

OBESITY

**AMSANT CQI
21 JUNE 2022**

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Central Australian Aboriginal
Congress



IN THE INTERESTS OF TRANSPARENCY:

- 100% of my mother's family was diabetic from a relatively young age
- My mother died earlier this year at 91 after 50 yrs of diabetes, slim and very active; her brother, her paternal aunt and grandmother were all diabetic and lived into their 80s and 90s
- My grandfather was active, overweight and smoked cigarettes and died when he was 52 yrs old
- I have had pre-diabetes (fasting blood sugar 6.7 mmol/L)



DiRECT

Diabetes Remission Clinical Trial



- **DISCLOSURES:**

DIRECT IS FUNDED BY DIABETES UK, WITH SUPPORT IN KIND FROM COUNTERWEIGHT LTD. DEPARTMENTAL RESEARCH FUNDS, SUPPORT FOR CONFERENCE ATTENDANCE AND FEES FOR ADVISORY BOARDS AND LECTURING FROM NOVO NORDISK, LILLY, ROCHE AND SANOFI.

- DIRECT SLIDES ARE POSTED ON:
WWW.DIRECTCLINICALTRIAL.ORG.UK





WHAT I AM HOPING TO ACHIEVE:

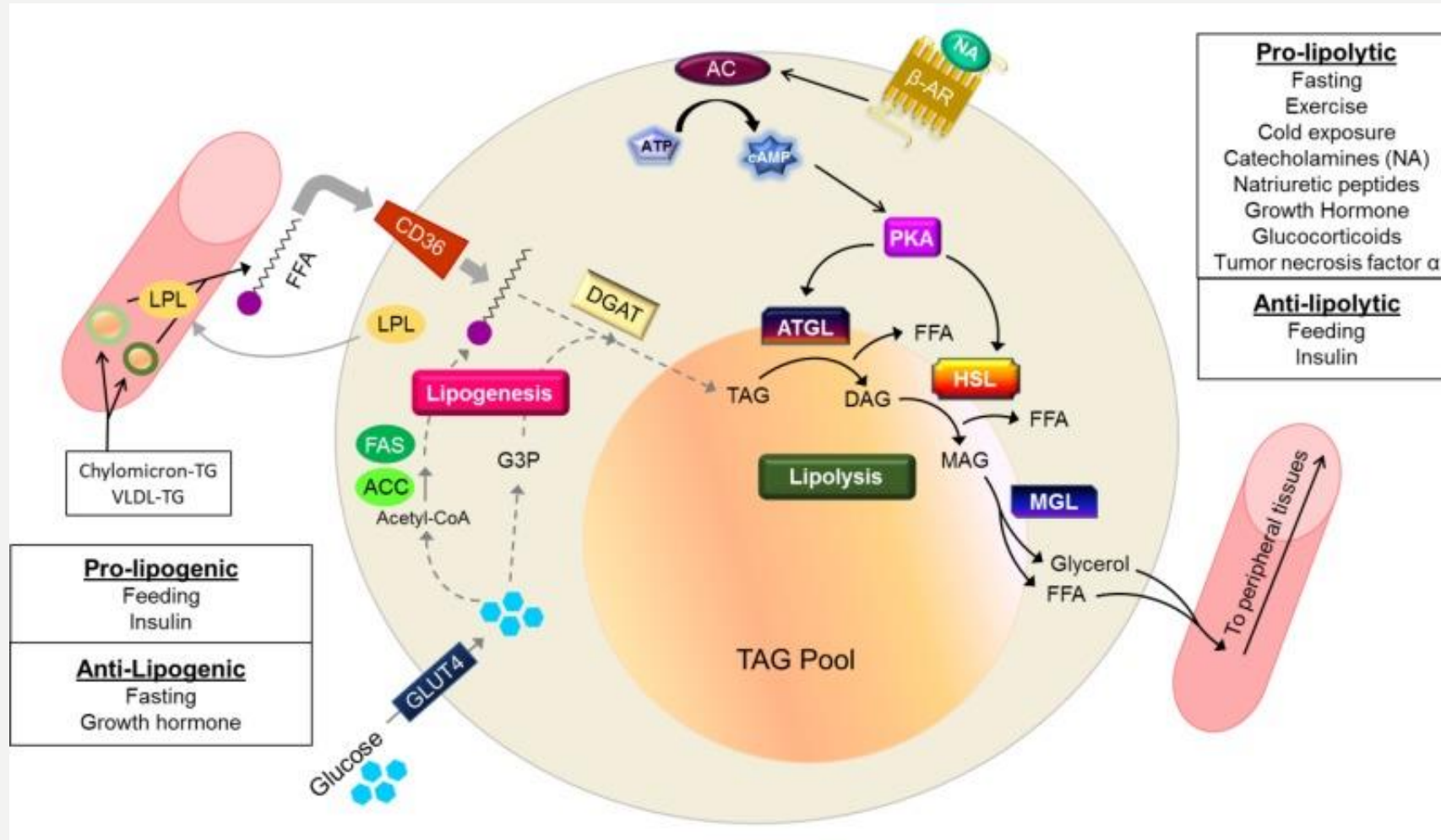
- When you meet a person who has one or more of:
 - High blood pressure
 - Fatty liver
 - Gout
 - Diabetes or (preferably) pre-diabetes
 - Early kidney disease
- You recognize that it is likely that the most important thing you can do to assist them in their health is to:
 - 1) Help that person understand the role of obesity in their condition, and
 - 2) Help that person lose weight

HISTORY

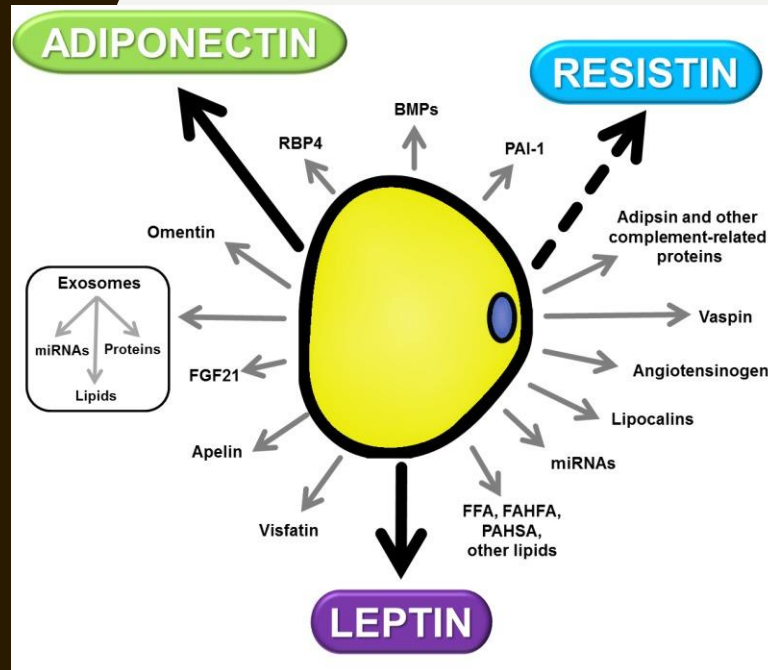
- 1837: Adipose cells first described (Fat cells)
 - Thought to be passive and inert energy storage (Tri-acyl-glycerols TAG)
- 1980s: Secretory function and specific fat cell hormones described
 - 1994 **Leptin** – signals fat mass to the brain, reduces appetite, impacts glucose metabolism, and immune system
 - Understood that fat cells are highly sensitive to insulin
 - taking up glucose, and
 - inhibiting the break down of TAG (triacylglycerols)



