Obesity

Dr Tahir Majeed

Introduction

- Definition
- The scale of the problem
- Causes of obesity
- Endocrine causes of obesity
- Complications of obesity
- Management of obesity
- Evidence based therapies for obesity
  - Diet
  - Exercise
  - Drugs
  - Bariatric surgery
- Obesity and diabetes

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Definition of obesity

Body Mass Index (kg/m^2)	**Category**
<18.5	**Underweight**
18.5-25	**Healthy weight**
25-30	**Overweight**
30-35	**Grade 1 obese**
35-40	**Grade 2 obese**
>40	**Grade 3 obese**

BMI

- Kg/m^2
- Easily calculated, repeatable measure
- Lean plus fat mass
- Clinically significant

Waist circumference

- Cm
- Waist circumference
  - >102cm in men (40 inches)
  - >88cm women
  - Leads to increased risk even if weigh/BMI normal
- Reflects visceral adiposity that releases pro-inflammatory cytokines

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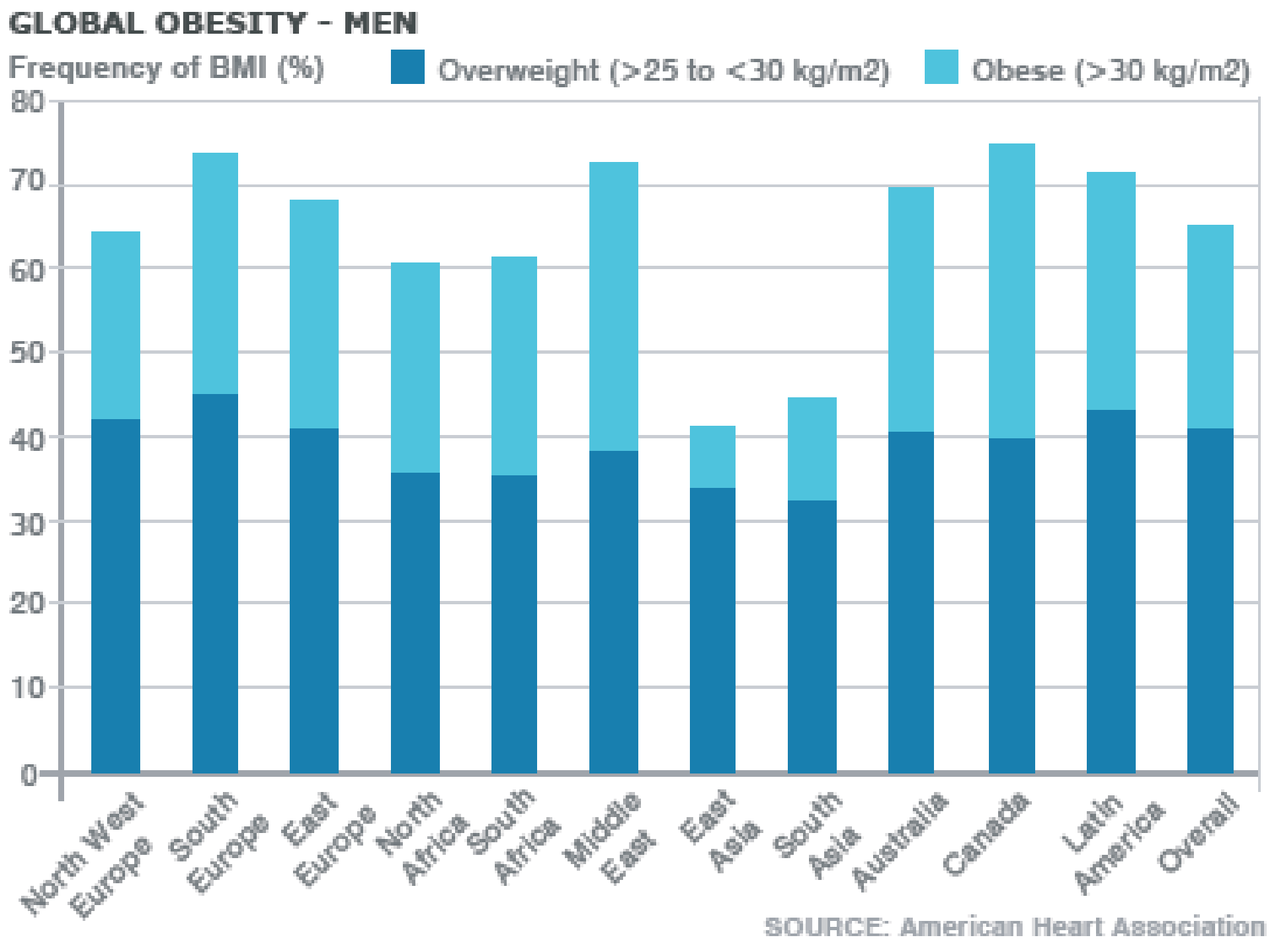
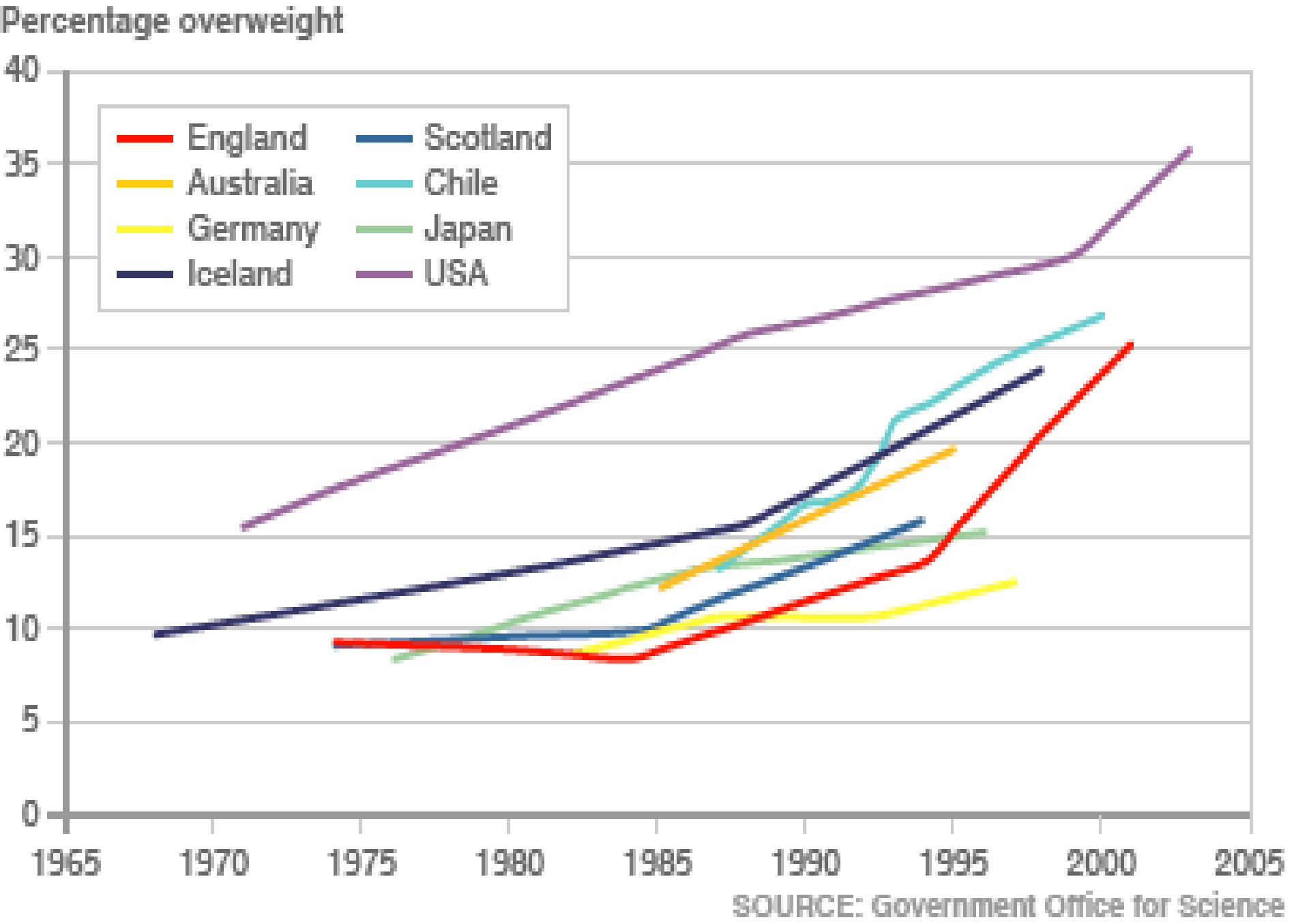
A global epidemic

- WHO estimates
- Currently
  - 1.5 billion adults are overweight
  - 400 million obese
- By 2015
  - 2.2 billion overweight
  - 700 million obese


GLOBAL OBESITY - MEN
Frequency of BMI (%)
Overweight (>25 to <30 kg/m2)
Obese (>30 kg/m2)
80
70
60
50
40
30
20
10
0
North West Europe
South Europe
East Europe
North Africa
South Africa
Middle East
East Asia
South Asia
Australia
Canada
Latin America
Overall
SOURCE: American Heart Association


GLOBAL OBESITY - WOMEN
Frequency of BMI (%)
Overweight (>25 to <30 kg/m2)
Obese (>30 kg/m2)
80
70
60
50
40
30
20
10
0
North West Europe
South Europe
East Europe
North Africa
South Africa
Middle East
East Asia
South Asia
Australia
Canada
Latin America
Overall
SOURCE: American Heart Association

