

# Management of obesity

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Alex Miras

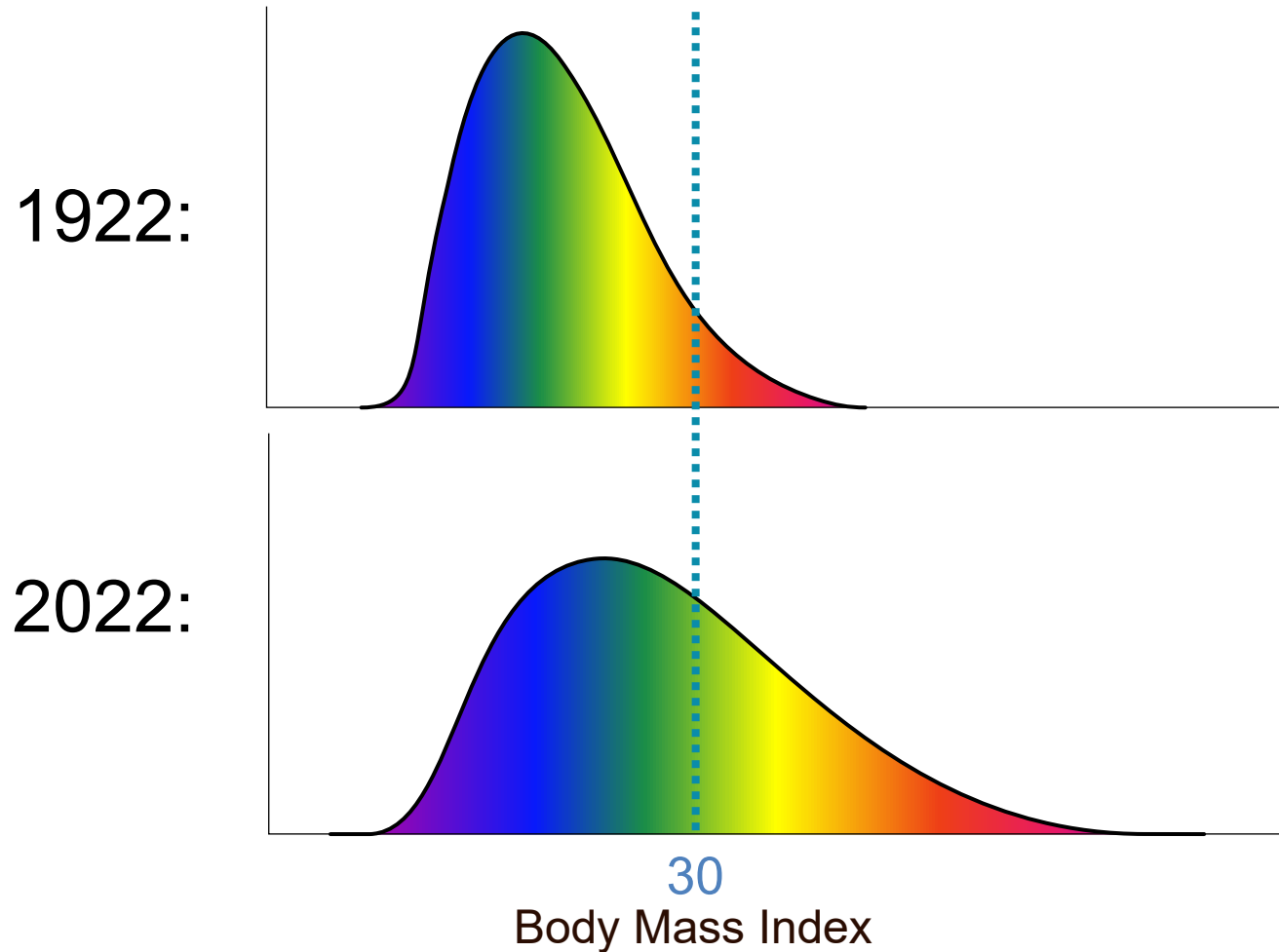
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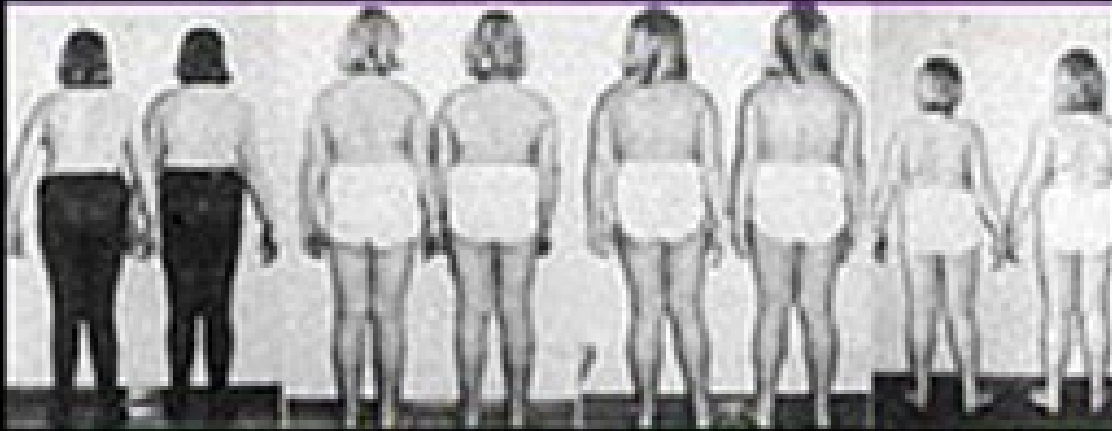
# Gene-Environment Interactions



# Landmark twin studies

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**Identical Twins**



**Fraternal Twins**





Robert Plomin



## Identical twins

differences all environmental

## Non-identical twins

have both genetic and  
environmental differences

Over 5,000 same-sex twin pairs

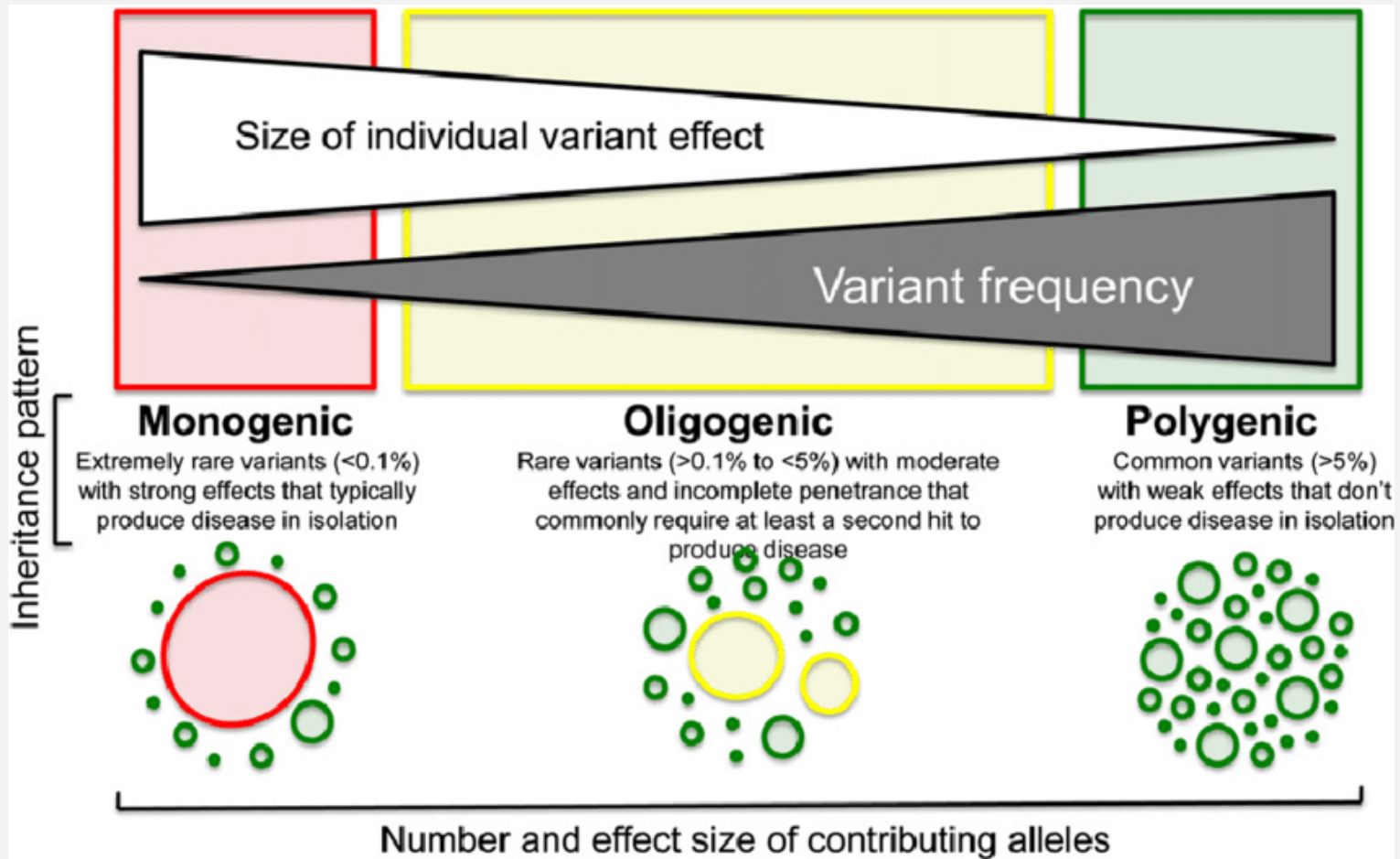
## Heritability:

**BMI 77%**

**Waist circ. 77%**

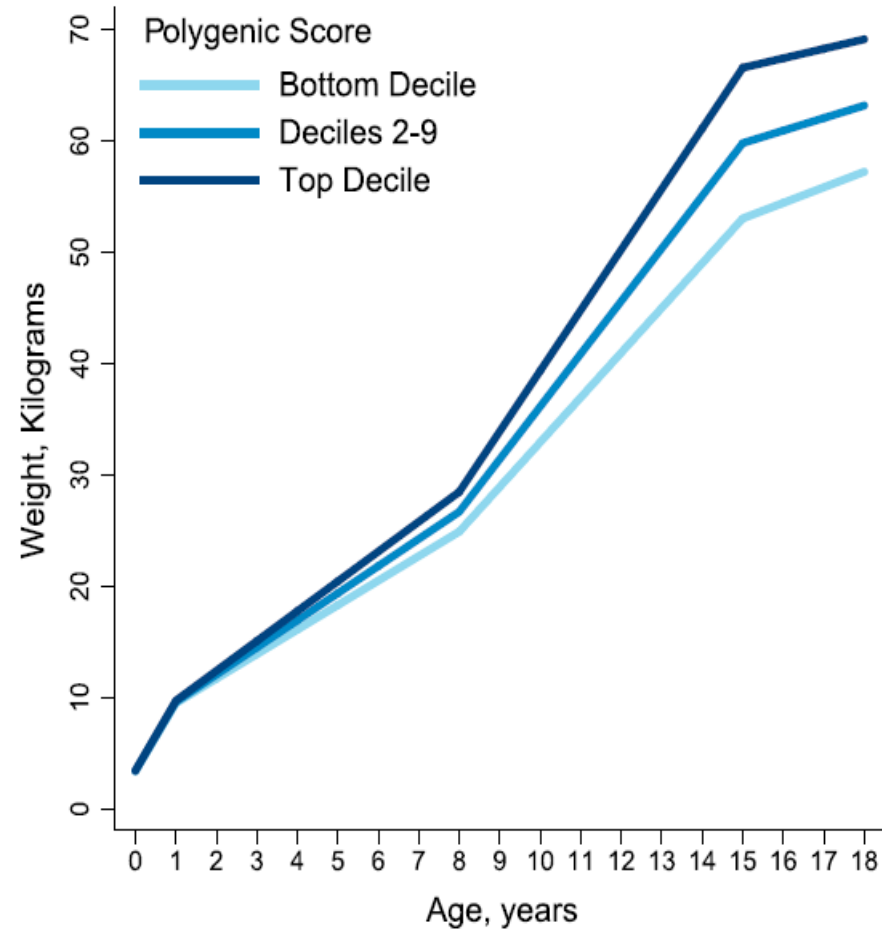
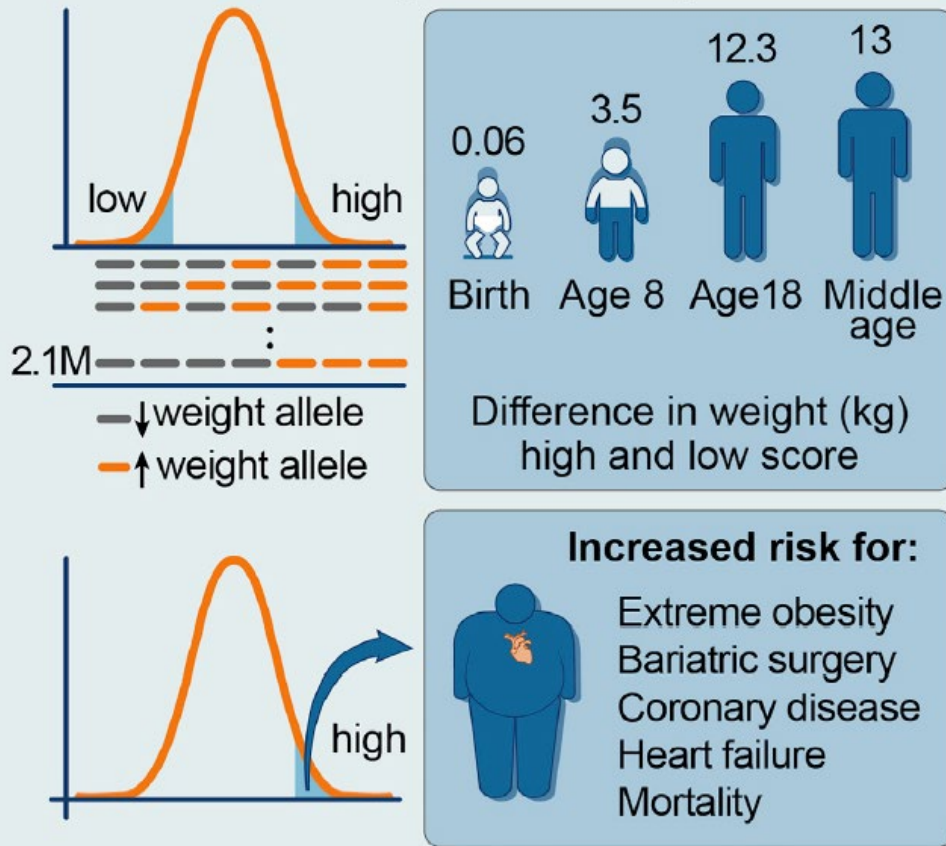


