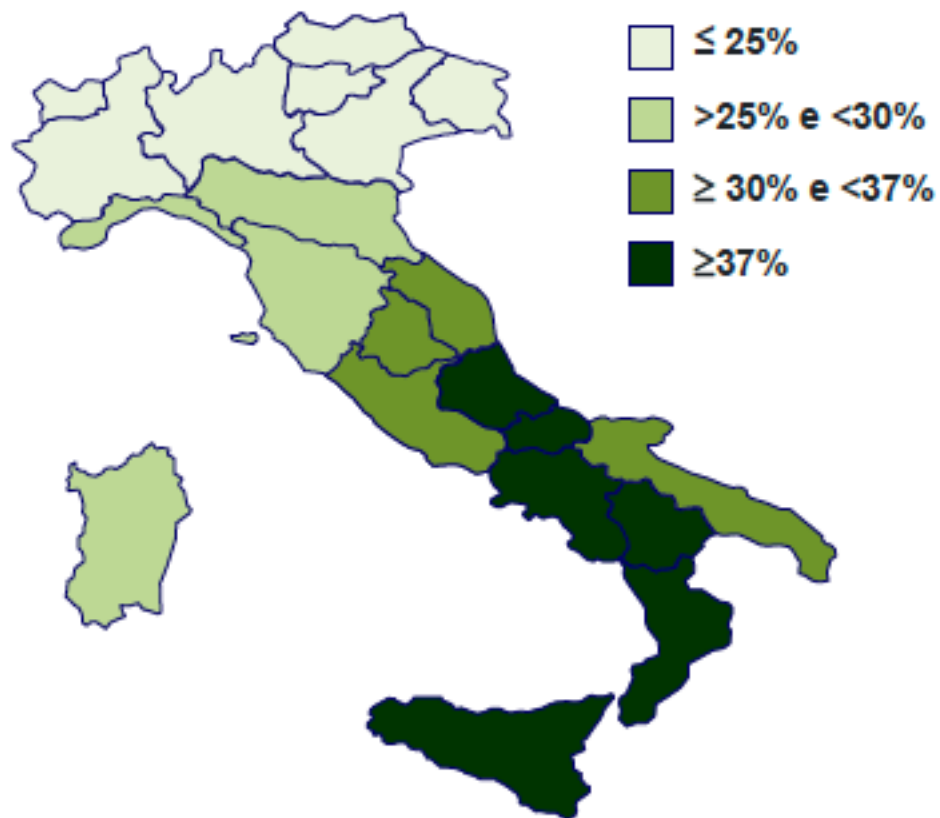
Prevalence of Adult Obesity (BMI ≥ 30.0 kg/m²): 2000 to Present



World Obesity Federation.

http://www.worldobesity.org/site_media/library/resource_images/Adults_and_children_earliest_and_most_recent_available_timepoints_combined_gender_November_14.pdf.

Prevalence of overweight and obesity (%), children aged 8-9 by Italian Regions. 2014 data.



Education

- Individuals with college degrees have lower risk of obesity compared to those with less education
- Generally, obesity rates are lower for children if head of household has college degree versus not finishing high school

<http://www.cdc.gov/obesity/data/childhood.html>

<http://www.cdc.gov/obesity/data/adult.html>

Geography & culture

- Higher prevalence of obesity in rural areas
- Risk for obesity among immigrants increases with time spent in the U.S.
- States with highest rates of obesity also have lowest physical activity rates for adults
- Unhealthy food and physical activity environments

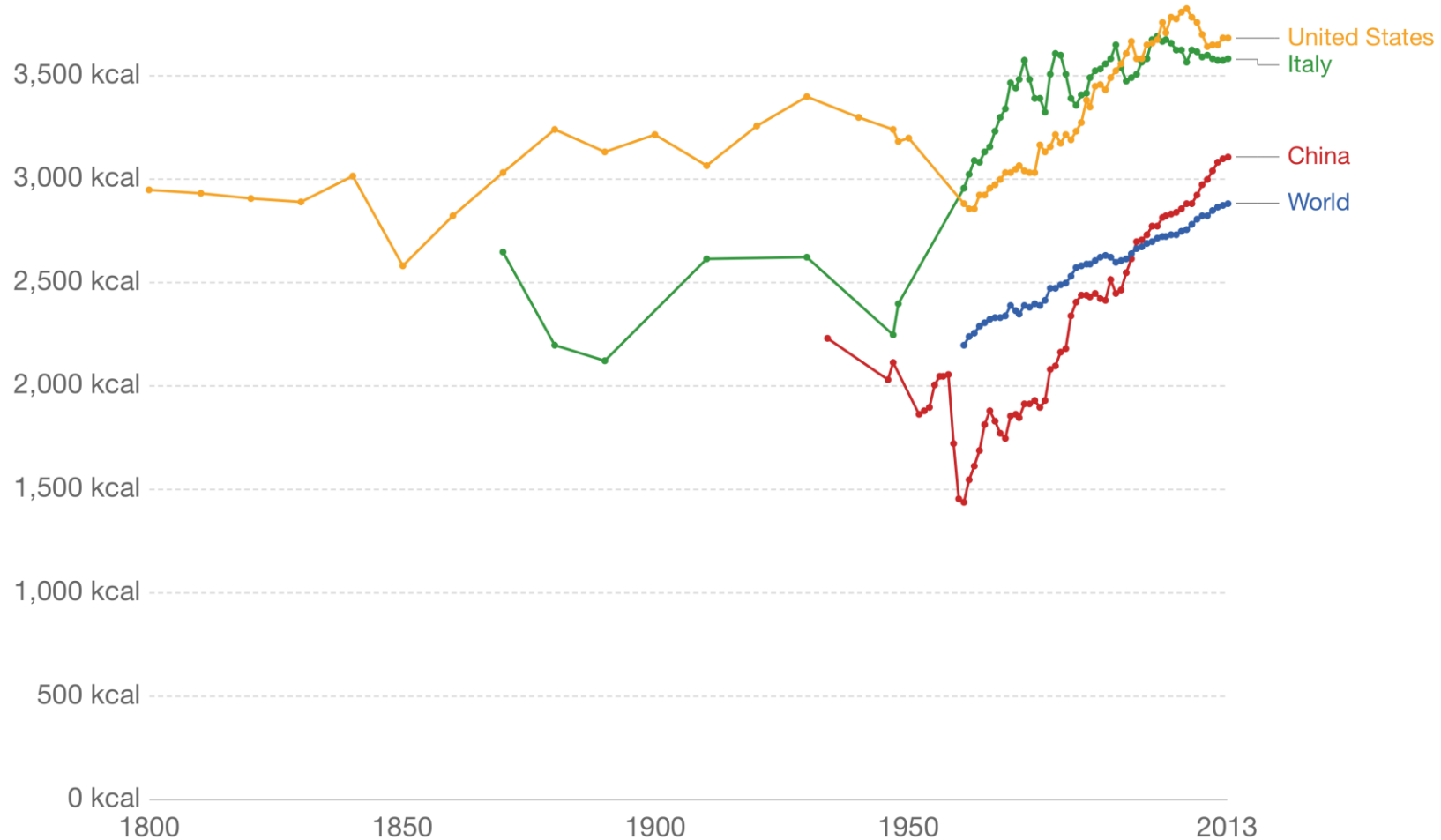
http://www.commed.vcu.edu/Chronic_Disease/Obesity/2016/activity&health_IOMNov.pdf

http://www.commed.vcu.edu/Chronic_Disease/2008/obesityRx_AHA.pdf

<https://ourworldindata.org/food-per-person>

Daily per capita supply of calories

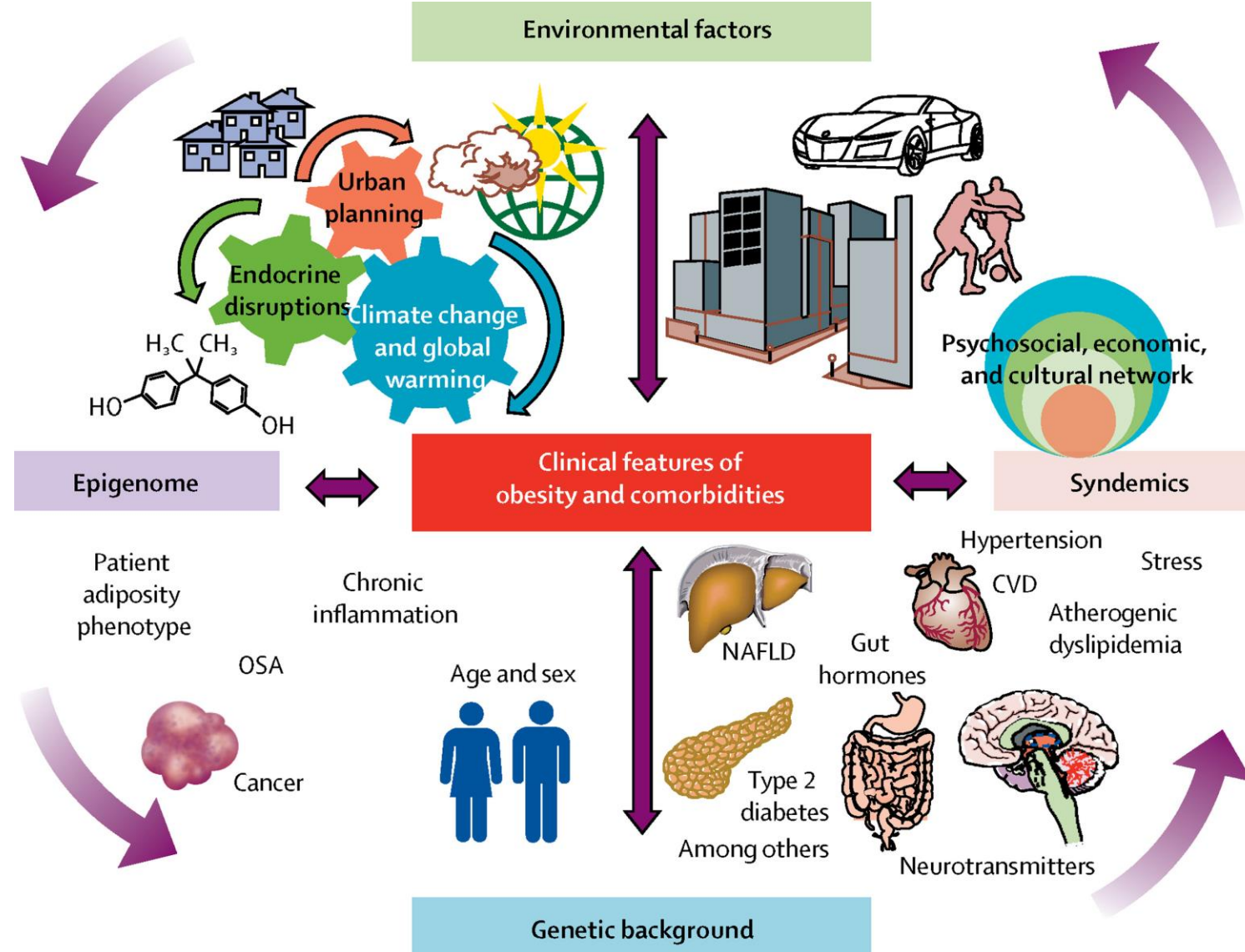
Average daily per capita supply of calories over the long-run, measured in kilocalories per person per day.



Source: Daily caloric supply per capita long-term - FAO (2017)

OurWorldInData.org/food-per-person/ • CC BY-SA

The complex interaction of diverse factors and networks underlying the development of obesity



Obesity is a complex disease

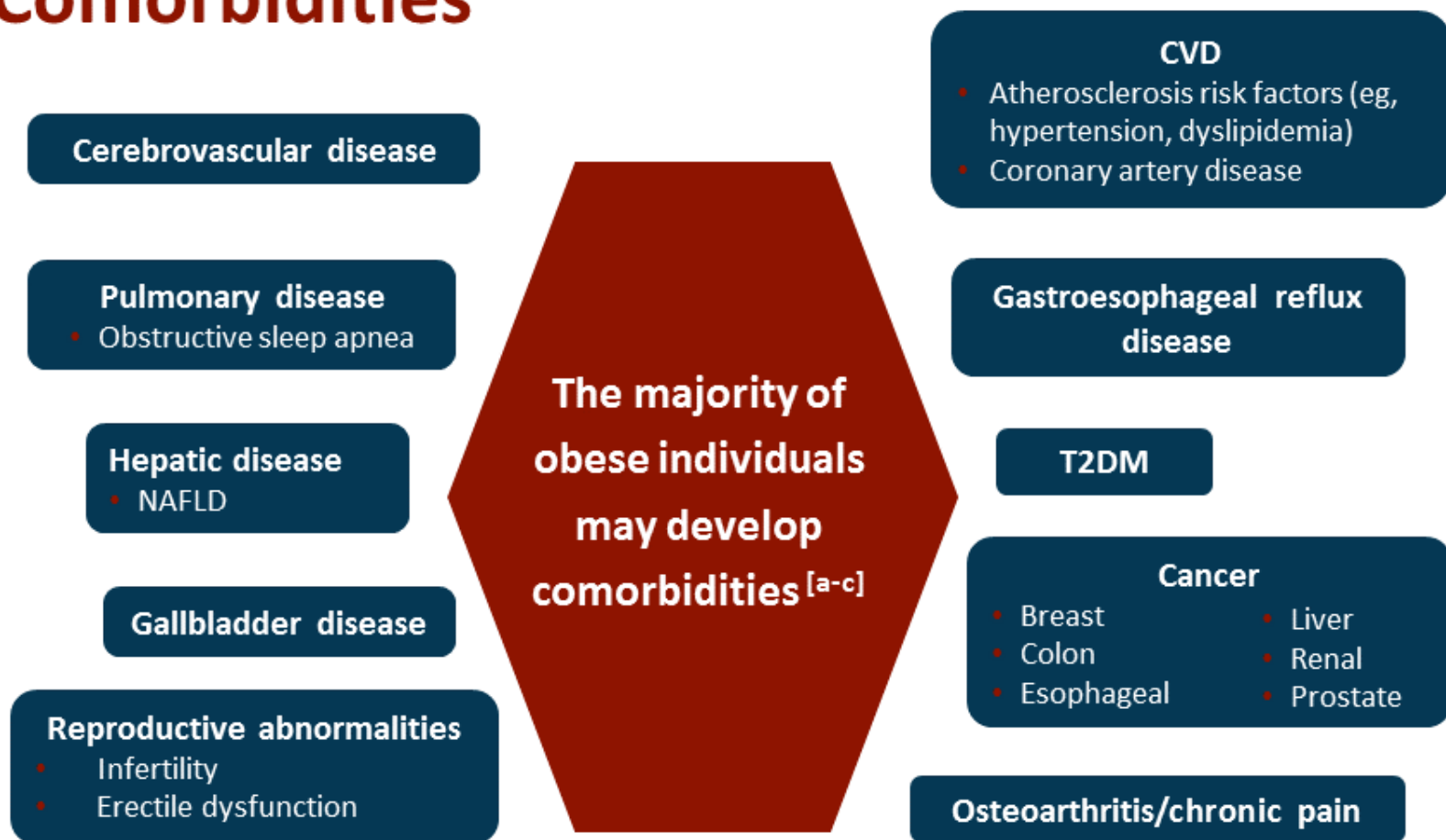
Drivers of obesity

Physiological ¹	Genetic ²	Environmental ¹
• Central nervous system pathways — Hunger and reward • Neuroendocrine signals — Long-term — Short-term	• High heritability of body weight, especially at BMI extremes • Genes in hypothalamus leptin-melanocortin pathway • Single genetic mutations leading to obesity are rare, but variations in many genes may predispose to obesity	• Socio-cultural factors — Traditions, belief systems, peer pressure • Socio-economic factors — Education level — Affordability of healthy food • Food environment — Availability of inexpensive, highly palatable food with high fat, sugar and salt content