INCREASING NUMBER OF OVERWEIGHT CHILDREN AROUND THE WORLD



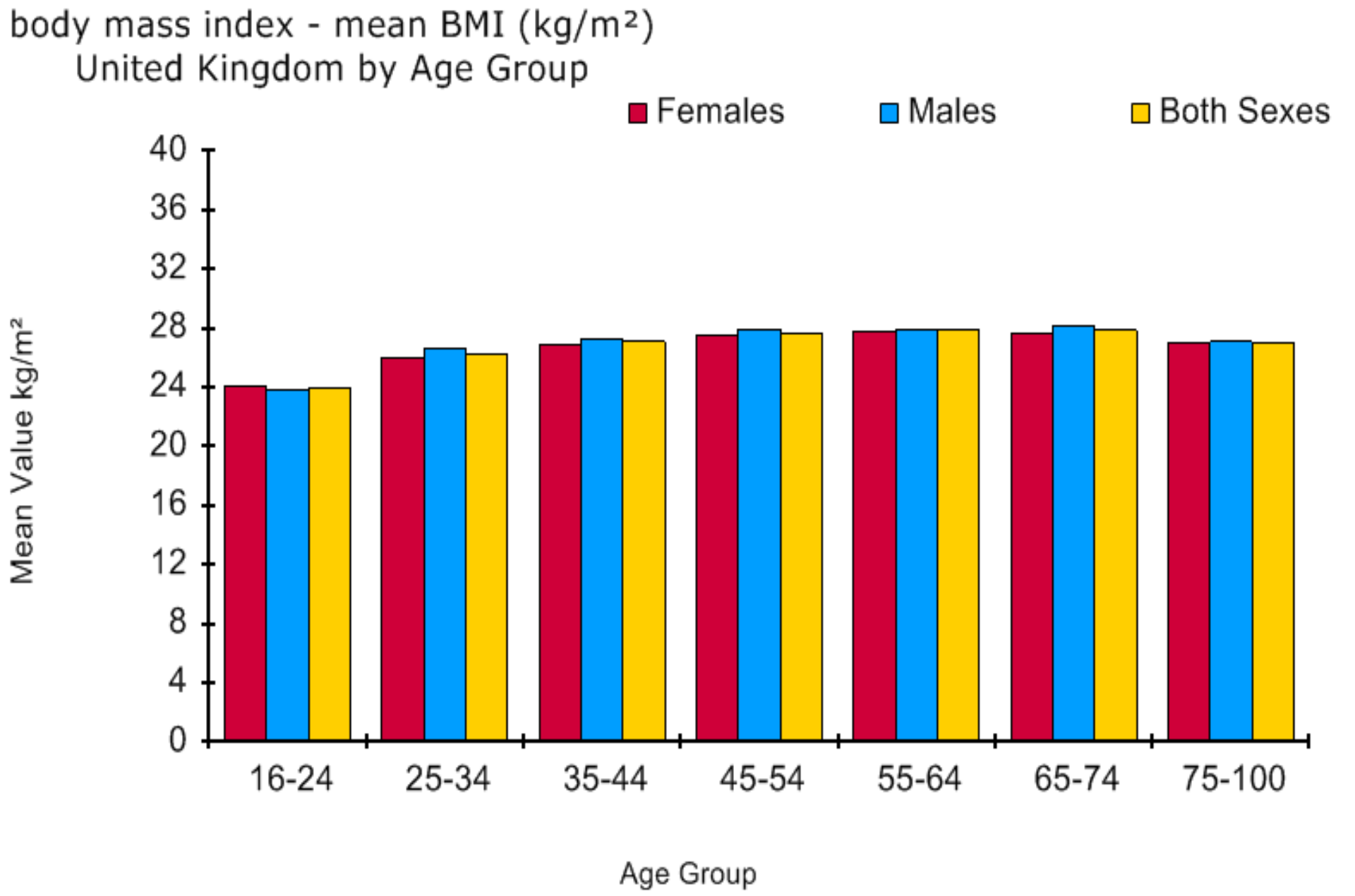
Health Survey England 2005 (HSE)

- Ideal weight (BMI 18.5-25) fell from 1993-2005
  - Men
    - 41% to 32.2%
  - Women
    - 49.5% – 40.7%
- Obese (BMI >30) rose from 1993-2005
  - Men
    - 13.2%-22.1%
  - Women
  - 16.4% - 21.8%

Gender, age and obesity in UK

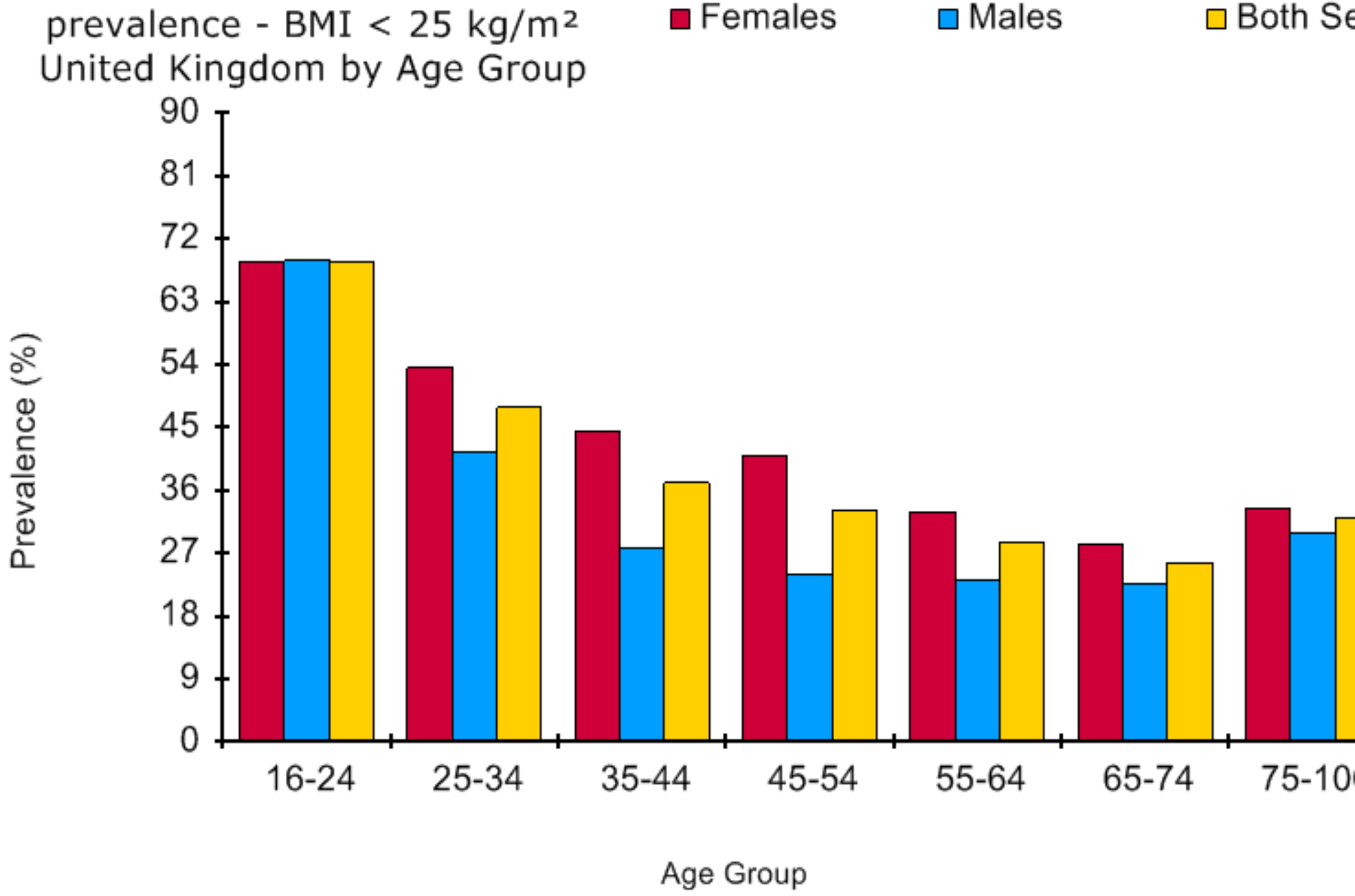
- Similar mean BMI men vs women (26.9 Kg/m^2)
- More men overweight (42% vs 32%) but higher proportion of women are morbidly obese 0.9% vs 2.7%)
- Obesity increases with age