IN AND OUT OF THE FAT CELL

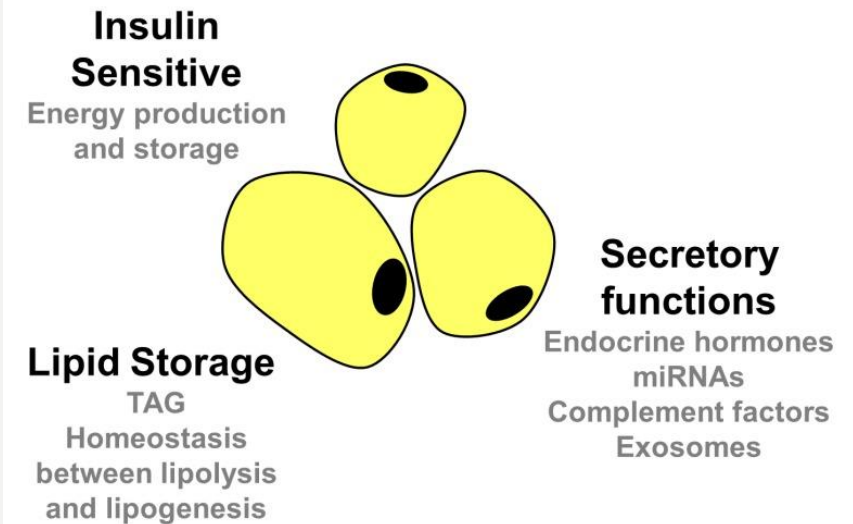
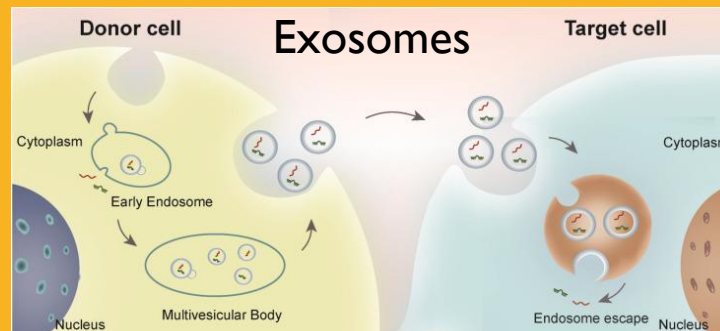
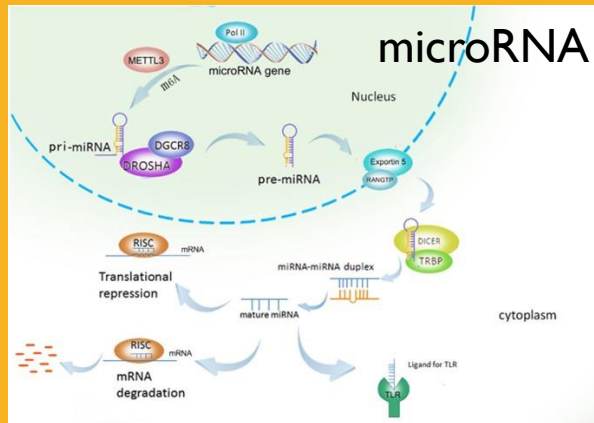


HORMONES AND FAT CELLS



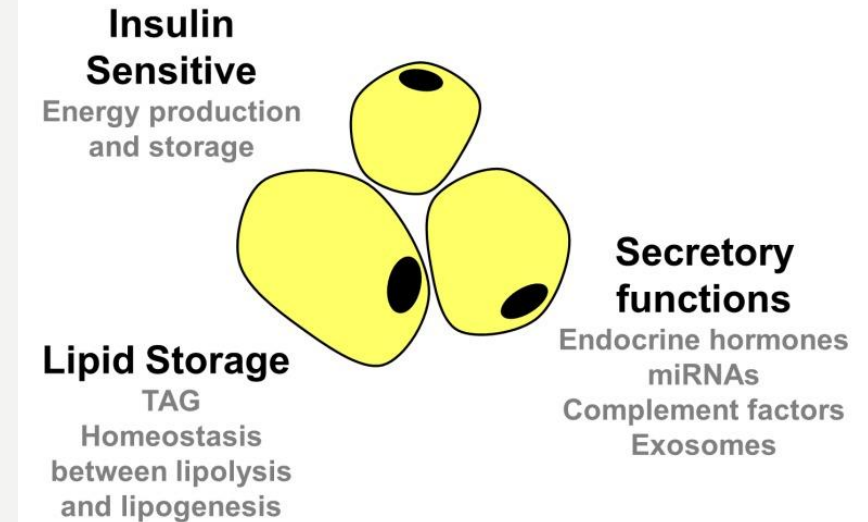
	LEPTIN		ADIPONECTIN	RESISTIN
Expression in Obesity	↑		↓	↑
Receptor(s)	Leptin Receptor (LR) (multiple isoforms)		T-cadherin, AdipoR1, & AdipoR2	TLR4 & CAP1
Target Tissues	Brain & CNS	Hepatocytes & β-cells	Liver, Skeletal Muscle, AT, Bone, Cartilage, Heart	AT, Liver, Endothelium, & Heart
Main Metabolic Actions	↓ Food Intake ↑ Energy Expenditure	Glucose & Lipid Metabolism	↓ Gluconeogenesis, glucose output, lipogenesis & TAG accumulation in liver ↑ Insulin Sensitivity, FAO, & EE in muscle	↑ Insulin Resistance ↓ Adipogenesis & ↑ Proinflammatory response in AT ↓ Glucose uptake & ↑ gluconeogenesis in liver
Other Functions	Reproduction Angiogenesis Bone homeostasis Wound healing Immune Responses Cancer		↓ Liver fibrosis & inflammation ↑ Cell survival ↑ Cardioprotection Reproduction	↑ Vascular Dysfunction ↑ Cell Adhesion ↓ Contractility ↑ Heart Failure

THE ROLES OF ADIPOSE TISSUE



THE ROLES OF ADIPOSE TISSUE

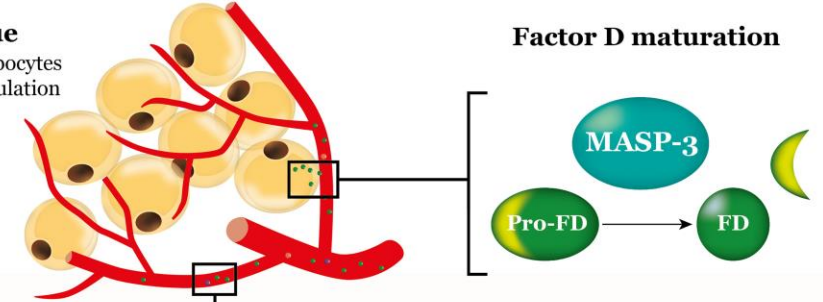
- One component involved in the **immune response** is the complement system, which, although also linked with modulation of adaptive immune responses, plays a vital role in innate immunity. It is especially important in the early stages of life, during which adaptive immunity has not yet been fully developed.
- Three pathways
 - Classical – antibody meets antigen
 - Lectin – recognition of foreign protein
 - Alternative - "slow tick"