1. Sharma AM et al. *Obes Rev* 2010;11:362–370;

2. Chesi A et al. *Trends Endocrinol Metab* 2015;26:711–721

Obesity Is Associated With Multiple Comorbidities

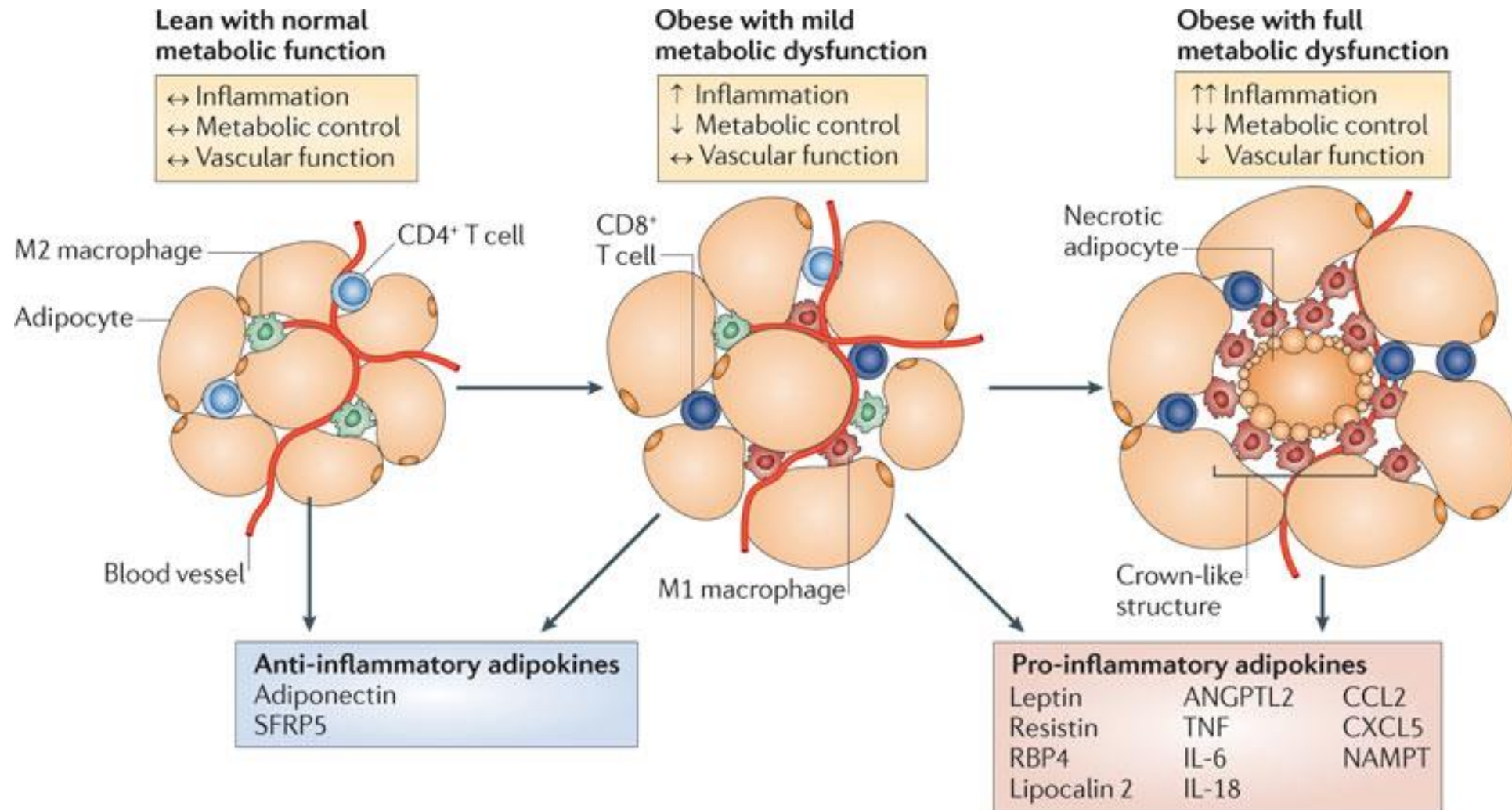


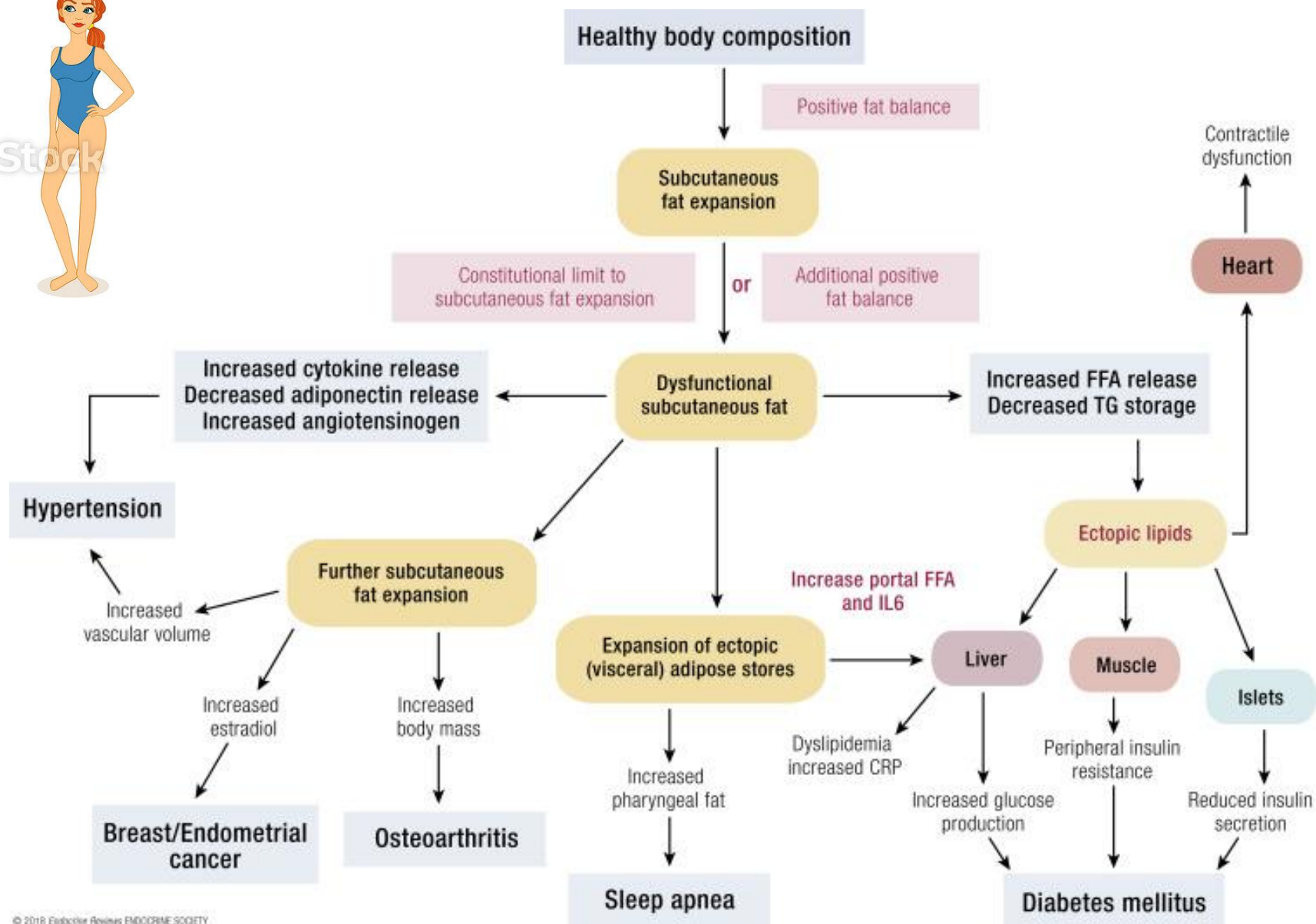
a. Catenacci VA et al. *Clin Chest Med*. 2009;30:415-444.

b. Calle EE et al. *N Engl J Med*. 2003;348:1625-1638.

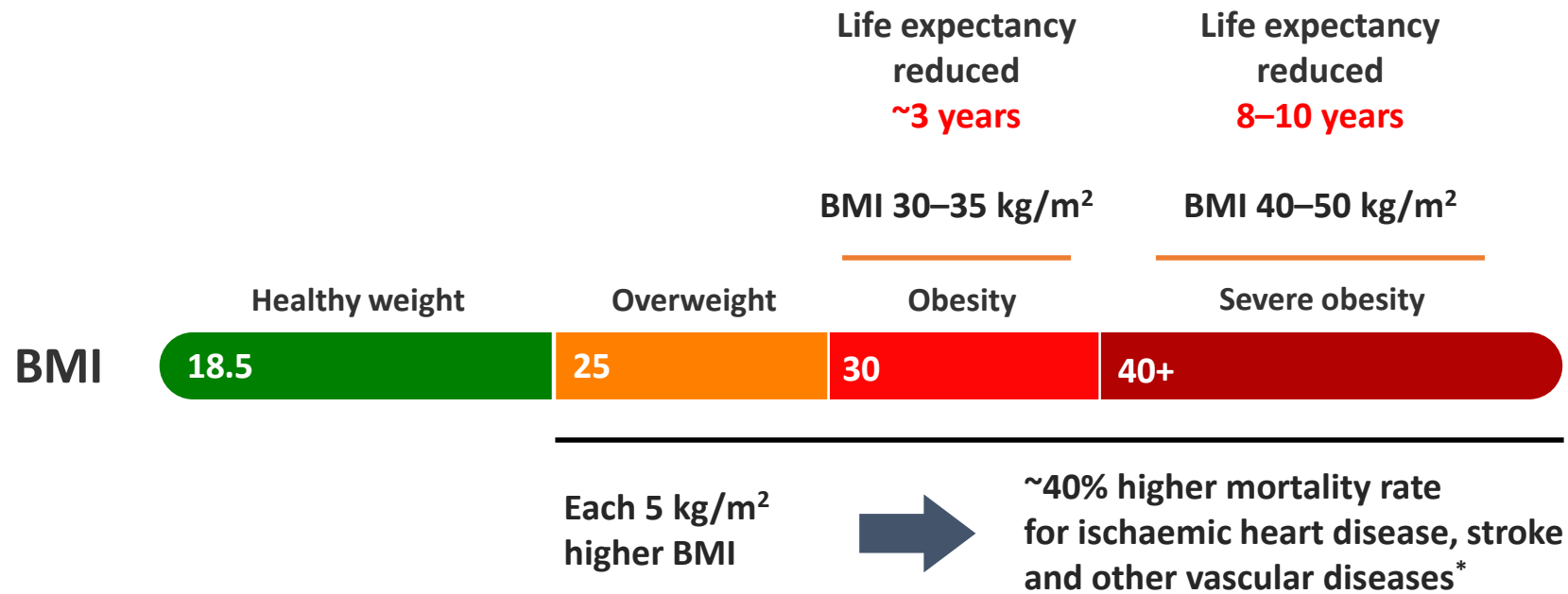
c. Bluher M. *Exp Clin Endocrinol Diabetes*. 2009;117:241-250.