body mass index - mean BMI (kg/m²)
United Kingdom by Age Group



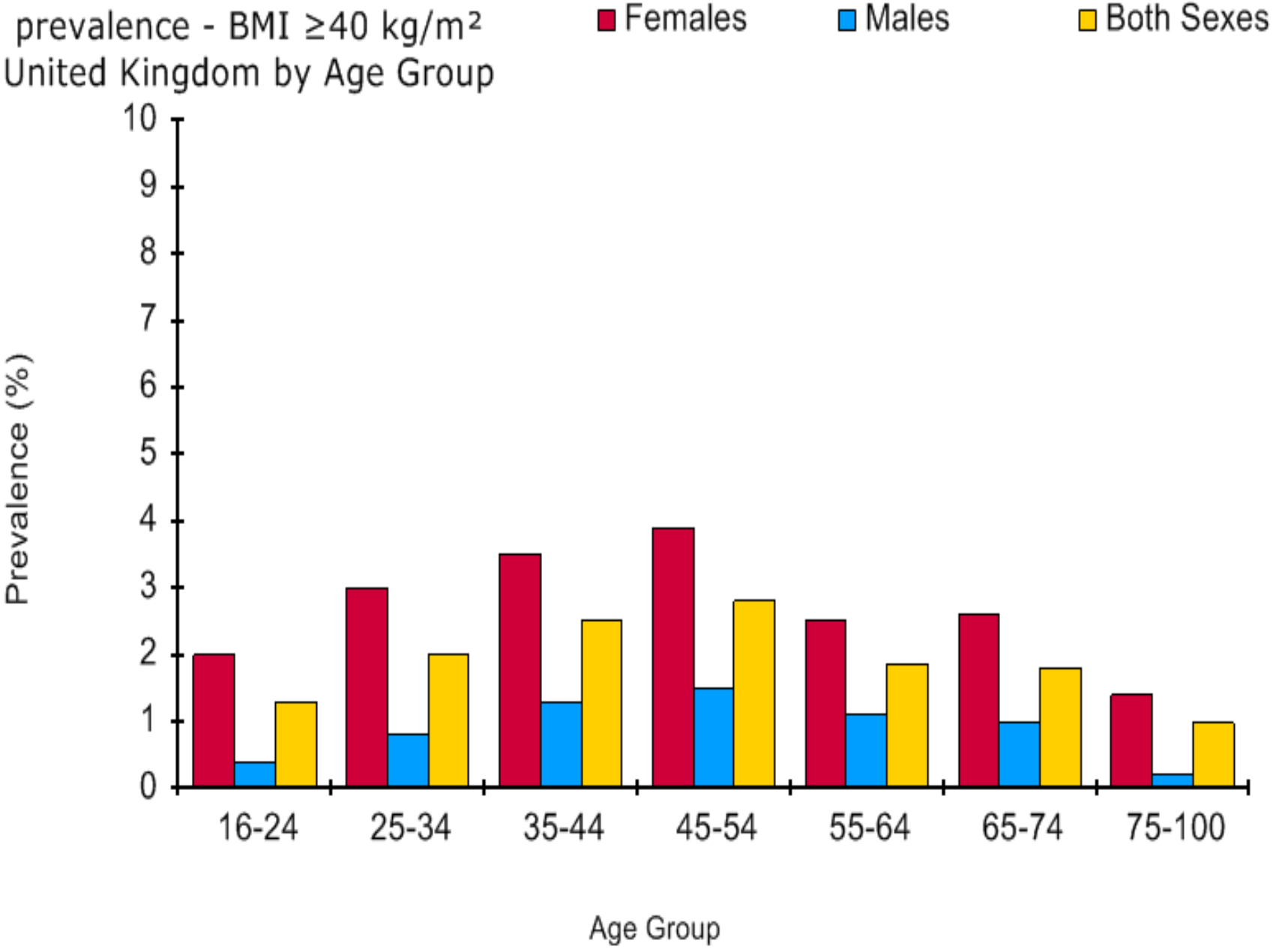
Source: Department of Health. Health Survey for England, 2002 (http://www.who.int/infobase IBRef: 101069)

prevalence - BMI < 25 kg/m²
United Kingdom by Age Group



Source: Department of Health. Health Survey for England, 2002 (http://www.who.int/infob
IBRef: 101069)

prevalence - BMI ≥40 kg/m²
United Kingdom by Age Group



Source: Department of Health. Health Survey for England, 2002 (http://www.who.int/infobase IBRef: 101069)

Ethnicity and Obesity rates BMI>30kg/m^2 (UK)

- Females
  - Black African (38%)
  - Black Caribbean (32%)
  - Pakistani (28%)
  - General population (23%)
  - Chinese (7%)
- Males
  - Black Carribean (25%)
  - General population (22%)
  - Chinese (6%)
  - Bangladeshi (6%)

Social class and obesity

- In women 25% were obese in lowest socio-economic class vs 15% in highest
- No such relationship found in men

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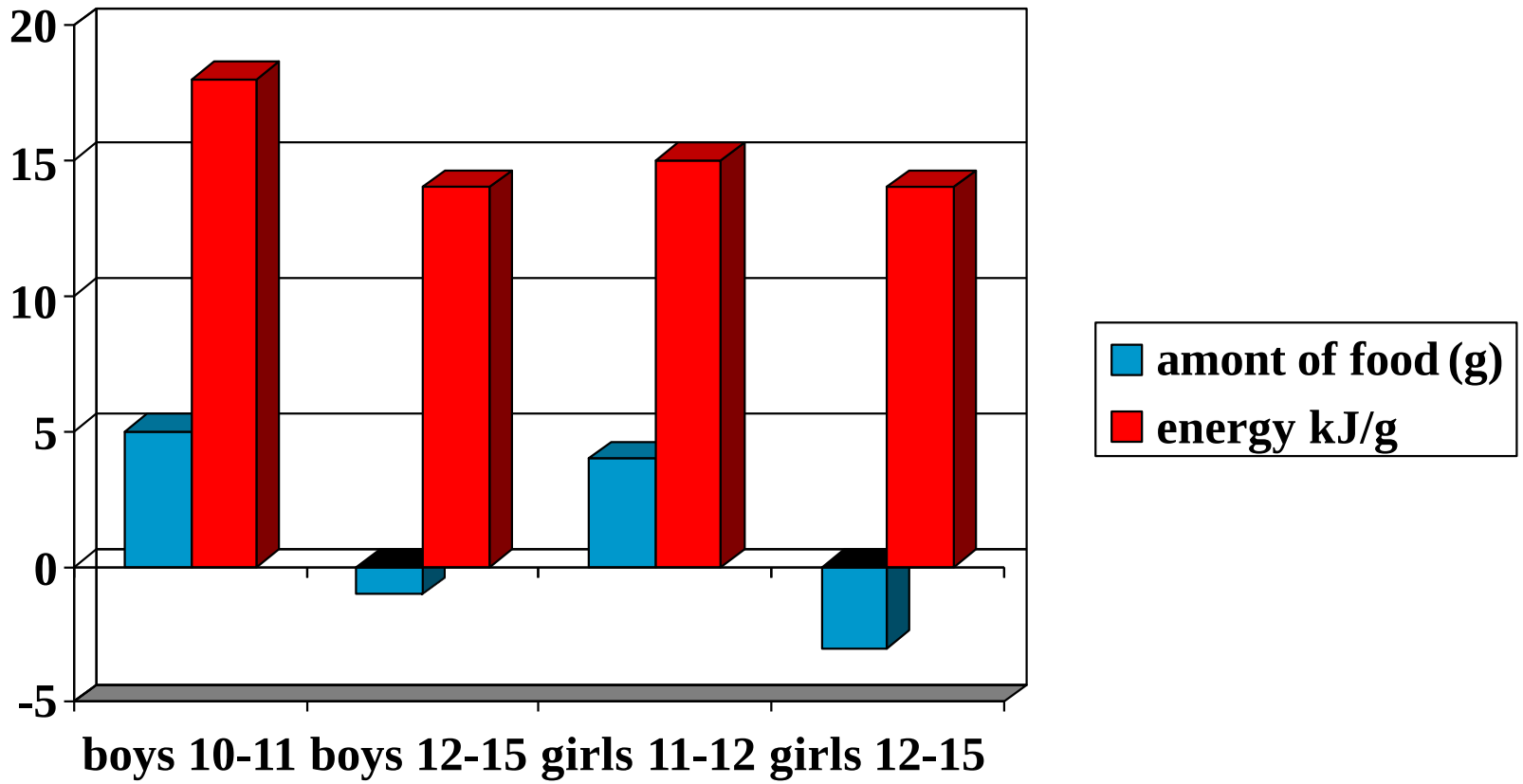
Causes of obesity - food

- Food production
- Portion size
- Food hoarding behaviour
- Increased proportion of meals eaten out
- Increased non-meal eating (snacking)

- Leading to removal of constraints of cost and availability

Percentage change in amount of food and energy contained between 1985-95 in Australia



Between 1985-95 in Australian children (Magarey *et al* 2005)

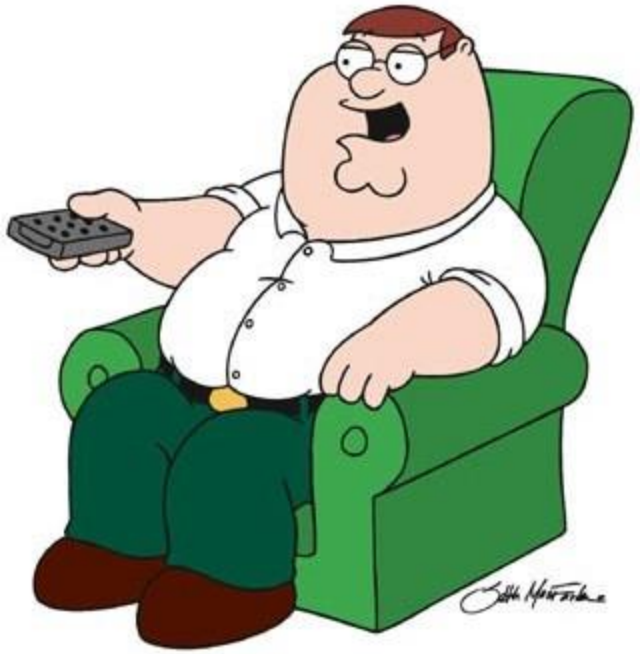
- 40-50% rise in confectionary consumption
- 29-48% rise soft beverage intake
- 46% increase intake in cereal based products (cakes, biscuits)
- 59-136% increase intake of sugar based products