# Genetic architecture of obesity

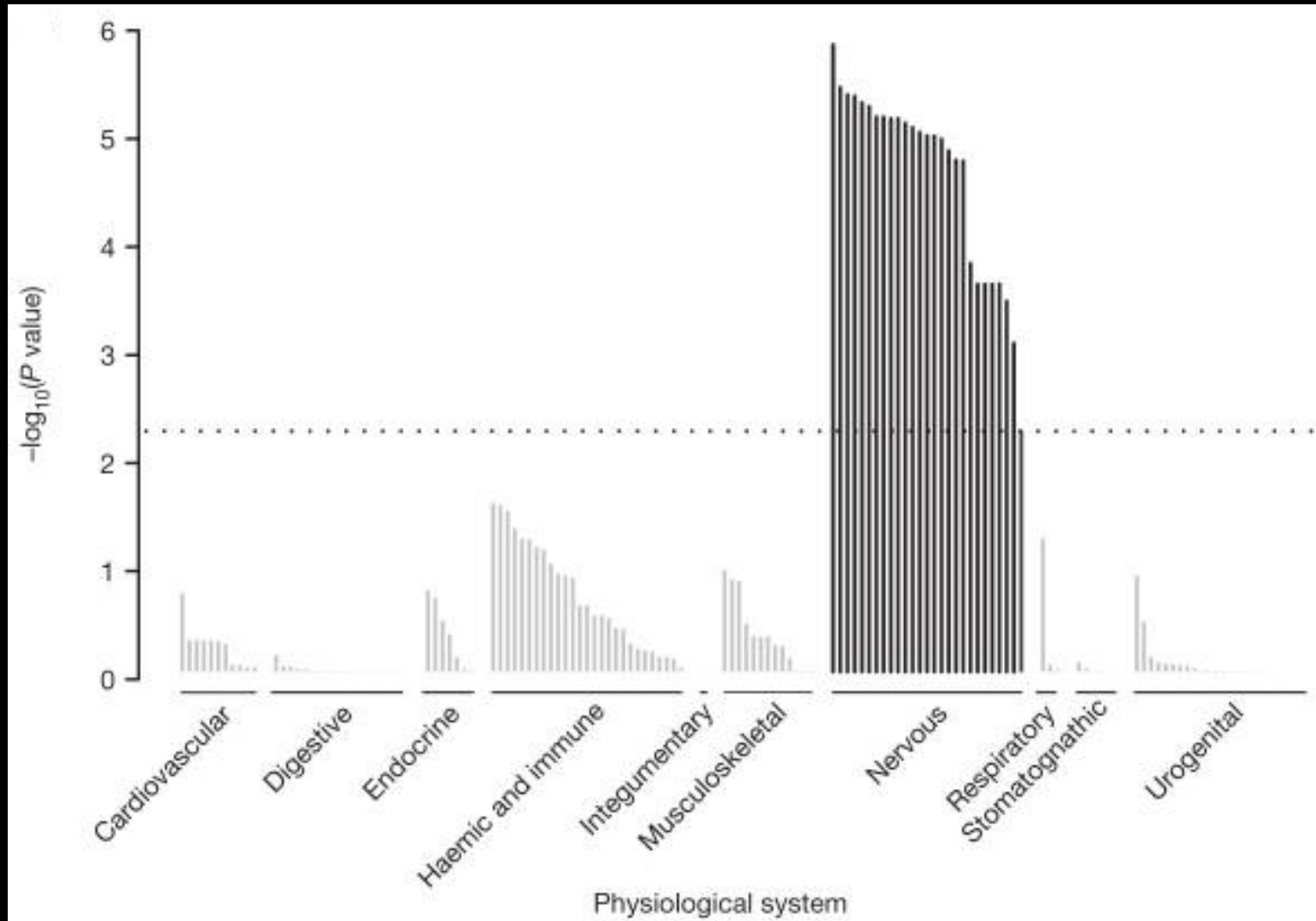


# Weight gain and risky genes

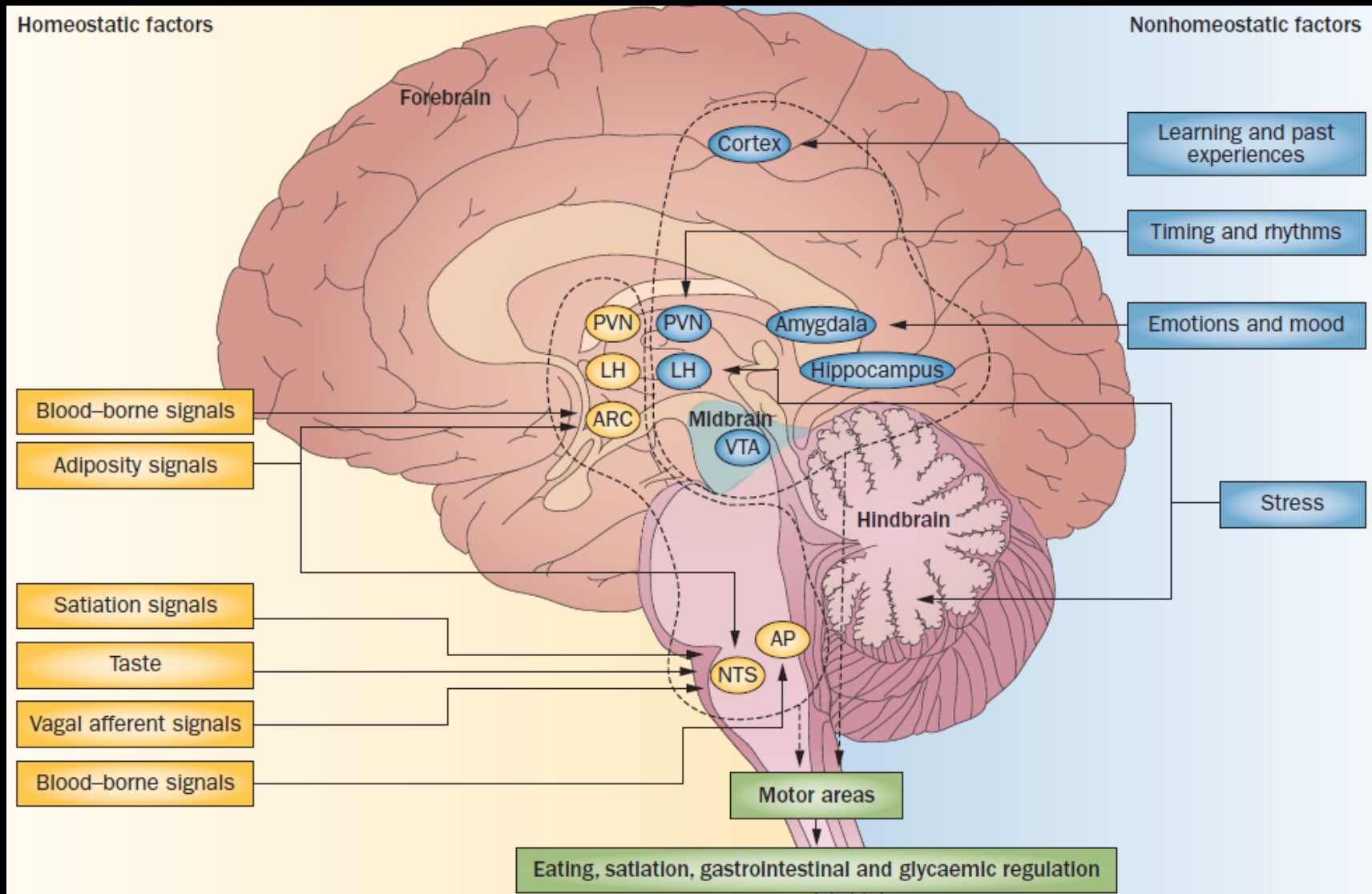
## Genome-wide polygenic score for weight and obesity



