•This meeting is organised and paid for by Janssen

•Slide content has been reviewed by Janssen to ensure compliance with the ABPI Code of Practice for the Pharmaceutical Industry.

•Speakers may express personal opinions that are not necessarily shared by Janssen.

•Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Janssen-Cilag Ltd on 01494 567447.

•Prescribing Information is available at this meeting.

Janssen-Cilag Ltd, 50-100 Holmers Farm Way, Buckinghamshire, HP12 4EG, UK

▼***Invokana® (canagliflozin)*** *This medicinal product is subject to additional monitoring and it is therefore important to report any suspect adverse reactions related to this medicinal product.*

Job number: PHGB/VOK/0415/0071 Date of preparation: April 2015

Managing obesity in patients with diabetes

Dr Matthew S Capehorn
GPwSI and bariatric physician
Clinical Director - National Obesity Forum
Clinical Manager – Rotherham Institute for Obesity

Declaration of interests

Unpaid

- Clinical Director, NOF

Paid

- Medical Director, Lighter Life

Advisory Boards

- BI/Lilly Alliance (national and global)
- Novo Nordisk
- MSD

Speaker fees/travel:

- BI/Lilly, Novo, MSD, Janssen

To discuss:

1) Prevalence of diabetes and obesity and impact on the NHS
2) Why does weight gain (visceral fat) matter
3) Why do we care about obesity?
4) How do we manage obesity?
5) Treatment interventions for managing obesity and diabetes
6) Questions?

Financial Cost of Diabetes – UK

- In 2010, 10% of NHS budget was spent on treating diabetes and its complications[1]
  - £9 Billion per year
  - £173 Million per week
  - £25 Million per day
  - £1 Million per hour
  - £17 000 per minute
  - £286 per second
- 80% of the cost of treating diabetes comes from treating complications

Diabetes_in_the_UK_2010.pdf: http://www.diabetes.org.uk/Documents/Reports/

Prevalence of diabetes in the UK is increasing

Year	Prevalence
1940	200,000
1960	400,000
1980	800,000
1996	1,400,000
2004	1,800,000
2010	3,000, 0000

Diabetes in the UK 2004 – A Report from Diabetes UK: Oct 2004 pages 19-20

Over 2 million people diagnosed[1]

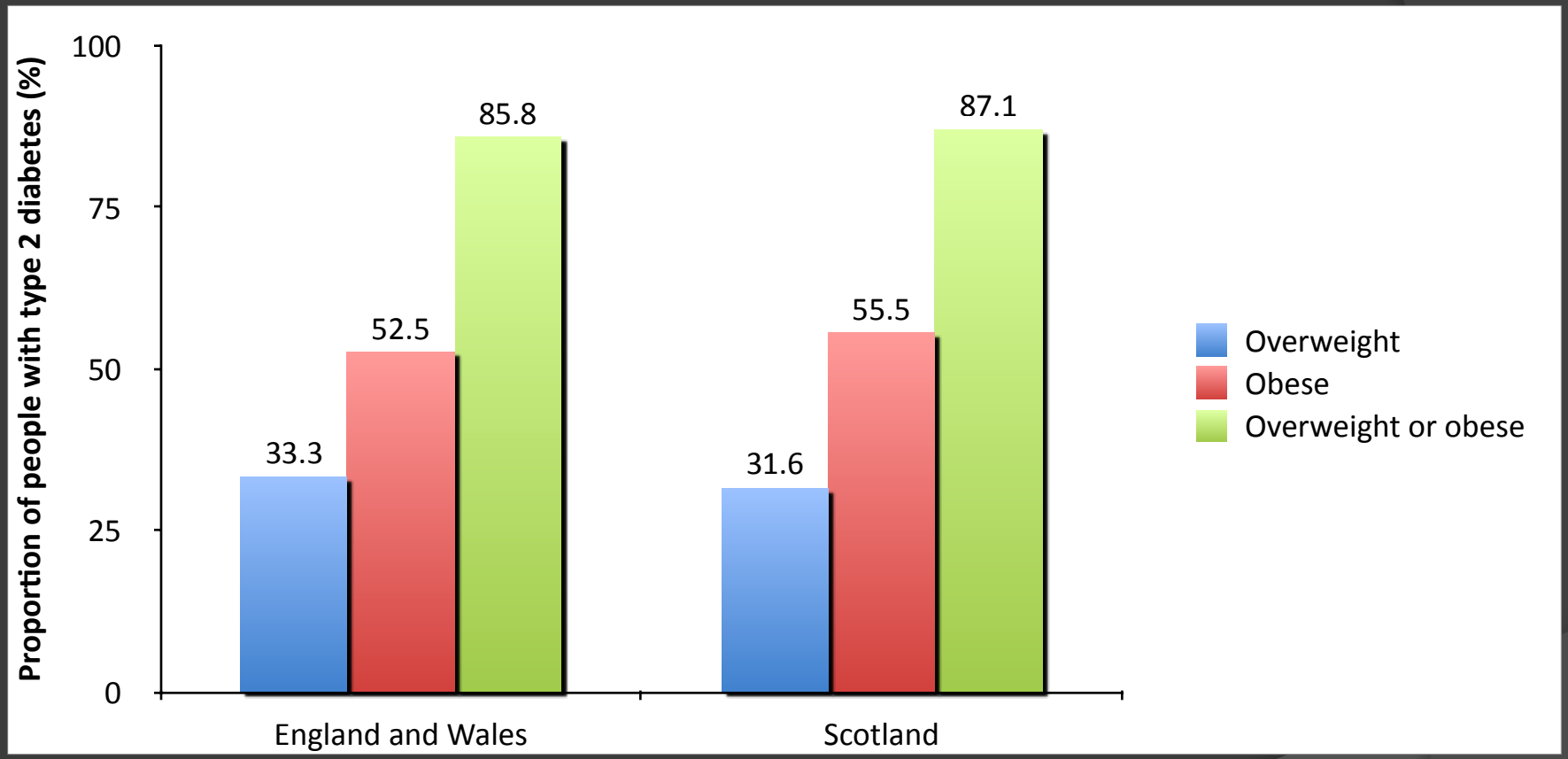
Approx 4.9% of UK adult population[1]

T2DM accounts for 85-95% of all cases[2]

The total number of people with diabetes in the UK could increase to >5.5 million by 2030[3]

All references accessed in May 2012
1. Diabetes UK. *Diabetes in the UK Report* (2010) http://www.diabetes.org.uk/Documents/Reports/Diabetes_in_the_UK_2010.pdf .
2. International Diabetes Federation. *IDF Diabetes Atlas, 3rd edn.*(2006) Brussels, Belgium. http://www.idf.org/sites/default/files/Diabetes%20Atlas%203rd%20edition.pdf
3. International Diabetes Federation. *IDF Diabetes Atlas, 4th edn.*(2009) Brussels, Belgium. http://www.idf.org/sites/default/files/The_Global_Burden.pdf

Prevalence of overweight and obesity in people with T2DM



Overweight refers to BMI 25–29.9 kg/m^2; obese refers to BMI ≥30 kg/m^2

1. Health and Social Care Information Centre (2014) *National Diabetes Audit 2012–2013. Report 1: Care Processes and Treatment Targets.* Available at: http://bit.ly/ZuxniQ (accessed 02.10.2014)
2. Scottish Diabetes Survey Monitoring Group (2012) *Scottish Diabetes Survey 2012.* Available at: http://bit.ly/1gdzGGV (accessed 12.03.2014)

Almost two thirds of adults and one third of children have a weight problem

- **67.1% of men and 57.2% of women** are overweight or obese[1]
  - 1 in 4 adults were obese in 2013 (26.0% men and 23.8% women)

- Children in 2013-14
  - 22.5% of Reception children were either overweight or obese[2]
  - 33.5% of Year 6 children were either overweight or obese[2]
  - 9.5% of Reception children and 19.1% of Year 6 children were classed as obese, showing a doubling between the two age groups[2]

- **Foresight report (Oct07):**
  - estimates on current trends **>50%** of the UK will be obese by **2050**
  - Currently 2/3 adults and 1/3 children overweight or obese
  - Without action 9/10 adults and 2/3 children overweight or obese by 2050