THE ROLES OF ADIPOSE TISSUE

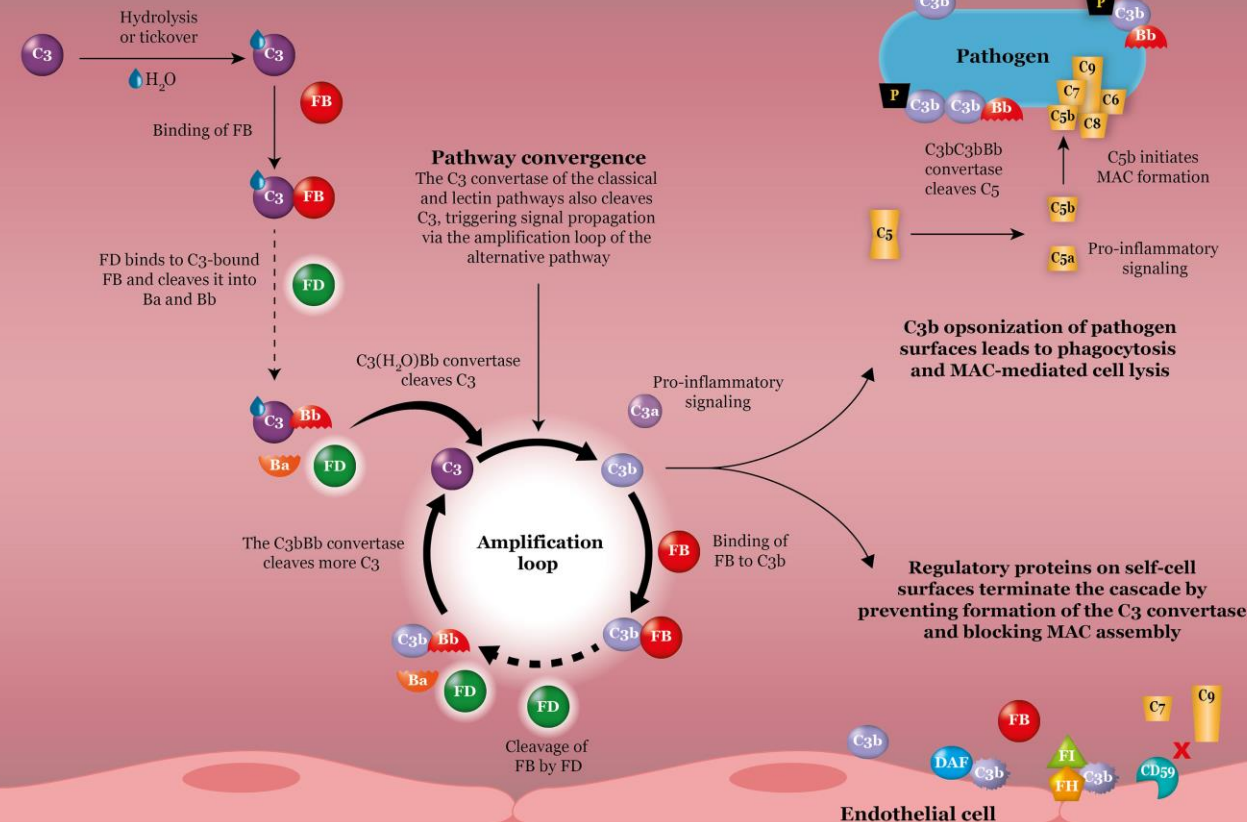
- Factor D is produced by adipose tissue
- The earliest complement pathway in evolution
- Complement dysregulation, and most commonly dysregulation of the alternative pathway, is known to cause or accentuate several different inflammatory glomerular diseases.

Adipose tissue
FD is produced by adipocytes and secreted into circulation

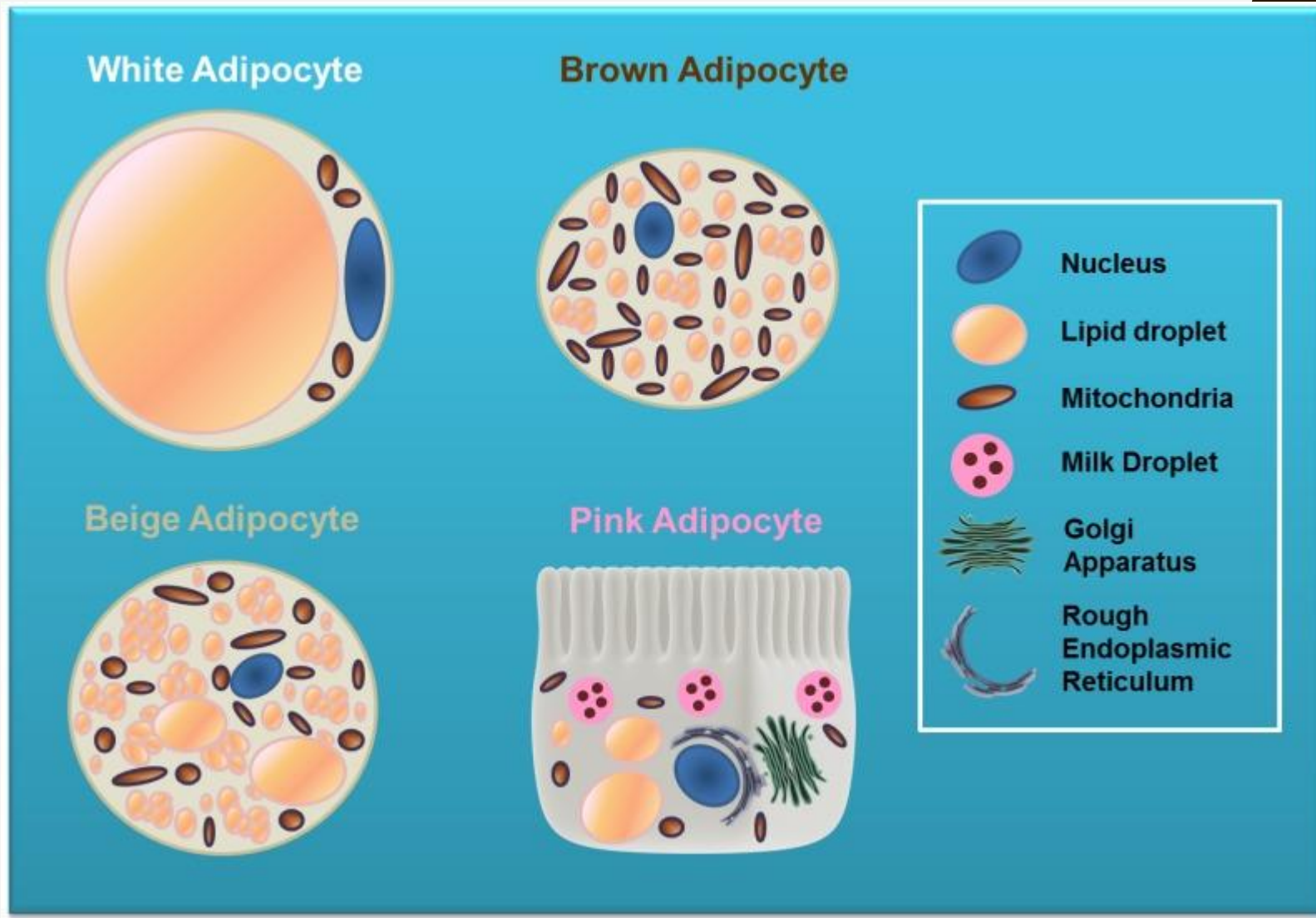


Proximal cascade of the alternative pathway
Initiation Amplification

Terminal cascade
(common to all complement pathways)



