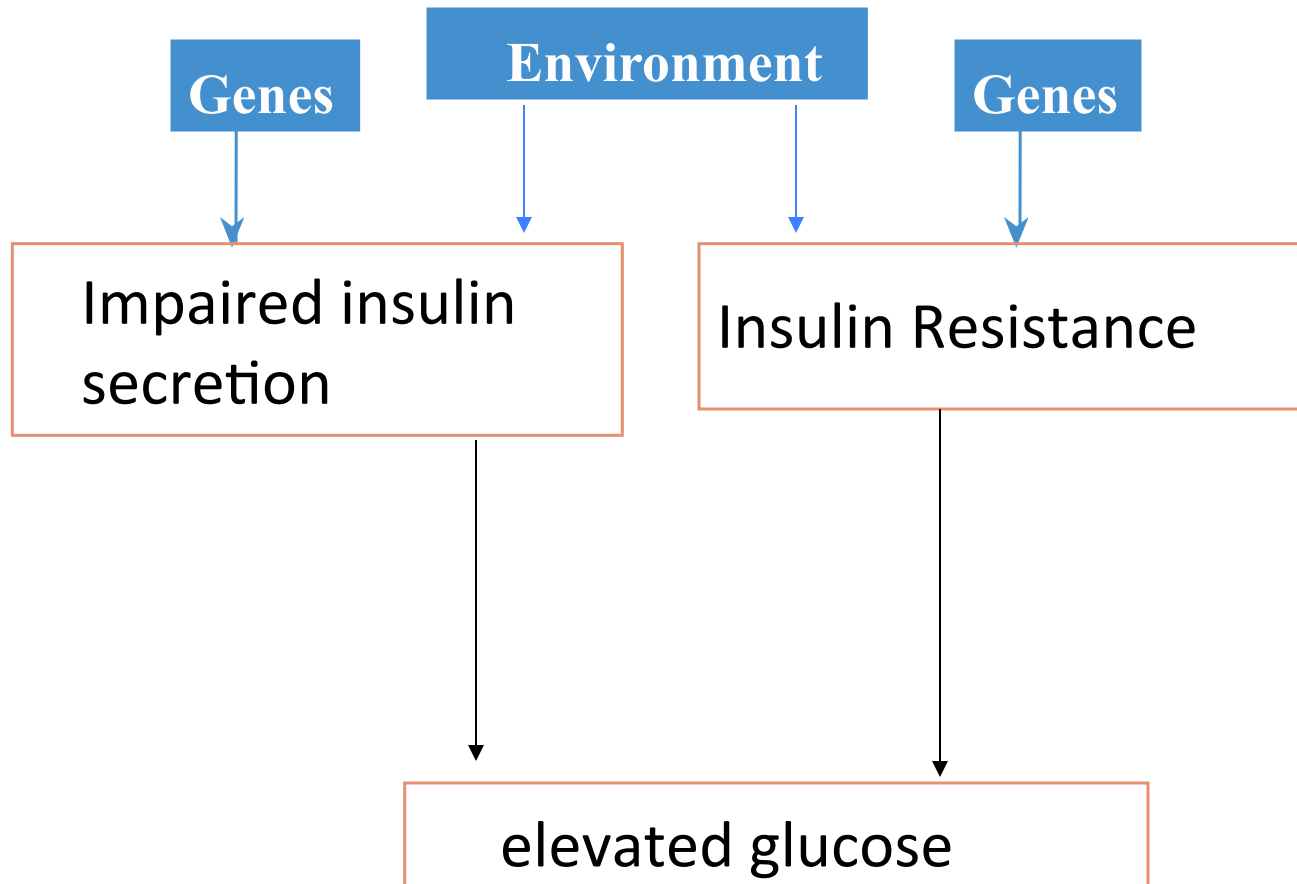


Overview of Type 2 diabetes and Prediabetes

Classification of Diabetes

- Type 1 (a) & (b)
- Type 2
- Other specific types
 - Hormones; drugs; liver disease; muscle disorders; pancreatitis; iron overload syndromes
- Gestational