# Where do most risky genes work?

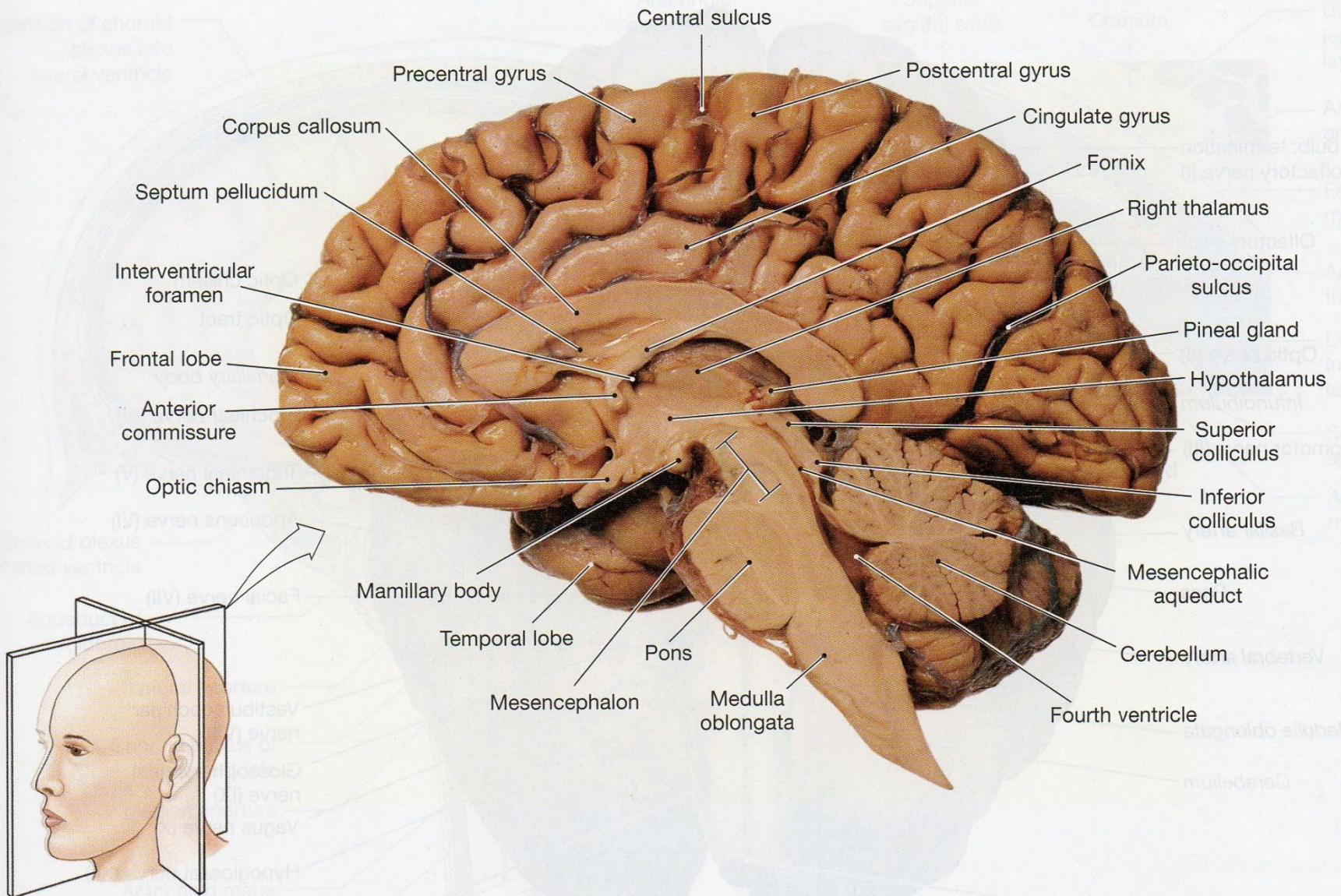


# Brain control of appetite





# Obesity is a neurological disease of the appetite centres of the brain



# Prevention vs. Treatment

## Prevention *and* Treatment

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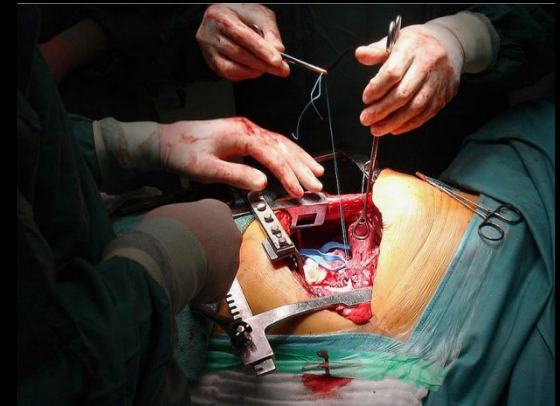
Prevention



Disease



Treatment





# Prevention vs. Treatment

## Prevention *and* Treatment

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Prevention



Disease

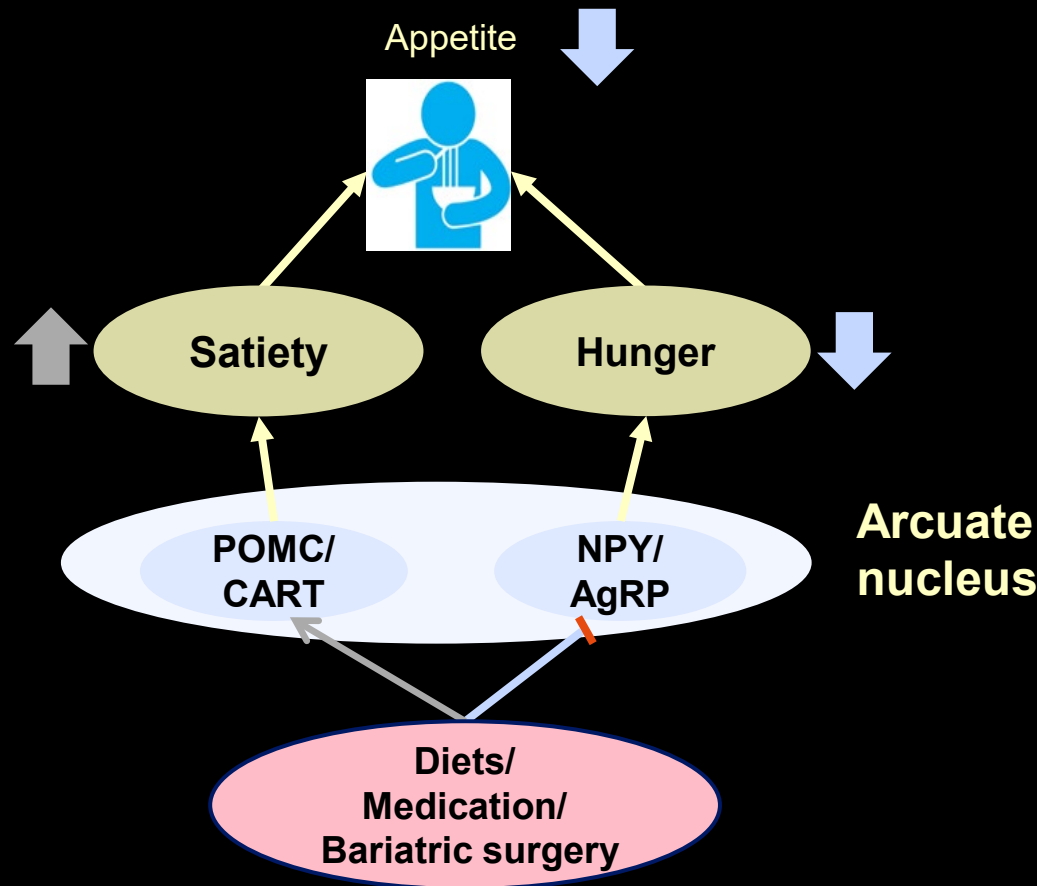


Treatment



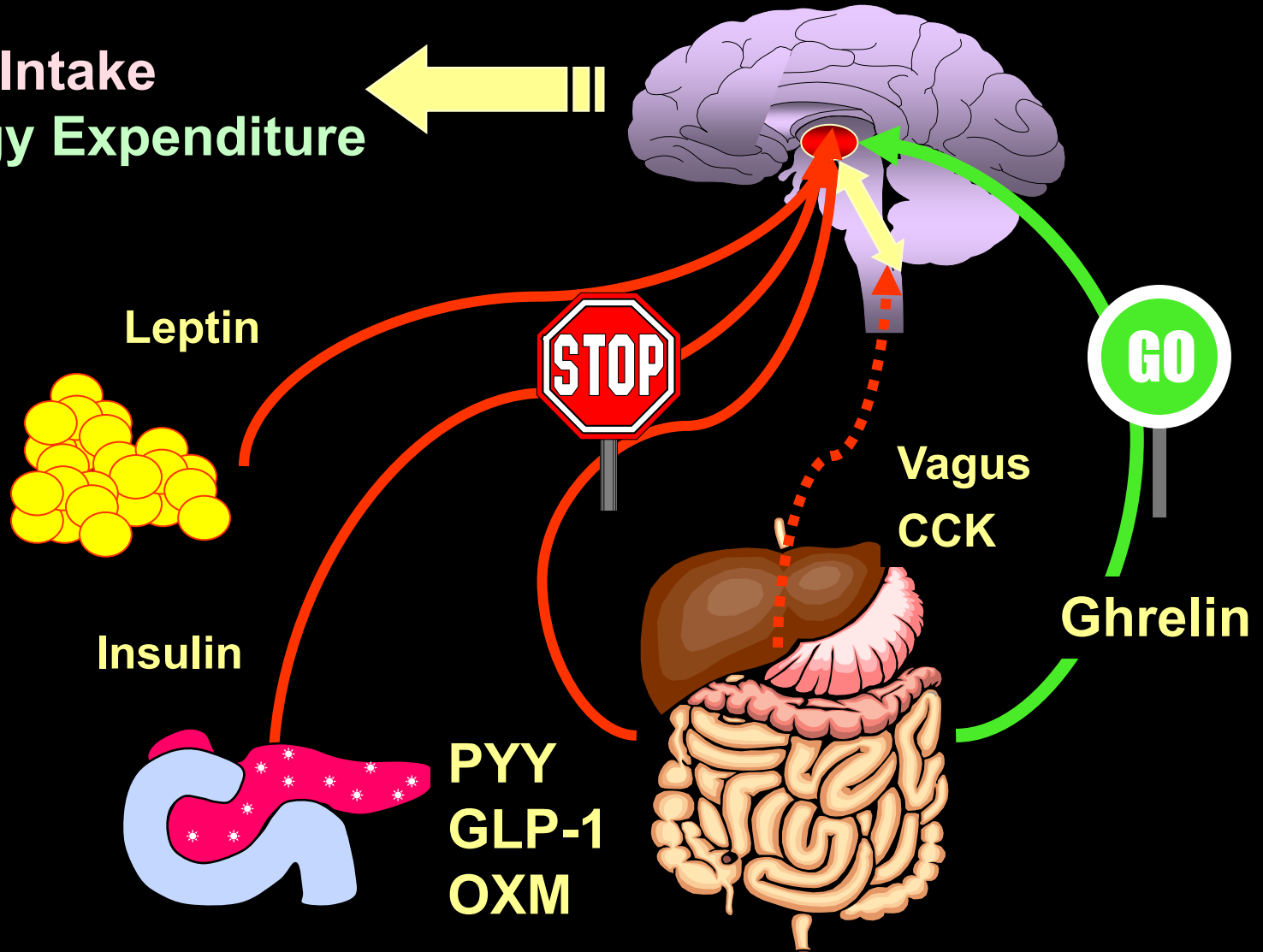
# Successful weight loss treatments increase satiety and reduce hunger

Via neurons in the hypothalamus

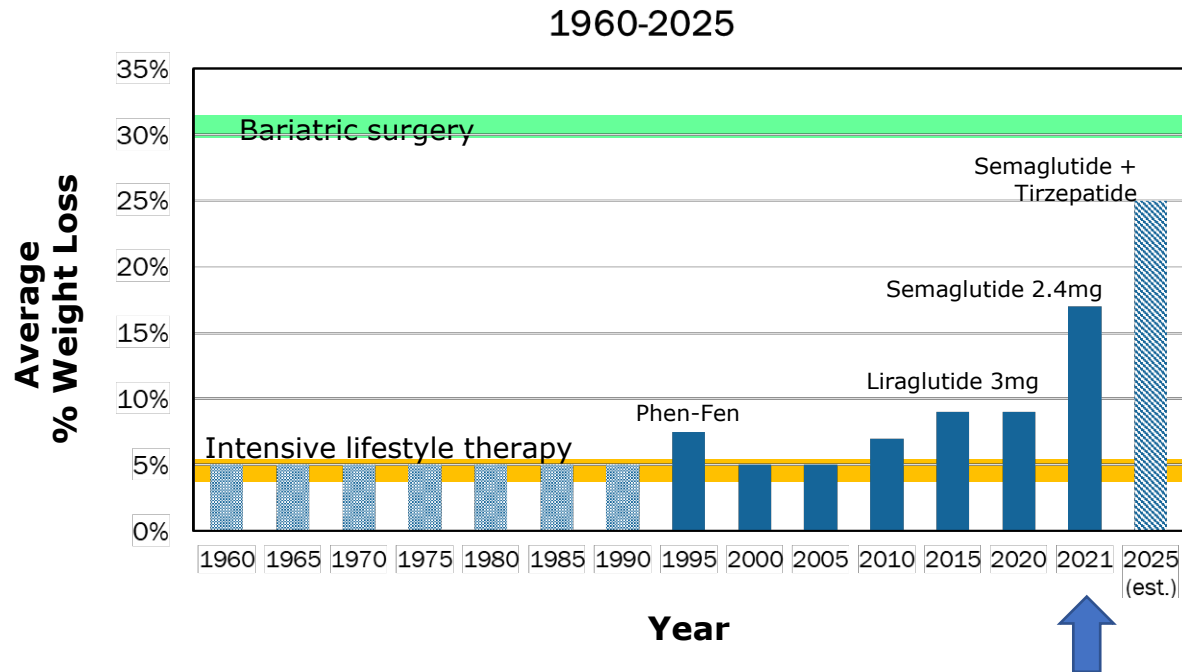


# SUMMARY

Food Intake  
Energy Expenditure



# Revolution in pharmacotherapy happening today



# Liraglutide injection 3 mg\* : drug overview



- Saxenda® (liraglutide injection 3 mg) is a glucagon-like peptide 1 (GLP-1) receptor agonist
- GLP-1 is a physiological regulator of appetite and glucose metabolism

The peptide precursor of liraglutide has been engineered to be 97% homologous to native human GLP-1 by substituting arginine for lysine at position 34