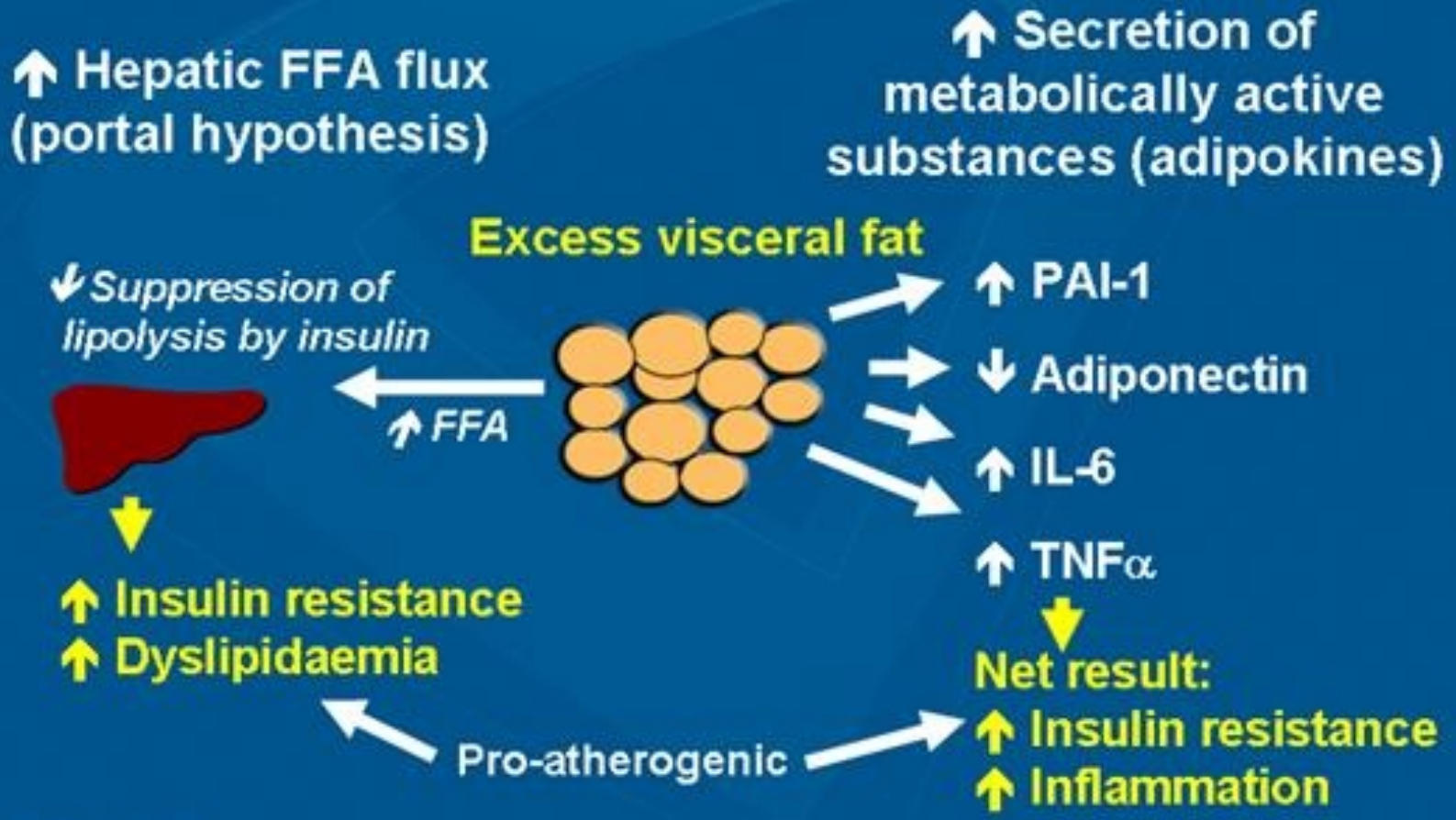
By 2050 total direct and indirect costs of obesity may increase to **£49.9bn**

1. Health and Social Care Information Centre (2013) *Health Survey for England - 2015*
2. Health and Social Care Information Centre (2013) *National Child Measurement Programme - England, 2013-14 school year*.
3. Foresight Report: Reducing Obesity: Future Choices (2007) Government office for science and Department of Health

Obesity is everywhere!

- and it leads to diabetes

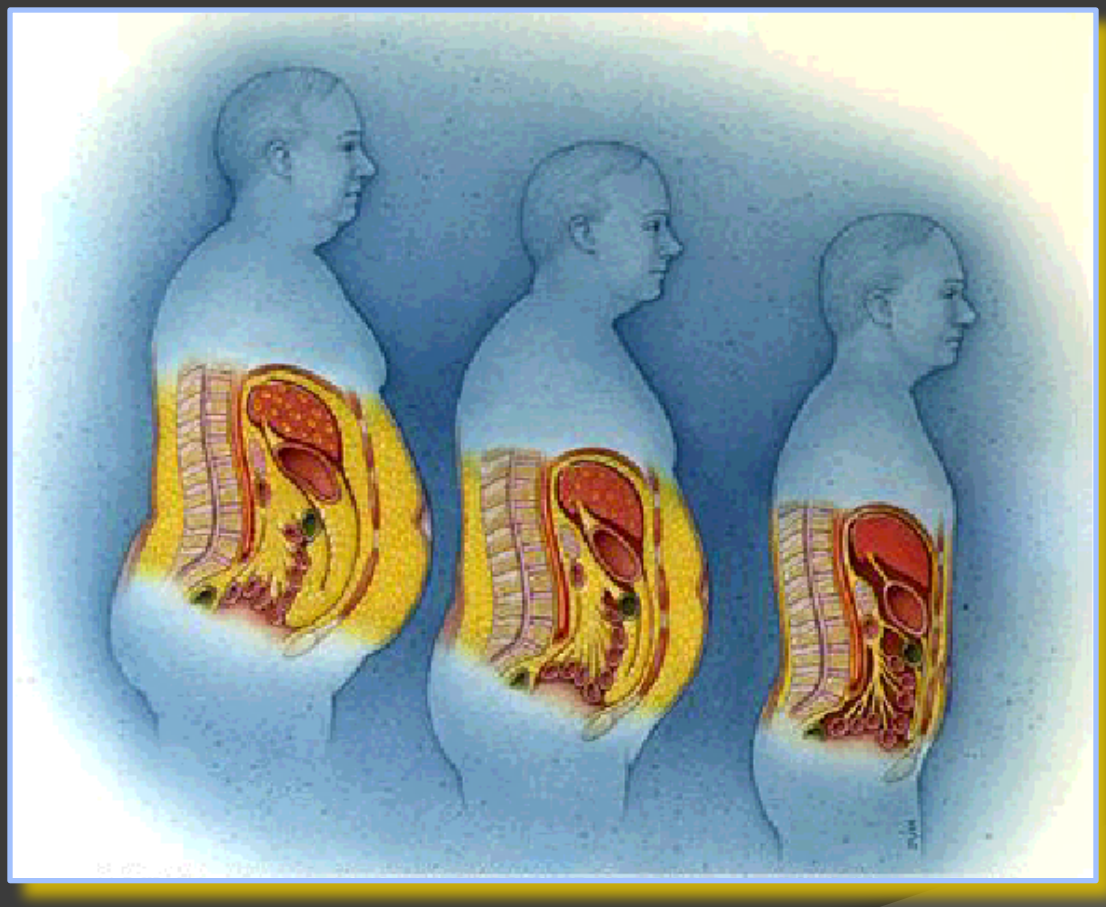
Excess visceral fat promotes insulin resistance and increased CV risk



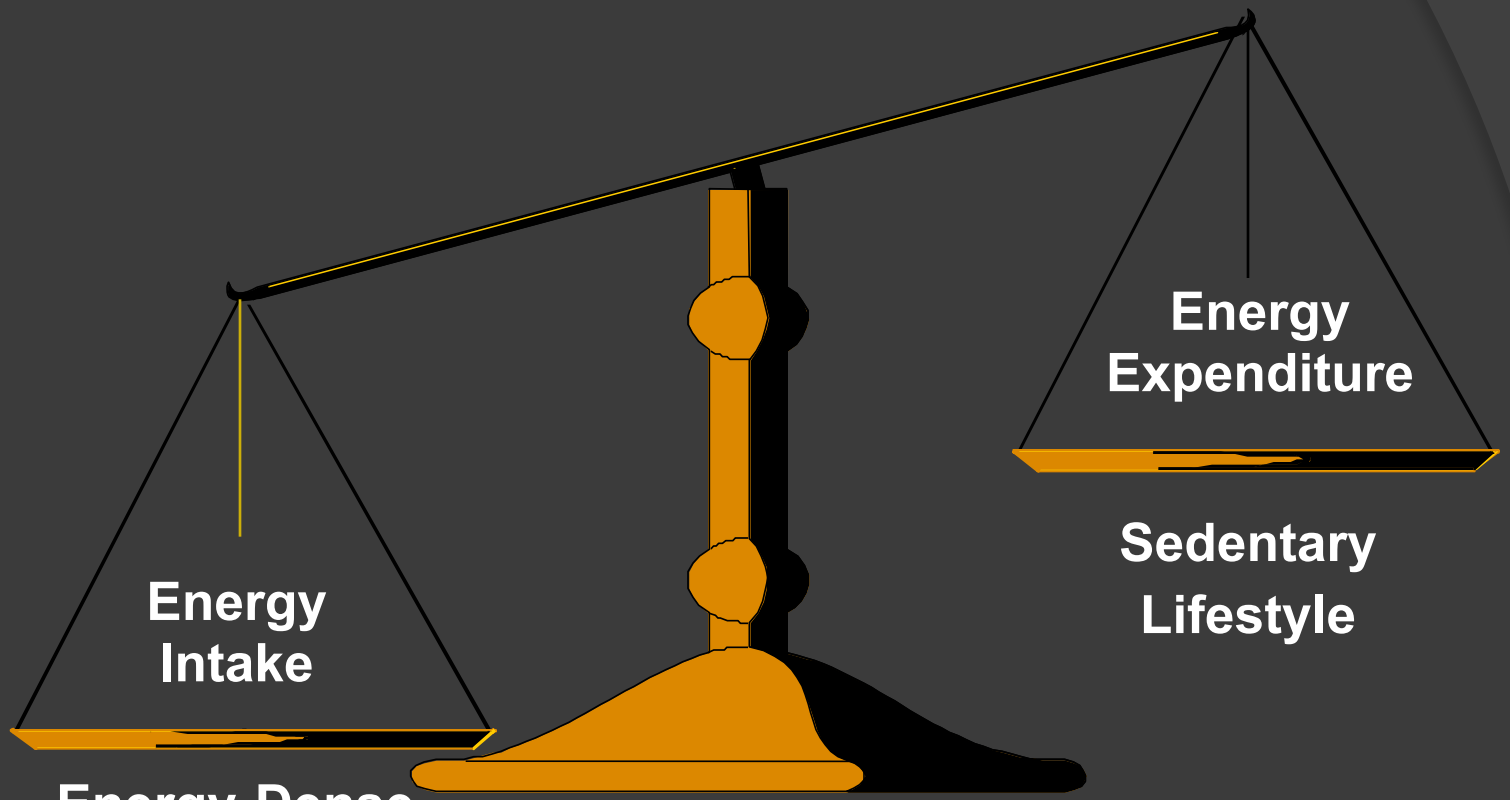
FFA = free fatty acids

1. Heilbronn L, *et al. Int J Obes Relat Metab Disord.* 2004;28 Suppl. 4:S12–21
2. Coppack S W. *Proc Nutr Soc.* 2001;60:349–56
3. Skurk T, *et al. Int J Obes Relat Metab Disord.* 2004;28:1357–64