Australian National Nutritional Survey of Children 1995 - snapshot

- 40% ate no fruit
- 30% ate no vegetables
- Potatoes accounted for 50% of all vegetables (75% of which were fried or fat added)
- Only 25% drank water
- 1/3 ate snacks (crisps, confectionary)
- 38% drank soft drinks
- 70% drank fruit juice

Causes of obesity – physical activity (HSE 2005)

- Higher rate of obesity in men reporting lower rates of physical activity (28% vs 17%)
- Higher rate of obesity in women reporting lower rates of activity (29% vs 15%)



Influence of genetic and environmental factors on prevalence of type 2 diabetes

(Schulz LO *et al* 2006)

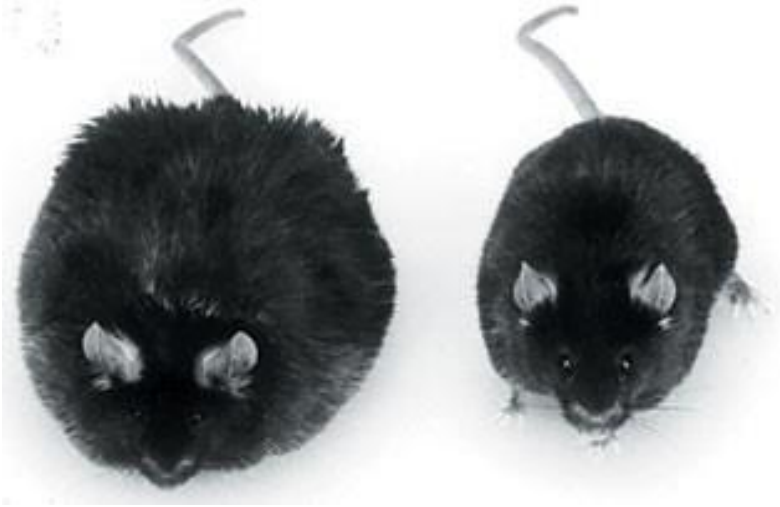
	Arizona Pima Indians N=888	**Mexican Pima Indians** n-=223	**Mexicans** N=193
BMI (kg/m^2)	34.6	25.1	25.8
Calorie intake (kcal/day)	1751	2458	2593
Lipid intake (%)	36.3	26.3	25.6
Physical activity (hr/week)	7	27	27
Prevalence TIIDM (%)	38.1	7.1	2.6

“It’s my metabolism Doctor”

- Multiple hormones control hunger and may contribute to obesity
- Ghrelin (peptide hormone) orexigenic hormone
  - Derived from the stomach
  - Double blinded placebo controlled trial subjects injected with ghrelin
  - 30% increased consumption at a buffet
  - No effect on gastric emptying

- Peptide YY performs opposite role
- Secreted by small bowel and colon postpradially
- Acts on the hypothalamus
  - Suppresses gastric emptying
  - Reduces gastric secretion
- When injected into subjects leads to decreased food consumption compared with placebo
- Other appetite suppressants
  - GLP-1
  - Cholecystokinin

Leptin



- Produced by adipocytes
- Internal control of energy fat stores
- Binds to specific receptors on arcuate nucleus in the hypothalamus
- Leptin deficient mice
  - Are hyperphagic
  - Become obese
  - Have reduced energy expenditure

Pharmacological causes of obesity

- TCAs
- Anti-psychotics
- Steroids
- Lithium
- Anti-conuilsants (sodium valproate)

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Endocrine causes of obesity

- Cushings' syndrome
- Hypothyroidism
- Hypopituitrism
- Prader-Willi syndrome
- Laurence-Moon syndrome

Cushing's syndrome

- First described by Harvey Cushing 1912
- 99% due to exogenous steroid use
- Endogenous Cushing's incidence 1-2/million per year
  - 90% ACTH dependent in>5y/o
  - Of those 90% are due to pituitary adenoma (Cushing's Disease)
  - Ectopic ACTH due to carcinoid (bronchial and intestinal) and as part of MEN 1
  - CRH dependent tumours very rare
  - Adrenocortical Cushing's 50% of cases in <5y/o with increased risk of malignancy

Cushings and obesity

- Excessive glucocorticoids bind to intracellular GC receptors and lead to gene transcription
- In adults
  - centripoedal obesity with intrascapular fat pad
- In children
  - more generalised obesity and growth delay
- Usual adult daily cortisol production is 6-8mg/m^2 but this can increase ten-fold under physiological stress

Exogenous glucocorticoids

- Exogenous glucocorticoids have 50-60% bioavailability of endogenous glucocorticoids
- Synthetically produced steroids have differing pharmacokinetc and pharmacodynamic effects
- i.e. 20mg cortisol equivalent effect on GR as
  - 25mg hydrocortisone
  - 5mg prednisolone
  - 4 mg methylprednisolone
  - 0.5mg dexamethasone

Prader-Willi syndrome

- 1/15000 new borns affected
- Genetic defect on 15q11-q13
- Poor intrauterine movements
- Neonatal hypotonia
- Short-stature
- Developmental delay/erratic behaviour
- Severe obesity and hyperphagia
- Hypogonadism and GH deficiency

Laurence-Moon syndrome

- Developmental delay
- Retinitis pigmentosa
- Mental retardation
- Spastic paraparesis
- Obesity
- Autosomal recessive condition

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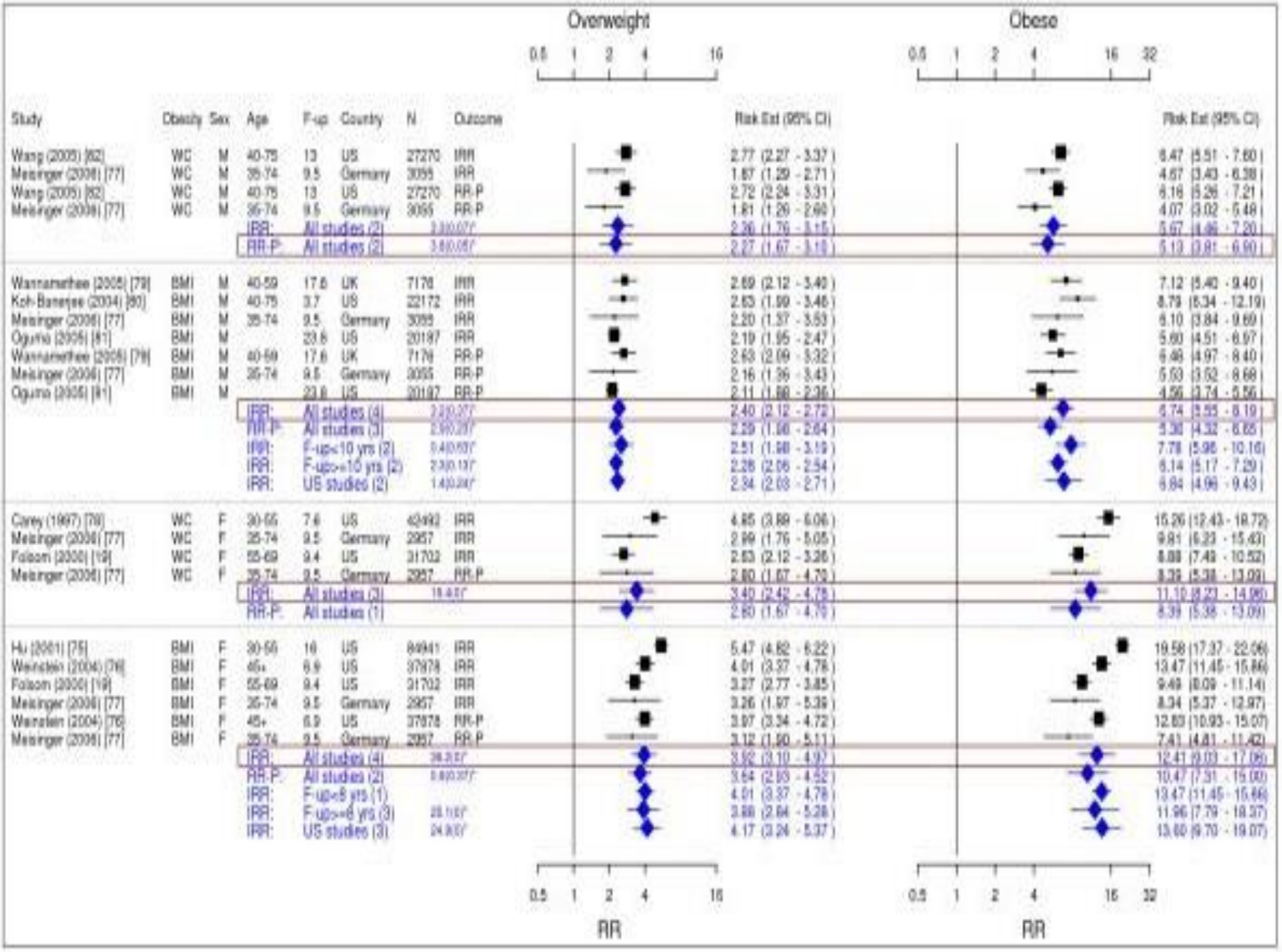
Health effect of obesity

- Increased rates of
  - Cardiovascular disease
  - Type II diabetes
  - Hyperlipidaemia
  - Hypertension
  - Cancer (breast, endometrial, colonic etc)
  - Osteoarthritis
  - Biliary disease
  - NASH and cirrhosis
  - Obstructive sleep apnoea
  - Type II respiratory failure
  - Depression
  - (Social isolation)