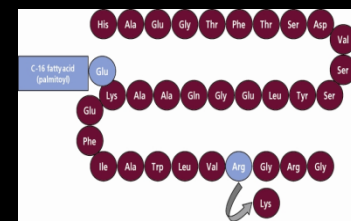
Liraglutide is made by attaching a C-16 fatty acid (palmitic acid) with a glutamic acid spacer on the remaining lysine residue at position 26 of the peptide precursor

**C-16 fatty acid (palmitoyl)**

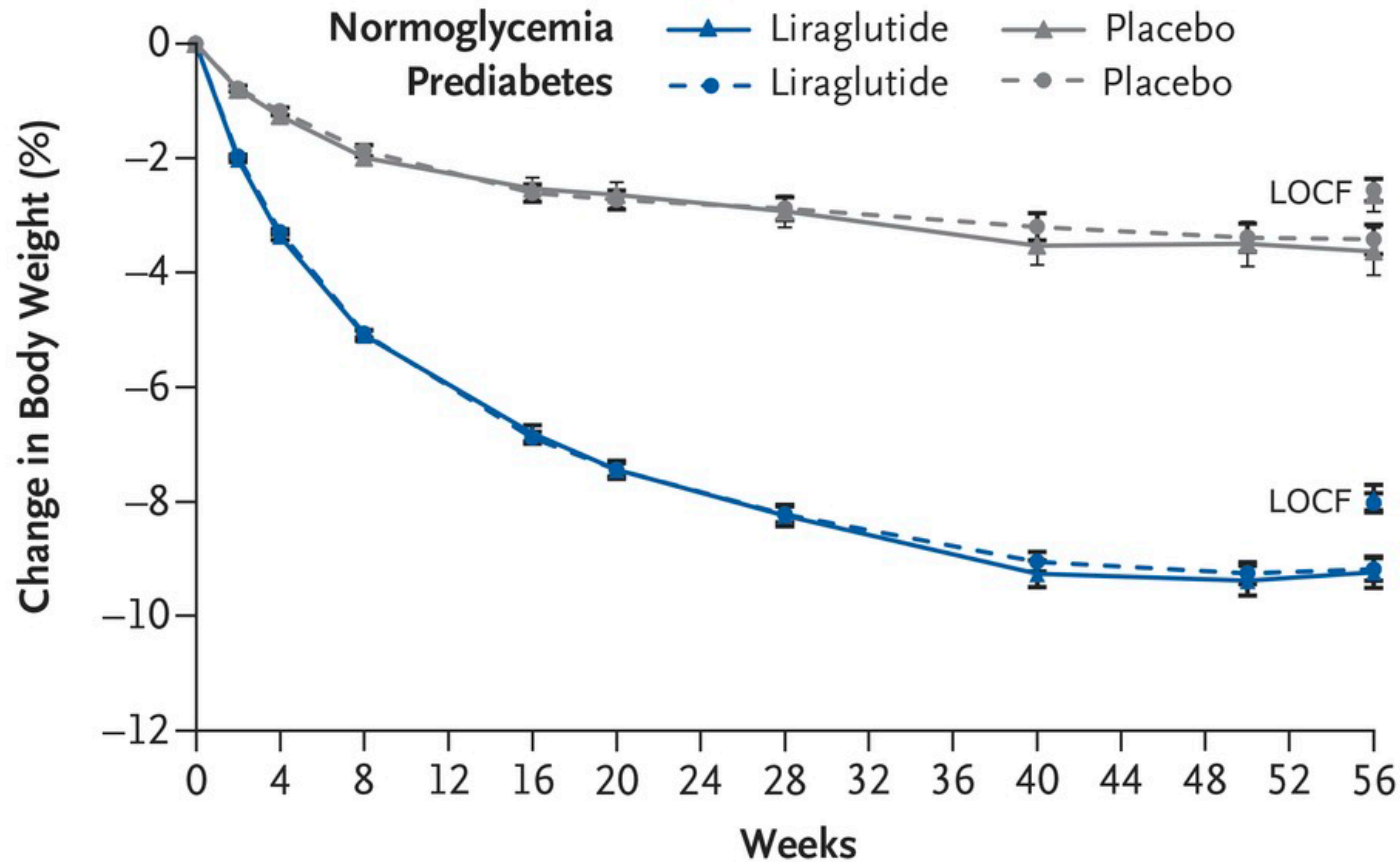


\*Liraglutide injection 3 mg is not indicated for glycaemic control

# Liraglutide and Body Weight



A



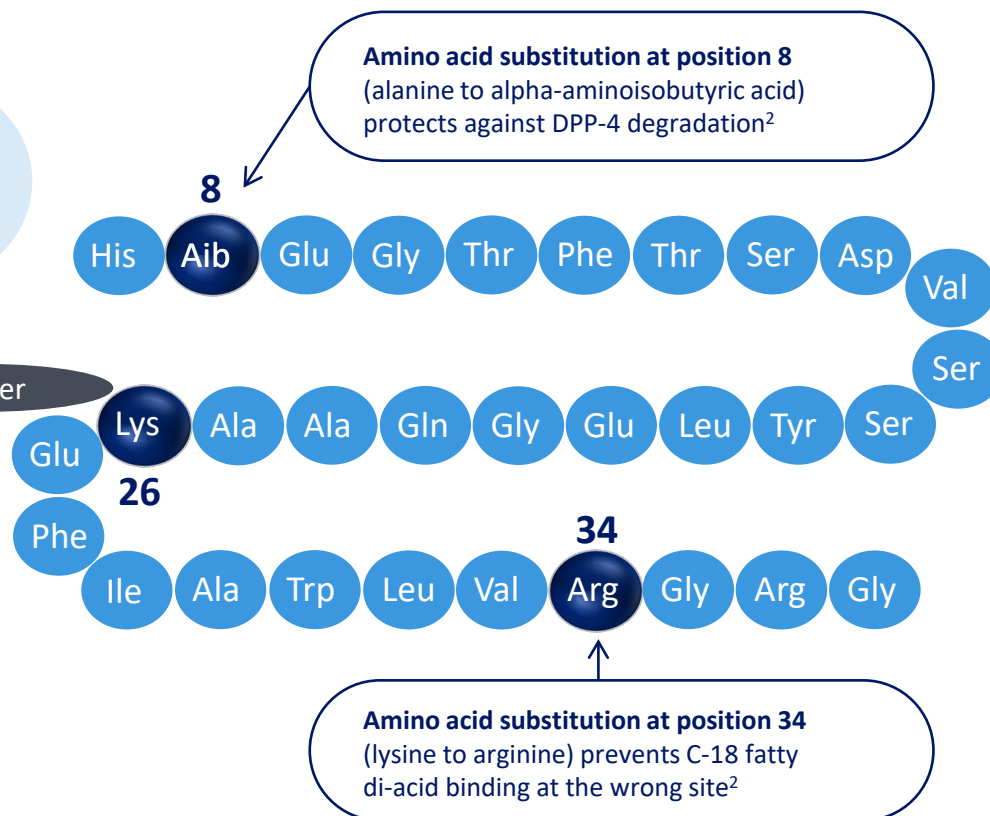


# Semaglutide 2.4 mg is a once weekly human GLP-1 analogue

- **94% homology to human GLP-1<sup>1</sup>**
- **t<sub>½</sub> of approximately 1 week<sup>3</sup>**



**Spacer and C-18 fatty di-acid chain to lysine in position 26 provide strong binding to albumin<sup>2</sup>**



DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; t<sub>½</sub>, half-life.

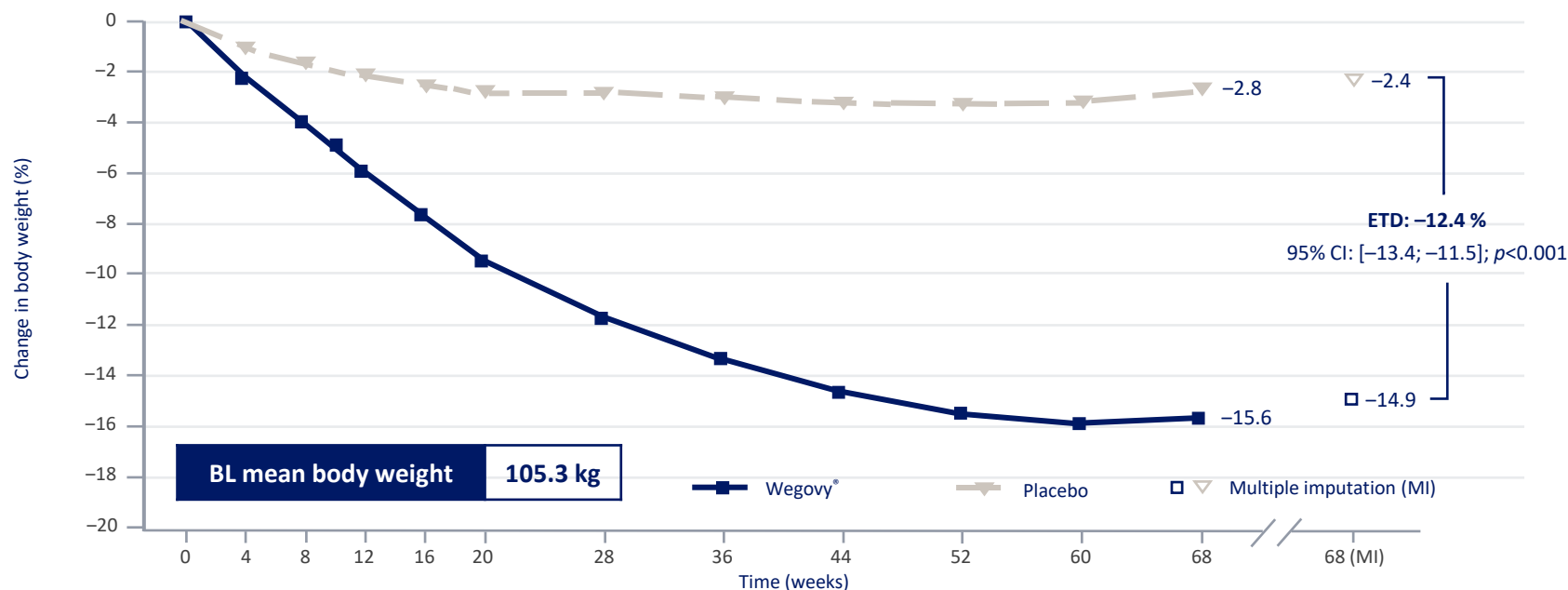
1. Novo Nordisk Limited; GB & NI Wegovy® SmPCs. 2. Lau et al. *J Med Chem* 2015;58:7370–80; 3. Marbury et al. *Clin Pharmacokinet* 2017;56:1381–90.