Visceral Fat



Etiology of Obesity



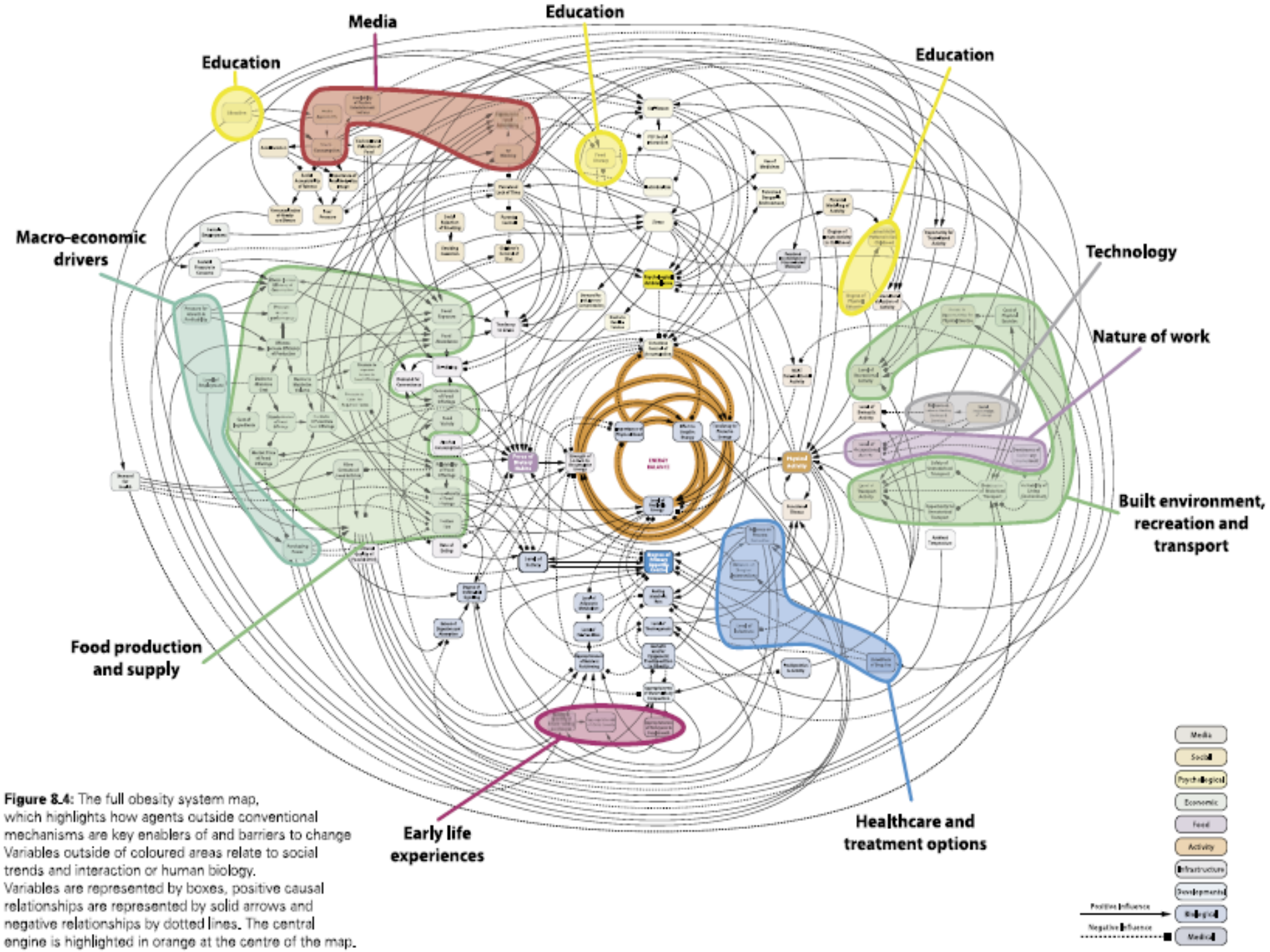


Figure 8.4: The full obesity system map, which highlights how agents outside conventional mechanisms are key enablers of and barriers to change Variables outside of coloured areas relate to social trends and interaction or human biology. Variables are represented by boxes, positive causal relationships are represented by solid arrows and negative relationships by dotted lines. The central engine is highlighted in orange at the centre of the map.

How can we solve a problem like obesity?

1) Tackle all 100+ causes

Nanny state or “nudge”
Increase physical activity
Decrease food consumption
Food tax/subsidy
Etc
Where is the evidence that we can “prevent” obesity?

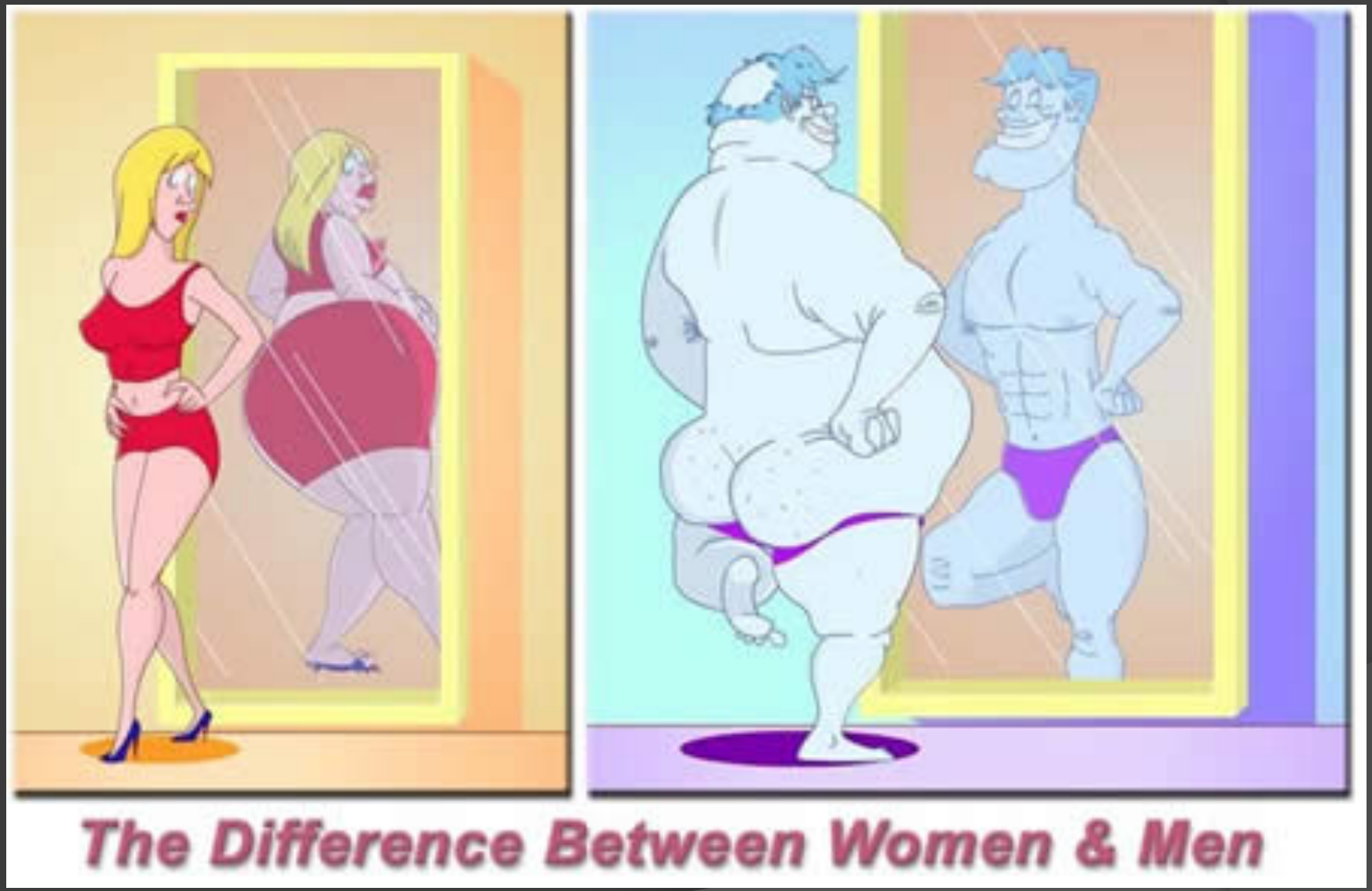
2) Treat the overweight/obese

“Treating” the overweight “prevents” more obesity etc
NICE Recommends (for adults):

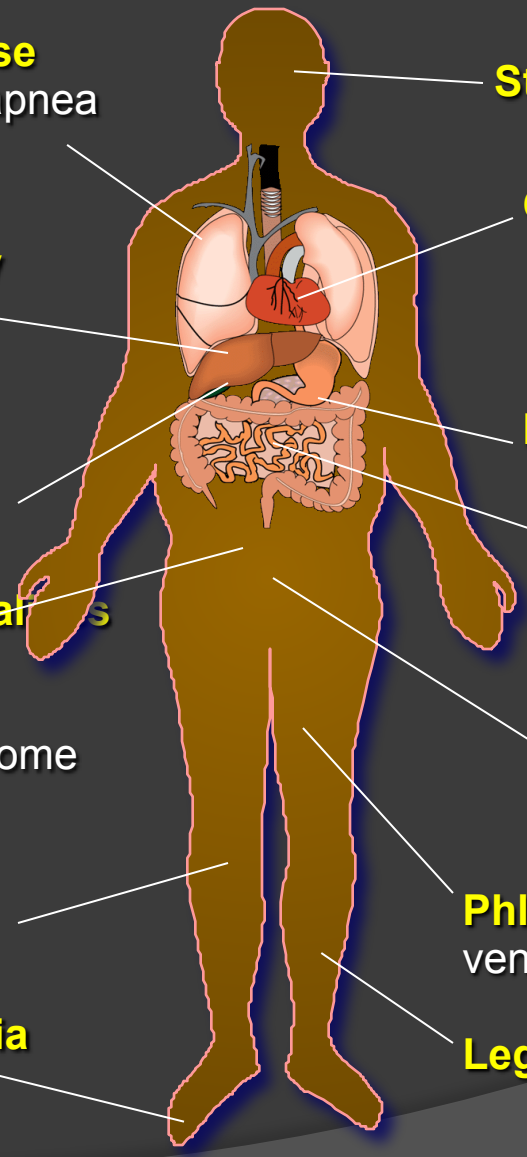
- Diet
- Exercise
- Behavioural therapy
- Drug treatment
- Surgery (if BMI >40, or >35 with co-morbidities)

NICE Clinical Guideline 43; Treating people who are overweight or obese. Dec 1996

Does the patient think they have a weight problem?