Overweight
Obese
0.5 1 2 4 16
0.5 1 2 4 16 32
Study
Obesity
Sex
Age
F-up
Country
N
Outcome
Risk Est (95% CI)
Risk Est (95% CI)
Wang (2005) [82] WC M 40-75 13 US 27270 IRR 2.77 (2.27 - 3.37) 6.47 (5.51 - 7.60)
Meisinger (2006) [77] WC M 35-74 9.5 Germany 3055 IRR 1.87 (1.29 - 2.71) 4.67 (3.43 - 6.38)
Wang (2005) [82] WC M 40-75 13 US 27270 RR-P 2.72 (2.24 - 3.31) 6.16 (5.26 - 7.21)
Meisinger (2006) [77] WC M 35-74 9.5 Germany 3055 RR-P 1.81 (1.26 - 2.60) 4.07 (3.02 - 5.48)
IRR: All studies (2) 2.36 (1.76 - 3.15) 5.67 (4.46 - 7.20)
RR-P: All studies (2) 2.27 (1.67 - 3.10) 5.13 (3.91 - 6.90)
Wannamethee (2005) [79] BMI M 40-59 17.6 UK 7176 IRR 2.69 (2.12 - 3.40) 7.12 (5.40 - 9.40)
Koh-Banerjee (2004) [80] BMI M 40-75 3.7 US 22172 IRR 2.63 (1.99 - 3.46) 8.79 (6.34 - 12.19)
Meisinger (2006) [77] BMI M 35-74 9.5 Germany 3055 IRR 2.20 (1.37 - 3.53) 6.10 (3.84 - 9.69)
Oguma (2006) [81] BMI M 33.6 US 20197 IRR 2.19 (1.95 - 2.47) 5.69 (4.51 - 6.97)
Wannamethee (2005) [79] BMI M 40-59 17.6 UK 7176 RR-P 2.63 (2.09 - 3.32) 6.46 (4.97 - 8.40)
Meisinger (2006) [77] BMI M 35-74 9.5 Germany 3055 RR-P 2.16 (1.36 - 3.43) 5.53 (3.52 - 8.68)
Oguma (2006) [81] BMI M 33.6 US 20197 RR-P 2.11 (1.88 - 2.36) 4.56 (3.74 - 5.56)
IRR: All studies (4) 2.40 (2.12 - 2.72) 6.74 (5.55 - 8.19)
RR-P: All studies (3) 2.29 (1.88 - 2.64) 5.30 (4.32 - 6.65)
IRR: F-up<10 yrs (2) 2.51 (1.98 - 3.19) 7.78 (5.96 - 10.16)
IRR: F-up>=10 yrs (2) 2.26 (2.06 - 2.54) 6.14 (5.17 - 7.29)
IRR: US studies (2) 2.34 (2.03 - 2.71) 6.84 (4.96 - 9.43)
Carey (1997) [78] WC F 30-55 7.6 US 42492 IRR 4.85 (3.89 - 6.06) 15.26 (12.43 - 18.72)
Meisinger (2006) [77] WC F 35-74 9.5 Germany 2957 IRR 2.99 (1.76 - 5.05) 9.81 (6.23 - 15.43)
Folsom (2000) [19] WC F 55-69 9.4 US 31702 IRR 2.83 (2.12 - 3.26) 8.88 (7.49 - 10.52)
Meisinger (2006) [77] WC F 35-74 9.5 Germany 2957 RR-P 2.80 (1.67 - 4.70) 8.39 (5.38 - 13.09)
IRR: All studies (3) 3.40 (2.42 - 4.78) 11.10 (8.23 - 14.96)
RR-P: All studies (1) 2.80 (1.67 - 4.70) 8.39 (5.38 - 13.09)
Hu (2001) [75] BMI F 30-55 16 US 84941 IRR 5.47 (4.82 - 6.22) 19.58 (17.37 - 22.06)
Weinstein (2004) [76] BMI F 45+ 6.9 US 37878 IRR 4.01 (3.37 - 4.76) 13.47 (11.45 - 15.86)
Folsom (2000) [19] BMI F 55-69 9.4 US 31702 IRR 3.27 (2.77 - 3.85) 9.49 (8.09 - 11.14)
Meisinger (2006) [77] BMI F 35-74 9.5 Germany 2957 IRR 3.26 (1.97 - 5.39) 8.34 (5.37 - 12.97)
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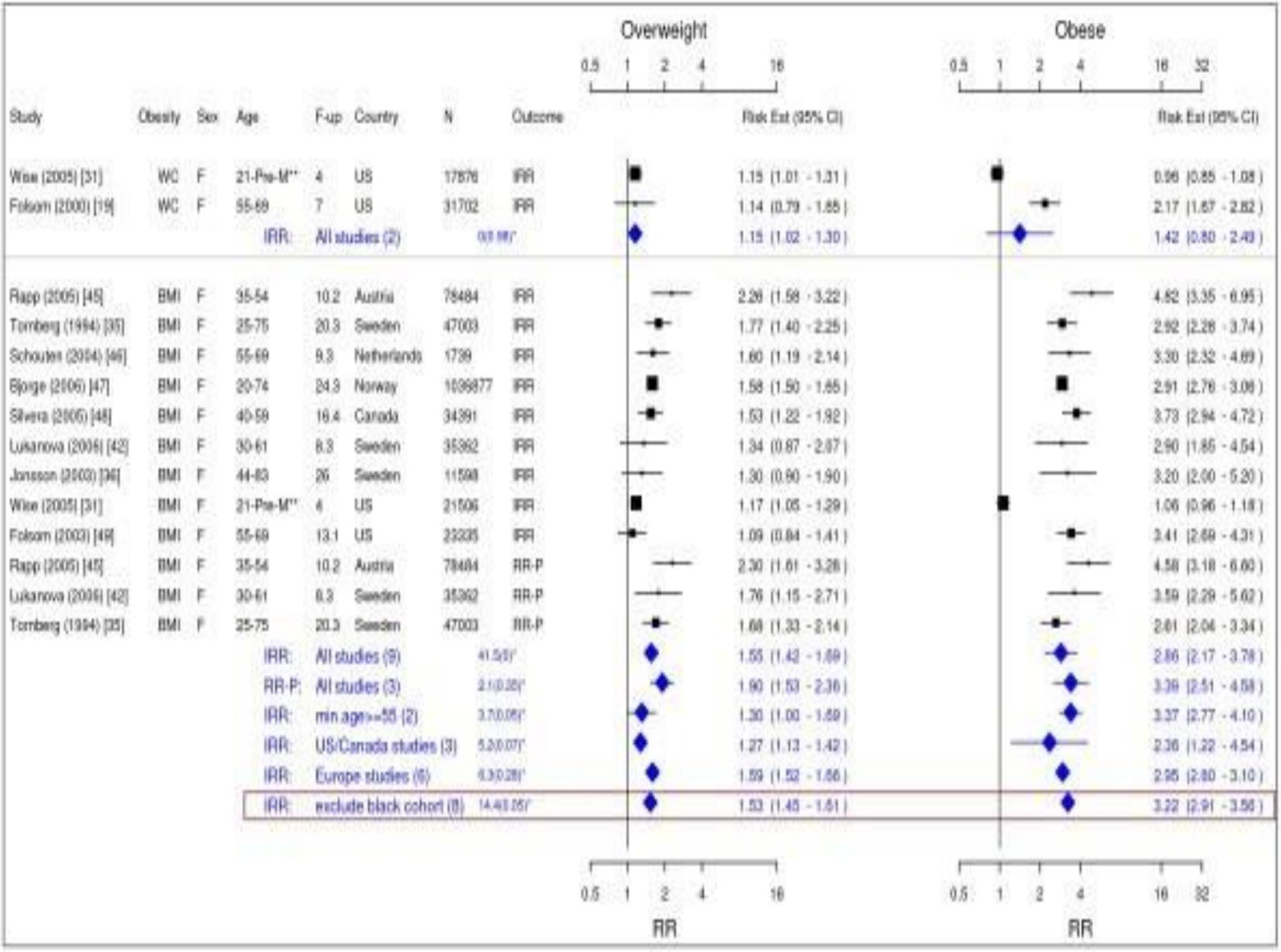
Meisinger (2006) [77] BMI F 35-74 9.5 Germany 2957 RR-P 3.12 (1.80 - 5.41) 7.41 (4.81 - 11.42)
IRR: All studies (4) 3.92 (3.10 - 4.97) 12.41 (9.03 - 17.06)
RR-P: All studies (2) 3.64 (2.03 - 4.52) 10.47 (7.31 - 15.00)
IRR: F-up<8 yrs (1) 4.01 (3.37 - 4.76) 13.47 (11.45 - 15.86)
IRR: F-up>=8 yrs (3) 3.88 (2.64 - 5.28) 11.96 (7.79 - 18.37)
IRR: US studies (3) 4.17 (3.24 - 5.37) 13.60 (9.70 - 19.07)
0.5 1 2 4 16
0.5 1 2 4 16 32
RR
RR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Obese
0.5 1 2 4 16
0.5 1 2 4 16 32
Study Obesity Sex Age F-up Country N Outcome Risk Est (95% CI)
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Wise (2005) [31] WC F 21-Pre-M** 4 US 17876 IRR 1.15 (1.01 - 1.31) 0.96 (0.85 - 1.08)
Folsom (2000) [19] WC F 55-69 7 US 31702 IRR 1.14 (0.79 - 1.65) 2.17 (1.67 - 2.82)
IRR: All studies (2) 1.15 (1.02 - 1.30) 1.42 (0.80 - 2.49)
Rapp (2005) [45] BMI F 35-54 10.2 Austria 78484 IRR 2.26 (1.58 - 3.22) 4.62 (3.35 - 6.95)
Tornberg (1994) [35] BMI F 25-75 20.3 Sweden 47003 IRR 1.77 (1.40 - 2.25) 2.92 (2.28 - 3.74)
Schouten (2004) [46] BMI F 55-69 9.3 Netherlands 1739 IRR 1.60 (1.19 - 2.14) 3.30 (2.32 - 4.69)
Bjorge (2006) [47] BMI F 20-74 24.3 Norway 1696877 IRR 1.58 (1.50 - 1.65) 2.91 (2.76 - 3.06)
Silvera (2005) [48] BMI F 40-59 16.4 Canada 34391 IRR 1.53 (1.22 - 1.92) 3.73 (2.94 - 4.72)
Lukanova (2006) [42] BMI F 30-61 8.3 Sweden 35362 IRR 1.34 (0.87 - 2.07) 2.90 (1.85 - 4.54)
Jonsson (2003) [36] BMI F 44-83 26 Sweden 11598 IRR 1.30 (0.90 - 1.90) 3.20 (2.00 - 5.20)
Wise (2005) [31] BMI F 21-Pre-M** 4 US 21506 IRR 1.17 (1.05 - 1.29) 1.06 (0.96 - 1.18)
Folsom (2003) [49] BMI F 55-69 13.1 US 23235 IRR 1.09 (0.84 - 1.41) 3.41 (2.69 - 4.31)
Rapp (2005) [45] BMI F 35-54 10.2 Austria 78484 RR-P 2.30 (1.61 - 3.28) 4.58 (3.18 - 6.60)
Lukanova (2006) [42] BMI F 30-61 8.3 Sweden 35362 RR-P 1.76 (1.15 - 2.71) 3.59 (2.29 - 5.62)
Tornberg (1994) [35] BMI F 25-75 20.3 Sweden 47003 RR-P 1.68 (1.33 - 2.14) 2.61 (2.04 - 3.34)
IRR: All studies (9) 1.55 (1.42 - 1.69) 2.86 (2.17 - 3.78)
RR-P: All studies (3) 1.90 (1.53 - 2.36) 3.39 (2.51 - 4.58)
IRR: min age>=55 (2) 1.30 (1.00 - 1.69) 3.37 (2.77 - 4.10)
IRR: US/Canada studies (3) 1.27 (1.13 - 1.42) 2.36 (1.22 - 4.54)
IRR: Europe studies (6) 1.59 (1.52 - 1.66) 2.95 (2.80 - 3.10)
IRR: exclude black cohort (8) 1.53 (1.45 - 1.61) 3.22 (2.91 - 3.56)
0.5 1 2 4 16
0.5 1 2 4 16 32
RR
RR