TYPES OF FAT CELLS

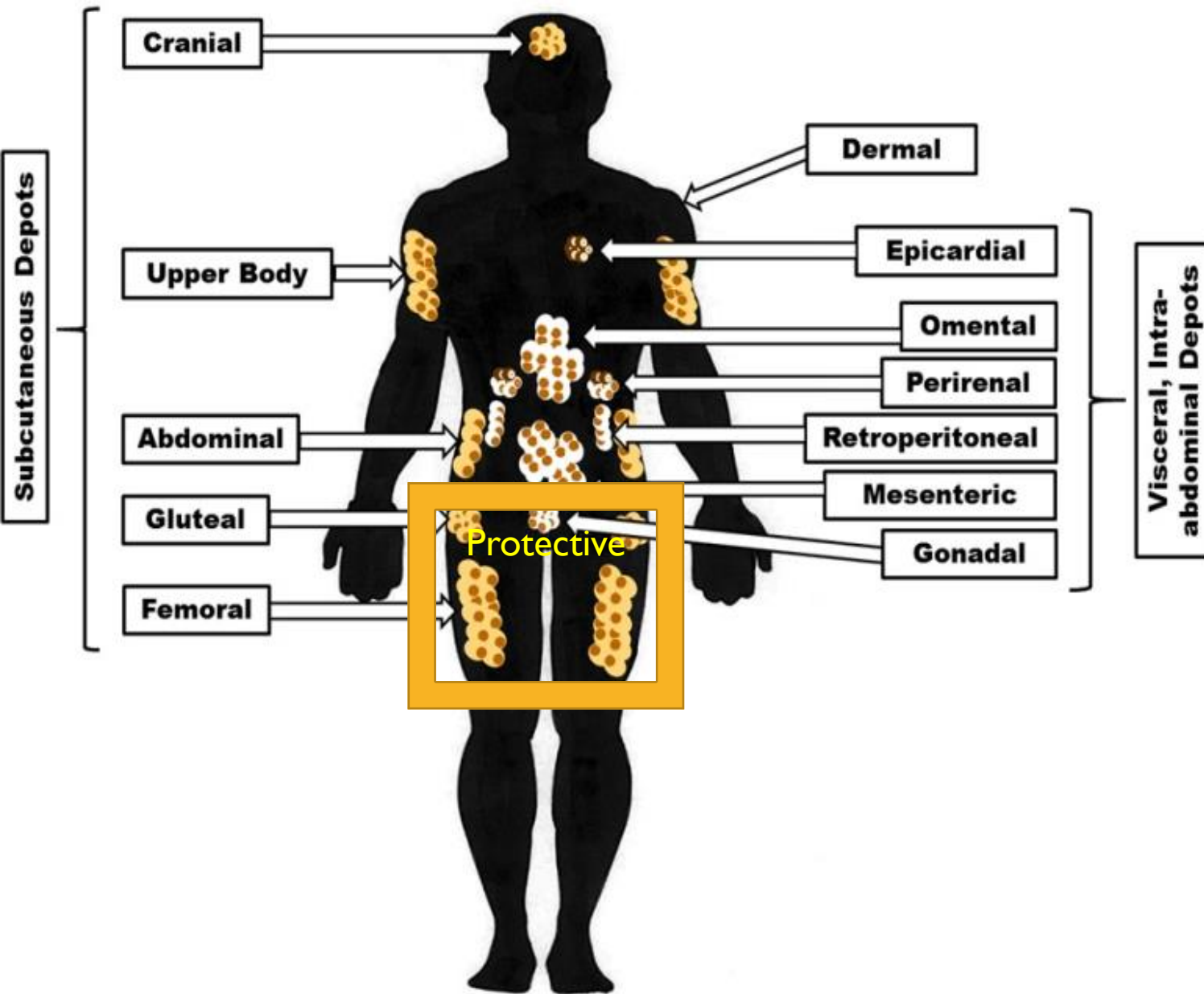


- White are for storage
- Brown for generation of heat
- Beige appear to be white under temperature stress
- Pink found in many mammals ? humans

HEALTHY AND UNHEALTHY ADIPOSE TISSUE

- Where are the fat cells?
- Are there too many fat cells?
- Are the fat cells getting too big?



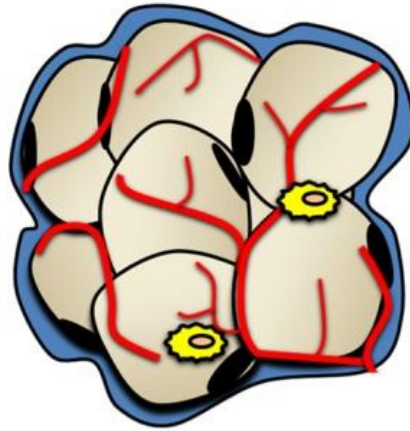


LOCATIONS OF ADIPOSE TISSUE

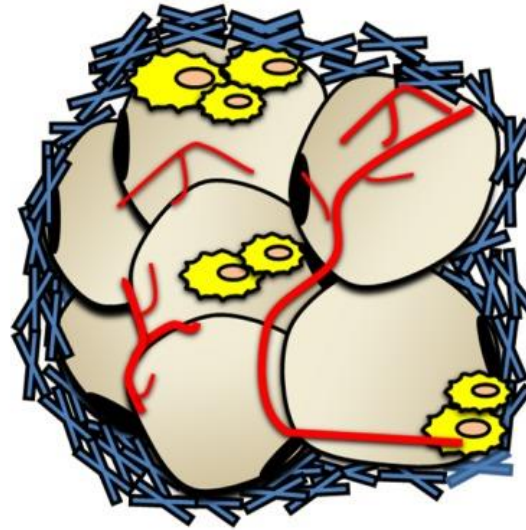
- Upper body and visceral adipose deposits are all linked to metabolic dysfunction
- Lower body adipose deposits can be protective
- Epicardial (one the surface of the heart)
 - brown fat and protect the heart from hypothermia
 - become inflamed with excessive deposits

FROM NORMAL TO FIBROSIS

Lean Adipose



Obese Adipose



 Blood vessel

 Extracellular matrix

 Immune cell

 Fat cell

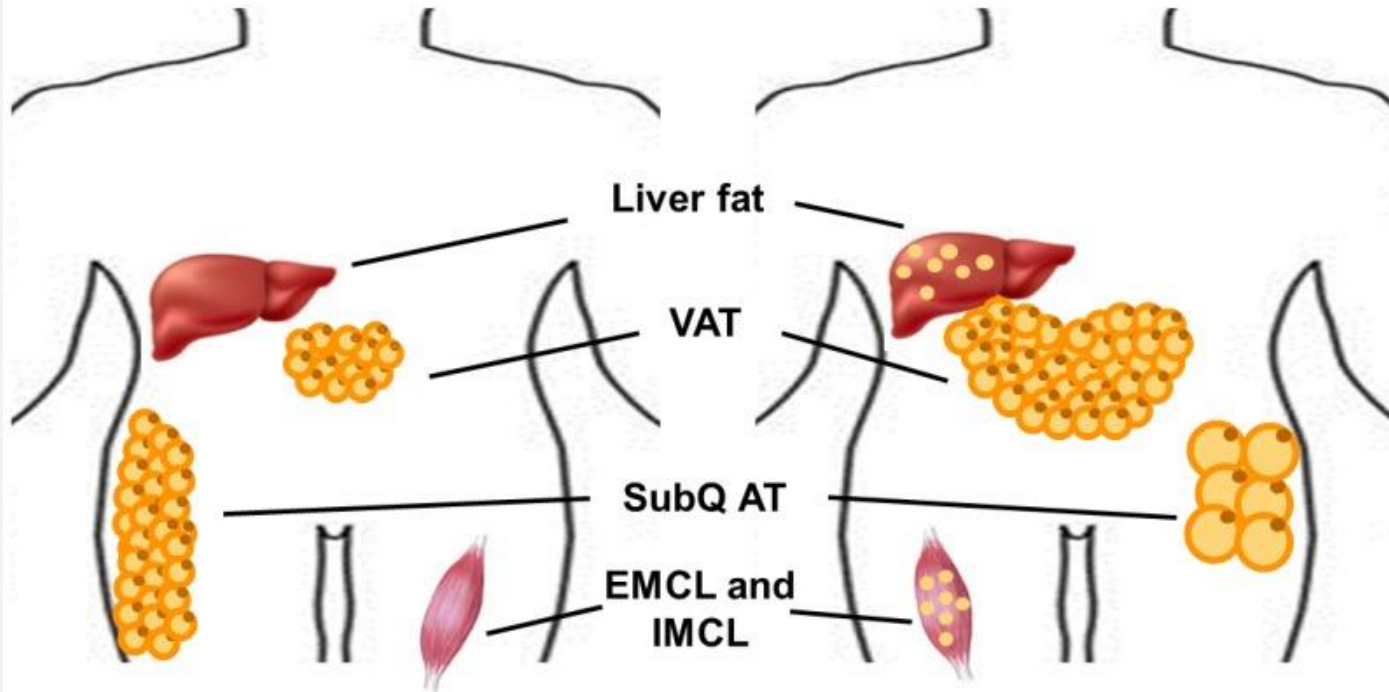
METABOLIC HEALTH REQUIRES:

- The ability to expand lipid stores if there is excess calorie intake
 - More cells
 - Enlarged cells
- Adipose tissue has not expanded to the point of becoming inflamed
- Normal insulin sensitivity
- Normal fasting glucose levels
- Normal blood pressure
- Blood lipid profiles in the healthy range



Metabolically Healthy Obesity (MHO)

Metabolically Unhealthy Obesity (MUO)



High fat mass
 High insulin sensitivity
 Adequate subQ AT expansion
 Low ectopic fat
 Normal blood pressure
 Low inflammation
 Low triglycerides
 High HDL-cholesterol
 High adiponectin

High fat mass
 Low insulin sensitivity
 Impaired subQ AT expansion
 High ectopic fat
 Hypertension
 High inflammation
 High triglycerides
 Low HDL-cholesterol
 Low adiponectin

“HEALTHY” & “UNHEALTHY” OBESITY

- 10-30% of people who are obese do not have metabolic problems
- Hypertrophic (large fat cells) associated with fat deposits in non-adipose tissue such as the liver and pancreas
- Age is associated with a shift from subQ AT to VAT
- 30% of MHO progress to MUO over 5 to 10 years
 - VAT = Visceral adipose tissue
 - subQ AT = subcutaneous adipose tissue
 - EMCL and IMCL = Extra and Intra Muscular adipose tissue

WHAT EVIDENCE DO WE HAVE THAT FAT CELLS ARE VERY IMPORTANT?

- What happens if you have no fat cells?
- What diseases are more likely if you have too many or extra large fat cells?
- What happens if you have too many fat cells and you lose weight?

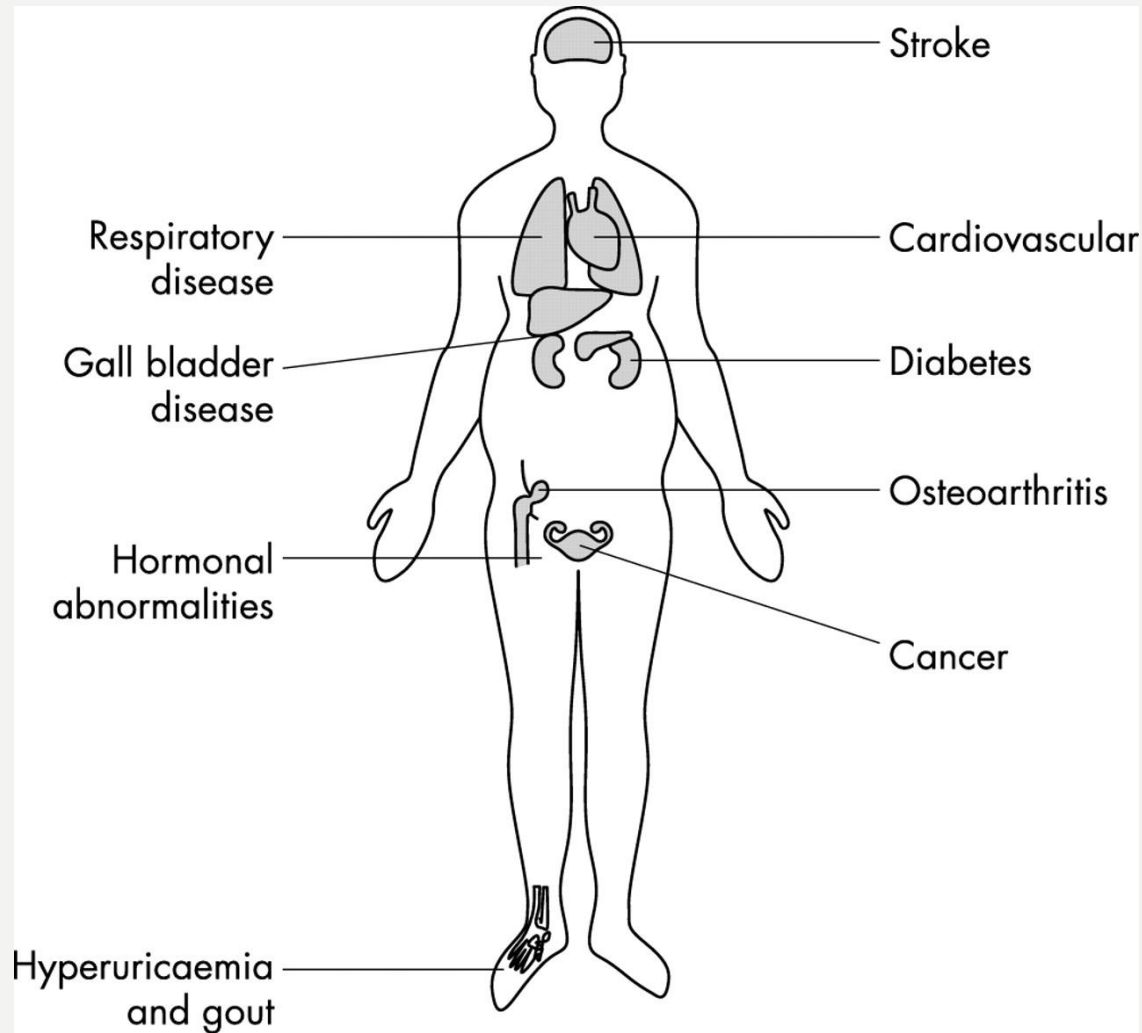


LIPODYSTROPHY – TOO LITTLE ADIPOSE TISSUE

- Genetic or as a result of medication (eg HIV anti-viral treatments)
- Metabolically like people with severe obesity
 - High insulin resistance
 - Type 2 Diabetes
 - Fatty liver
- Shortened life expectancy
 - Myocardial disease
 - Vascular disease



DISEASE AND OBESITY



- Hypertension (High blood pressure)
- Dyslipidaemia (Blood fat disorders)
- Type 2 diabetes
- Coronary heart disease
- Stroke
- Gallbladder disease
- Osteoarthritis
- Sleep apnoea and respiratory problems
- Increased cancer
 - Endometrial
 - Breast
 - Prostate
 - colon cancers
- Increases in all cause mortality
- Social stigmatisation and discrimination