Diseases related to obesity (*)



Pulmonary disease
obstructive sleep apnea
Asthma/COPD

Nonalcoholic fatty liver disease
steatohepatitis
cirrhosis

Gall bladder disease

Gynaecologic abnormalities
abnormal menses
infertility
polycystic ovarian syndrome

Osteoarthritis

Hyperuricaemia and Gout

Stroke

Coronary heart disease
Dyslipidemia
Hypertension

Diabetes

Cancer
breast, uterus, cervix
colon, esophagus, pancreas
kidney, prostate

Stress incontinence

Phlebitis
venous stasis

Leg ulcers
pressure sores

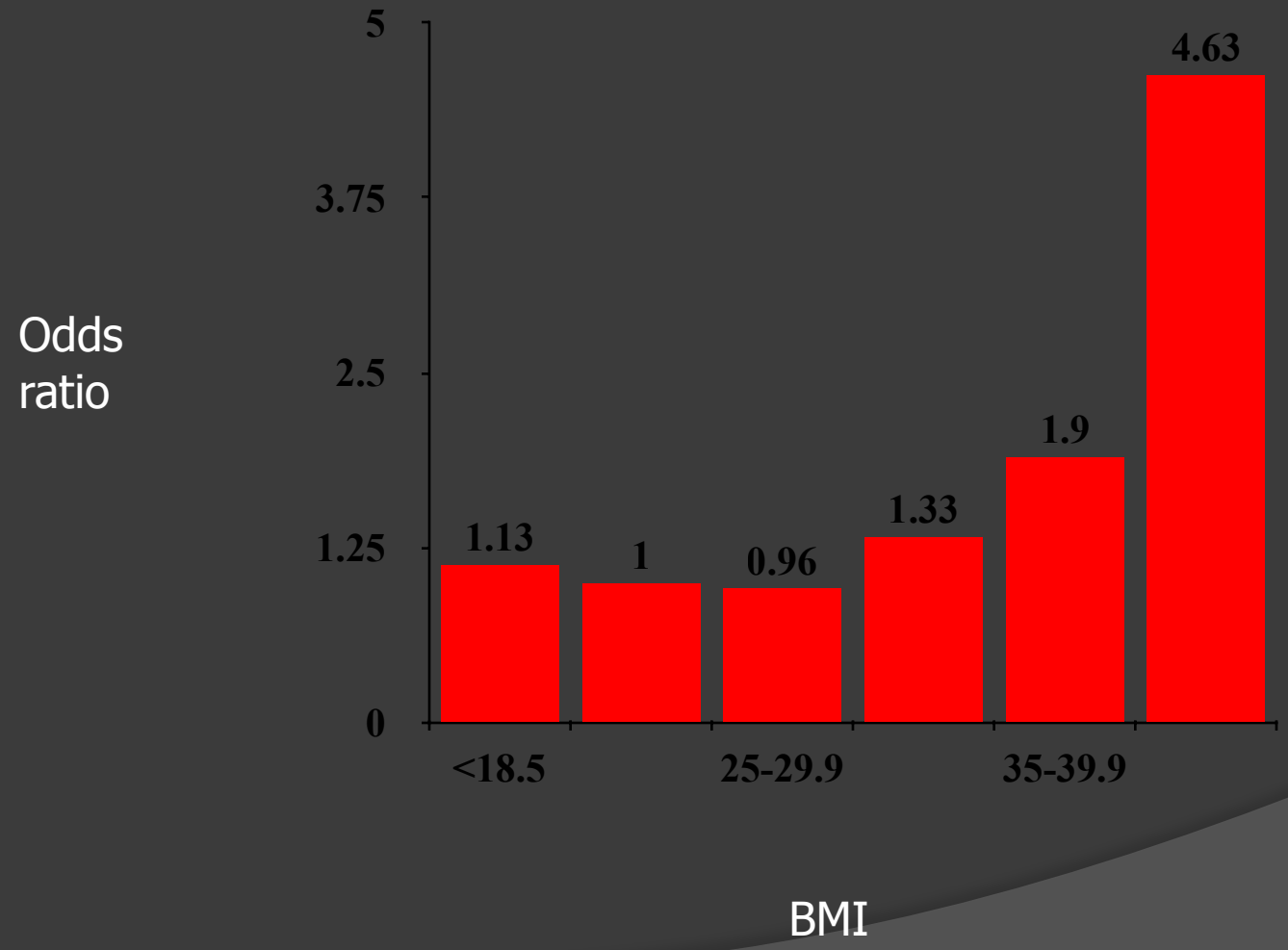
* Speakers own opinion

Relative risk of health problems associated with obesity

Disease	Women	Men
T2D	12.7	5.2
Hypertension	4.2	2.6
Myocardial infarction	3.2	1.5
Colon cancer	2.7	3.0
Angina	1.8	1.8
Gall bladder disease	1.8	1.8
Ovarian Cancer	1.7	-
Osteoarthritis	1.4	1.9
Stroke	1.3	1.3

National Audit Office Report. Tackling Obesity in England. London, 2001.

Risk of Major Depression with Extreme Obesity



Onyike, et al. Amer J Epidemiology 2003;158:1139-1147.

Weight Loss Reduces Mortality

Mortality	◉ **> 20-25% fall in mortality** ◉ **> 30-40% fall in diabetes-related deaths** ◉ **> 40-50% fall in obesity-related cancer deaths**
Blood pressure	◉ **Fall of approximately 10 mmHg SBP and DBP**
Diabetes	◉ **Fall of 50% in fasting glucose**
Lipids	◉ **Fall of 10% in total cholesterol** ◉ **Fall of 15% in LDL-C** ◉ **Fall of 30% in triglycerides** ◉ **Rise of 8% in HDL-C**

Weight loss of 10 kg produces a marked improvement in mortality

Betteridge DJ and Morrell JM *Clinicians' Guide to Lipids and Coronary Heart Disease* Second edition Arnold, London 2003 p173 (based on Jung R. Obesity as a disease. Br Med Bull 1997; 53 (2): 307-321

So, what works?

NICE Recommends (for adults):

- Diet
- Exercise
- Behavioural therapy
- Drug treatment
- Surgery (if BMI >40, or >35 with co-morbidities)

NICE Clinical Guideline 43; Treating people who are overweight or obese. Dec 1996

The eatwell plate

FOOD STANDARDS AGENCY
food.gov.uk

Use the eatwell plate to help you get the balance right. It shows how much of what you eat should come from each food group.

Which is healthiest?

- Big Mac

- Subway Melt

- Tesco BLT

Which has the highest :

- Calories?
- Fat?
- Salt?

*Big Mac vs Subway Melt vs packaged sandwich**

	Big Mac	Subway Melt (6”)	Tesco BLT Packaged sandwich
Calories (kcal)	495	351	520
Protein (g)	29	27	25.4
Carbohydrate (g)	41	40	46.4
Of which sugars (g)	9	3.2	8.3
Fat (g)	24	11.1	25.8
Of which saturates (g)	9	5.2	7.1
Fibre (g)	5.0	4.0	5.5
Salt (g)	2.0	4.3	3.1

*Reference to manufacturer’s own data (*McDonalds*, *Subway*, *Tesco*)

Common mistakes

All sugars are the same (4kcal/g) i.e., sucrose = fructose etc

- Coco pop straws 34g/100g = 2 finger kitkat
- Fruit juice approx 9g/100mls

All fats (satd/polyunsatd/monounsatd) are the same (9kcal/g)

- Jordan's Country Crisp Cereal: 28.5g/100g = McDonalds McBacon Roll
- Thick pork sausages: 20.3g/100g

Alcohol (think of each drink as a chocolate bar!)