# Efficacy of Wegovy®

Adults with BMI >30 kg/m<sup>2</sup> OR ≥27 kg/m<sup>2</sup>  
with ≥1 weight-related comorbidity

## STEP 1: Mean change in body weight (%) from Baseline to Week 68, co-primary endpoint

Adult patients (n=1961) were randomised (2:1) to semaglutide 2.4 mg (n=1306) or placebo (n=655) for a 16-week dose escalation period, followed by a 52-week treatment period, and a 7-week off-treatment follow-up period

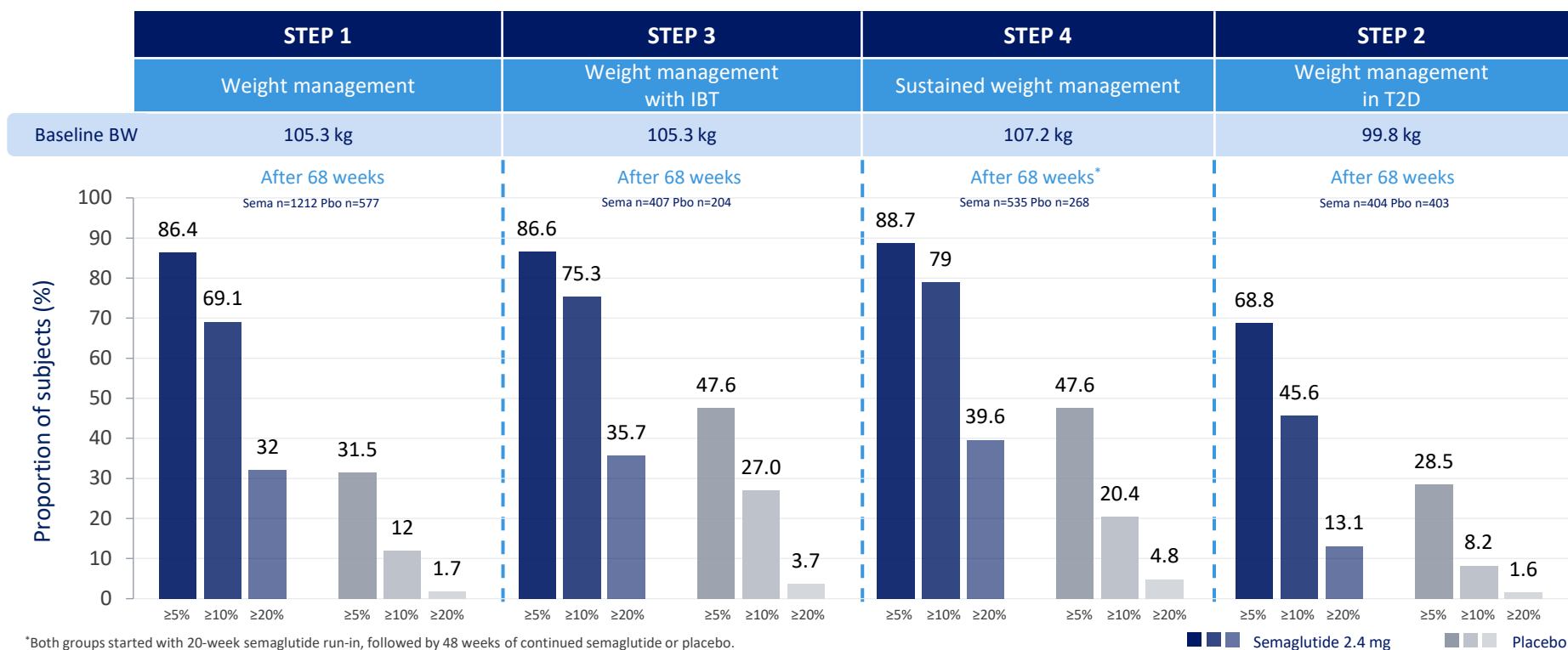


Data are from FAS. Observed values for patients completing each scheduled visit and estimates with multiple imputations (MI) from retrieved dropouts.

BL, baseline; ETD, estimated treatment difference; FAS, full analysis set.

Wilding JPH et al. *N Engl J Med* 2021;384:989–1002.

# STEP 1–4: subjects achieving weight loss



\*Both groups started with 20-week semaglutide run-in, followed by 48 weeks of continued semaglutide or placebo.

Data are for the in-trial period. In STEP 1 and 3, subjects achieving  $\geq 5\%$  weight loss was a co-primary endpoint and subjects achieving  $\geq 10\%$  and  $\geq 15\%$  were confirmatory secondary endpoints and  $\geq 20\%$  was a supportive secondary endpoint. In STEP 2, subjects achieving  $\geq 5\%$  weight loss was a co-primary endpoint and subjects achieving  $\geq 10\%$  and  $\geq 15\%$  were confirmatory secondary endpoints. In STEP 4, subjects achieving  $\geq 5\%$ ,  $\geq 10\%$ ,  $\geq 15\%$  and  $\geq 20\%$  were supportive secondary endpoints.

BW, body weight; IBT, intensive behavioural therapy; Sema, semaglutide; Pbo, placebo.

1. Wilding JPH et al. *N Engl J Med* 2021;384:989-1002. 2. Davies M et al. *Lancet* 2021;397(10278):971-984. 3. Wadden TA et al. *JAMA* 2021;325(14):1403-1413. 4. Rubino DM et al. *JAMA* 2021;325(14):1414-1425.

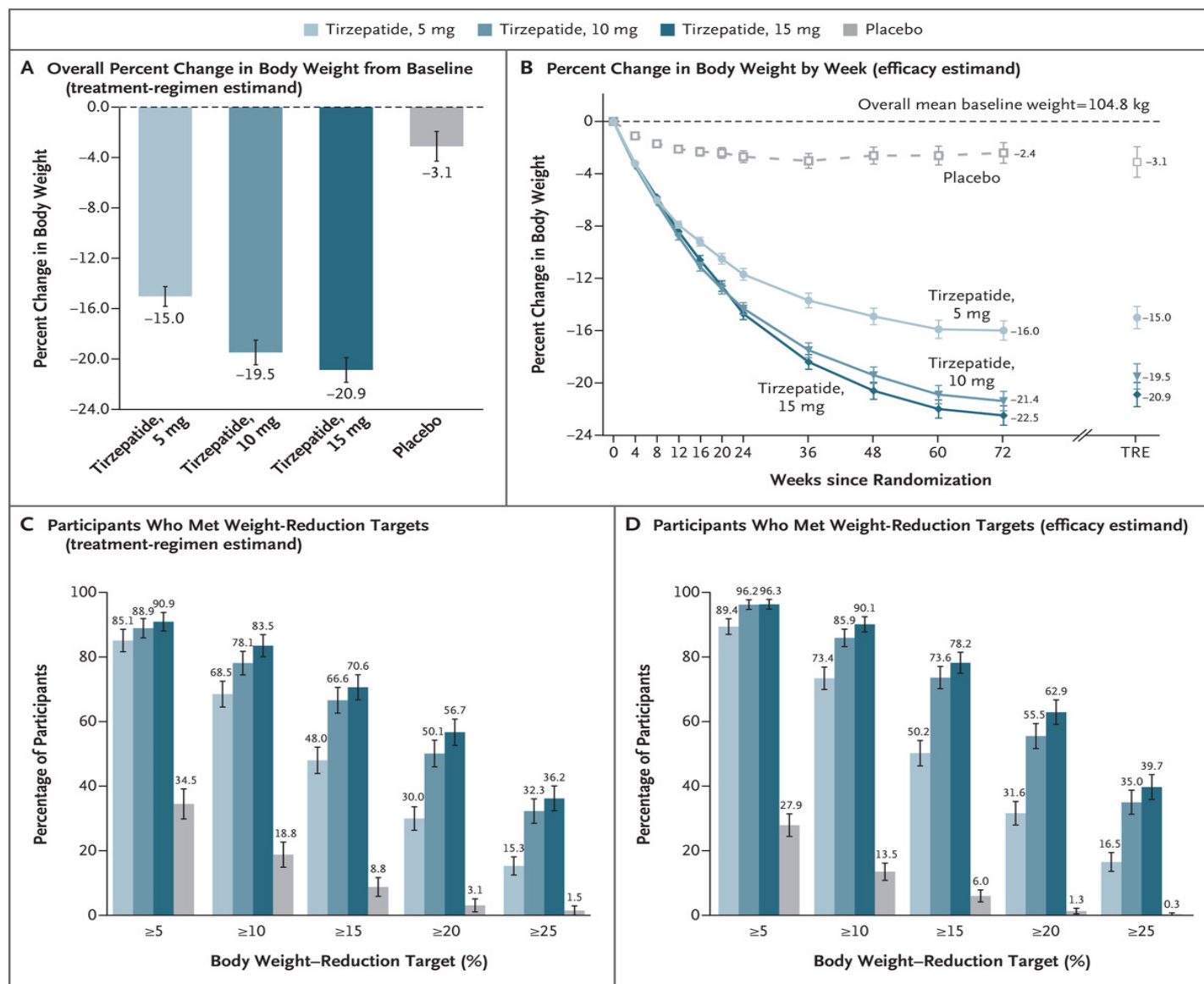
# NICE guidance on Wegovy 2022

Semaglutide is recommended as an option for weight management, including weight loss and weight maintenance, alongside a reduced-calorie diet and increased physical activity in adults, only if:

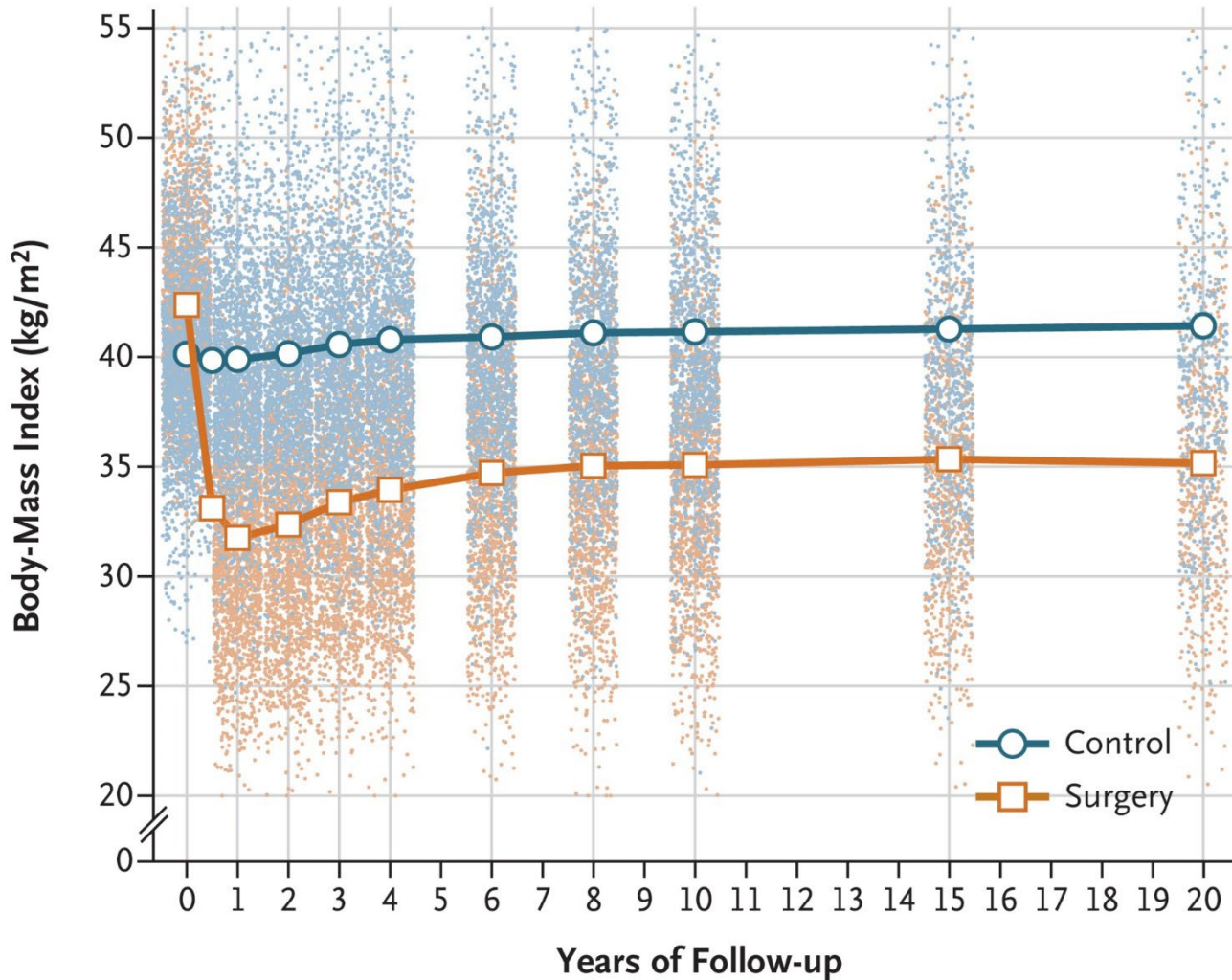
- it is used for a maximum of 2 years, and within a specialist weight management service providing multidisciplinary management of overweight or obesity (including but not limited to tiers 3 and 4), and
- they have at least 1 weight-related comorbidity and:
  - a body mass index (BMI) of at least 35.0 kg/m<sup>2</sup>, or
  - a BMI of 30.0 kg/m<sup>2</sup> to 34.9 kg/m<sup>2</sup> and meet the criteria for referral to specialist weight management services in [NICE's clinical guideline on obesity: identification, assessment and management](#).