ADIPOSE TISSUE AND REPRODUCTION

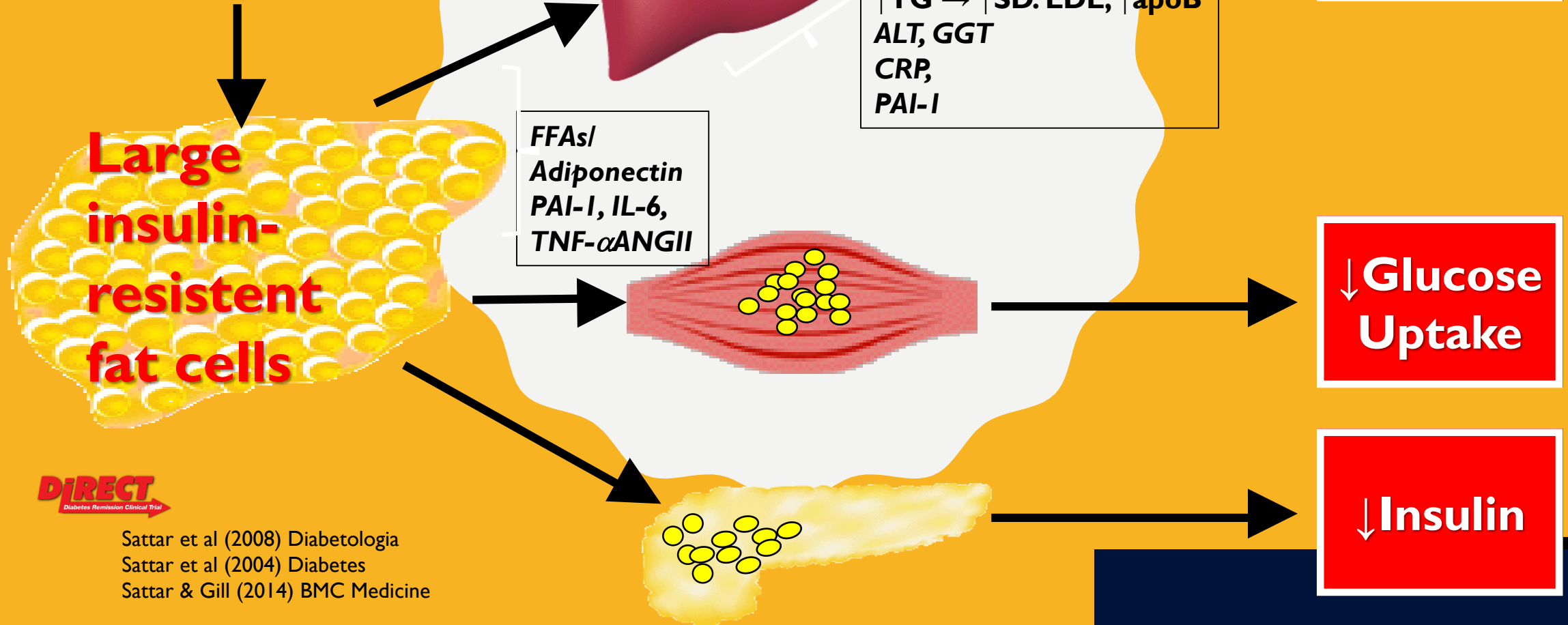
- Adipose tissue is important in:
 - production and regulation of sex and reproductive hormones
 - pubertal development
 - maintenance of pregnancy and lactation
- Receptors for both leptin and adiponectin have been identified in all major reproductive tissues, including the testes, placenta, ovaries, oviducts and endometrium
- Obesity is associated with polycystic ovarian syndrome, reduced fertility, amenorrhoea in women
- Obesity is known to increase the risk of breast, uterine, cervical, and prostate cancers



Excess fat in key organs.