Metabolic dysfunction: the metaflammation





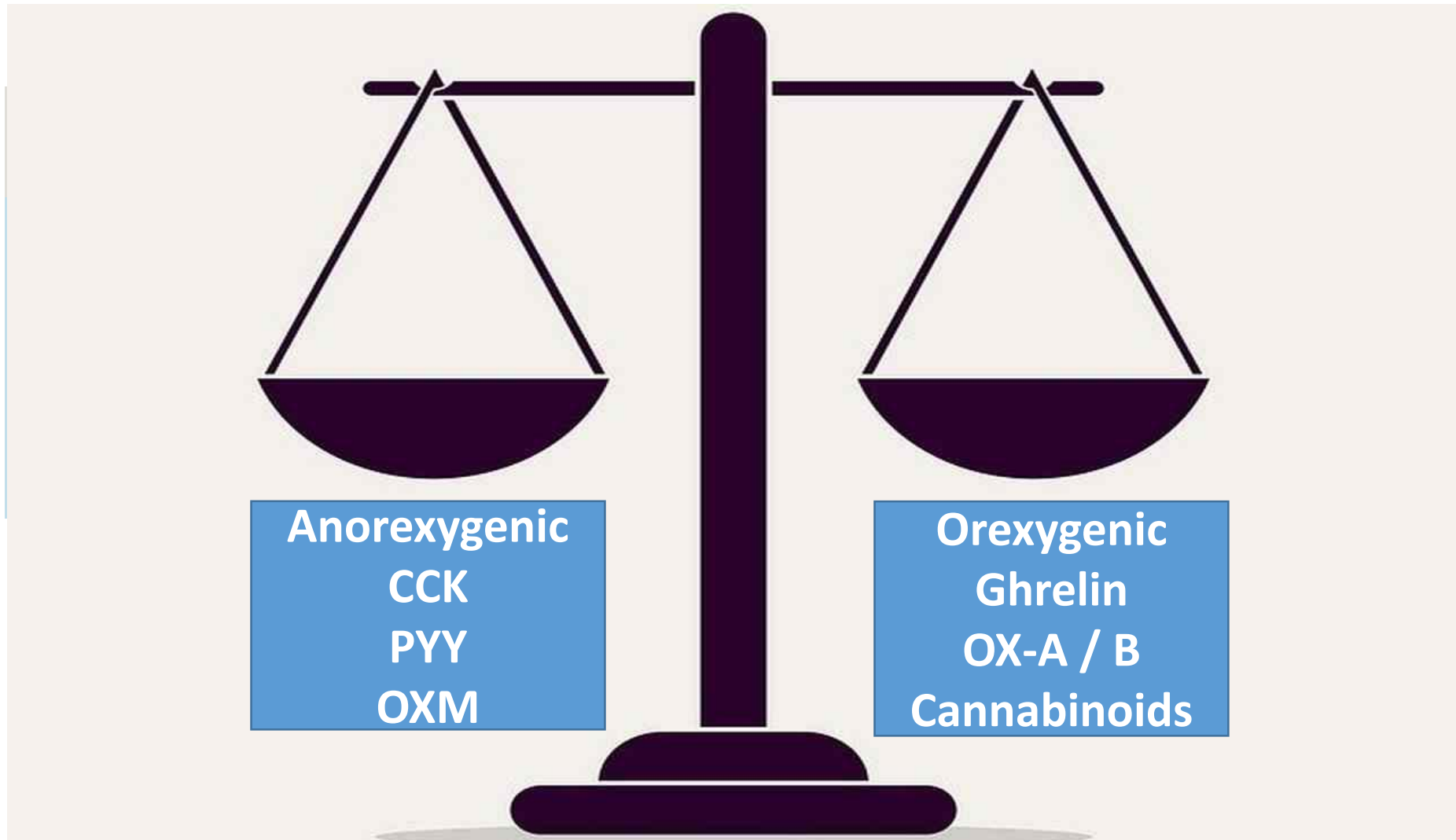
Obesity is a chronic condition/disease with serious implications for life expectancy¹



*Based on a meta-analysis of 57 international prospective studies predominantly based in Europe, the United States, Israel and Australia, including BMI information for 894,576 adults. BMI, body mass index

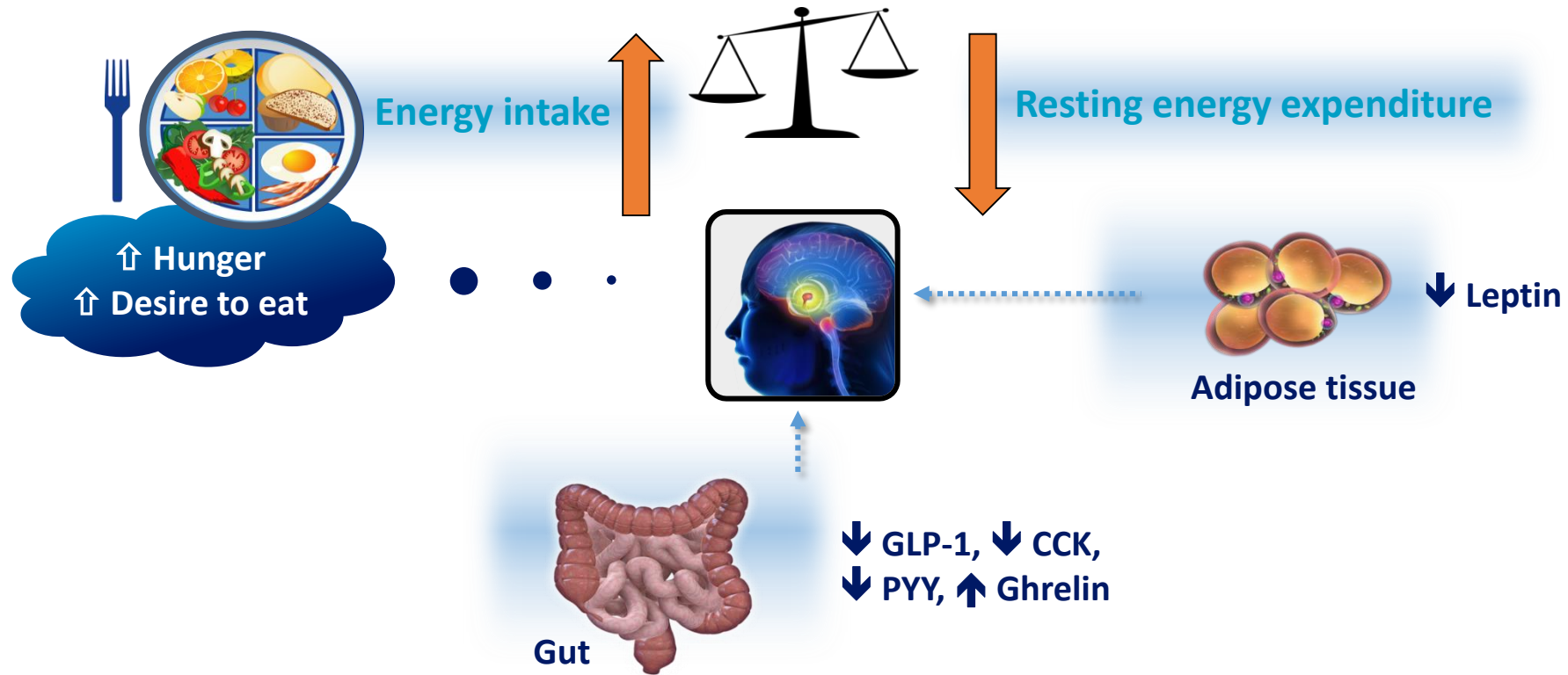
1. Prospective Studies Collaboration. *Lancet* 2009;373:1083–1096

Homeostatic regulation of appetite



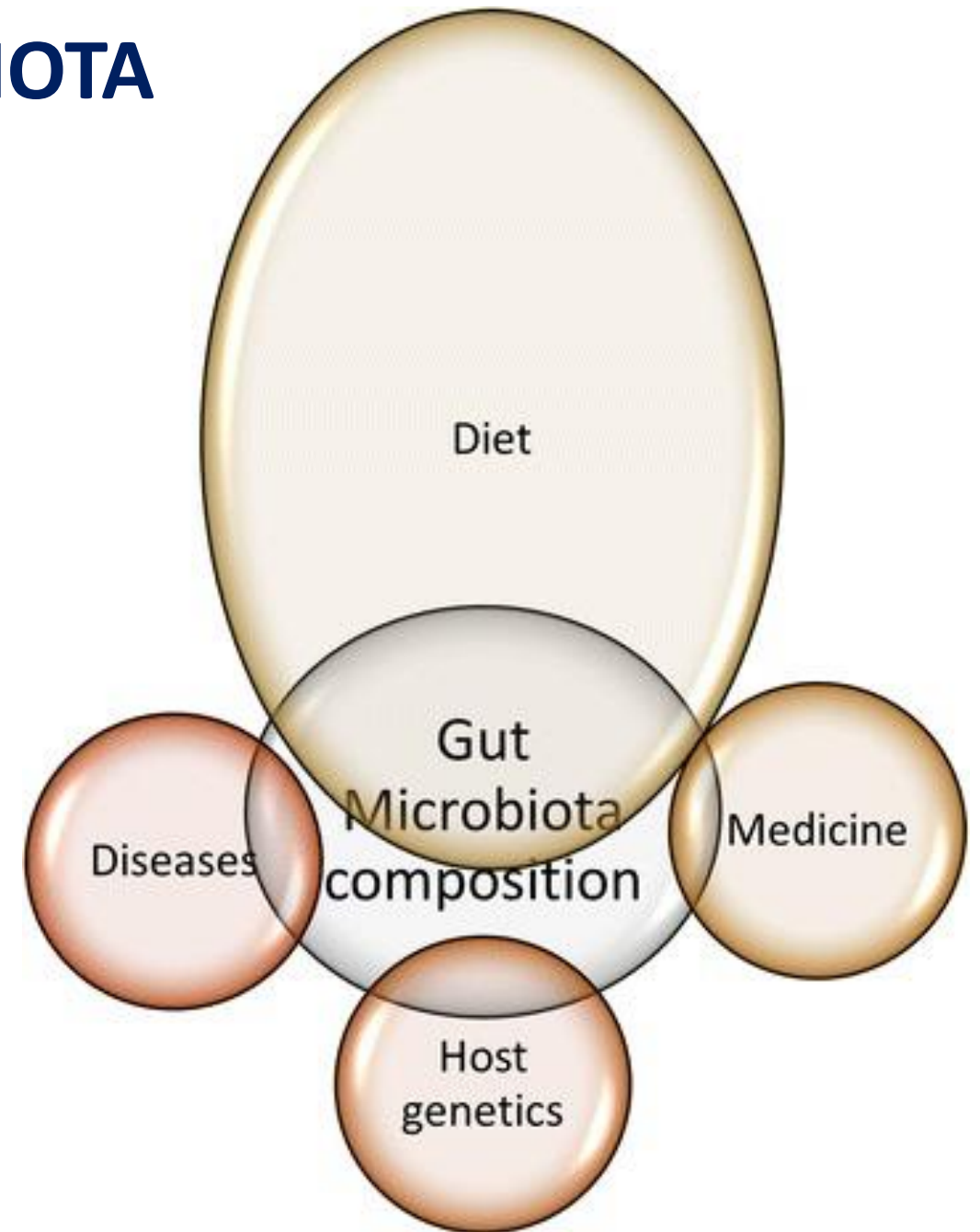
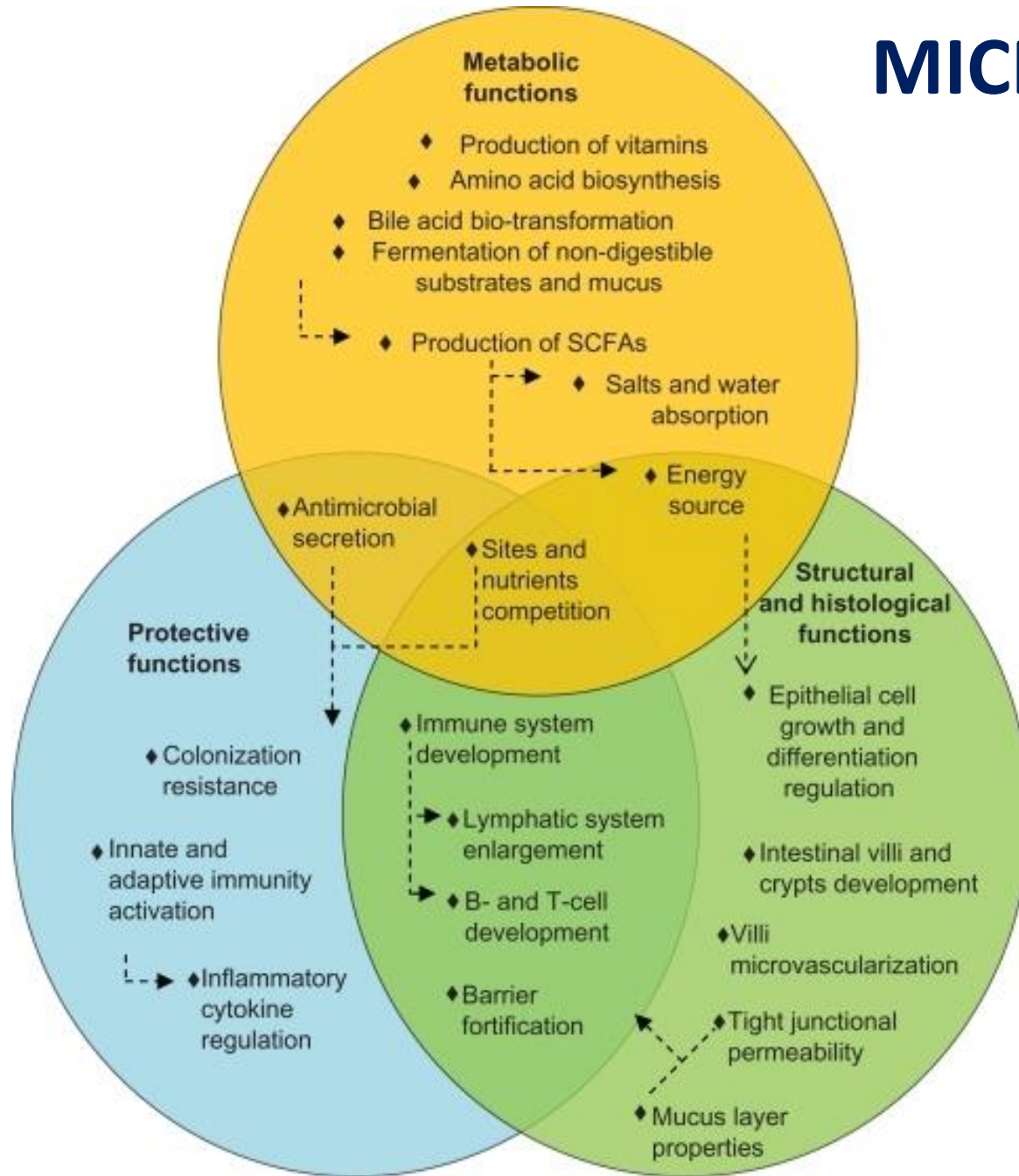
amphetamine-
otide Y; OXM,
5 receptor
et al. *J Clin*