Use lower BMI thresholds (usually reduced by 2.5 kg/m<sup>2</sup>) for people from south Asian, Chinese, and Black African or Caribbean family

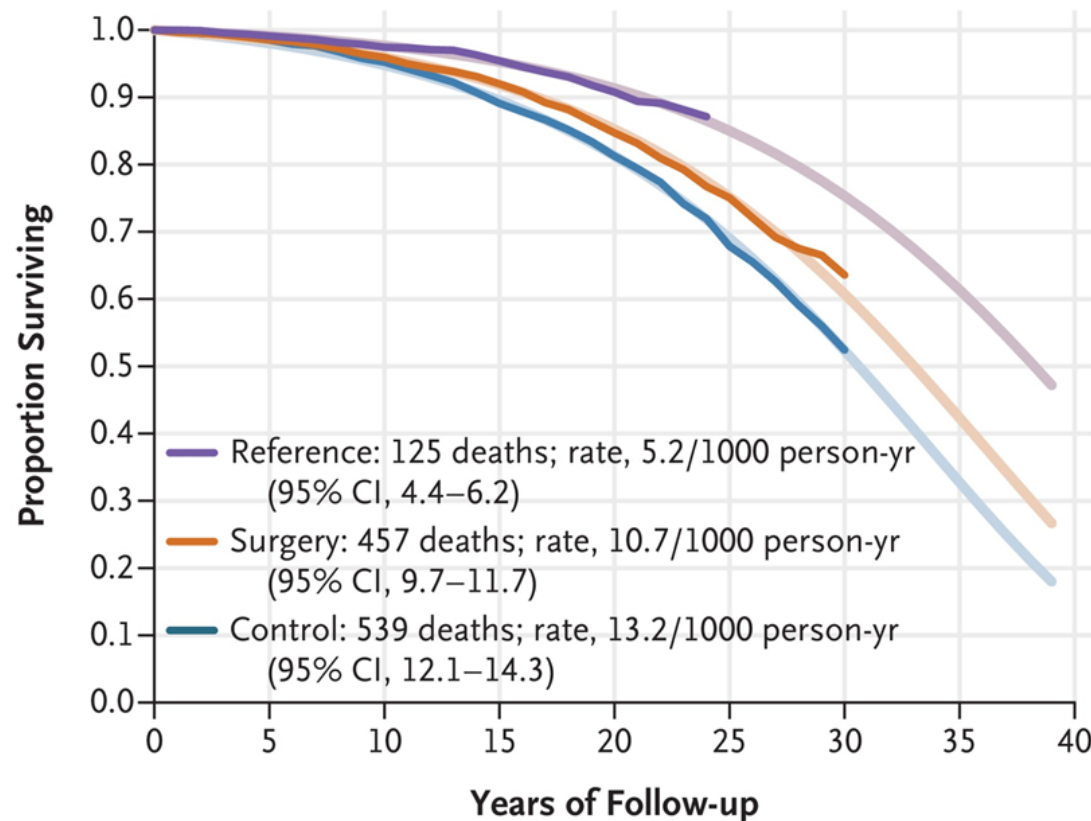
# Tirzepatide for Obesity



# Obesity Surgery



# Obesity Surgery - Mortality benefit



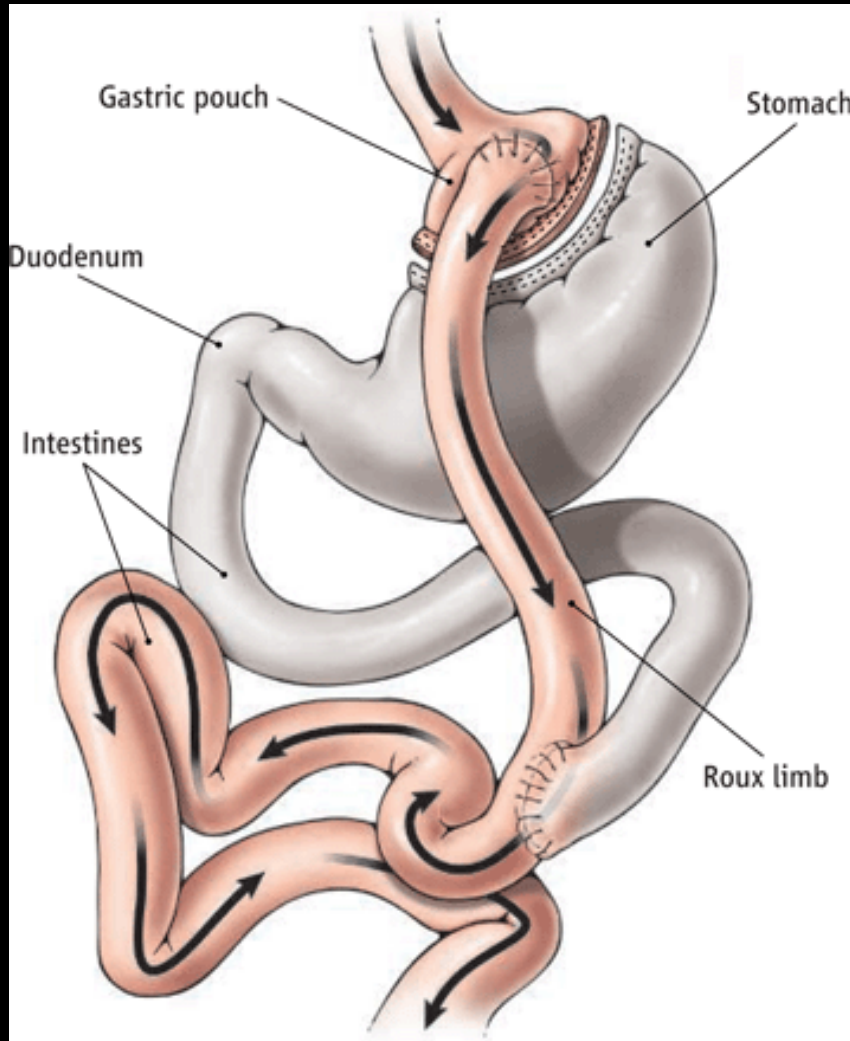
## No. at Risk

Reference	1135	1125	1106	1083	905	0	0
Surgery	2007	1915	1837	1744	1390	580	34
Control	2040	1961	1815	1589	1238	488	26



# Roux-en-Y gastric Bypass

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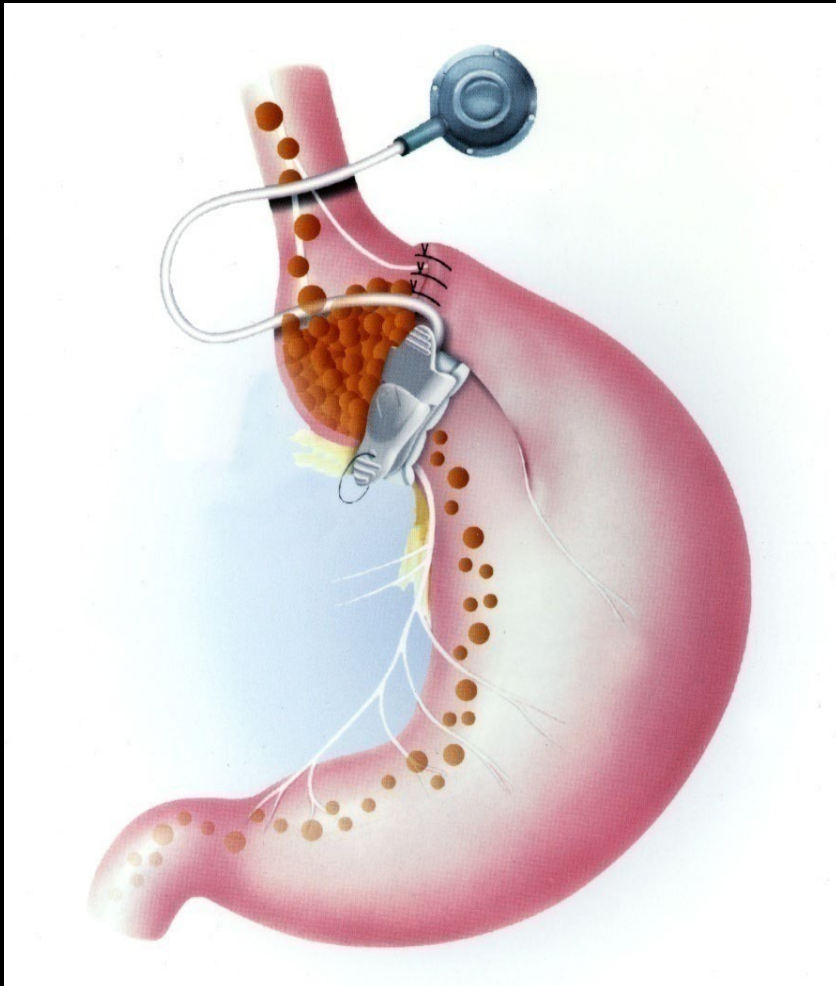


- Laparoscopic
- 90-120 minutes
- 1-2 day in-patient stay
- 25% weight loss



# Adjustable Silastic Gastric Banding

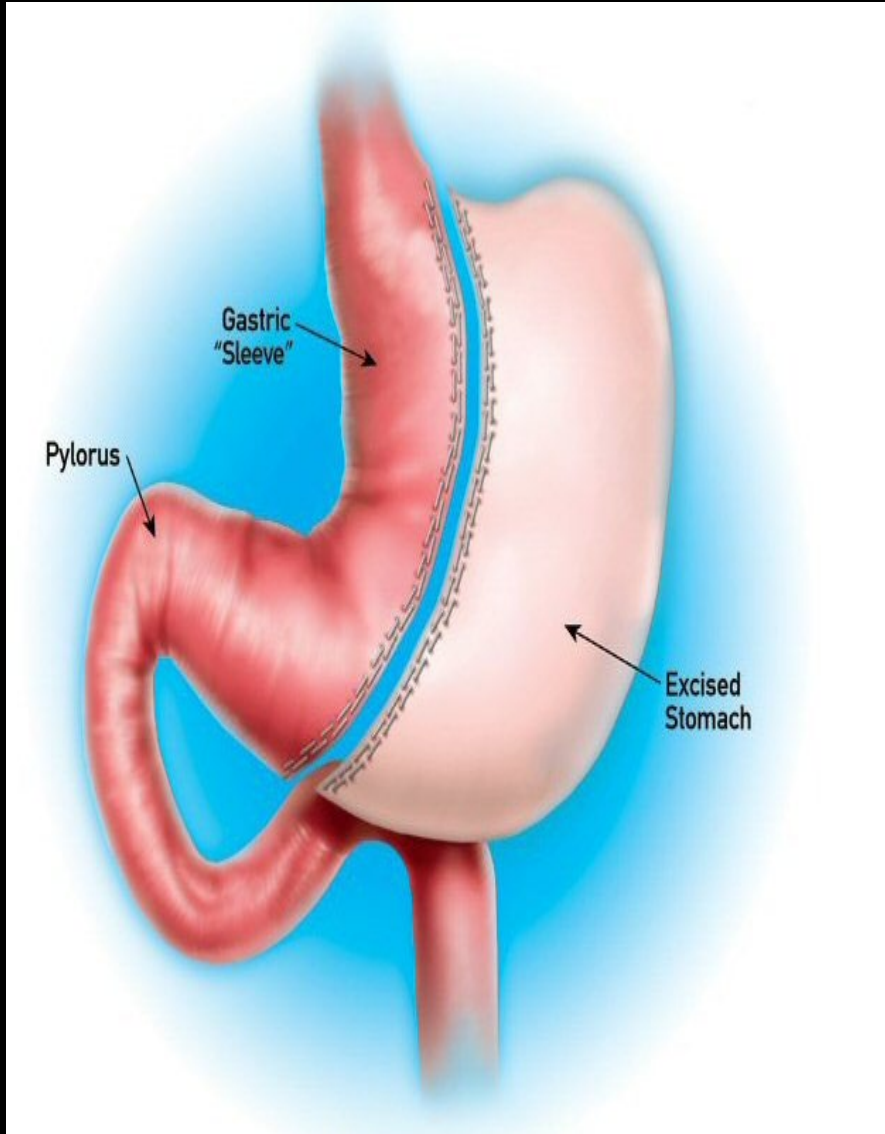
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- Laparoscopic
  - <1 hr procedure
  - 1 day in-patient
  - 20% weight loss
  - High risk of re-operation
  - Self-sabotage easier
  - Reversible