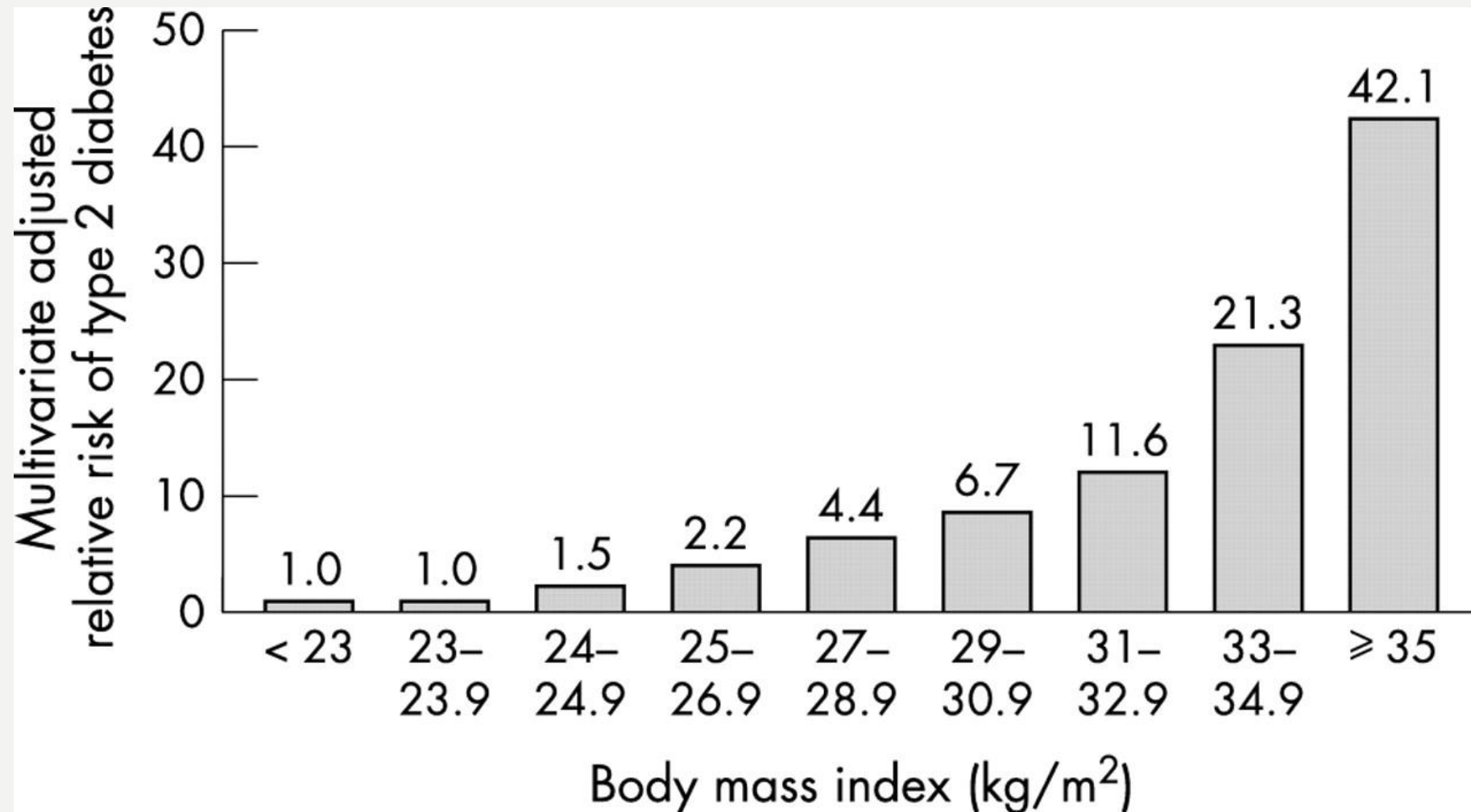
Outcome: **Diabetes**

Diet energy > exercise
Sat Fat, Low Fruit & Veg

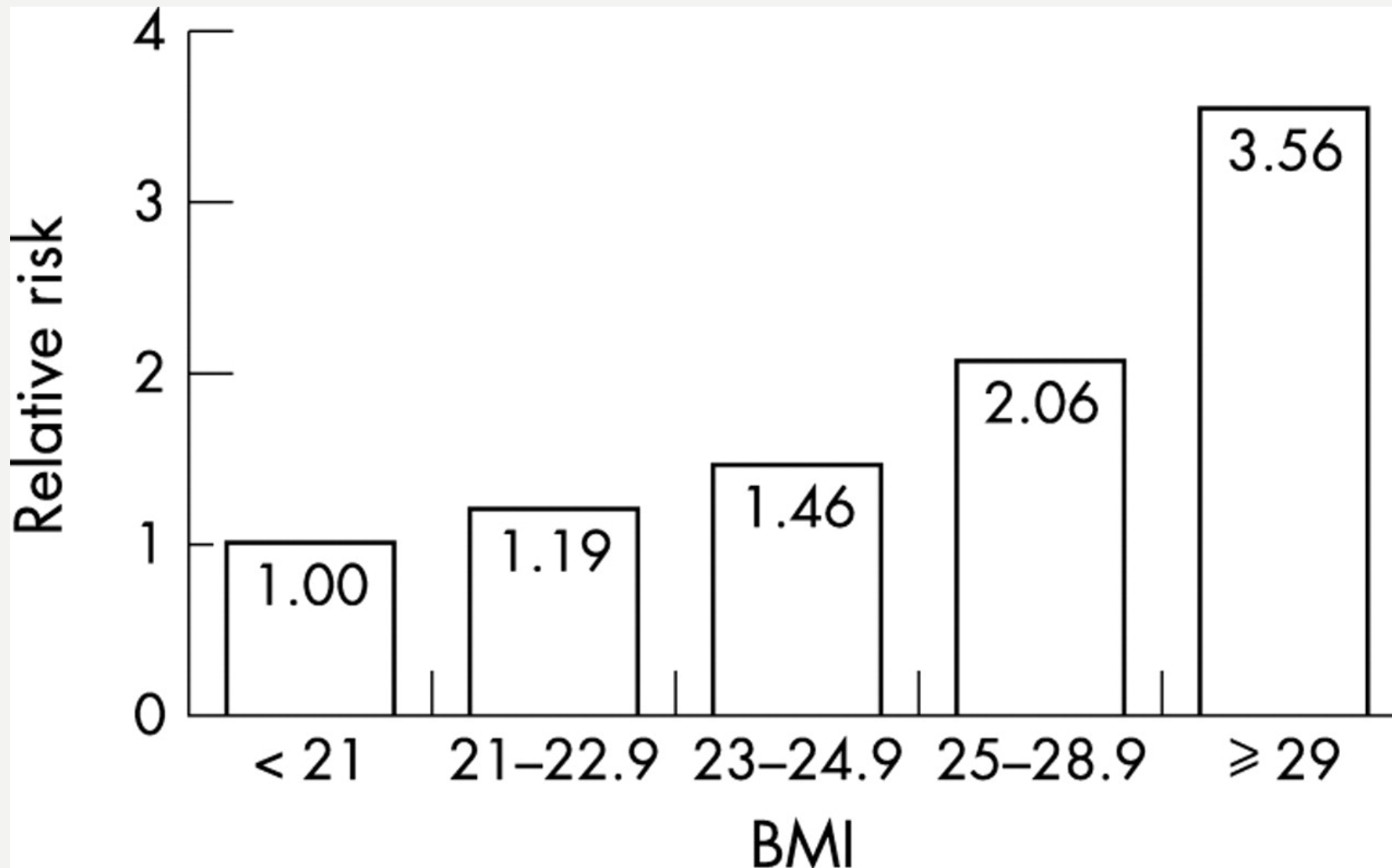


Sattar et al (2008) Diabetologia
Sattar et al (2004) Diabetes
Sattar & Gill (2014) BMC Medicine

RELATIVE RISK OF DEVELOPING TYPE 2 DIABETES



RELATIVE RISK OF HEART ATTACK



OBESITY AND KIDNEYS

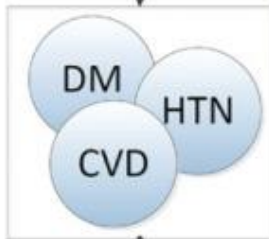
- Obesity causes diseases that damage kidneys
 - Hypertension
 - Cardiovascular disease
 - Diabetes
- Obesity requires higher filtration rates of kidneys
 - Fibrosis
- Activation of alternative complement pathway (inflammation)
- Obesity is associated with kidney stones



Adiposity

↓ Adiponectin, ↑ Leptin, ↑ Resistin, ↑ Visfatin
?Other adipokines

↑ Insulin resistance
↑ Insulin level
↑ RAAS activation
↑ Inflammation
↑ Oxidative stress
Abnormal lipid
metabolism



CKD

OBESITY AND KIDNEY DISEASE

Proposed mechanisms of action whereby obesity causes chronic kidney disease

Note. DM = diabetes mellitus; CVD = cardiovascular disease; HTN = hypertension; CKD = chronic kidney disease. RAAS = Renin-Angiotensin-Aldosterone-System

Can J Kidney Health Dis. 2017; 4

RELATIVE BENEFIT FROM 10KG OF WEIGHT LOSS

- Mortality

- Overall - *minus 20 to 25%*
- Diabetes related - *minus 35-40%*
- Obesity related cancer
 - *minus 40 - 50%*

- Blood pressure

- Systolic – *minus 20 mm Hg*
- Diastolic – *minus 10 mm Hg*

- Diabetes

- Blood sugar – *minus 30 – 50%*

- Lipids

- Total cholesterol – *minus 10%*
- LDL (bad cholesterol) – *minus 15%*
- HDL (good cholesterol) – *plus 8%*
- Triglycerides – *minus 30%*

Jung RT. Obesity as a disease. Br Med Bull 1997;53:307–21



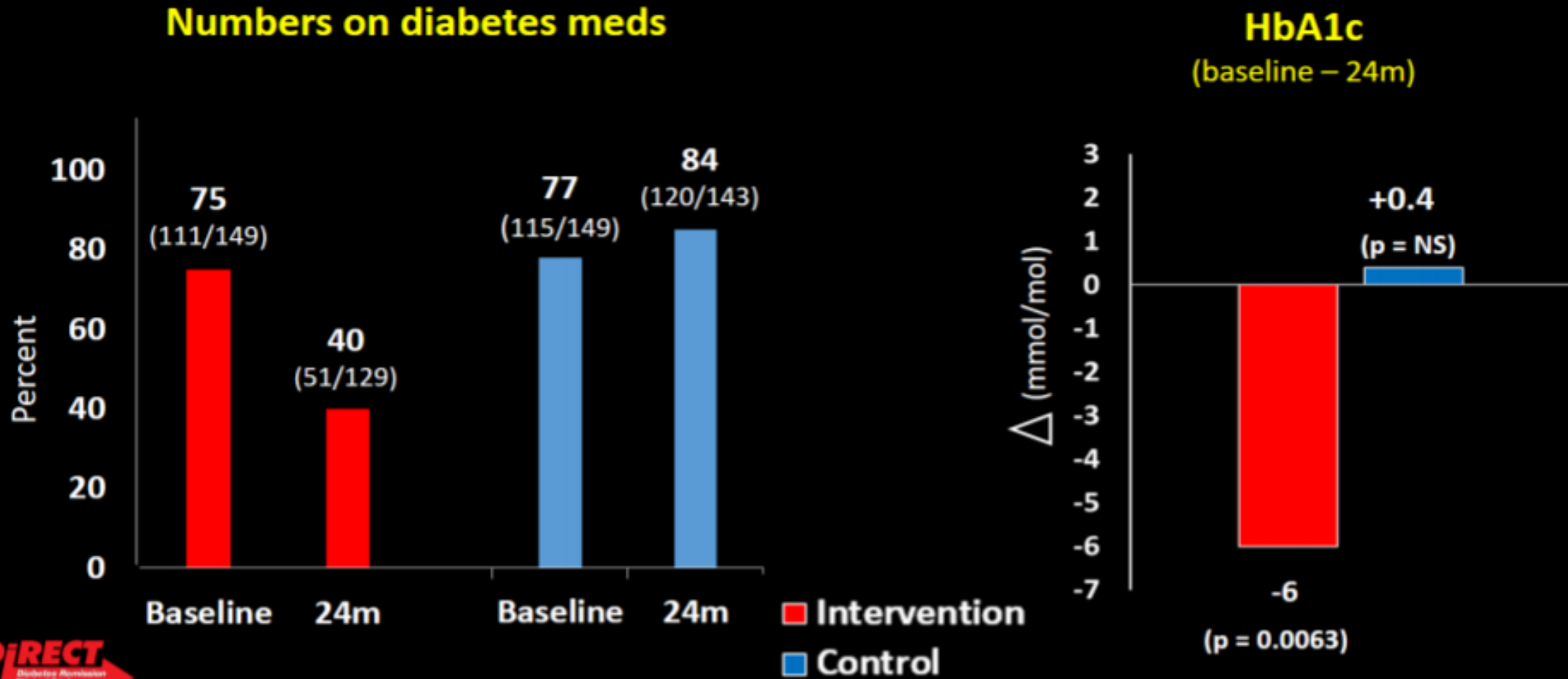
WEIGHTLOSS AND DISEASE REVERSAL

DIABETES, HYPERTENSION, FATTY LIVER...