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Management of obesity

- Aims
- Diet
- Dietetics input
- Exercise
- Pharmacotherapy
- Bariatric surgery

Aims of weight loss

- Normalise body weight
- Improved mobility and quality of life
- Improved health and reduced mortality
  - Loss of 5-10% body weight beneficial in reducing cardiovascular disease
  - *Diabetic prevention programme* – 5-6% weight loss in BMI>34kg/m^2 lead to 34% reduction in incidence of diabetes

Diet

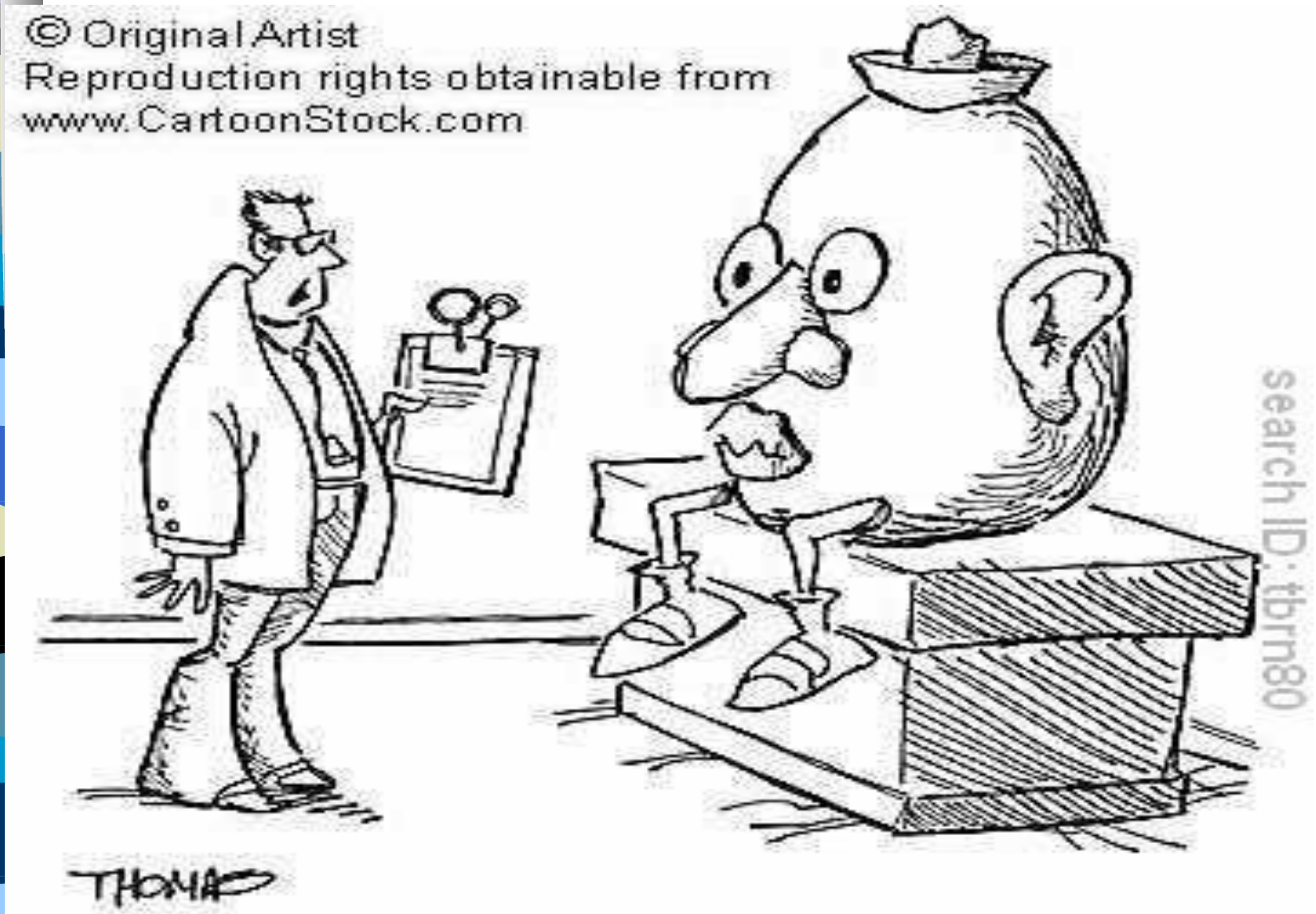
- Types of diets
  - Low calorie diets (500kcal/day deficit)
  - Very low calorie diets (less than 800kcal/day ***total***) not recommended for >14 weeks
  - Low carbohydrate, high protein diets (Dr Atkins)
  - Low fat diets
  - Meal replacement diets

Low calorie diets

- *Weight Watchers* multicentre trial 423 subjects
- RCT *Weight Watchers vs* self-help program (plus 2 dietician reviews)
- Dropout rate 27%
- Weight loss significantly more on WW
  - WW 5.3% at 1 year and 3.2% 2 year
  - Control 0.5% at 1 year and 0% at 2 years
- Similar results in 3 further RCTs
- Current cost around £20 per month or £6 per weekly meeting

Very low calorie diets

- Severe calorie deficiency (800kcal/day only)
- Meals often replaced by liquids
- One review found
  - average weight loss of 1.2-2.5kg per week and up to 20kg at 12-16 weeks on VLCD
  - Compared to 0.5kg/week and total of 6-8kg on LCD



"I'm going to put you on a low carb diet."

Low carbohydrate diets

- I.e. Atkins Diet
- Initiation phase of very low carbohydrate <20g/day) 2 weeks
- Then maintenance phase – add 5g carbohydrate per week to max of 50g
- Unlimited protein and fat
- Induces ketogenic state and fat metabolism

Samaha *et al*, NEJM 2003

- 64 pt each group
- Ranomised to Aktkins vs low calorie diet (1600/1800 kcal/day)
- Dietician input at 3,6 and 12 months
- Weight loss
  - 3 months -6.8% vs -2.9% (*p=0.001*)
  - 6 moths -7% vs –3.2% (*p=0.02*
  - 12 months –4.4% vs –2.5% (*p=0.26*)

Meta-analysis: the effect of dietary counselling for weight loss. Dansinger ML *et al* 2007

- Meta-analysis of dietary counselling vs usual care for obese and overweight of 46 trials
- Meta-analysis of changes in weight over time (slopes) and meta-regression suggest a change of approximately -0.1 BMI unit per month from 3 to 12 months of active programs and a regain of approximately 0.02 to 0.03 BMI unit per month during subsequent maintenance phases
- Issues identified were of high drop-out rate and poor study data quality

Exercise

- Helps to mobilise fatty acids rrom stored fat metabolised to produce energy
- Exercise increases energy expenditure
- 30-45 mins of moderate exercise 3 times/week burns 150kcal/day (1000kcl/week)
- Any exercise – walking, swimming, cycling that increases HR and makes patient breathless

"What fits your busy schedule better, exercising one hour a day or being dead 24 hours a day?"