# Vertical Sleeve Gastrectomy

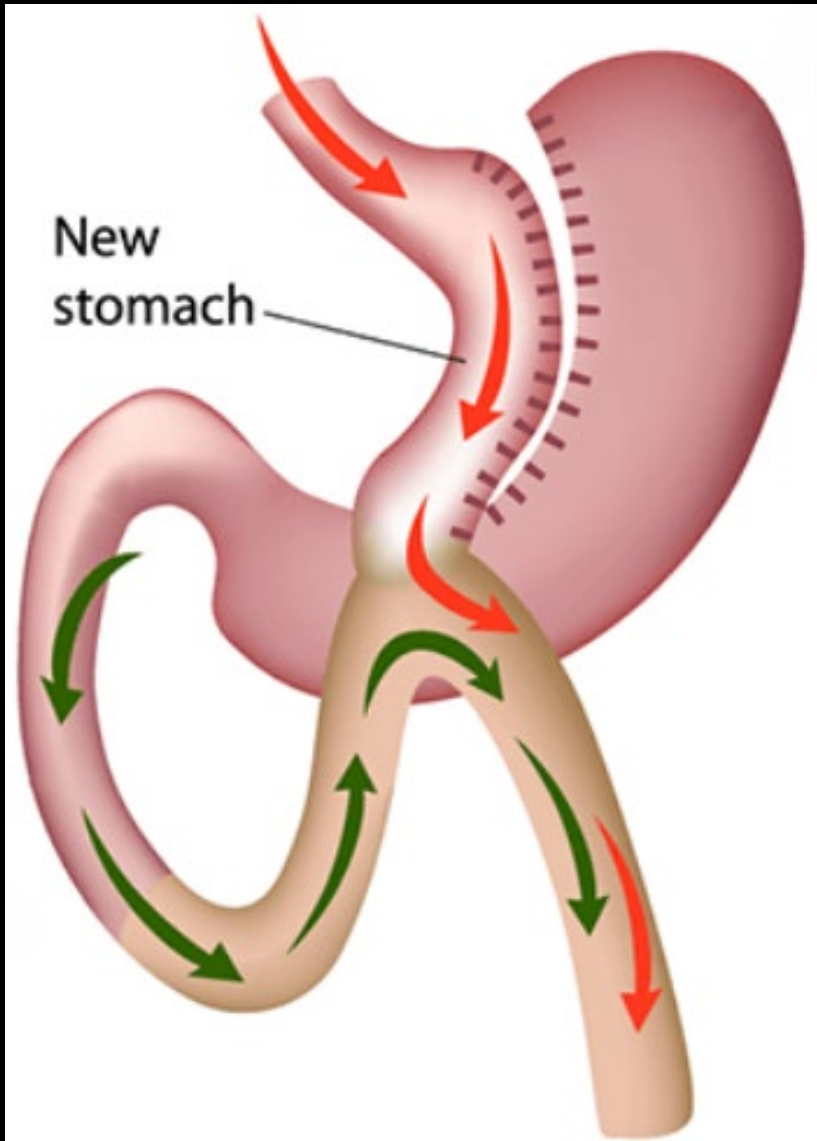
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- **Laparoscopic**
  - 1-2 hour procedure
  - 1-2 days in-patient
  - 25% weight loss
  - ? 1<sup>st</sup> choice for very obese

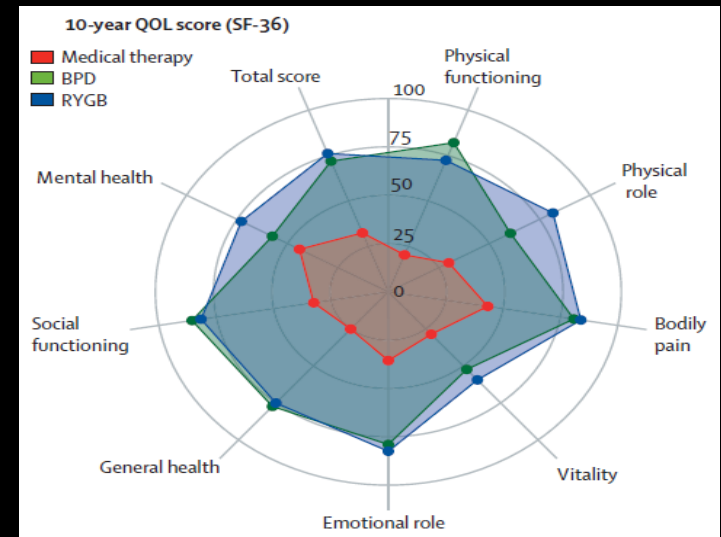
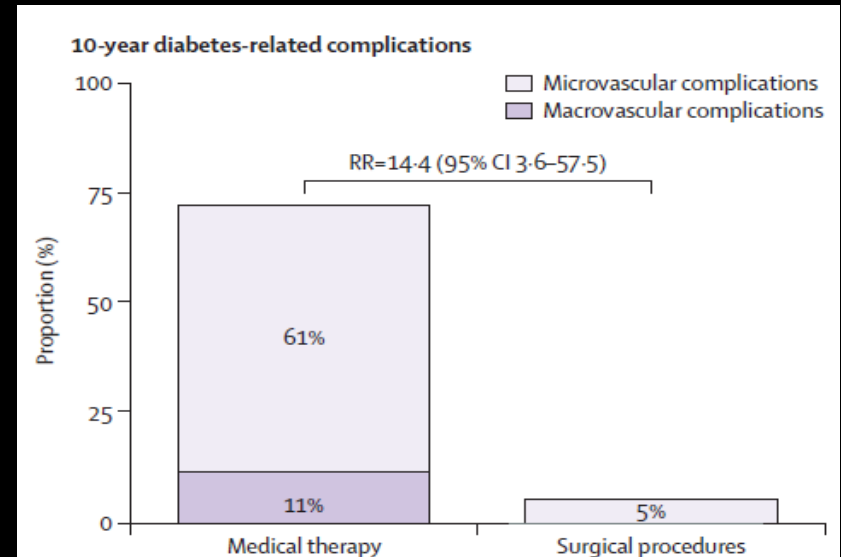
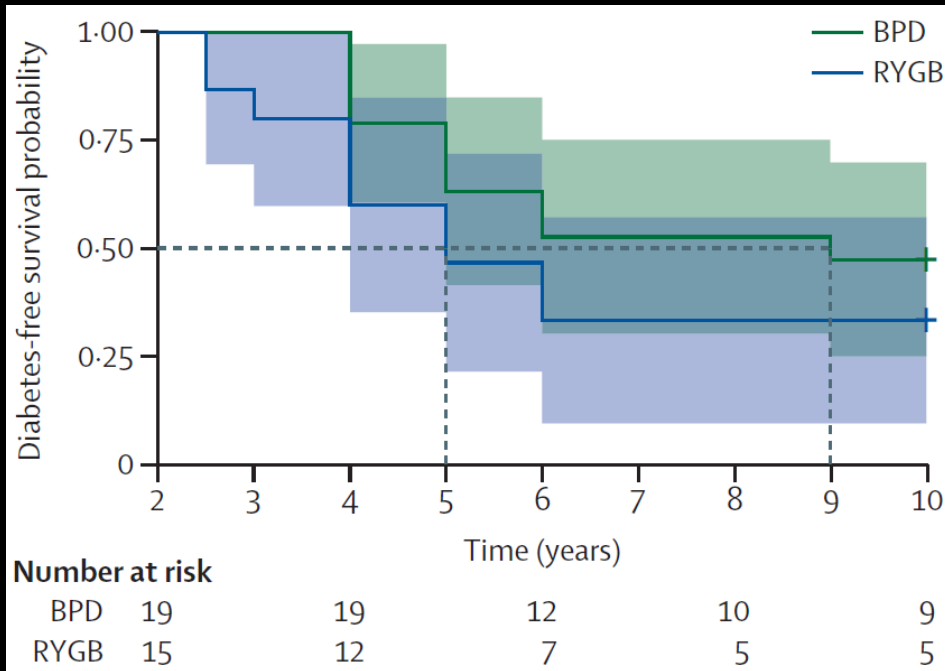
# One-anastomosis gastric bypass

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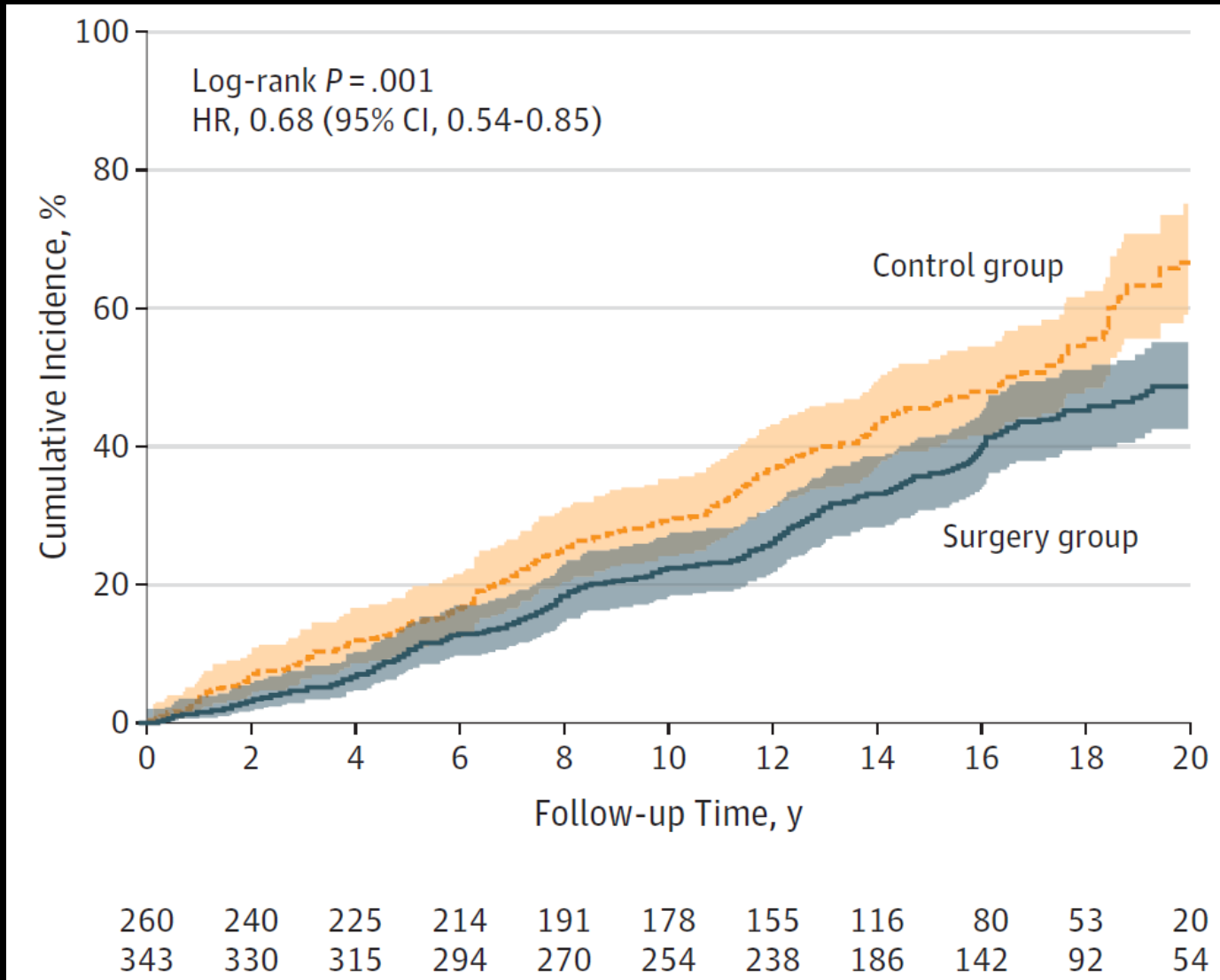