Weightloss	Reverse diabetes	Reverse High BP	Reverse fatty liver
10kg	64%	15%	80%
15kg	83%	50%	100%
20kg	90%	?	100%
	Over 3 months	Reduce 2 mmHg per Kg	Over 2 months



LOWER HbA1c, WITH FEWER ON ANTI-DIABETES DRUGS AT 24 MONTHS



5/106

From all Chemists & Price 2/6 and 4/6

Antipon

Regd Trade Mark

PERMANENTLY CURES OBESITY

"ANTIPON" is an Absolutely Perfect Remedy for Obesity, Permanently Curing the most Obstinate Cases. As a Medicine it attains the Highest Standards: It is Reliable, Efficient, Pure, Harmless, Agreeable to the palate and Easy to take. Last, but not least, it is comparatively Inexpensive.

"ANTIPON" is not only the most Powerful Fat Absorbent ever discovered, Radically Eliminating all Superabundant and Diseased Fatty Deposits, and Effectually Destroying the Distressing Tendency to develop Excessive Adipose, but it is Permanently Beneficial to Health.

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"ANTIPON" Reduces Weight to normal and Restores Beauty of Form in the Shortest Possible Time; and on the Required Reduction being attained the Treatment may be discontinued.

"ANTIPON," a Liquid Tonic, contains nothing of a mineral or otherwise objectionable nature, and is Approved by the most Competent Authorities as the most Rational, Effective and Truly Beneficial Cure for Obesity known to Science.

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13 BUCKINGHAM STREET, STRAND, LONDON, W.C.

Telegraphic Address: "CORPULOR, LONDON." TRADE MARK: Union of London and South's Bank.

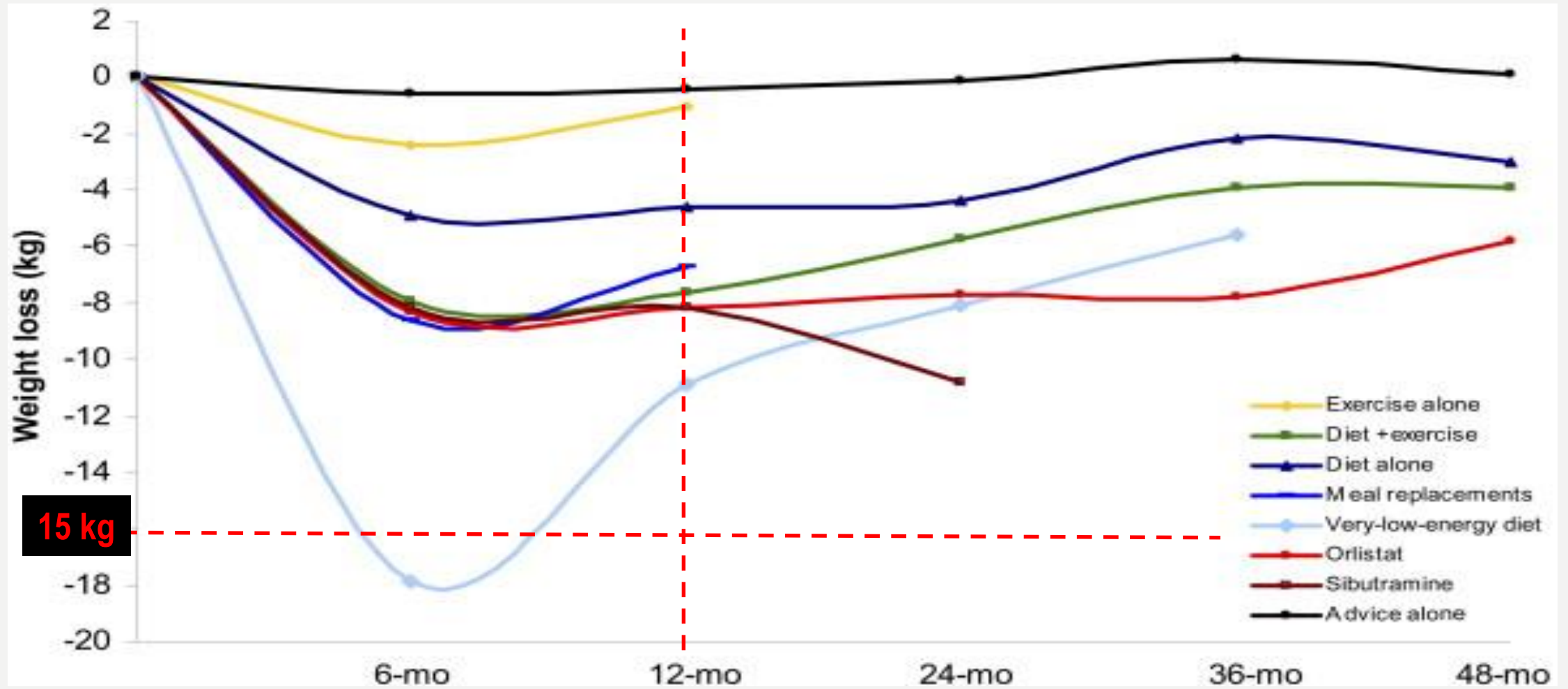
THE EASY HOME TREATMENT

WHAT TO DO ABOUT OBESITY?

- Food industry (less high calorie food)
- Food and drink sales point (esp supermarkets)
- Education
- Controlled diets
- Taxing high calorie foods and drinks
- Weight loss treatments
 - Very low calorie shakes
 - Medications
 - Bariatric surgery

VLCD RELIABLY ACHIEVES 15KG WEIGHT LOSS

BEST LONG-TERM RESULTS ARE WITH MOST RAPID EARLY WEIGHT LOSS



Subjects completing 1-year in 80 studies: n = 26,455,
completers = 18,199 (69%) (Franz MJ et al JADA 2007;107(10):1755-67)



THE ROOT CAUSE OF OBESITY?

- The energy balance model
 - Eat less, exercise more
 - Would you rather have a big glass of water instead of Coke
 - OR
 - Not eat an egg
 - OR
 - Walk for an hour
- The carbohydrate-insulin model
 - Eat very few highly processed carbohydrates
 - Eat food and not edible food-like substances



WHO IS MOST AT RISK

THEN



NOW

- US Data

- Food insecurity – doubles risk of obesity
- Food insecurity with hunger associated with obesity:
 - Whites: 20% reduction in obesity
 - Asians, Blacks, Hispanics: 3 times the risk

Paradox

WORLD RECORD HOLDER: 30,000 BIG MACS



CREDITS

THANK YOU

Title slide: Adipose Tissue, Odra Noel

Prof. Mike Lean, Glasgow University

Cheek Docs, Congress and Flinders University

[Adipose tissue: Physiology to metabolic dysfunction](#) Allison J et al.