Exercise

- Alone results in 2-4% reduction in BMI
- Combined with dietary modification results in greater weight loss and better maintenance.

Pharmacotherapy

- 2 commonly used
  - Orlistat
  - Sibutramijne
- Mata-analysis; pharmacologic treatment of obesity (*Zhaoping et al*, Annals of Internal Medicine 2005)

Sibutramine

- Norepinepherine and serotonin reuptake inhibitor
- MOA – appetite suppression and thermogenesis
- 10-20mg/day
- SE – hypertension, tachycardia, insomnia,
- CI – use with SSRI
- Average weight loss of **4.6kg** vs placebo at 1 year
- Minimal effect on HbA1C
- No deaths on sibutramine

Orlistat

- Reversible lipase inhibitor
- Prevents absorption of 30% dietary fat
- Inhibits fat soluble vitamin absorption
- SE – oily rectal discharge, bloating, diarrhoea, faecal incontinence, flatulence (RR approx 3)
- A meta-analysis of 22 TRCTs
  - Meanwt loss 2.75kg vs placebo after 12 months treatment

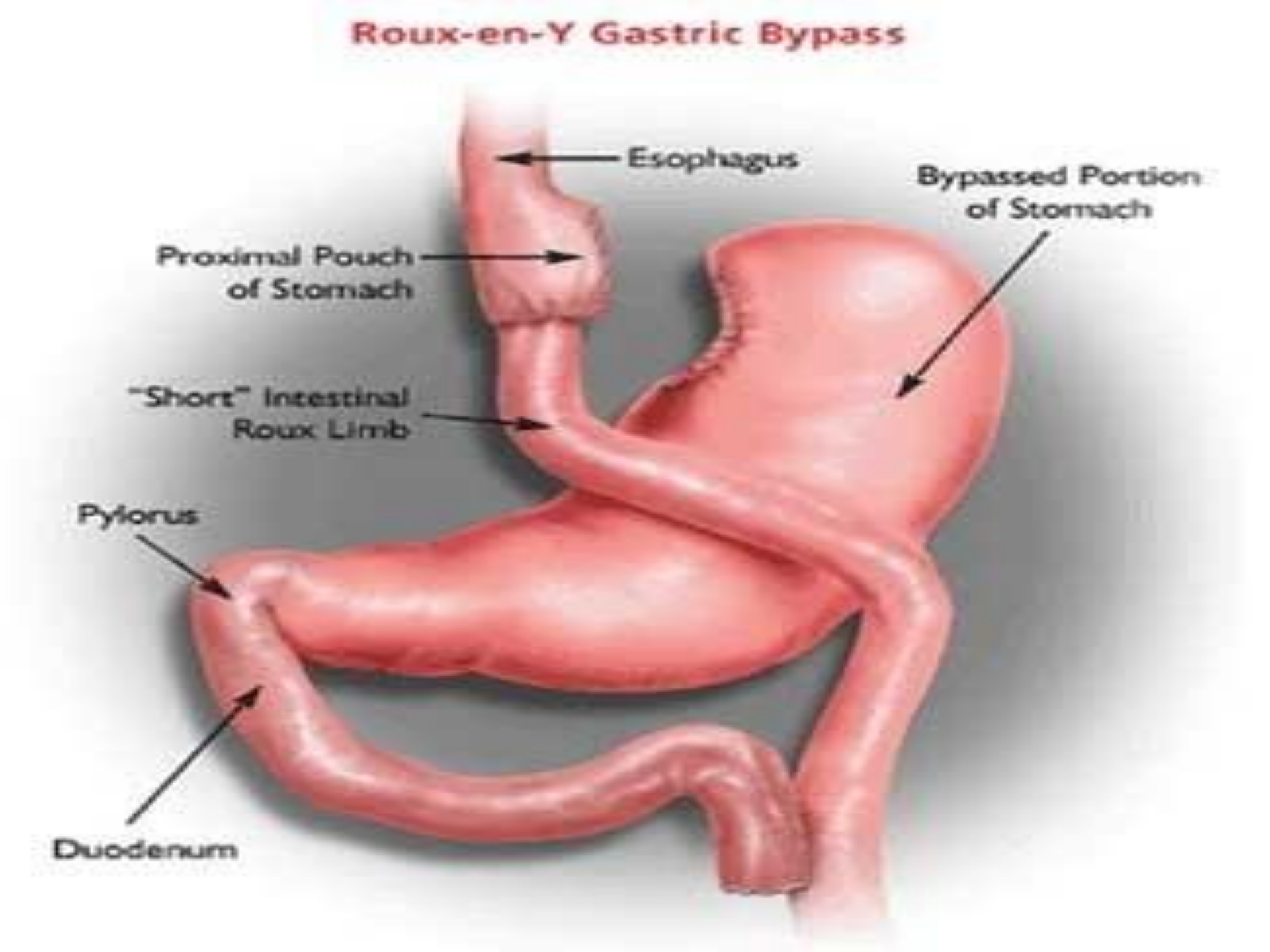
Bariatric surgery

- First procedures 1950s
  - Jejunoileal bypass
- Becoming increasingly common
  - Procedures increased 6-fold in from 1996-2000 in California
  - 140,000 performed in USA in 2004
- 2 procedures now commonly performed

Roux-en-Y

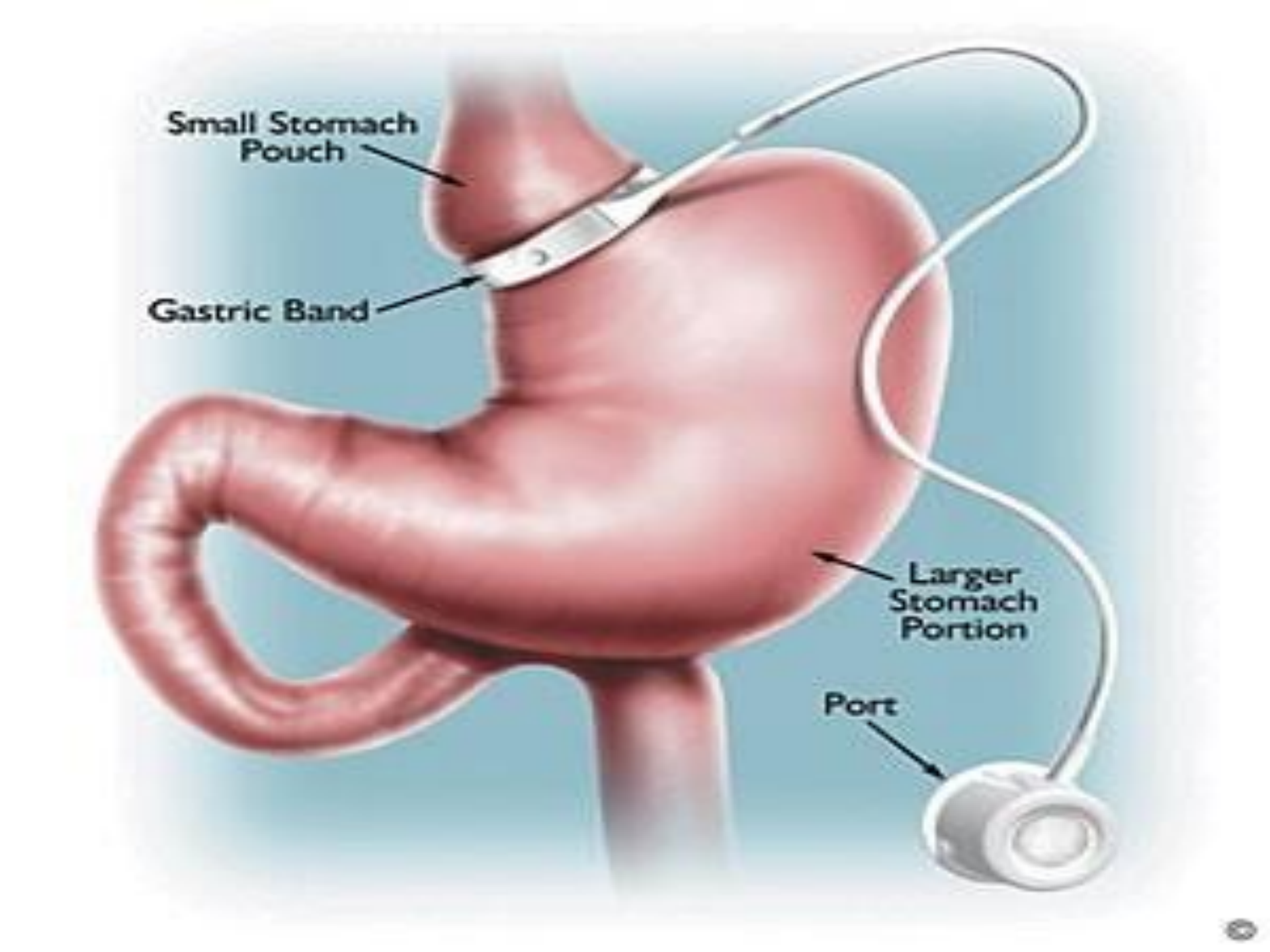
- Laparoscopic or open
- Most common procedure worldwide in 2002 (65%)
- Causes malabsorption and restriction