High fat foods vs Low fat foods

Premium vs Economy ranges vs Home cooked food:

Premium	- likely to have high fat and high sugar (high calories)
Economy	- likely to have high salt
Home cooked	- likely to have high fat (depends on how it is cooked) ?better

The role for Meal Replacement

Meal Replacement Systems:

Eg, SlimFast, Celebrity Slim, The Biggest Loser, many "own brands"

- Most MRs aim for 1200-1400
- Replace 2 meals (breakfast/lunch) + nutritional meal in evening
- European Directive givens nutritional composition (NOT complete)

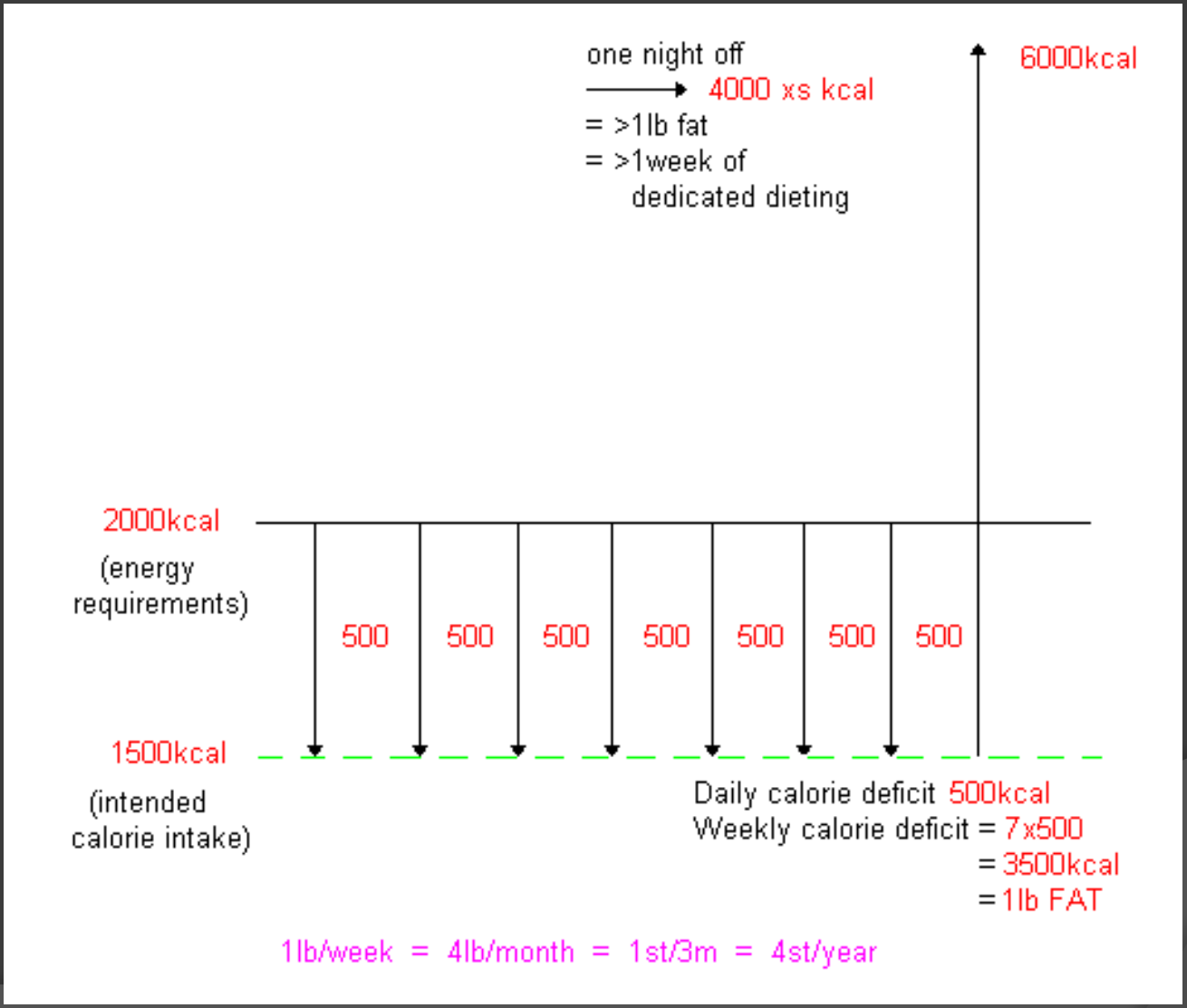
  products must contain 200-400kcal, >25% protein, 23 vitamins and minerals, 5-6g fibre

VLCDs (VLEDs):

Eg, Lighter Life, Cambridge Weight Plan, Lipotrim

- Defined as < 800 kcal (3,300 kJ) per day or less
- Nutritionally complete (normally liquid) meals
- Carbohydrate may be entirely absent (although mostly > 50g)

Explaining calories



The role of Exercise

- Isolated exercise is an inefficient way of burning calories and losing weight
- 1 mile (15 mins) burns up 100kcals
- Regular exercise has a huge effect on burning calories and losing weight

- Energy expenditure = BMR x PAL **(modified Harris Benedict equation)**

- BMR (kcal/day):

Age (yrs)	Men	Women
10-18	17.5 x Kg + 651	12.2 x Kg + 746
18-30	15.3 x Kg + 679	14.7 x Kg + 496
31-60	11.6 x Kg + 879	8.7 x Kg + 829
>60	13.5 x Kg + 487	10.5 x Kg + 696

- PAL (Patient Activity Level)

Activity level	Men	Women
Inactive	1.3	1.3
Light	1.55	1.56
Moderate	1.78	1.64
Heavy	2.1	1.82

eg,
24yr old man 80kg
BMR = 1903
PAL = 1.3
energy = 2474

PAL = 1.55
energy = 2950

Rotherham Institute for Obesity protocol for calorie estimation 2015

Relationship between Physical Activity & Health

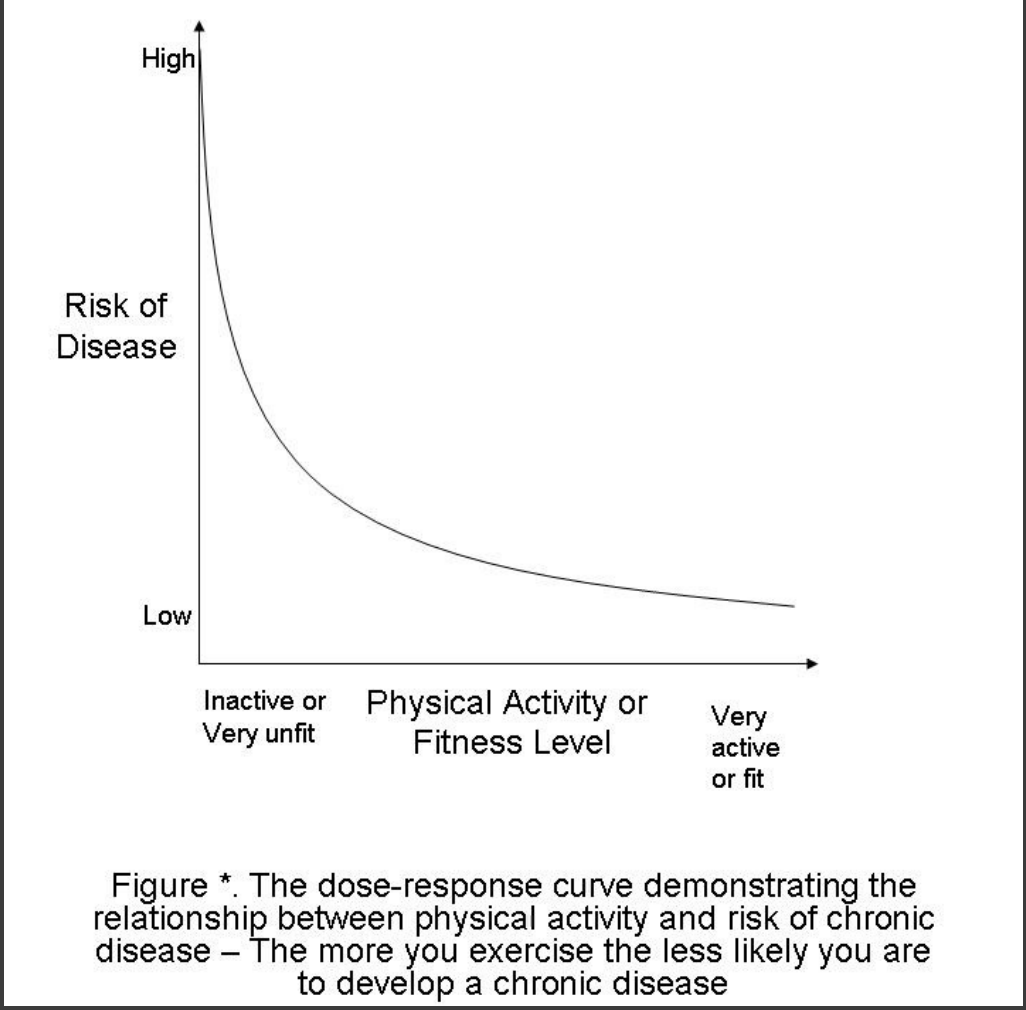
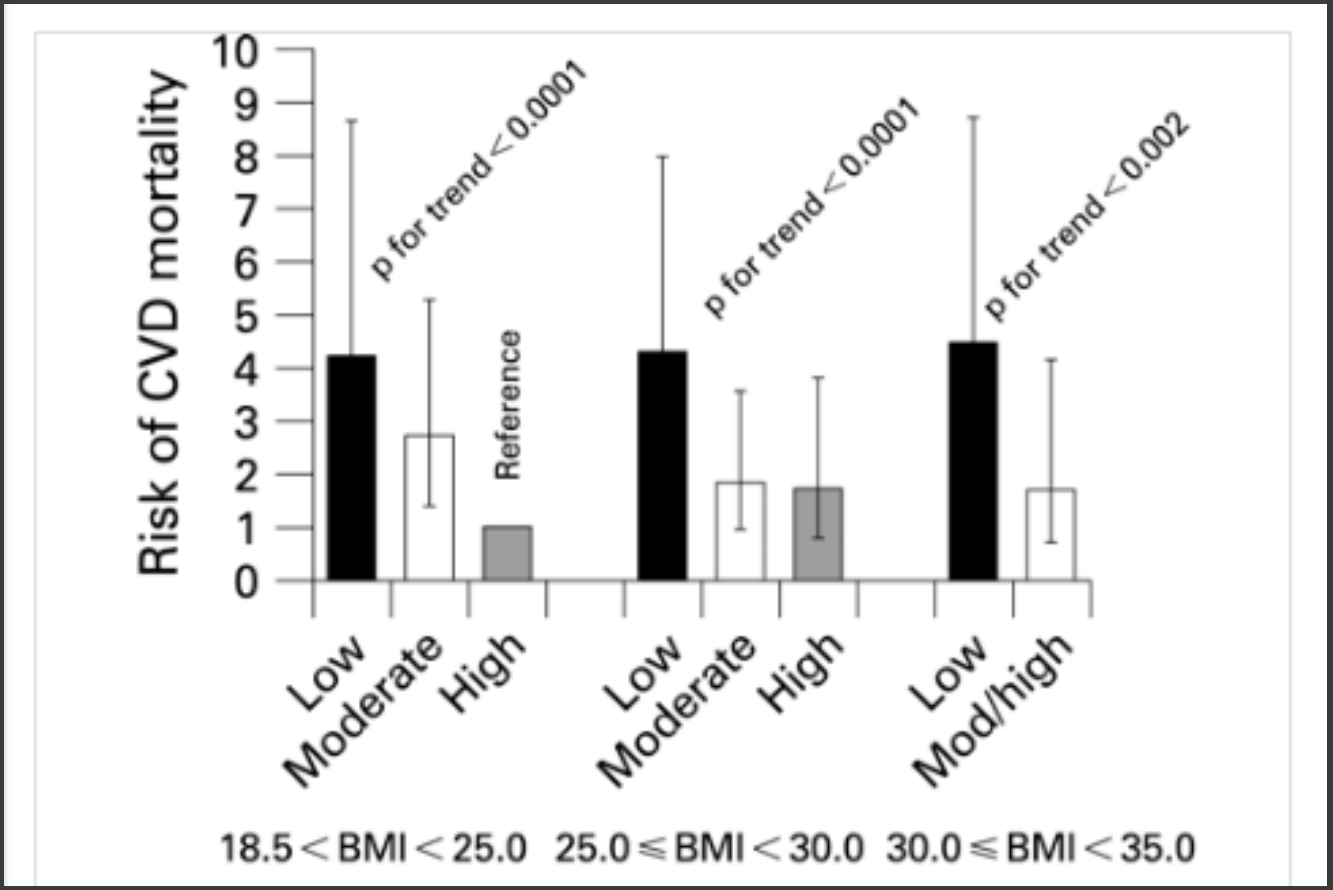