Type 2 diabetes



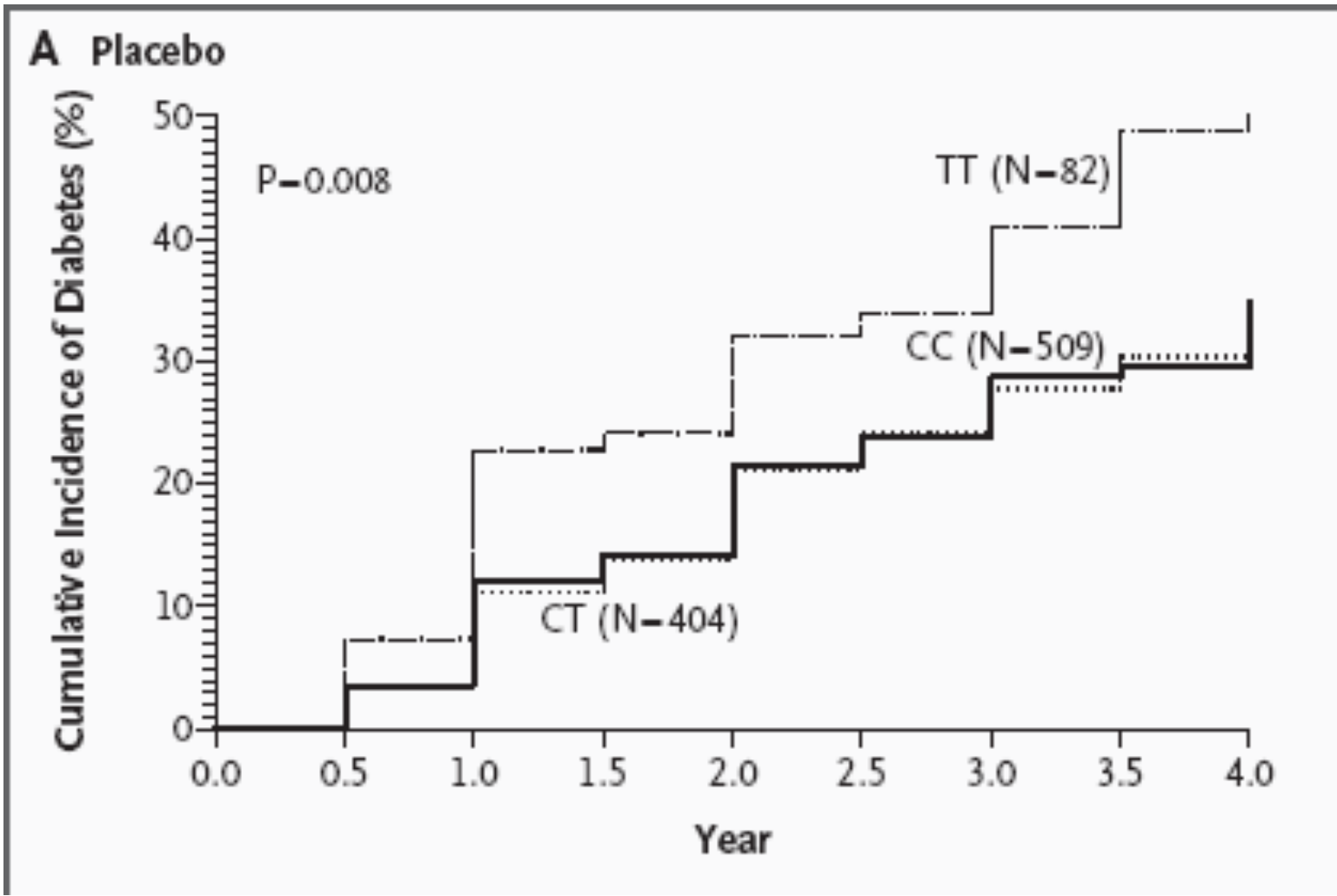
Risk for developing type 2 diabetes

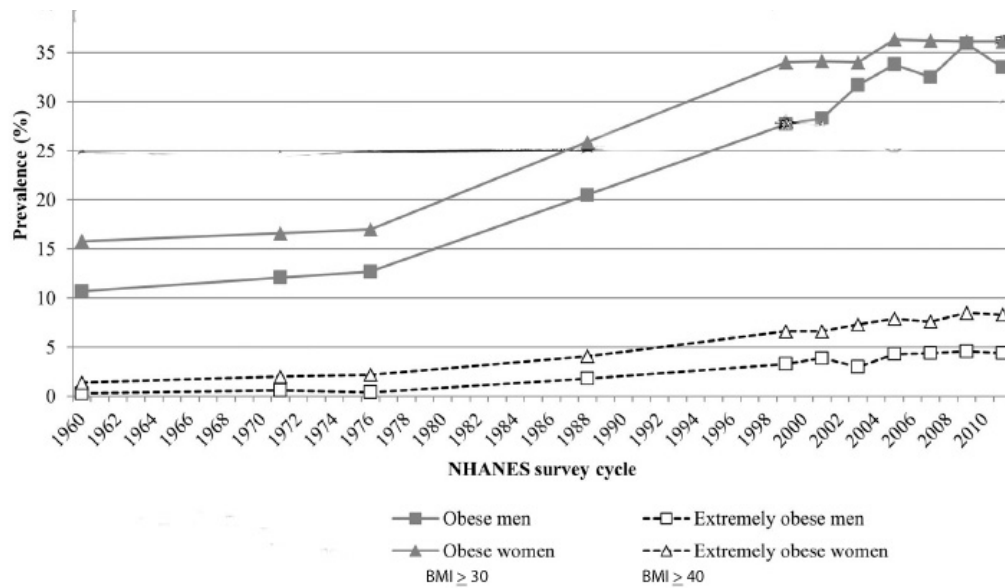
Background population	10%
Average risk for siblings	30-40%
One parent with T2D	30-40%
Both parents with T2D	50-80%