Physiological responses to weight loss favour weight regain

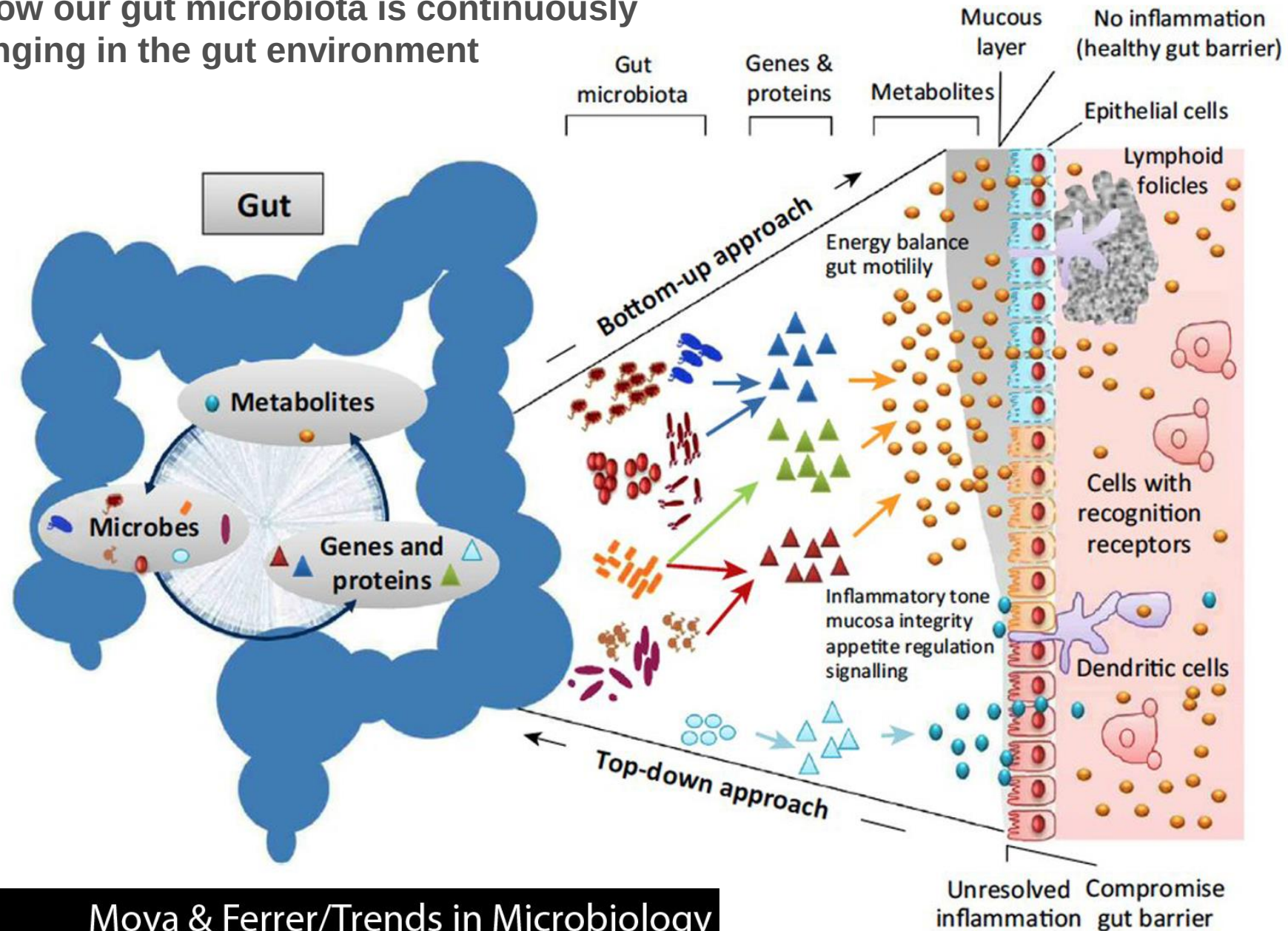


A new actor on stage : the gut microbiota

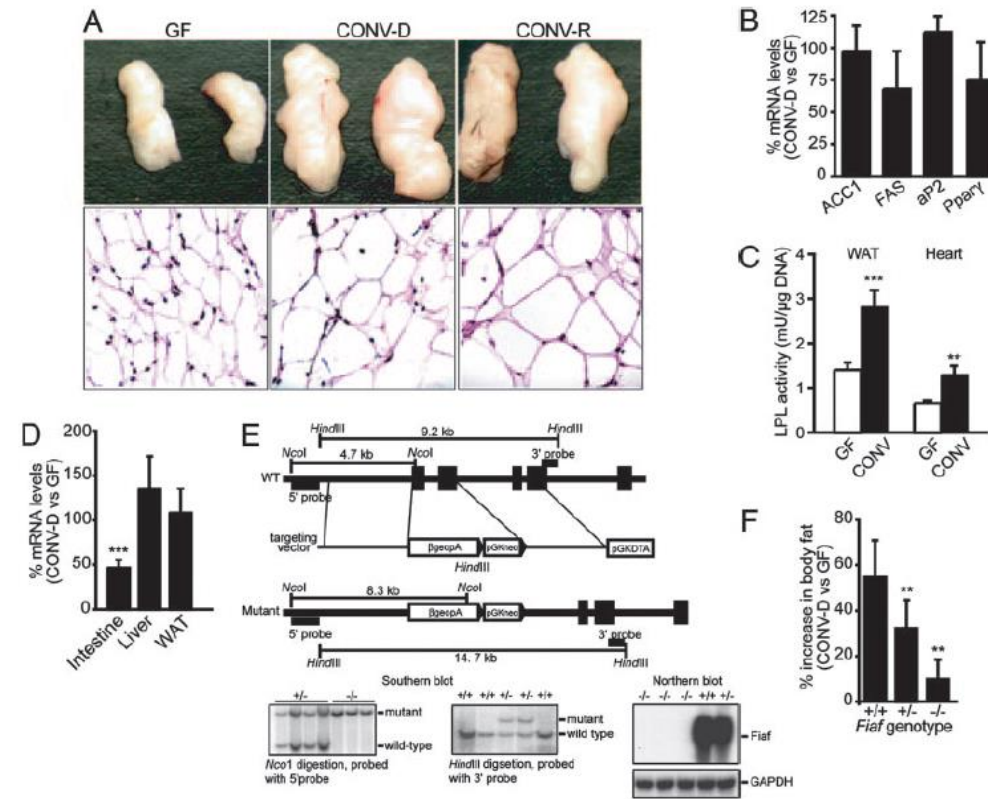
MICROBIOTA



The network-biology approach can help us to understand how our gut microbiota is continuously changing in the gut environment

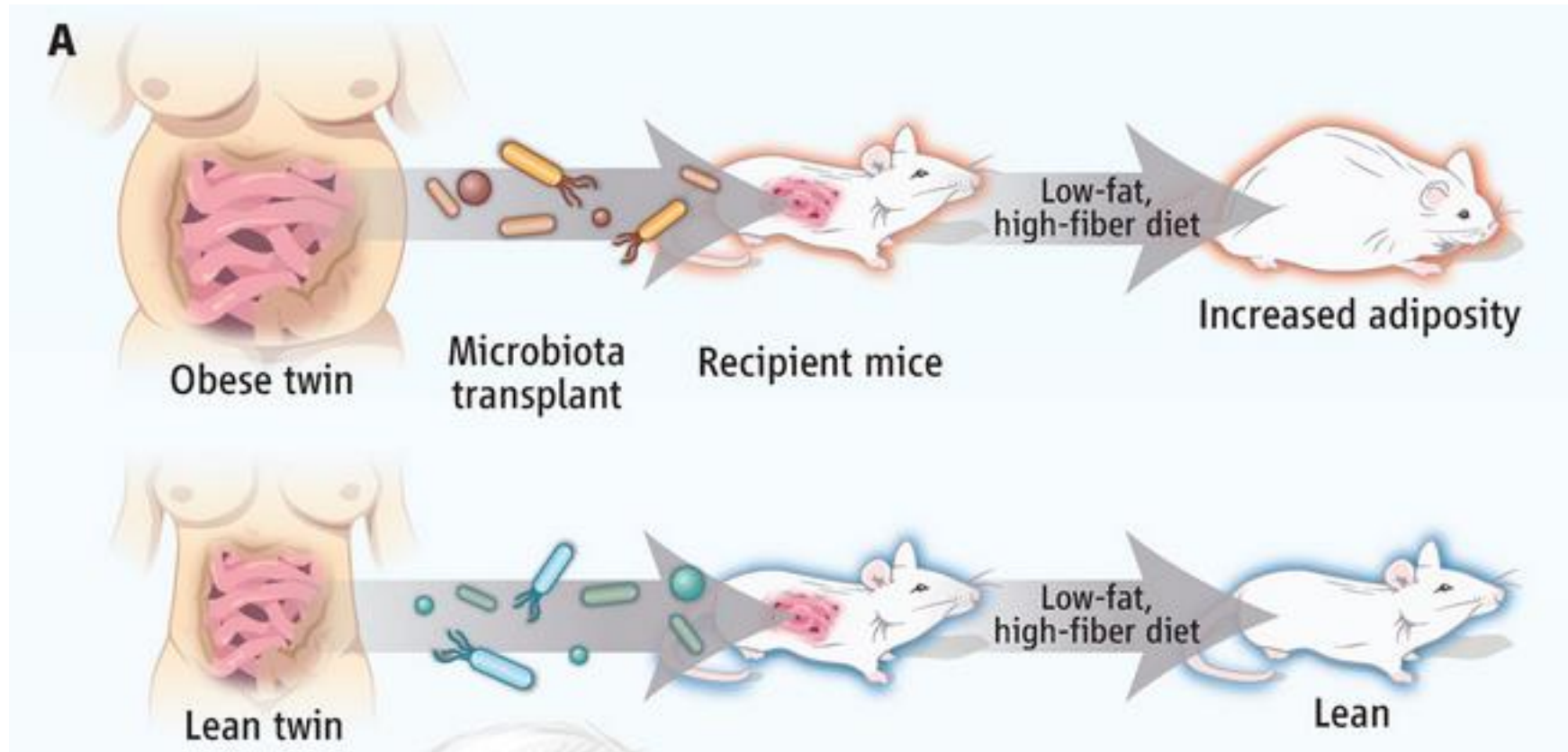


Microbiota and obesity : the mouse model



Significant weight gain in germ free mice with microbiota sample taken from fecal cultures of obese mice

Microbiota and obesity : the mouse model



Hypothesis on the mechanism of action

1.

Particular bacterial strains would be able to ferment indigestible fibers. The products of this intestinal fermentation would be short-chain fatty acids such as acetate, propionate, butyrate which would then be absorbed by the intestinal mucosa to be used for the de novo synthesis of lipids and glucose. Short-chain fatty acids would thus provide an additional form of energy for the body which is estimated to be around 10%

2.

Type of bacterial strains: particular bacterial strains are attributed pro-inflammatory and anti-inflammatory properties that could contribute to the development of obesity

3.

The intestinal flora and its products (lipopolysaccharides LPS and SCFAs) could regulate host gene expression (genes that code for enzymes involved in the oxidation of fatty acids)

4.

There is a significant difference in the composition of the intestinal flora of genetically obese mice and normal weight mice: 50% reduction in the abundance of Bacteroidetes with a proportional increase in Firmicutes in obese phyla compared to normal weight

Gut microbiota and obesity : a role for probiotics

Source	Study Subjects	Type of Trial	Probiotic(s) Administered	Placebo Arm	Duration	Major Findings
Gomes et al. [97]	43 obese Women (20–59 years); 21 probiotic/22 placebo	Randomized, double-blind, placebo-controlled, two arm, parallel-group	<i>L. acidophilus</i> LA-14, <i>L. casei</i> LC-11, <i>Lactococcus lactis</i> LL-23, <i>B. bifidum</i> BB-06, <i>B. lactis</i> BL-4 (2×10^{10} CFU/day) + dietary intervention	1 cap/day placebo + dietary prescription	8 weeks	Lower WC
Higashikawa et al. (2016) [98]	Overweight adults aged 20–70 years ($n = 62$); Intervention I ($n = 21$); Intervention II ($n = 21$); placebo ($n = 20$)	Randomized, double-blind, placebo-controlled clinical trial	Intervention I: Living LP28; Intervention II Heat-killed LP28 (<i>Pediococcus pentosaceus</i>) (10^{11} CFU/day)	1 cap/day placebo	12 weeks	<BMI and WC after Intervention II
Jung et al. (2015) [96]	Obese adults aged 20–65 years ($n = 120$); intervention ($n = 60$); placebo ($n = 60$)	Double-blind, placebo-controlled, randomized clinical trial	<i>L. curvatus</i> HY7601 + <i>L. plantarum</i> KY1032 (2.5×10^9 CFU of probiotics/2 cap/day) + healthy lifestyle habits	2 cap/day placebo + healthy lifestyle measures	12 weeks	<Body weight, WC and body fat
Kadooka et al. (2010) [104]	Adults aged 33–63 years with obese tendencies ($n = 87$); intervention ($n = 43$); control group ($n = 44$)	Multicenter, double-blind, randomized, placebo-controlled intervention trial	Fermented milk containing <i>Lactobacillus gasseri</i> SBT2055 (5×10^{10} CFU/100 g fermented milk). Intake of 200 g/day	200 g/day of fermented milk without probiotic	12 weeks	Lower abdominal, subcutaneous fat deposition, body weight and BMI
Kim et al. (2018) [99]	Obese adults aged 20–75 years ($n = 90$); low-dose intervention ($n = 30$); high-dose intervention ($n = 30$); placebo ($n = 30$)	Randomized, double-blind, placebo-controlled trial	Low (10^9 CFU/day) and high (10^{10} CFU/2 cap/twice a day) dose of <i>Lactobacillus gasseri</i> BNR17 + lifestyle changes	2 cap/twice a day of placebo + lifestyle changes	12 weeks	Lower visceral adipose tissue; lower WC in high-dose and low-dose groups
Luoto et al. (2010) [89]	Mother–child pairs ($n = 113$); intervention ($n = 54$); placebo ($n = 59$)	Randomized, double-blind, prospective follow-up study	<i>Lactobacillus rhamnosus</i> GG (1×10^{10} CFU/day)	1 cap/day of placebo (microcrystalline cellulose)	Mothers 4 weeks before expected delivery; in infants up to 6 month old	Lower weight gain at 1 year of life and 4 years; no changes in later stages of development
Minami et al. (2018) [100]	Healthy pre-obese adults aged 20–64 years ($n = 80$); intervention ($n = 40$); placebo ($n = 40$)	Randomized, double-blind, placebo-controlled trial	<i>Bifidobacterium breve</i> B-3 (10^{10} CFU/2 cap/day)	2 cap/day of placebo	12 weeks	<Body fat mass