Roux-en-Y Gastric Bypass



Adjustable vertical banding gastroplasty

- Restrictive procedure
- 25% of procedures carried out worldwide


Small Stomach Pouch
Gastric Band
Larger Stomach Portion
Port

Swedish Obese Subjects

- 1703 subjects
- 10-year follow-up
- Average BMI 41kg/m^2, average age 47
- BMI> 34kg/m^2 in men and 38kg/m^2 in women
- Volunteered to bariatric surgery or best medical treatment

SOS 10 years

- Significantly greater weight-loss in bariatric surgery
  - 16.1% decrease in BS group
  - 1.6% weight increase in medically treated group
  - Significantly greater weight loss in the gastric bypass group
  - Risk reduction of diabetes (odds ratio 0.16) vs medical treatment
  - Reduced OSA, dyspnoea and angina

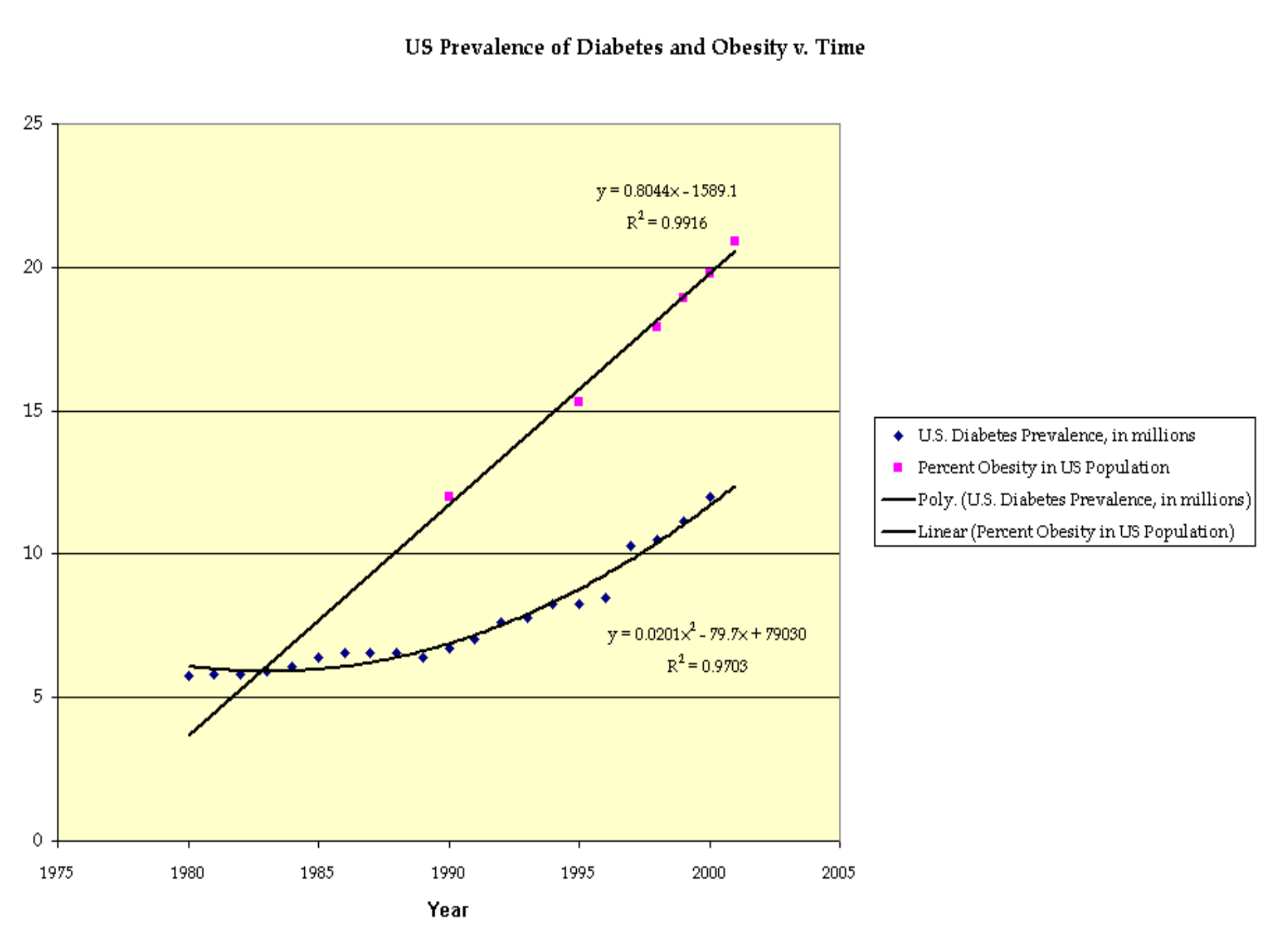
Banding vs RYGB

- Meta-analysis
  - >30kg weight loss for both procedures
  - 10kg excess weight loss at 36 months in those with RYGB vs gastric banfing

- Definition
- The scale of the problem
- Causes of obesity
- Endocrine causes of obesity
- Complications of obesity
- Management of obesity
- Evidence based therapies for obesity
  - Diet
  - Exercise
  - Drugs
  - Bariatric surgery
- Obesity and diabetes

Obesity and diabetes

- Epidemiology
- Aetiology
- Treatment


US Prevalence of Diabetes and Obesity v. Time
25
20
15
10
5
0
1975
1980
1985
1990
1995
2000
2005
Year
y = 0.8044x - 1589.1
R2 = 0.9916
y = 0.0201x2 - 79.7x + 79030
R2 = 0.9703
U.S. Diabetes Prevalence, in millions
Percent Obesity in US Population
Poly. (U.S. Diabetes Prevalence, in millions)
Linear (Percent Obesity in US Population)

Prevalence of diabetes 2008

- England 3.9 percent 2,088335
- Northern Ireland 3.3 percent 60,822
- Scotland 3.7 percent 200,669
- Wales 4.4 percent 138,988

Glycaemic control and exercise

- JAMA meta-analysis 2001 (G Normand *et al*)
- 14 random and non-randomised studies
- Mixture of aerobic and resistance training programmes
  - -0.66% in HbA1C (p-0.01)
  - No significant reduction in body weight
    - ?due to short duration of studies, increased food intake or reduced overall activity

Weight gain in treatment of diabetes

- General population gain weight at a rate of 1kg/year
- No ideal time to study weight gain
- Only a few studies weight gain as primary endpoint
- Wide variety of drugs cause weight gain
  - Sulphonylureas
  - Insulin
  - Thiazolidinedones
  - Steroids, TCAs, antipsychotics, beta blockers, sodium valproate, lithium

Insulin

- Often compared to insulin alone or insulin plus oral anti-diabetic agents
- In type II diabetics (in studies of drug efficacy rather than with obesity as primary endpoint)
  - +3.6-6.2kg over one year
- UKPDS
  - + 6.5kg over10 years

Sulphonylureas

- vs placebo, vs other oral-antidiabetic agents and vs insulin
  - +2.6-3.8kg weight gain over 1 year

Pioglitazone

- +1.5-1.9kg per year vs placebo

- (source W Leslie *et al* QJM 2007)

Newer therapies

- Incretinmmimetics and DPP-4 inhibitors
- Incretin response
- Incretins
  - Glucagon like peptide 1 (GLP-1) produced in l-cells of distal small intestine
  - Glucose dependent insulinotrophic polypeptide (GIP) produced in k-cells of proximal small intestine
- This response is reduced or absent in those with type II DM
- Type II DM tends to cause rise in post-prandial plasma glucose
- Can we restore the incretin response?

GLP-1

- Native GLP-1 causes rapid decrease in plasma glucose
- BUT is rapidly metabolised by dipeptidyl peptidase-4 (DPP-4)

- Therefore therapeutic targets are
  - DDP-4
  - GLP-1 agonists

DPP-4 inhibitors

- Sitagliptin licensed 2007 – 100mg daily
- Vildagliptin licensed 2008 – 50mg bd
- Use in TIIDM patients not controlled by SU and MF
- Reduction in HbA1c 0.5-1.0% vs placebo (alone, with Su plus or minus MF) p=0.001
- Weight neutral
- Caution in those with impaired hepatic function
- Some reports of hypersensitivity and Stevens-Johnson Syndrome

GLP-1 agonists

- Exenatide 5-10mcg bd sc
- Liraglutide
- Reduce HbA1C significantly by 0.6-1.1%
- Significant weights loss
  - 3-5% body weight
  - Appears sustained and progressive
  - Dose dependent
  - Less pronounced on liraglutide

Incretin levels and effect are markedly increased 1 month following Roux-en-Y gastric bypass surgery in obese patients with type II diabetes (*Laferere et al* 2007)

- 8 female TII DM go-on to have Roux-en-y gastric bypass
  - BMI>35
  - TII DM for 20 months
  - HbA1c 6.5%
  - Not on insulin or TZDs
- 7 obese, non-diabetic controls did not have surgery

- Pre-surgery equivalent fasting and stimulated glucose between groups
- Also equivalent levels of GIP and GLP1
- Post surgery all subjects free from diabetes
- OGTT and isoglycaemic iv test compared in all subjects 1 month post-surgery
  - Levels of GIP and GLP1 increased post-op
  - “Incretin effect” increased from 7% to 47%

Obesity summary

- Rapidly increasing problems
- Needs socialogical change in westen countries
- In those failing to lose weight is surgery the answer?
- Bariatric surgery to “cure” type II diabetes