Monozygotic twins	50-90 %

Genome wide study - SNPs

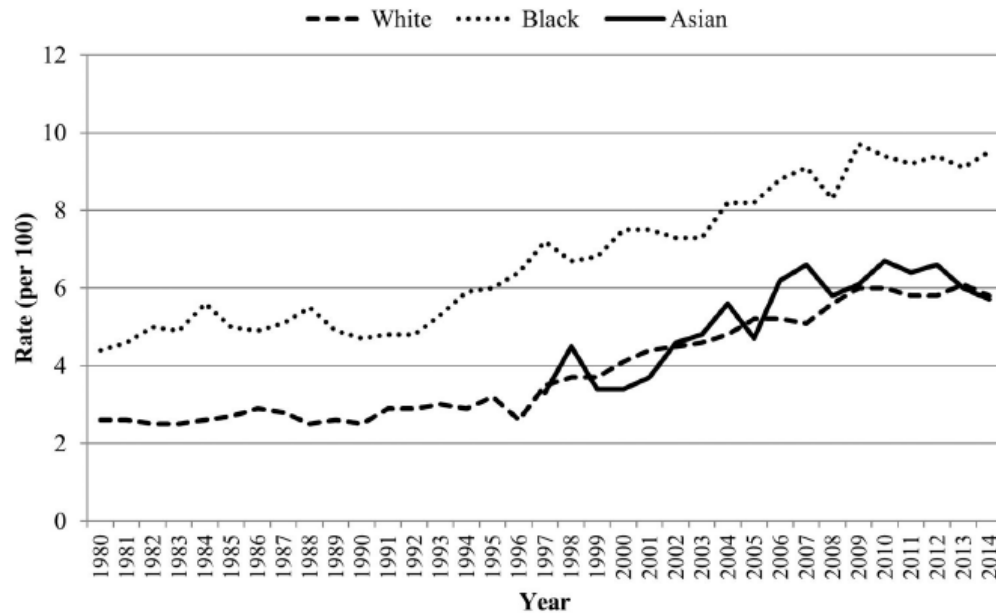
- *non coding region near CDKN2A/CDKN2B,*
- *intron of IGF2BP2*
- *Intron of CDKAL1*
- *Intron of TCF7L2*
- *SLC30A8 (Zinc transporter)*
- *HHEX*
- *PPARG*
- *KCNJ11*
- *FTO*
- *MC4R*