Gut microbiota and obesity : a role for probiotics

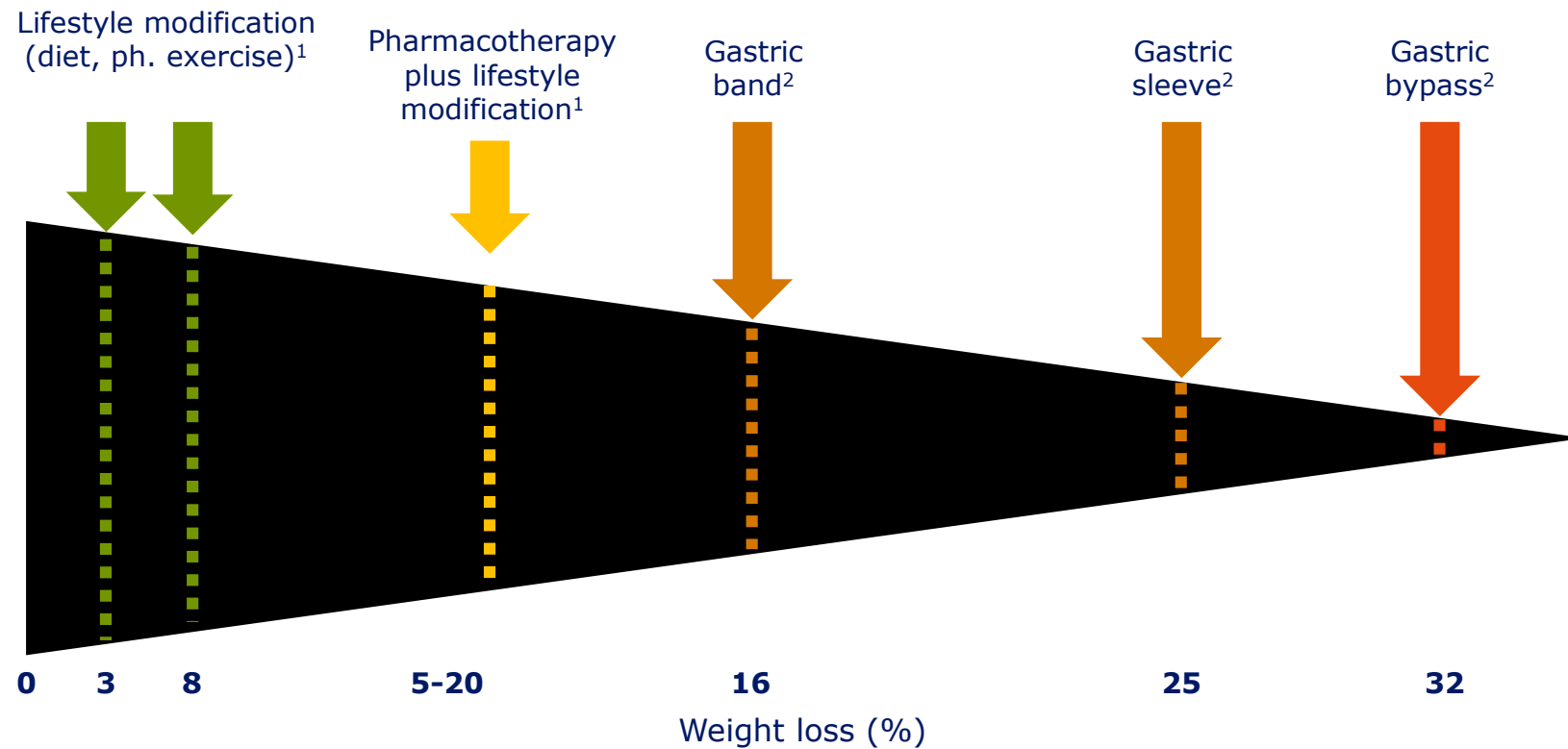
Source	Study Subjects	Type of Trial	Probiotic(s) Administered	Placebo Arm	Duration	Major Findings
Osterberg et al. (2015) [105]	Healthy non-obese young male adults (18–30 years) ($n = 20$); intervention ($n = 9$); placebo ($n = 11$)	Randomized, double-blind placebo-controlled clinical trial	Two vials of VSL#3 (450 billion bacteria per vial in milk shake/once a day) + high fat diet (HFD)	Two vials of placebo in milk shake/once a day + HFD	4 weeks	Lower weight and fat
Pedret et al. (2018) [101]	Abdominally obese adults ($n = 126$); Intervention I ($n = 42$); Intervention II ($n = 44$); placebo ($n = 40$)	Randomized, parallel, double-blind, placebo-controlled trial	Bifidobacterium animalis subsp. Lactis CECT 8145 (Intervention I) or its heat-killed form (Intervention II) (1010 CFU/cap/day)	1 cap/day of placebo	12 weeks	Lower BMI, WC and waist circumference/height ratio
Sánchez et al. (2017) [103]	Obese adults aged 18–55 years ($n = 125$); intervention ($n = 62$); placebo ($n = 63$)	Double-blind, randomized, placebo-controlled trial	L. rhamnosus CGMCC1.3724 (1.62×10^8 CFU/2 cap/day) + healthy eating behavior	250 mg of maltodextrin + 3 mg magnesium stearate + eating advices	12 weeks	Lower weight
Sanchis-Chordá et al. (2018) [93]	Obese children (aged 10–15 years) with insulin resistance ($n = 48$); intervention ($n = 23$); placebo ($n = 25$)	Double-blind, randomized, placebo-controlled trial	B. pseudocatenulatum CECT 7765 (109×10 CFU/day) + dietary recommendations	Placebo + dietary recommendations	13 weeks	Lower weight
Szulinska et al. (2018) [102]	Obese postmenopausal women aged 45–70 years ($n = 81$); low-dose intervention ($n = 27$); high-dose intervention ($n = 27$); placebo ($n = 27$)	Randomized-double-blind, placebo-controlled clinical trial	Low (2.5×10^9 CFU/day) and high dose (1010 CFU/day/two sachets per day) of probiotic mixture including nine different strains of Lactobacillus and Bifidobacterium	1 cap/day of placebo	12 weeks	Lower body weight, BMI and fat mass in low and high-dose group; improved lipid profile in the high-dose group
Vajro et al. (2011) [90]	Obese children (aged 10–13 years) with hypertransaminasemia and ultrasonographic bright liver ($n = 20$); intervention ($n = 10$); placebo ($n = 10$)	Double-blind, placebo-controlled pilot study	Lactobacillus rhamnosus GG (12 billion CFU/day)	1 cap/day of placebo	8 weeks	Lower hypertransaminasemia; lower BMI and visceral fat adding lifestyle interventions

BMI: body mass index; WC: waist circumference.



Treatment options

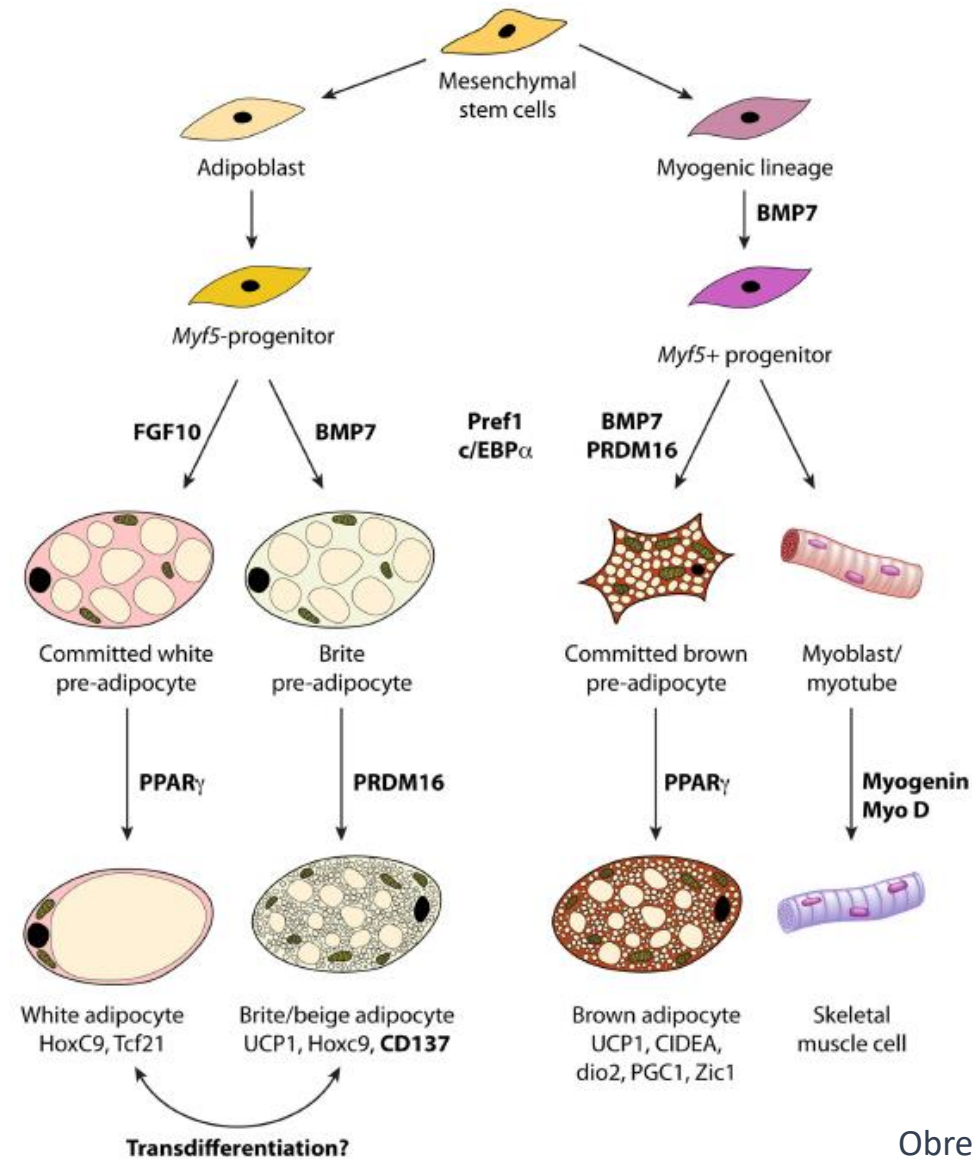
Treatment options for people with obesity: weigh loss target



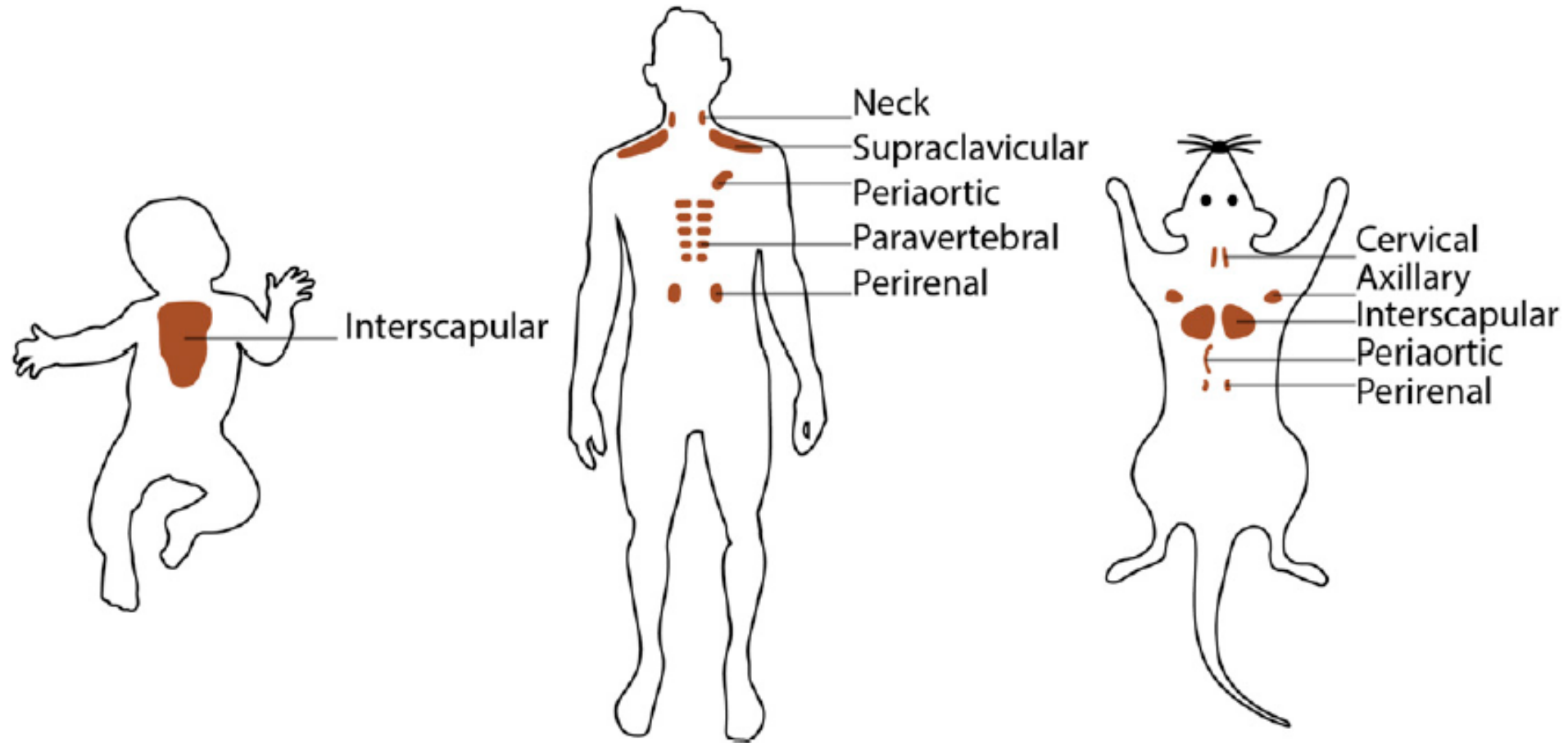
1. Jensen MD *et al. Circulation* 2014;129(25 Suppl. 2):S102-38; 2. Courcoulas AP *et al. JAMA* 2013;310:2416-2425