Figure *. The dose-response curve demonstrating the relationship between physical activity and risk of chronic disease – The more you exercise the less likely you are to develop a chronic disease

<u>Physical</u>
Metabolic Syndrome
- Insulin resistance
-Type II Diabetes
CVD
Stroke
Cancer
Asthma (pulmonary disease)
Hypertension
Hyperlipidemia
Orthopaedic incl.
- abnormal bone growth,
- degenerative disease,
- pain

<u>Psychological</u>
Low Self-Esteem
Depression
Substance abuse

Physical Inactivity



Risk of CVD mortality by CV fitness and BMI, 2,316 men with Type 2 diabetes

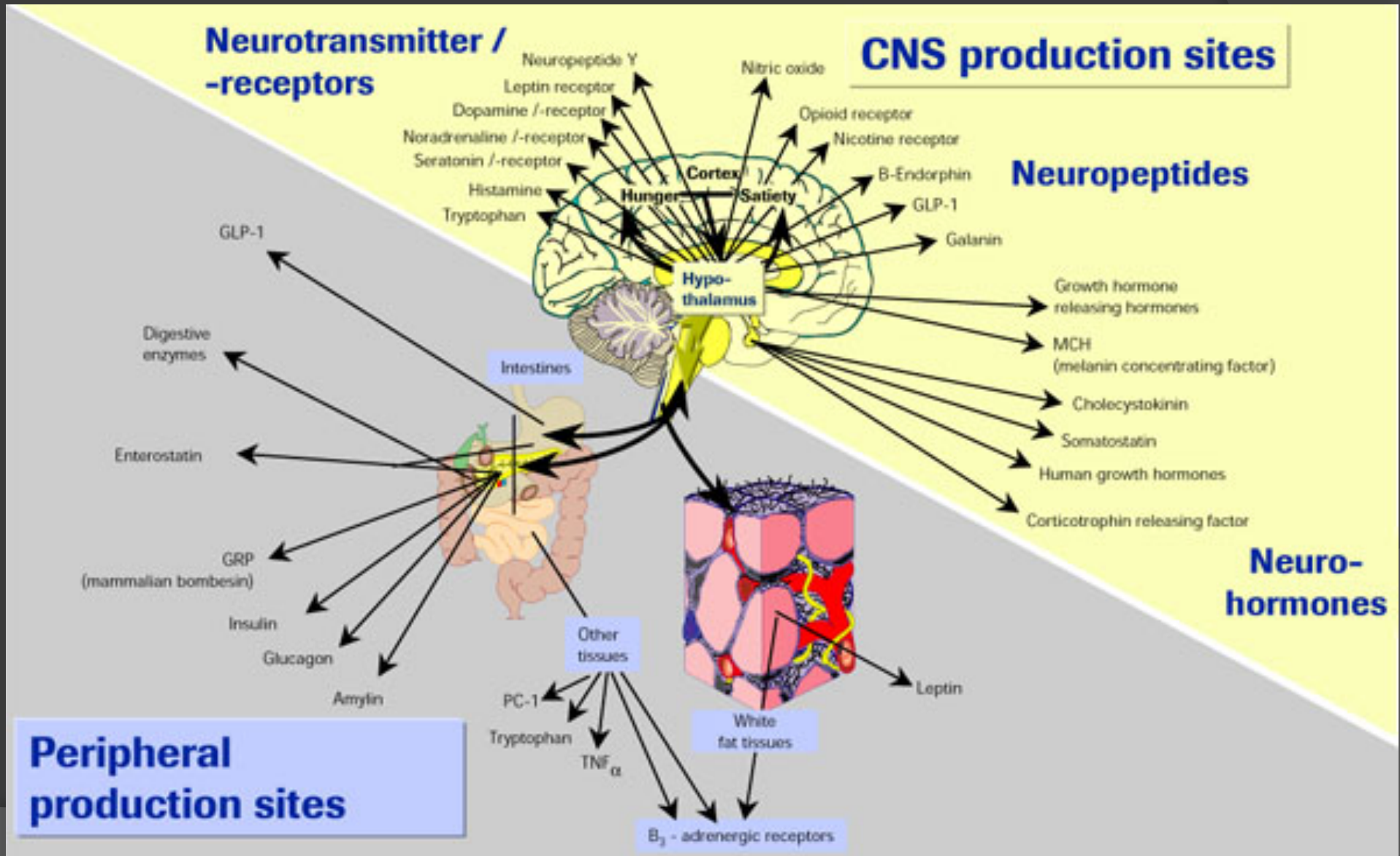
Church et al. Arch Int Med 2005;165:2114-20

COMFORT EATING AND BINGE EATING

Behaviour change:

- Talking Therapies:
  - Life coaching
  - Cognitive Behavioural Therapy (CBT)
  - Neurolinguistic Programming (NLP)
  - Emotional Freedom Techniques (EFT)
  - Hypotherapy
  - Hypnobanding
  - etc

Can we ever control appetite?



Pharmaceutical Strategies

Old Medications:

Am-Bar (amphetamine + barbiturate)
Phentermine,
Rimonabant,
Sibutramine

Current licensed medications:

Pancreatic lipase inhibitors – Orlistat (Xenical/Alli)

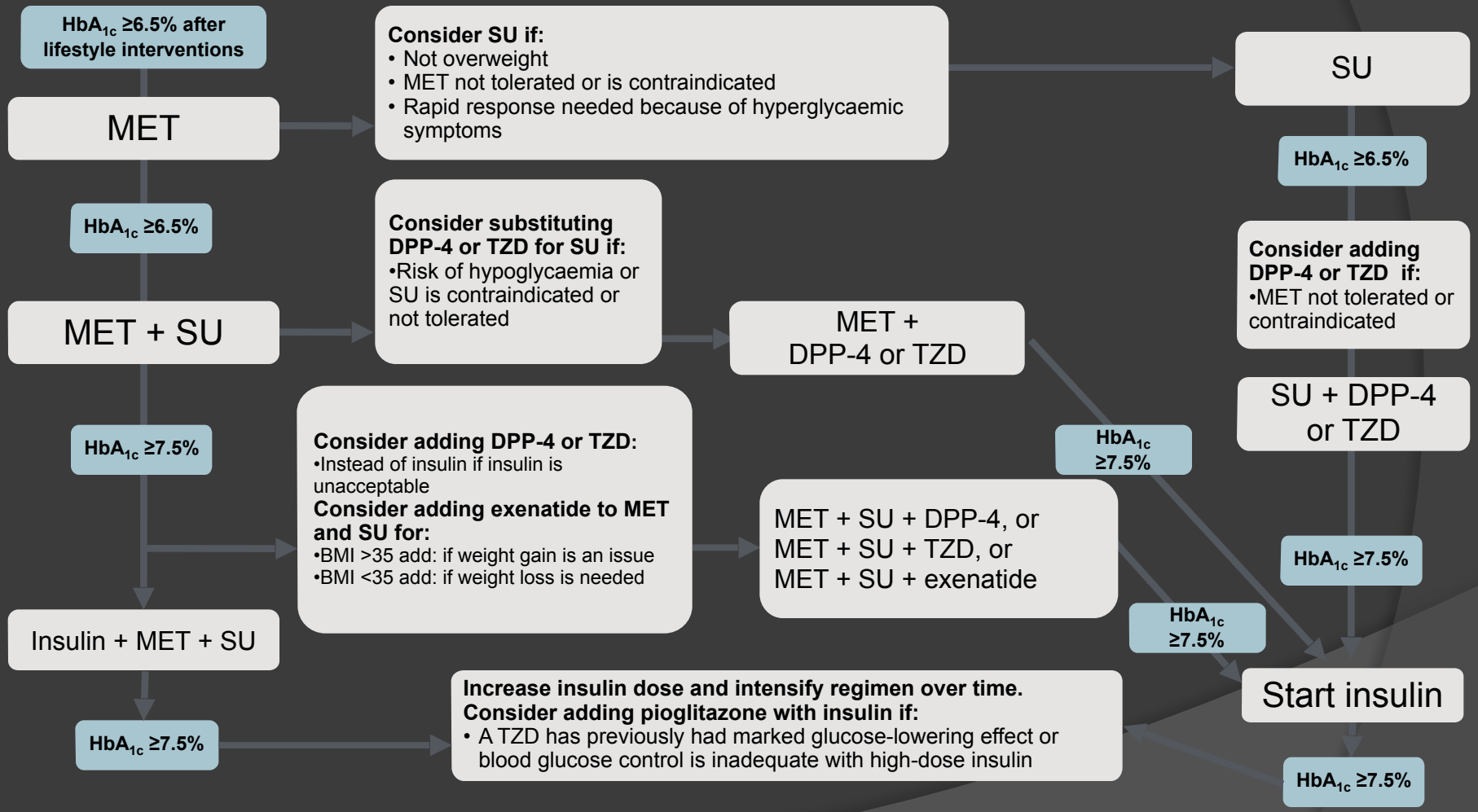
Weight friendly diabetic medications:

Metformin
DPP4 inhibitors ("gliptins")
SGLT2 inhibitors ("flozins") eg Canagliflozin
GLP1 analogues

Coming soon? (all available in the US)

Liraglutide 3.0mg
Lorcaserin
Qnexa/Qsymia (Phentermine + Topiramate)
Contrave (Naltrexone SR + Bupropion SR)

National Institute for Health and Clinical Excellence (NICE): T2D treatment algorithm



MET = metformin, SU = sulphonylureas, TZD = thiazolidinedione, DPP-4= dipeptidyl peptidase-4 inhibitor

Adapted from: National Institute for Health and Clinical Excellence. Clinical Guideline 87. Type 2 diabetes - newer agents (a partial update of CG66): quick reference guide. Available at: http://www.nice.org.uk/nicemedia/pdf/CG87ShortGuideline.pdf Accessed July 2013.

*Treatment options in T2D**

Drug/Class	Effect on			Adverse effects[4*]
	Weight[1,2,5]	Lipids[1,2]	BP[1–3,5]	
Metformin	↔/↓	✓	↔	Anorexia, nausea, vomiting, diarrhoea (usually transient), abdominal pain, taste disturbance
Acarbose	↓?	?	?	Flatulence, soft stools, diarrhoea (may need to reduce dose or withdraw), abdominal distention and pain
Meglitinides	↔?	?	?	Hypoglycaemia, hypersensitivity reactions (pruritus, rashes and urticaria), abdominal pain, diarrhoea, constipation, nausea, vomiting
Sulphonylureas	↑	✓ **mainly in TG**	?	Increased hypoglycaemia risk; gastrointestinal disturbances (nausea, vomiting, diarrhoea, and constipation); hyponatraemia
Pioglitazone	↑	✓ **HDL and TG**	✓ **(small improvement)**	Gastrointestinal disturbances, oedema, anaemia, headache, visual disturbances, dizziness, arthralgia, hypoaesthesia, haematuria, impotence, epidemiological data suggests a small increase in risk of bladder cancer
DPP-4 inhibitors	↔	?	✓ **(non-diabetics)**	Vomiting, dyspepsia, gastritis; peripheral oedema; headache, tremor, asthenia, dizziness, fatigue; upper respiratory tract infection, urinary tract infection, gastroenteritis, sinusitis, nasopharyngitis; pain; hypoglycaemia, myalgia, pancreatitis
GLP-1 receptor agonists	↓	✓	✓ **(lowers systolic pressure)**	Gastrointestinal disturbances; gastro-oesophageal reflux disease, decreased appetite, weight loss, headache, dizziness, agitation, asthenia, hypoglycaemia, increased sweating, injection-site reactions, antibody formation
SGLT2 inhibitors	↓	?	✓	Hypoglycaemia (in combination with other glucose lowering agents), constipation, dyslipidaemia, back pain, genital infection, urinary-tract infection, dysuria, polyuria, thirst, sweating
Insulin	↑	✓	↔	Transient oedema; local reactions and fat hypertrophy at injection site

***These are most common AEs as depicted by the BNF. Please consult individual product SPCs for a comprehensive list of AEs.** HDL, high-density lipoprotein; TG, triglycerides; BP: blood pressure. Table adapted from 1. Kurukulasuriya LR, Sowers JR. Cardiovasc Diabetol. 2010; 9:45; 2. Inzucchi SE, McGuire DK. Circulation. 2008; 117(4):574–84; 3. Unger JR, Parkin CG. Diabetes Ther. 2011; 2(1):29–39. 4. British National Formulary. Available at www.bnf.org (last accessed July 2013). 5. Valentine V. Clinical Diabetes. 2012; 30(4):151–155.

Case Study:

49 year old woman, who has 3 children and works as a teacher.

Diagnosed as having T2DM 6 years ago.

She has attended DESMOND but her control is worsening.

Rarely has time to monitor her blood sugars.

- BMI 36kg/m2 (increasing over time)
- HbA1c 65mmol/mol (8.1%) when last checked
- BP 130/85, Egfr 48ml/min/1.73m2 (stable)

Current medication:

- Ramipril 10mg od
- Metformin 1g bd
- Gliclazide 160 mg bd
- Linagliptin 5mg od

What would you consider next?

Things to consider:

- Is she a driver?
- She doesn't test BM's often
- Is she getting hypos?
- Her weight is going up – why?
- Renal function stable but needs monitoring

- Could consider reducing/stopping gliclazide (but HbA1c may go up)
- Could consider SGLT2i eg Canagliflozin (but egfr < 60)
- Could consider replacing linagliptin with GLP1 analogue

- **Should** consider referral to weight management clinic
  - Talking Therapy
  - Orlistat
  - VLCD
  - Bariatric Surgery??

The next surgical frontier

Who Would Have Thought It?

An Operation Proves to Be the Most Effective Therapy for Adult-Onset Diabetes Mellitus

1995

Walter J. Pories, M.D., Melvin S. Swanson, Ph.D., Kenneth G. MacDonald, M.D., Stuart B. Long, B.S., Patricia G. Morris, B.S.N., Brenda M. Brown, M.R.A., Hisham A. Barakat, Ph.D., Richard A. deRamon, M.D., Gay Israel, Ed.D., Jeanette M. Dolezal, Ph.D., and Lynis Dohm, Ph.D.

From the Departments of Surgery and Biochemistry o Performance Laboratory of East Carolina University, G

Objective

This report documents that the gastric bypass operatic and diabetes.

Summary Background Data

Obesity and diabetes, both notoriously resistant to me most common and serious diseases.

Methods

Over the last 14 years, 608 morbidly obese patients un

Surgery as an Effective Early Intervention for Diabesity

2006

Why the reluctance?

John B. Dixon, MBBS, PhD[1]
Walter J. Pories, MD[2]
Paul E. O'Brien, MD[1]
Phillip R. Schauer, MD[3]
Paul Zimmet, MD, PhD[4]

should be of highest priority ose already suffering from di- fective treatment is important. that provides remission of both ad obesity should attract enor- rest and activity. tically, weight loss is such a 1,12). However, although in- eight loss through diet and ex- associated with better control, plications, and reduced mortal- 4), achieving and sustaining s in those with type 2 diabetes n elusive goal (15). Poor weight mes for those with type 2 dia- e been consistently demon- h the standard range of weight

significant weight loss. Recent publications have confirmed earlier research that substantial and durable weight loss is achieved by current bariatric surgical procedures and that all these procedures provide a strongly beneficial effect in subjects with type 2 diabetes.

An early study to show this clinical improvement consisted of 608 patients followed for up to 14 years after a Greenville-type open gastric bypass (19). Weight loss was 35% of excess weight at 10 years and 40% at 14 years. There were 146 type 2 diabetic patients, and 121 (83%) achieved and maintained a nondiabetic clinical state with normal fasting plasma glucose, GHb, and serum insulin levels. Additionally, 150 of 152 patients with impaired glucose tolerance became normoglycemic. The weight loss was accompanied by major improvements or resolution of other obesity-related comorbidities, including hypertension, sleep

The Early Effect of the Roux-en-Y Gastric Bypass on Hormones Involved in Body Weight Regulation and Glucose Metabolism

2004

Francesco Rubino, MD, Michel Gagner, MD, FACS,‡ Paolo Gentile[illegible] MD,§ Subhash Kini, MD,§ Shoji Fukuyama, MD,§ John Feng, MD,§ and Ed L[illegible]*

Objective: To evaluate the early effect of Roux-en-Y (RYGB) gastric bypass on hormones involved in body weight regulation and glucose metabolism.

Significant Background Data: The RYGB is an effective bariatric procedure for which the mechanism of action has not been elucidated yet. Reports of hormonal changes after RYGB suggest a possible endocrine effect of the operation; however, it is unknown whether these changes are the cause or rather the effect of surgically induced weight loss. We speculated that if the mechanism of action of the RYGB involves an endocrine effect, then hormonal changes should occur early after surgery, prior to substantial body weight changes.

Methods: Ten patients with a mean preoperative body mass index (BMI) of 46.2 kg/m² (40–53 kg/m²) underwent laparoscopic RYGB. Six patients had type 2 diabetes treated by oral hypoglycemic agents. Preoperatively and 3 weeks following surgery, all patients were tested for fasting glucose, insulin, glucagon, insulin-like growth factor 1 (IGF-1), leptin, gastric inhibitory polypeptide (GIP), glucagon-like peptide-1 (GLP-1), cholecystokinin (CCK), adrenocorticotropic hormone (ACTH), corticosterone, and pancreatic polypeptide Y (PPY).

diabetic patients ($P < 0.01$), whereas no changes in GIP levels were found in nondiabetics.