Incidence of diabetes according to TCF7L2 allele in the DPP cohort



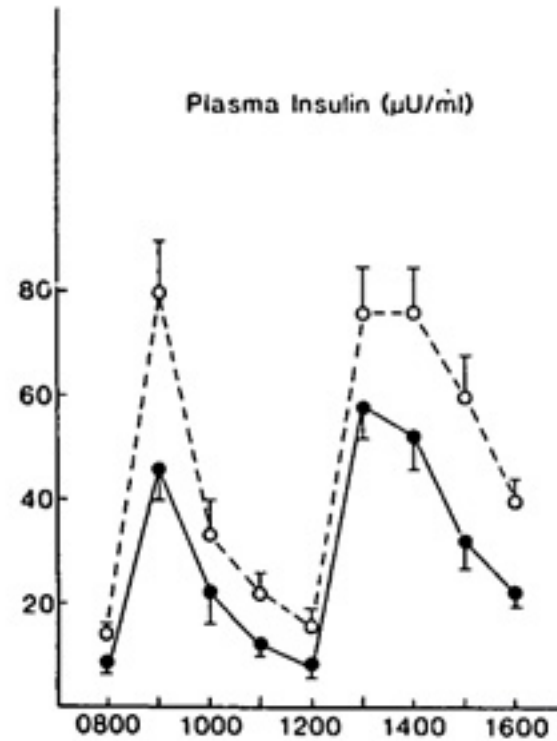
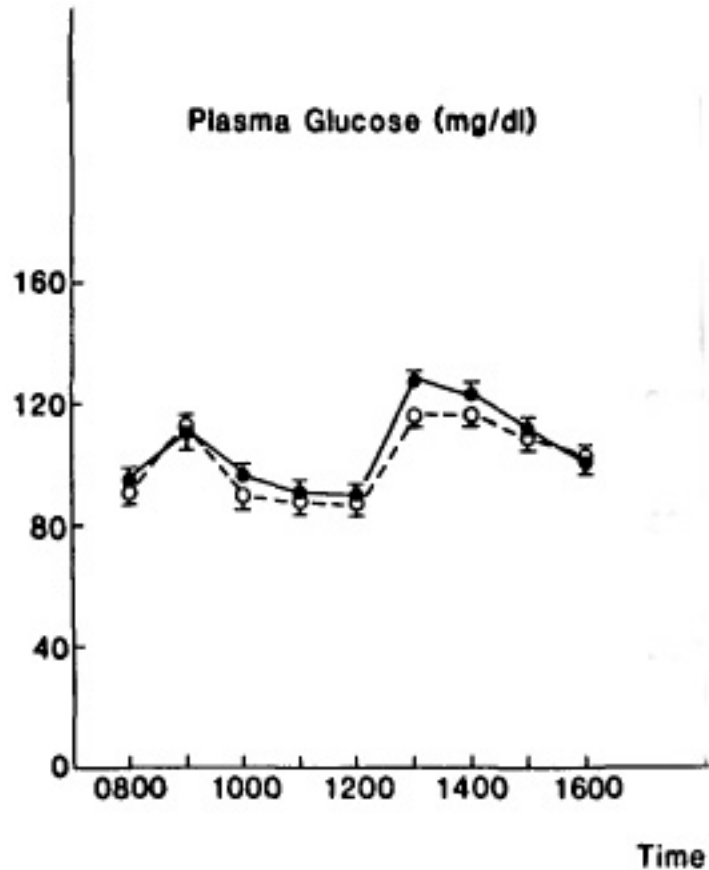