Lifestyle modifications

WHITE, BROWN e «BRITE/BEIGE» ADIPOCYTE



DEPOSIT LOCATIONS OF BROWN FAT TISSUE IN HUMAN AND MOUSE

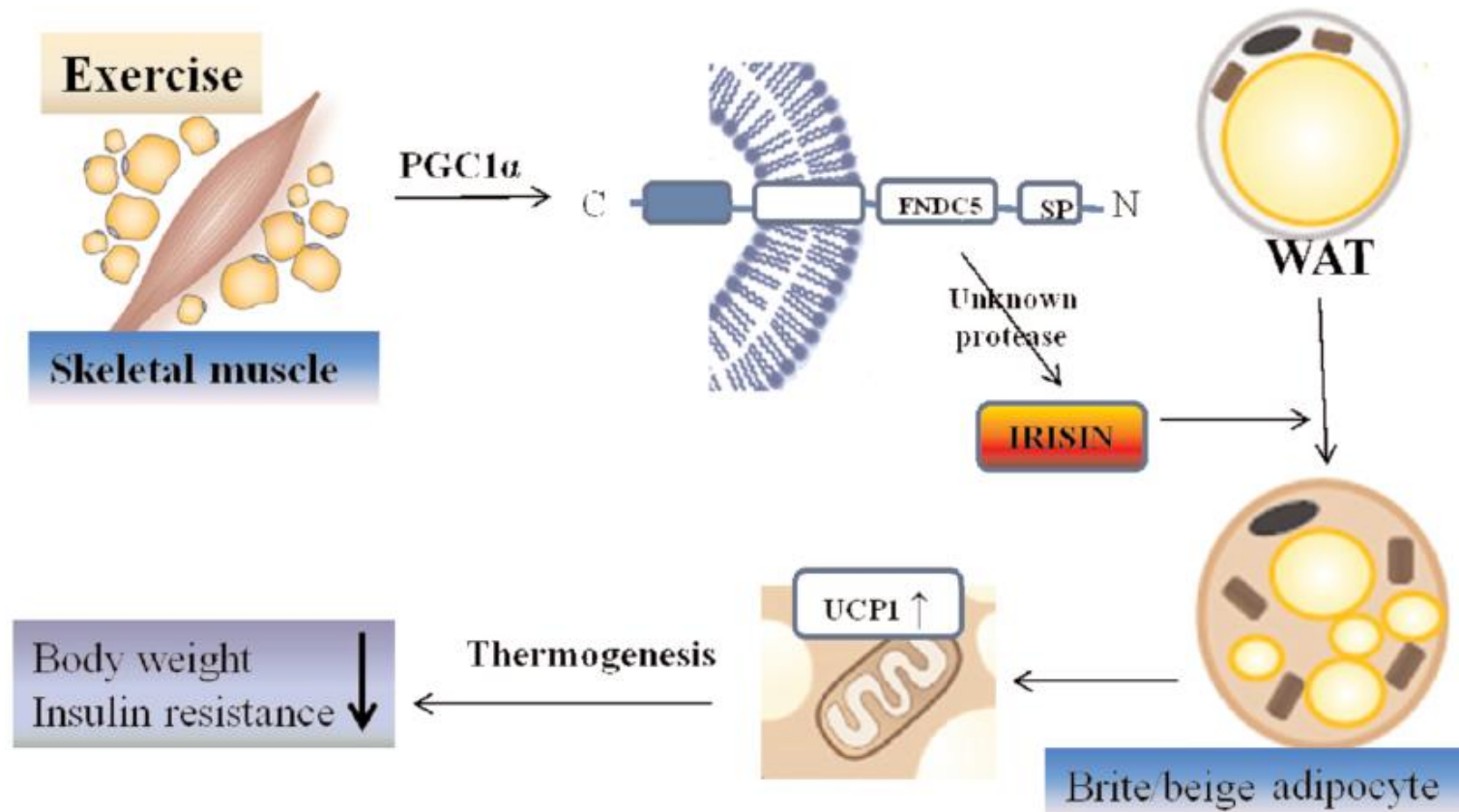




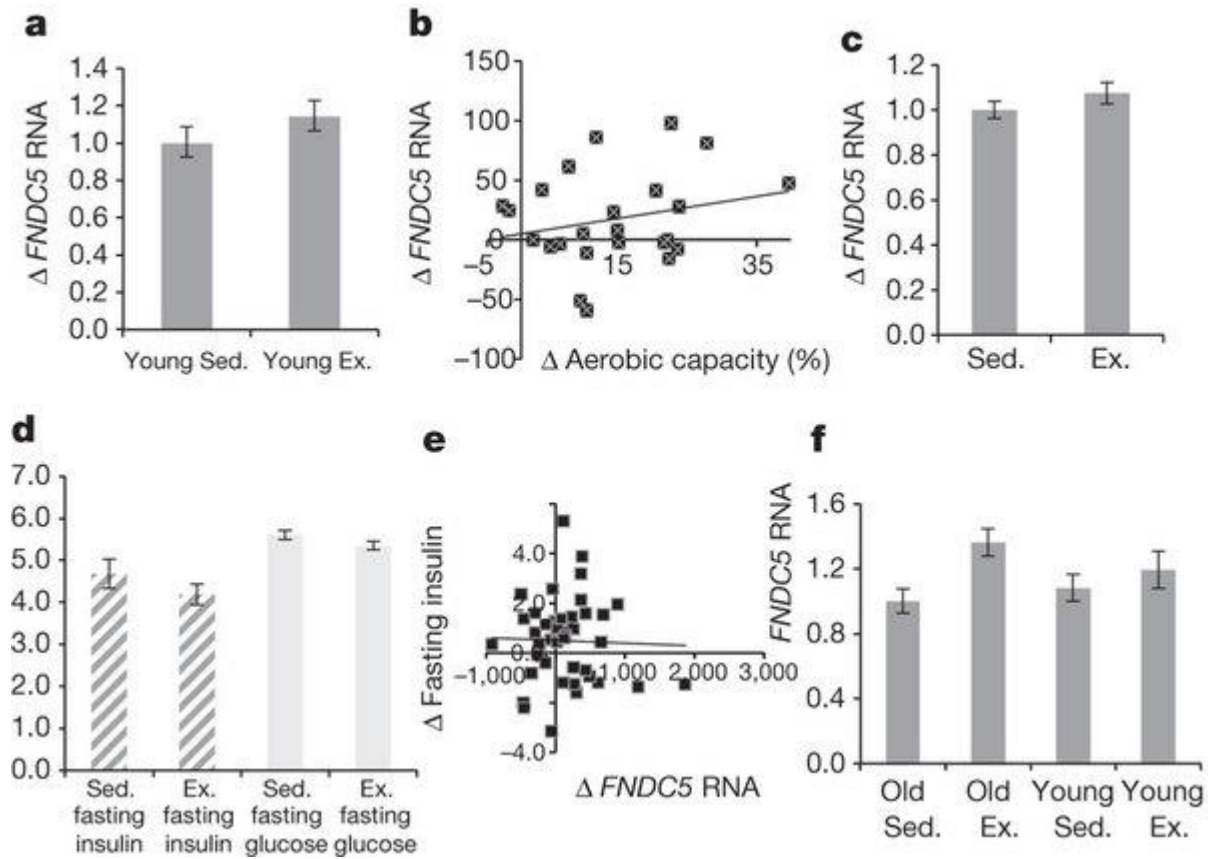
IRISIN

The health promoting hormone

PHYSICAL EXERCISE INDUCES THE RELEASE OF **PPAR γ coactivator-1 α (PGC1 α)** FROM THE SKELETAL MUSCLE TISSUE THAT INCREASES THE EXPRESSION OF **FIBRONECTIN TYPE III DOMAIN 5 (FNDC5)** WHOSE CLIVAGE BY UNKNOWN PROTEASE INDUCES **IRISIN** RELEASE

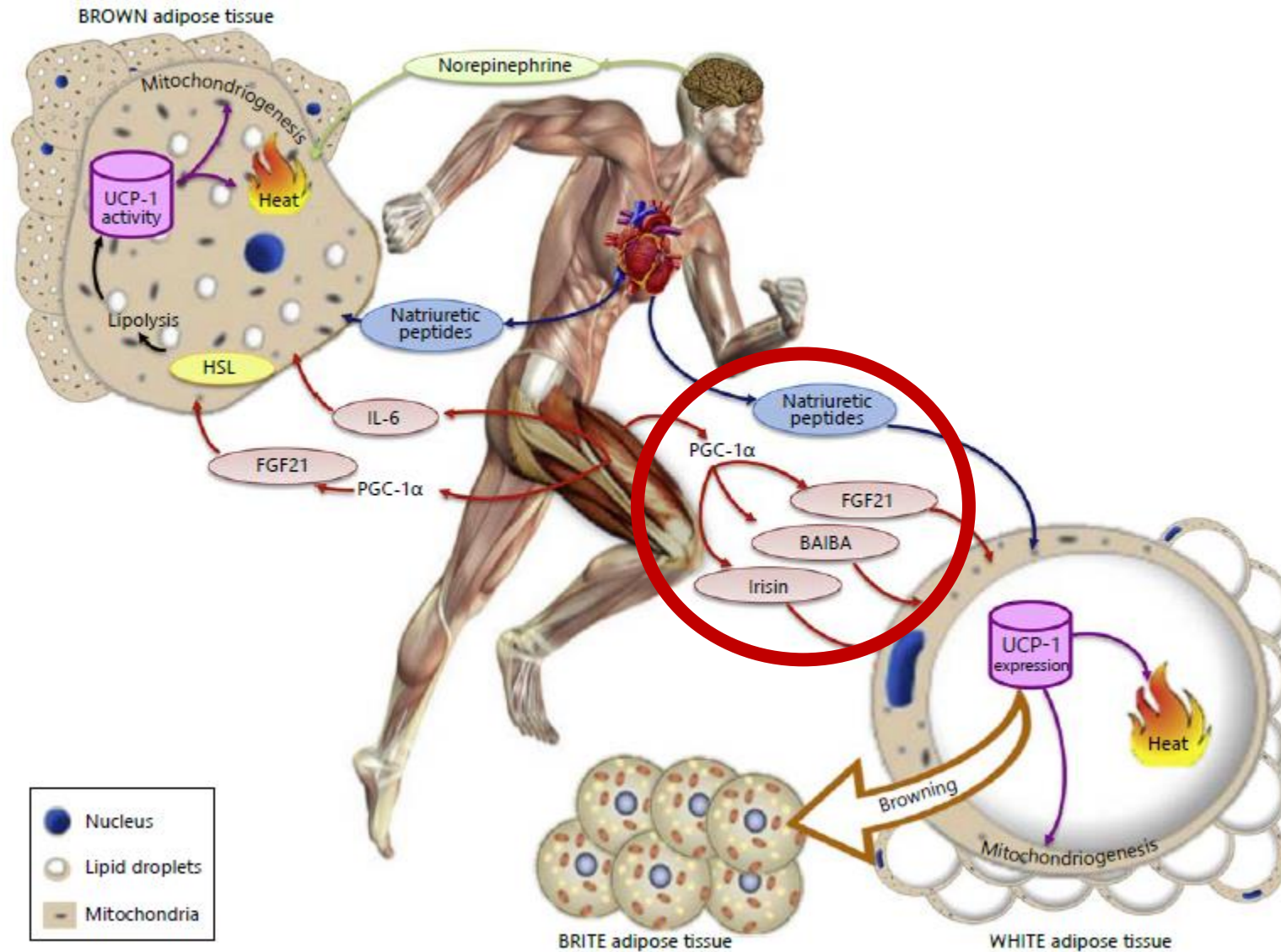


AEROBIC TRAINING INDUCES IRISIN EXPRESSION THAT CONVERTS WHITE IN BROWN FAT



Boström et al. *Nature* 2012

EXERCISE MODULATES THE ENDOCRINE CROSSTALK BETWEEN MUSCLE AND ADIPOSE TISSUE



How much activity do I need?

Moderate-intensity aerobic activity

Anything that gets your heart beating faster counts.