- 90 minutes
- 1-2 day in-patient stay
- 25% weight loss

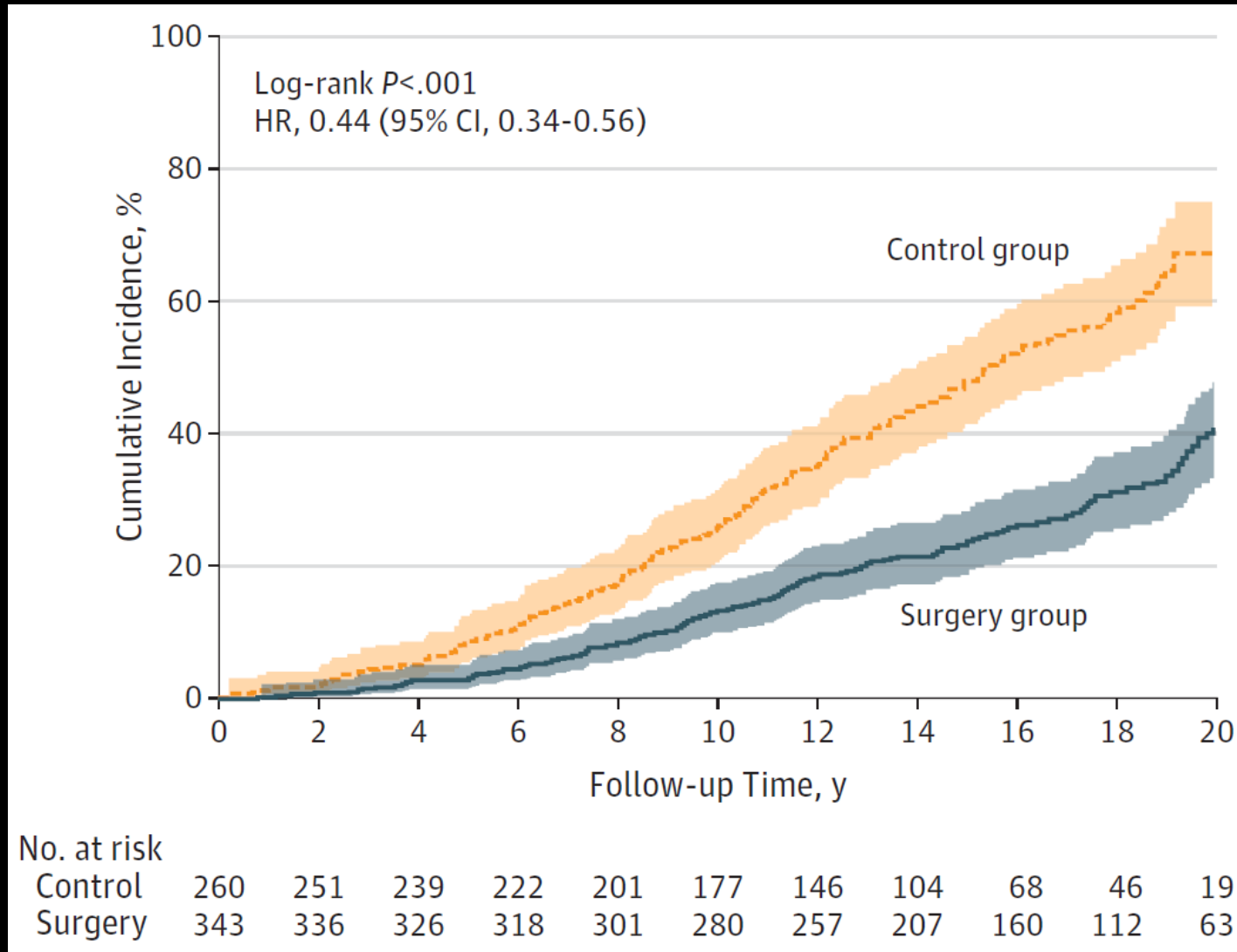
# 10 year metabolic effects of surgery



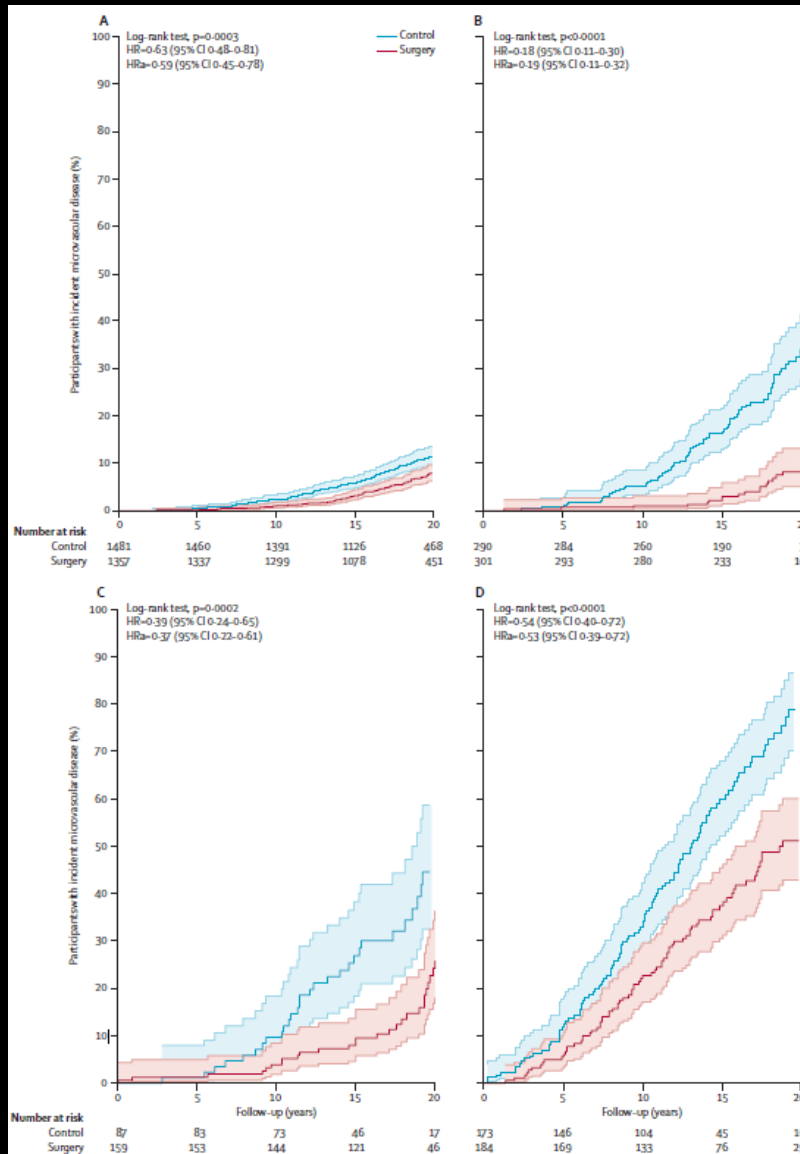
# Macrovascular complications



# Microvascular complications

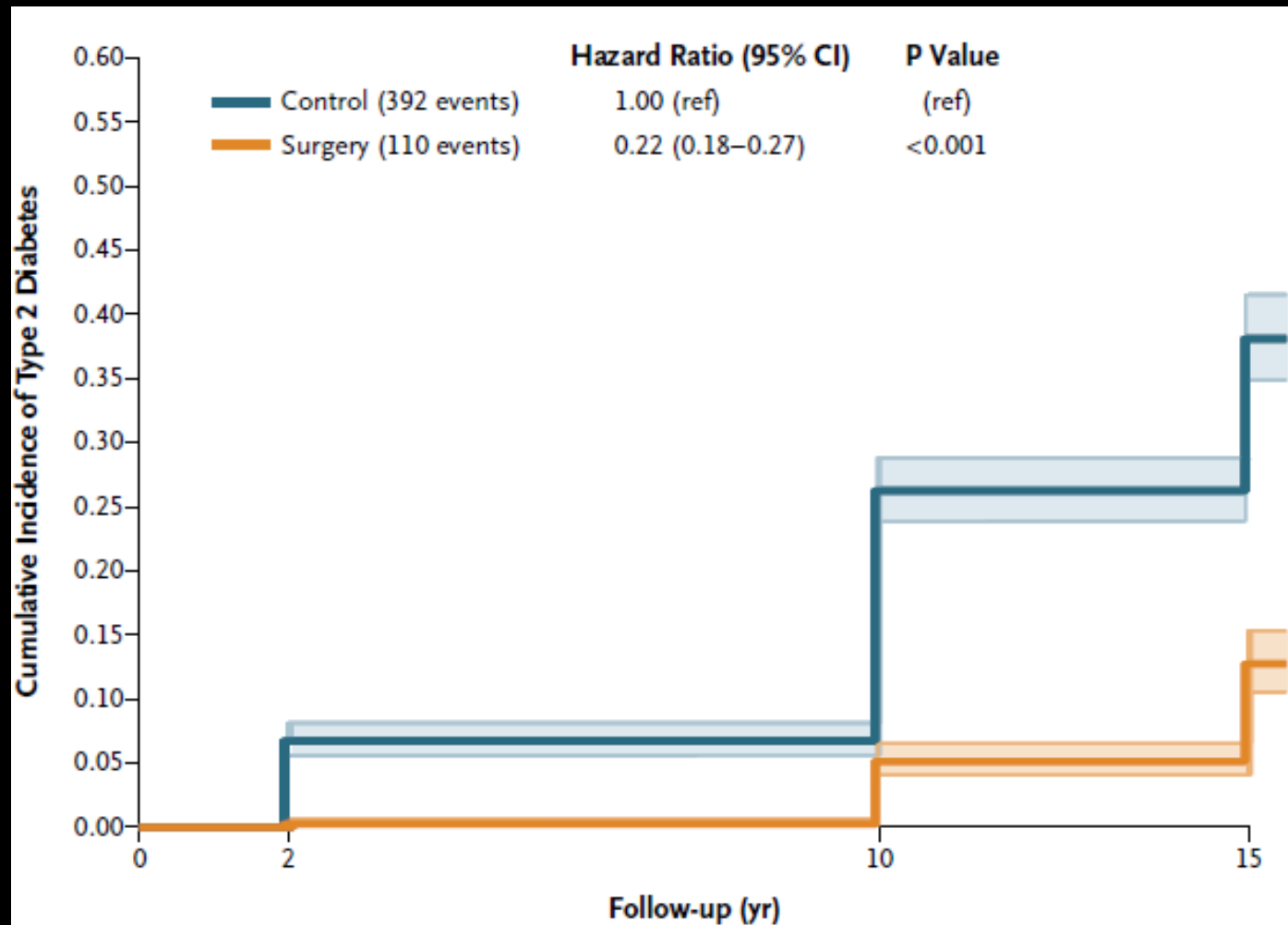


# Reduction in microvascular complications



A: normal glycaemia  
B: Prediabetes  
C: New T2DM  
D: Established T2DM

# Prevention of diabetes – SOS study





# Cost effectiveness

Variable	Condition	Bariatric surgery arm		Incremental		Cost per QALY (mean, 95% range) (UK£)
		Total costs (UK£M)	Total QALYs	Incremental costs (UK£M)	Incremental QALYs	
All	BMI $\geq 40$ kg/m <sup>2</sup>	67.25	14,509	15.26	2142	7129 (6775 to 7506)
Gender	Men	63.99	14,332	14.97	2087	7188 (6662 to 7796)
	Women	70.51	14,680	15.55	2201	7076 (6581 to 7638)
Age group (years)	20–34	68.18	17,153	13.62	1866	7344 (6478 to 8421)
	35–54	70.79	15,030	15.00	2139	7027 (6511 to 7569)
	55–74	59.49	11,545	17.01	2355	7230 (6862 to 7613)
Deprivation category	Least deprived	61.49	14,791	14.46	2052	7056 (6688 to 7448)
	Most deprived	70.00	14,187	16.32	2242	7287 (6930 to 7665)
Diabetes BMI $\geq 40$ kg/m <sup>2</sup>	BMI $\geq 40$ kg/m <sup>2</sup>	68.47	14,468	15.04	2437	6176 (5894 to 6457)
BMI 35–39 kg/m <sup>2</sup>	BMI 35–39 kg/m <sup>2</sup>	68.08	14,708	15.00	1995	7675 (7339 to 8037)
Costs of procedure	50% higher	71.83	14,511	19.84	2144	9261 (8800 to 9795)
	100% higher	76.41	14,512	24.42	2148	11,376 (10,763 to 11,950)
	Zero procedure cost	58.09	14,512	6.10	2148	2842 (2701 to 2998)
Decline of intervention effect over time	Year <sup>-0.25</sup>	64.25	13,786	12.25	1422	8637 (8009 to 9400)
	Year <sup>-0.50</sup>	63.15	13,516	11.16	1152	9720 (8860 to 10,706)

# Indications

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## NICE guidelines for the surgical therapy of morbid obesity

- Recommend BMI criteria
  - BMI  $\geq$  40
  - BMI  $\geq$  35 + significant comorbidities
  - BMI  $\geq$  30 + T2DM

# Multidisciplinary care before and after

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- Dietitian
- Physician
- Psychologist
- Surgeon
- Anaesthetist
- Nurse specialist

# Peri-operative complications

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- Death < 3 in 1000 (0.3%)
- Complication rates 4-25% at 30-180 days
- Most common:
  - Pulmonary
  - VTE
  - Wound infection, bleeding, leak
- Predictors: VTE, OSA, poor function, BMI>60, open surgery
- One of the safest operations in entire surgical field
- Doing nothing many times carries higher risk

# Conclusions

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- Obesity is a disease that needs biological treatments in addition to other measures
- Centre stage in new diabetes guidelines
- Medications are now safe and increasingly effective
- Bariatric surgery is safe and very effective
- Treatment has benefits to person, HSC and society

# Acknowledgements

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