Prevalence of obesity

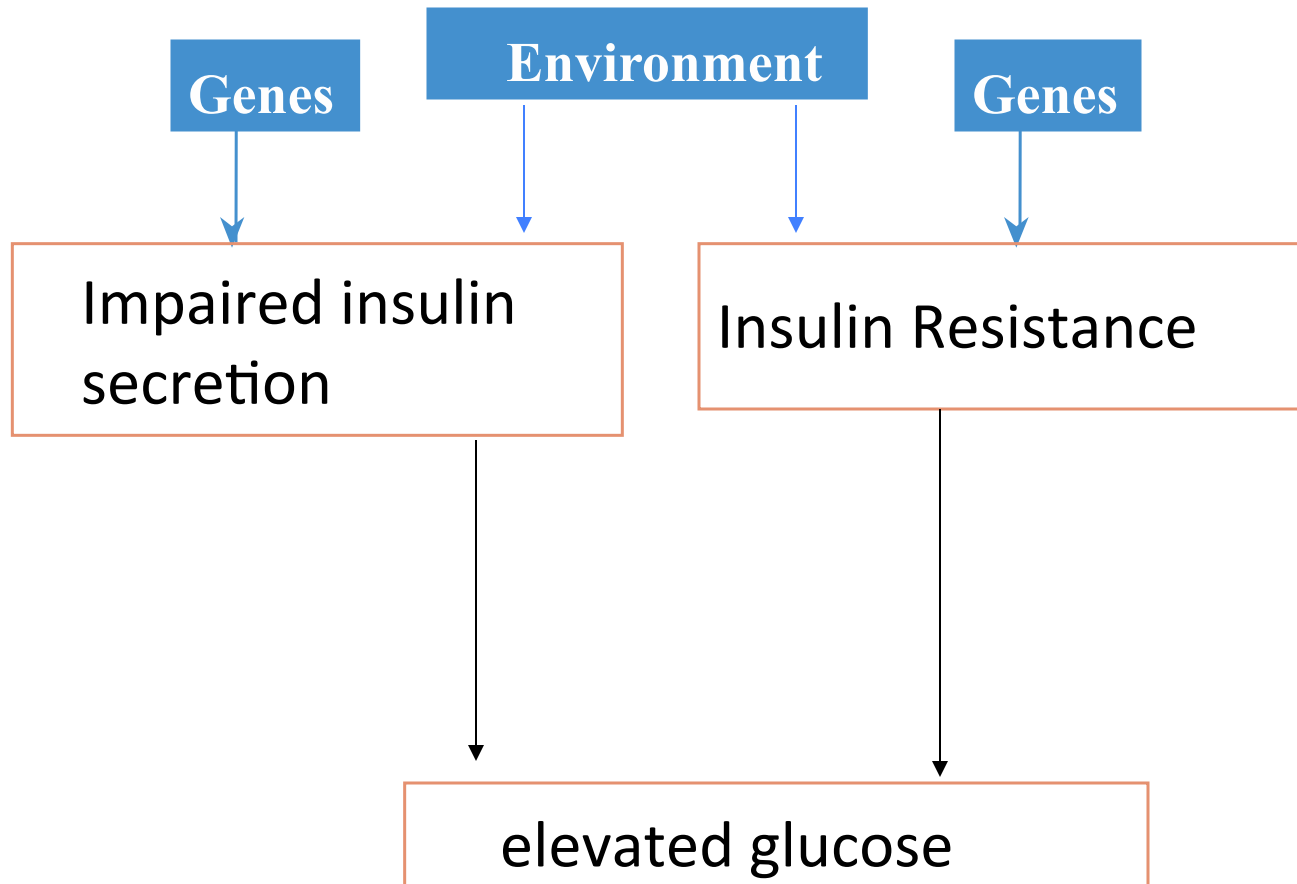


Prevalence of age adjusted rates of diabetes

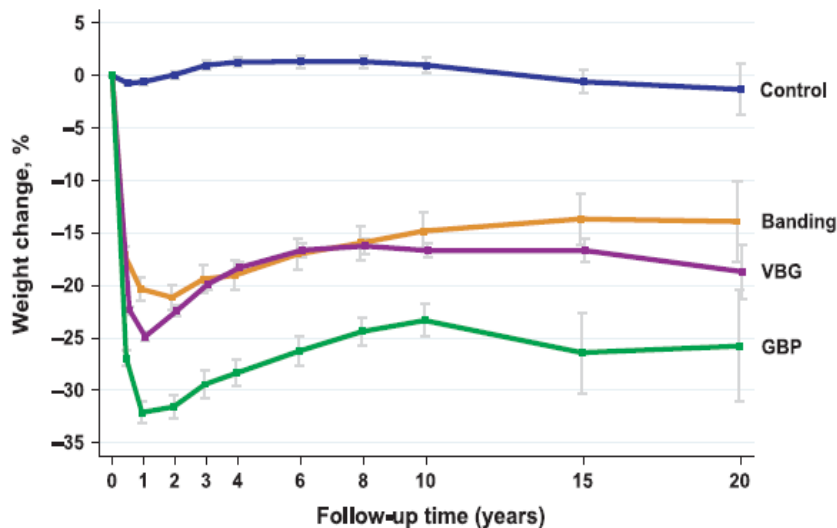
Effect of obesity on glucose & insulin



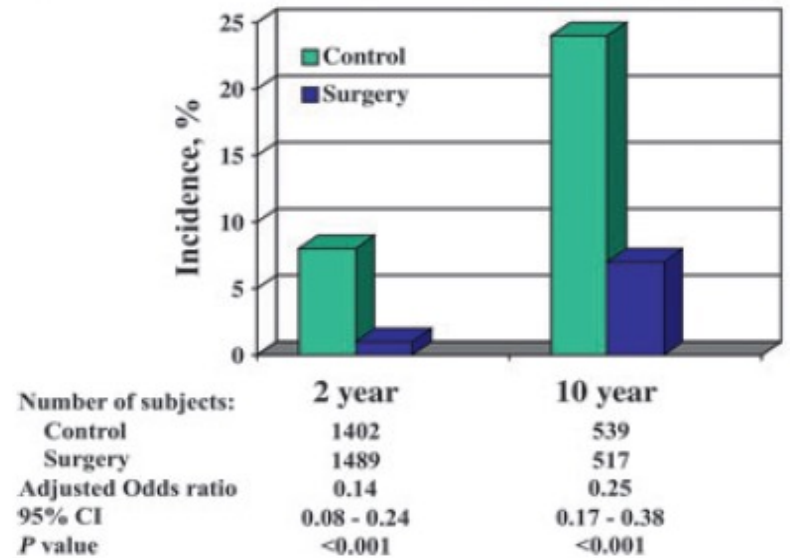
Type 2 diabetes



Swedish obesity study – bariatric surgery prevent development of diabetes [1402 controls; 1489 surgery patients]