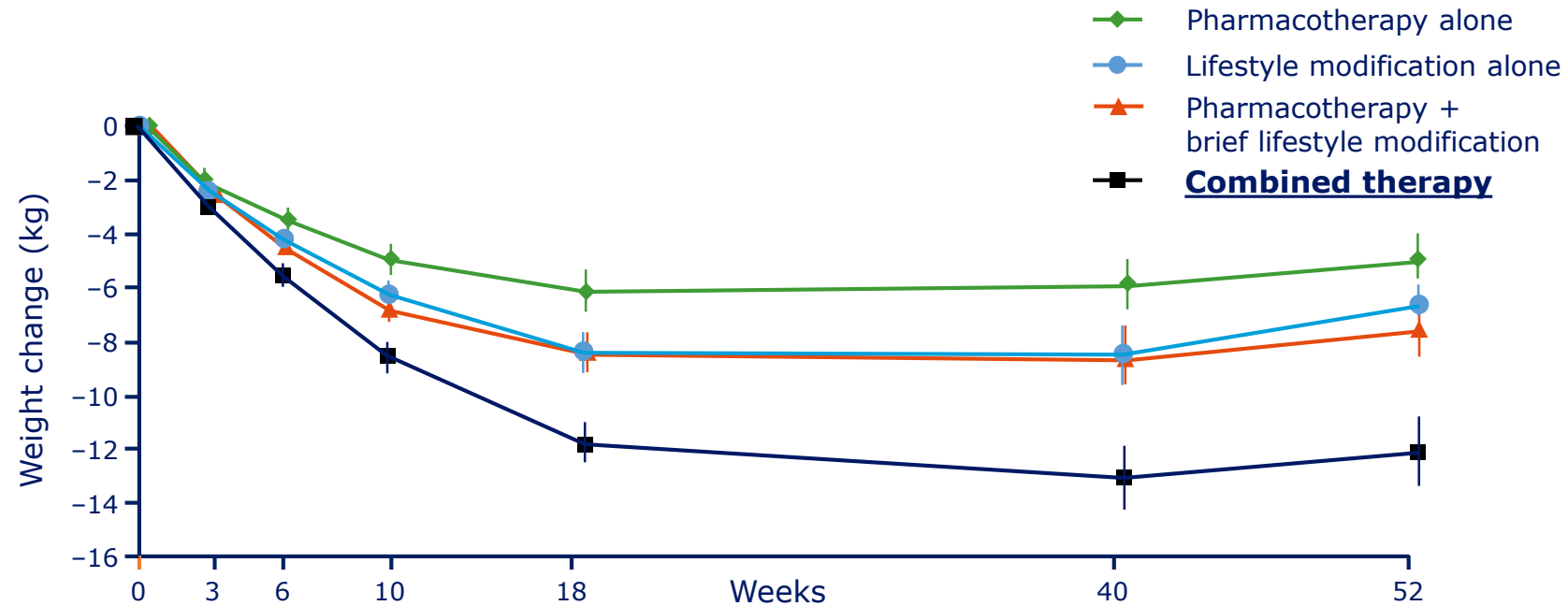


Tight on time this week? **Start with just 5 minutes.** It all adds up!

Or get the same benefits in half the time. If you step it up to **vigorous-intensity** aerobic activity, aim for at least **75 minutes** a week.

Pharmacotherapy

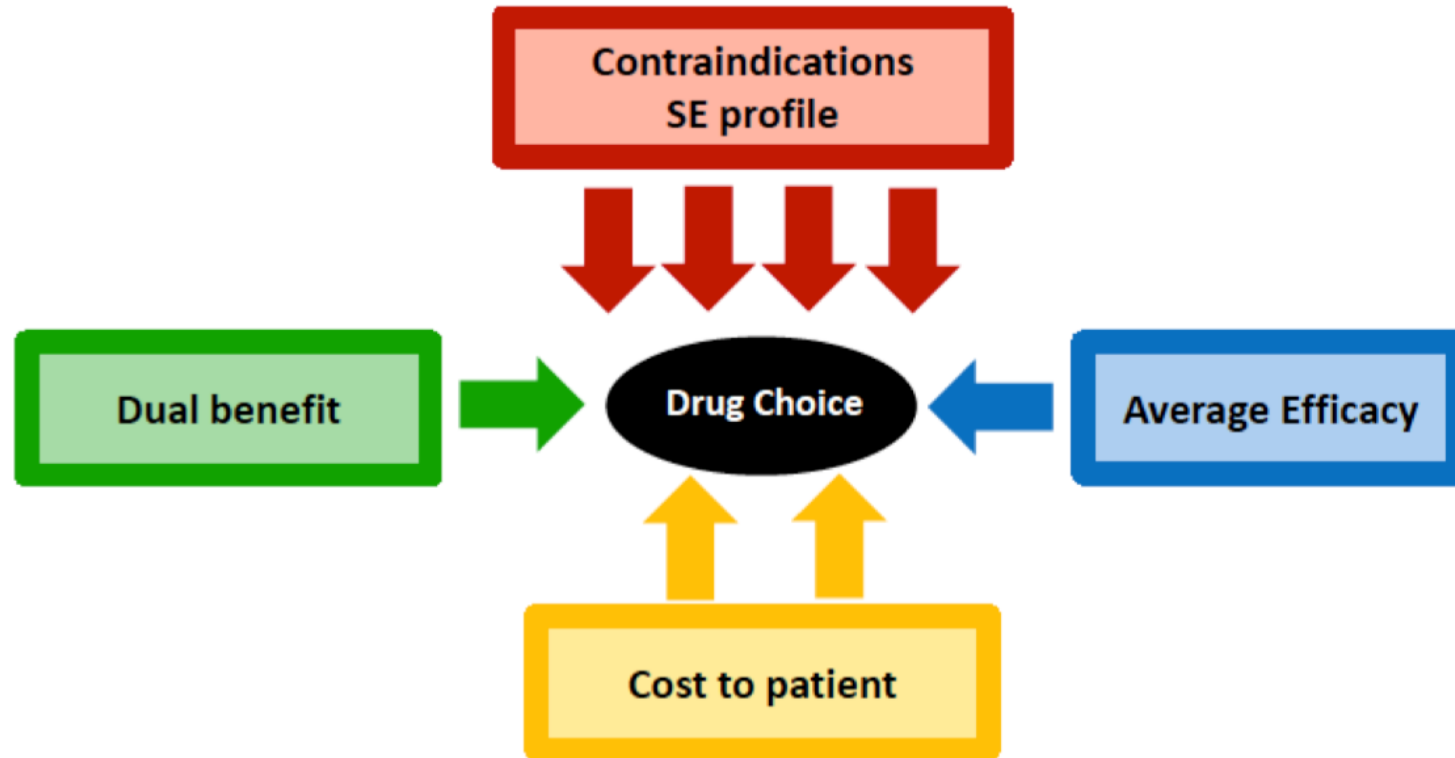
Pharmacotherapy in addition to diet and exercise can help patients achieve clinically relevant weight loss



Data are mean $\pm$ standard error
Pharmacotherapy: Sibutramine; Pharmacotherapy alone: Patients received a daily dose of 15 mg/day; Lifestyle modification alone: Patients attended 30 lifestyle counselling sessions; Pharmacotherapy + brief therapy: Patients were given sibutramine and received brief lifestyle counselling; Combined therapy: Patients received sibutramine and attended 30 lifestyle counselling sessions

Wadden TA et al. *N Engl J Med* 2005;353:2111–2120

Initial choice of the anti-obesity medications:



Pharmacotherapeutic options for weight management

Drug	USA	Canada	EU	UAE	Class
Phentermine*	✓	✗	✗	✗	Adrenergic agonist
Orlistat 120 mg tds	✓	✓	✓	✓	Lipase inhibitor
Orlistat 60 mg tds	✓	✓	✓	✓	Lipase inhibitor
Sibutramine	✗	✗	✗	✗	5-HT _{2c} /NE agonist
Naltrexone/bupropion	✓	✗	✓	✗	Combination
Phentermine/topiramate	✓	✗	✗	✗	Combination
Lorcaserin ER	✓	✗	✗	✗	5-HT _{2c} agonist
Liraglutide 3.0 mg	✓	✓	✓	✓	GLP-1R agonist

*Approved only for short-term use. In the EU and Canada, phentermine has marketing authorisation but approvals vary by country. Details available at: <http://ec.europa.eu/health/documents/community-register/html/ho1038.htm> (Accessed May 2017)

5-HT_{2c}, 5-hydroxytryptamine 2c; ER, extended release; GLP-1R, glucagon-like peptide-1 receptor; NE, norepinephrine; tds, three times daily
 EMA. <http://www.ema.europa.eu/ema>. Accessed 7 April 2017; Gadde K. *Pharmacother* 2014;15:809–822; UKMI new drug database. <http://www.ukmi.nhs.uk>. Accessed 7 April 2017; Central Drugs Standard Control Organization. <http://www.cdsco.nic.in>. Accessed 7 April 2017

GLP-1 reduces energy intake in humans

Flint *et al.* 1998 (n=19)

Näslund *et al.* 1998 (n=6)

Näslund *et al.* 1999 (n=8)

Long *et al.* 1999 (n=10)

Gutzwiller *et al.* 1999a (n=16); 0.38 pmol/L

Gutzwiller *et al.* 1999a (n=16); 0.75 pmol/L

Gutzwiller *et al.* 1999a (n=16); 1.50 pmol/L

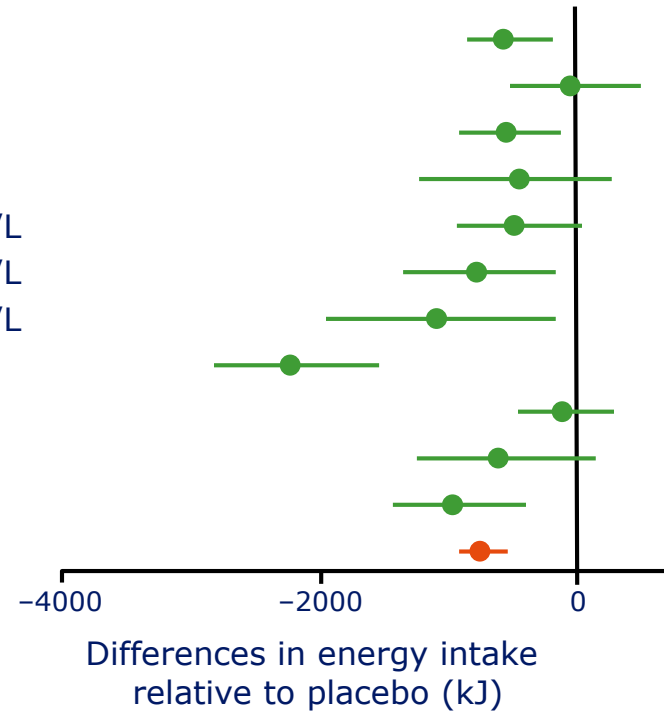
Gutzwiller *et al.* 1999b (n=12)

Flint *et al.* 2001 (n=17)

Beglinger *et al.* (unpublished b) (n=12)

Beglinger *et al.* (unpublished a) (n=15)

Meta-analysis



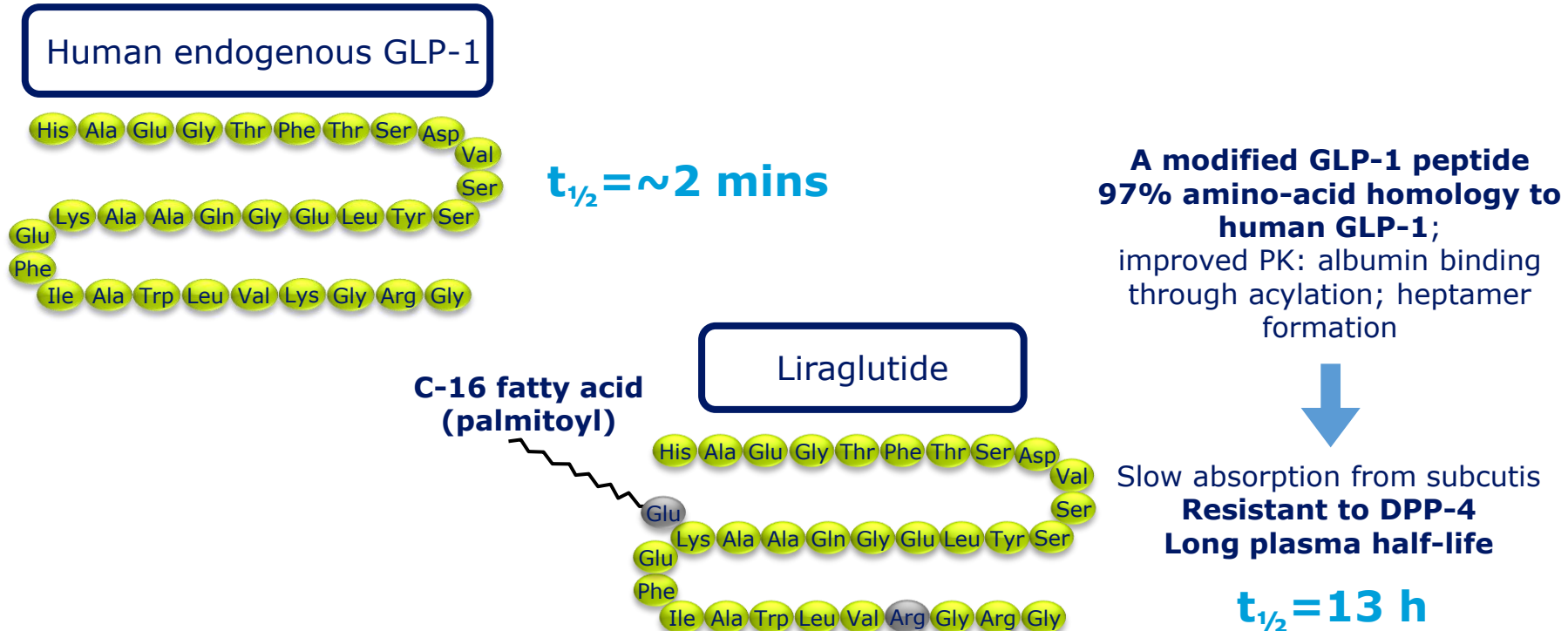
On average,
energy intake was
reduced by 727 kJ
(95% CI: 548–908 kJ)
during GLP-1 infusion,
corresponding to a
reduction of ~12%