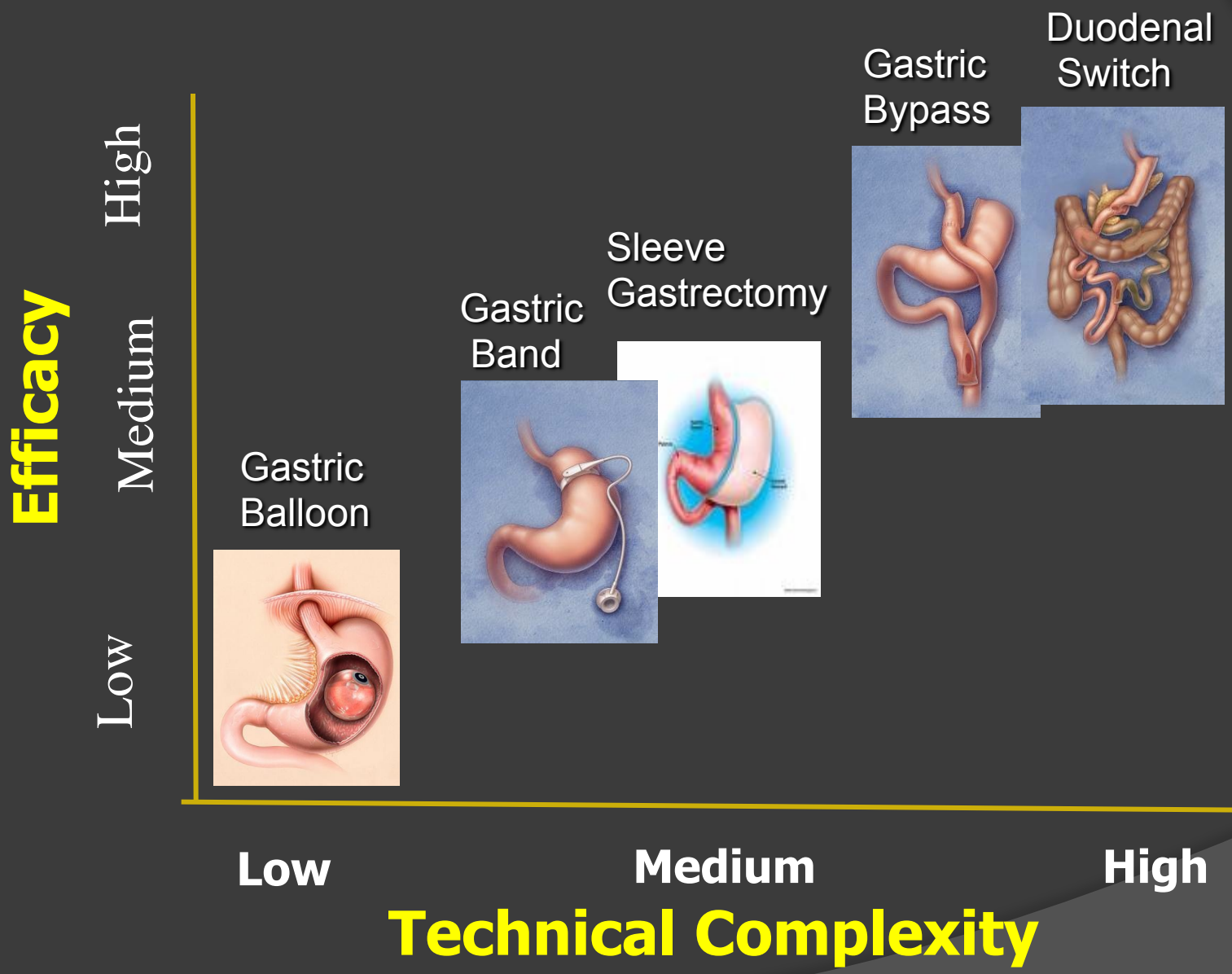
Conclusions: Roux-en-Y gastric bypass determines considerable hormonal changes before significant BMI changes take place. These results support the hypothesis of an endocrine effect as the possible mechanism of action of RYGB.

(*Ann Surg* 2004;240: 236–242)

Surgery represents the most effective therapeutic modality for morbid obesity.[1,2] Interestingly, the Roux-en-Y gastric bypass (RYGB), a procedure that includes the creation of a small proximal gastric pouch and the bypass of the duodenum and proximal jejunum from the transit of food, not only determines permanent reduction of excess body weight, but also induces resolution of type 2 diabetes mellitus in more than 80% of morbidly obese patients.[3]

Body weight is the result of complex physiologic mechanisms that control food intake and energy expenditure. Regulation of body weight involves several systems such as

Obesity Surgical Interventions



Surgery – a cure for T2DM?

ECO 2009 Metanalysis Presentation:

- Laparoscopic Band Surgery 56.7%
- Roux-En-Y Gastric Bypass 80.3%
- Biliopancreatic Duodenal Switch 95.1%

Favretti et al. J Ob Surg. 2007 17: 168
Buchwald et al. Am J Med 2009 122: 248

NHS Commissioning Board (2013)
Clinical Commissioning Policy: Complex and Specialised Obesity Surgery

Intended to address the postcode lottery of availability for bariatric surgery

Address “perverse incentives” of gaining weight to meet NHS criteria for surgery

Address the findings of the NCEPOD Report findings (2012)

Key changes:

- Nationwide BMI criteria meeting NICE recommendations (BMI 40 or 35 with comorbidity)
- BMI > 50 still needing to meet other criteria
- 4 surgical procedures available on NHS (band, bypass, sleeve, switch)
- Revisional procedures only considered for clinical reasons due to complications
- Surgical team post-op care for 2 years and lifelong in tier 3
- 12-24m (*6m) in a tier 3 non-surgical MDT for intensive medical management

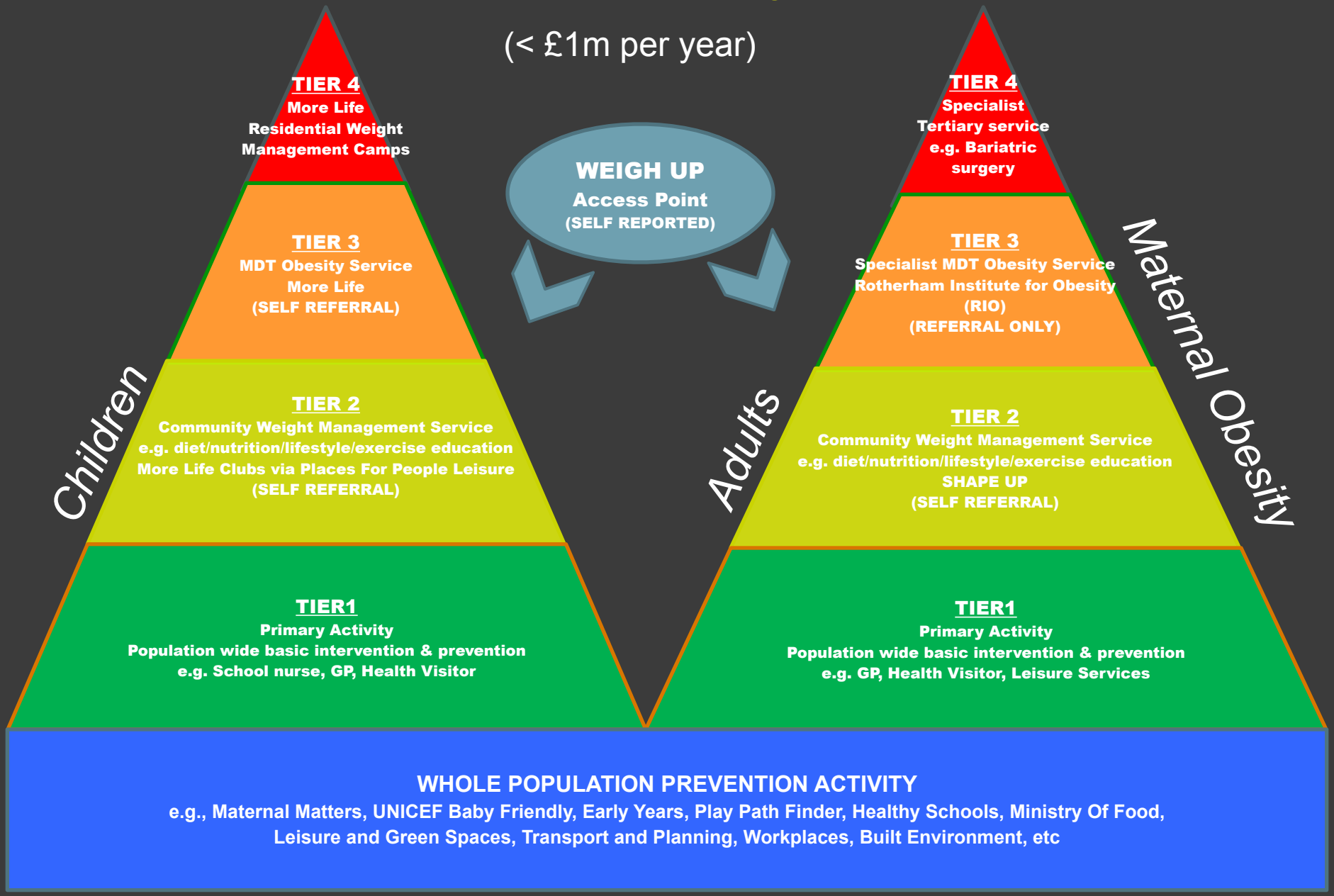
Problem:

- Highlighted the postcode lottery regarding the availability of tier 3 services

NHS Rotherham Healthy Weight Framework

(locally referred to as "Weigh Up")

(< £1m per year)



Dr Matthew S Capehorn

GPwSi Obesity
Clinical Director - NOF
Clinical Manager - RIO
mcapehorn@yahoo.co.uk
07786931007

The Health Village
Doncaster Gate Hospital
Doncaster Road
Rotherham
S65 1DA
0844 477 3622
www.RIONHS.co.uk

www.rotherhaminstituteforobesity.co.uk

www.rioweightmanagement.co.uk

www.nationalobesityforum.co.uk

Job number: PHGB/VOK/0415/0071 Date of preparation: April 2015