Data are mean and 95% CI

CI, confidence interval; GLP-1, glucagon-like peptide-1

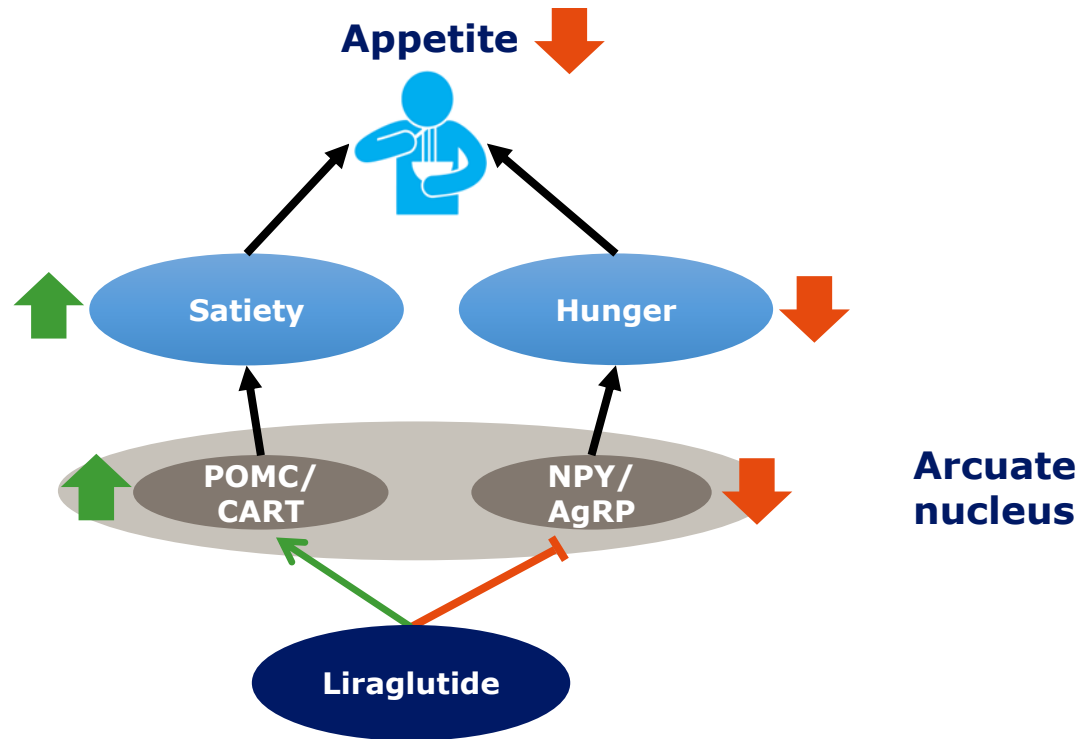
Adapted from: Verdich C *et al.* *J Clin Endocrinol Metab* 2001;86:4382–4389

Liraglutide is a once-daily, human GLP-1 analogue



DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; PK, pharmacokinetics; $t_{1/2}$, half-life
Knudsen LB *et al. J Med Chem* 2000;43:1664–1669; Degn KB *et al. Diabetes* 2004;53:1187–1194

Liraglutide reduces hunger and increases satiety via neurons in the arcuate nucleus



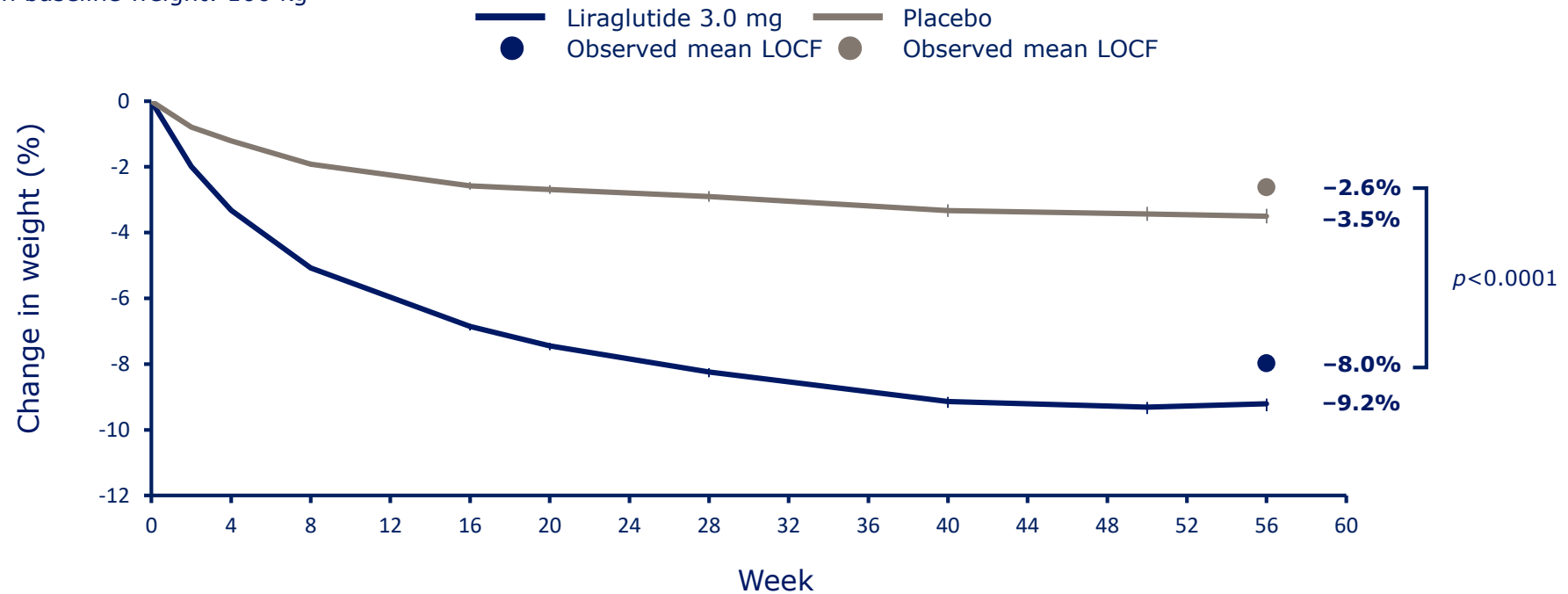
AgRP, agouti-related peptide; CART, cocaine- and amphetamine-regulated transcript; NPY, neuropeptide Y; POMC, pro-opiomelanocortin

Secher A *et al. J Clin Invest* 2014;124:4473–4488; van Can J *et al. Int J Obes (Lond)* 2014;38:784–793

Liraglutide vs placebo change in body weight (%)

SCALE Obesity and Prediabetes: 0–56 weeks

Mean baseline weight: 106 kg

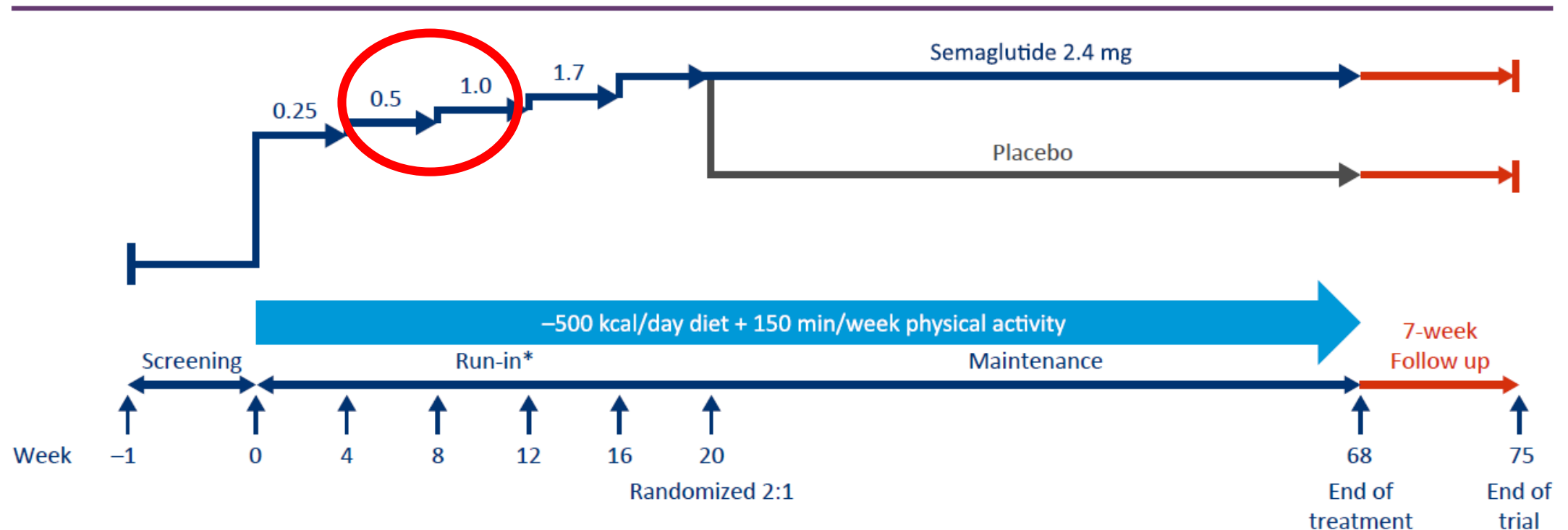


FAS, fasting visit data only. Line graphs are observed means ($\pm$ SE). Statistical analysis is ANCOVA

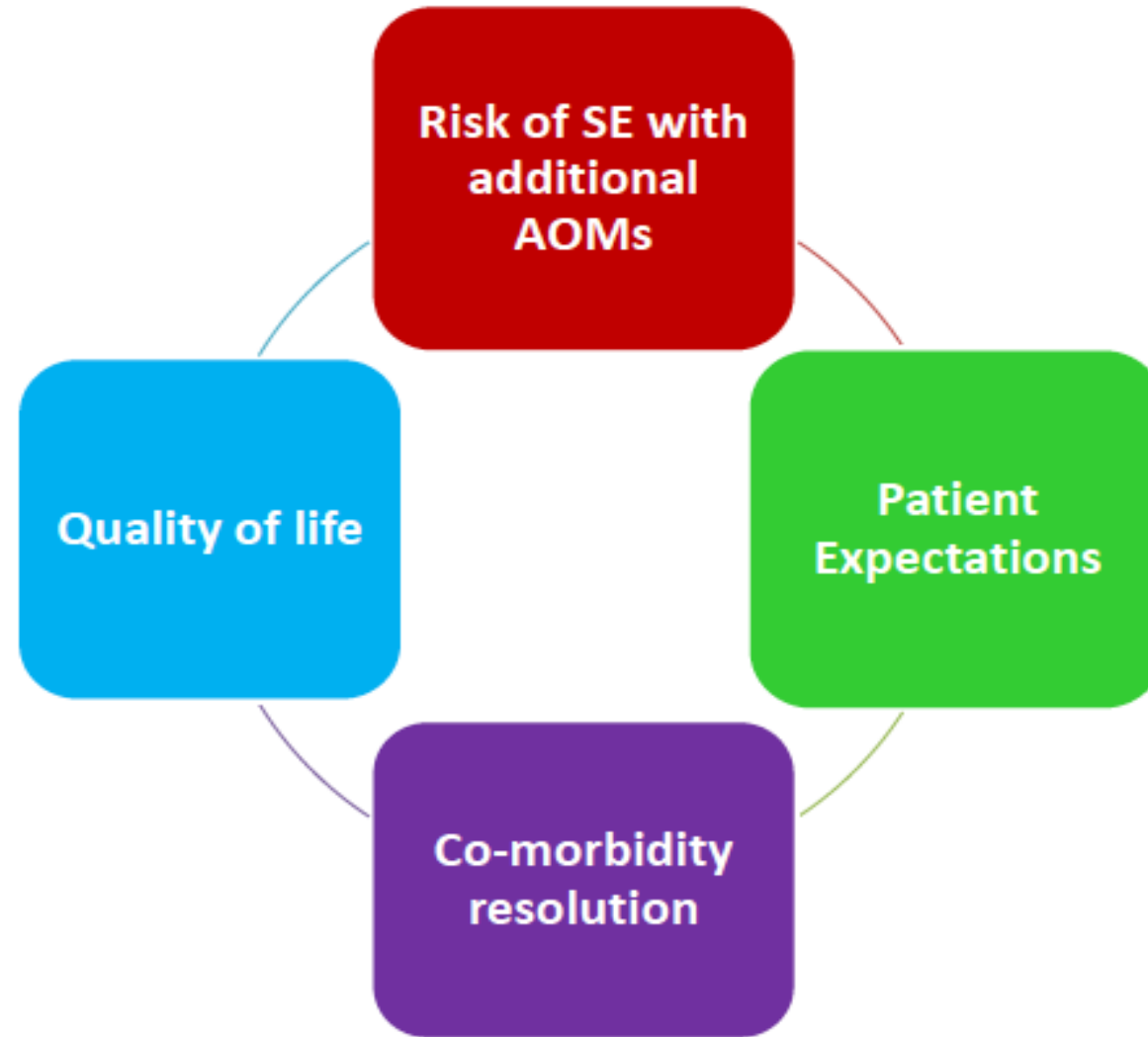
FAS, full analysis set; LOCF, last observation carried forward; SE, standard error

Pi-Sunyer *et al. Diabetologia* 2014;57(Suppl. 1): Abstract 73-OR

The GLP-1 receptor agonist Semaglutide 2.4 mg has greater efficacy than Liraglutide in reducing body weight (%)



Therapeutic endpoint



Take-home messages



- We don't need to get patients to an 'ideal' weight; moderate weight loss can bring health benefits
- The goal should be targeted health benefit
- When patients struggle, medications can help patients to achieve their health goals
- Successful weight maintenance is possible, especially if medications are continued

Fat is not a feeling