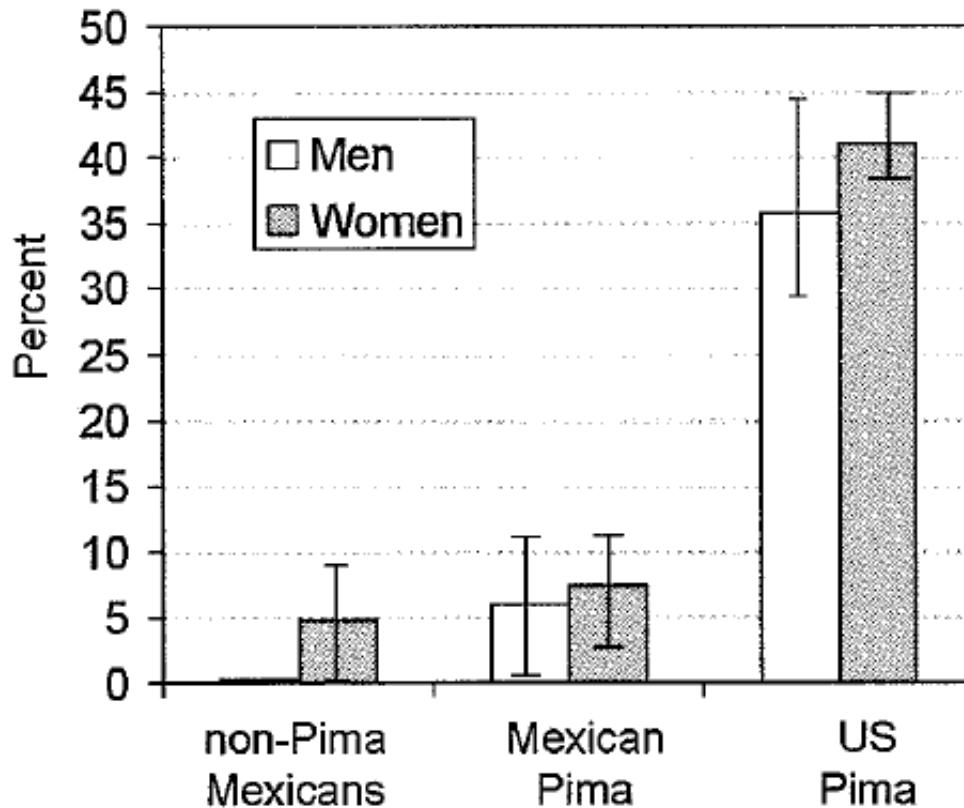


(b) SOS. Incidence of diabetes over 2 and 10 years



Bariatric surgery reduces the incidence of type 2 diabetes by 78%

Prevalence of type 2 diabetes in Pima Indians in Sonora, Mexico and Arizona, USA



BMI:

Non Pima Mexicans 24 -27

Mexican Pima 24-26

US Pima 33 - 35

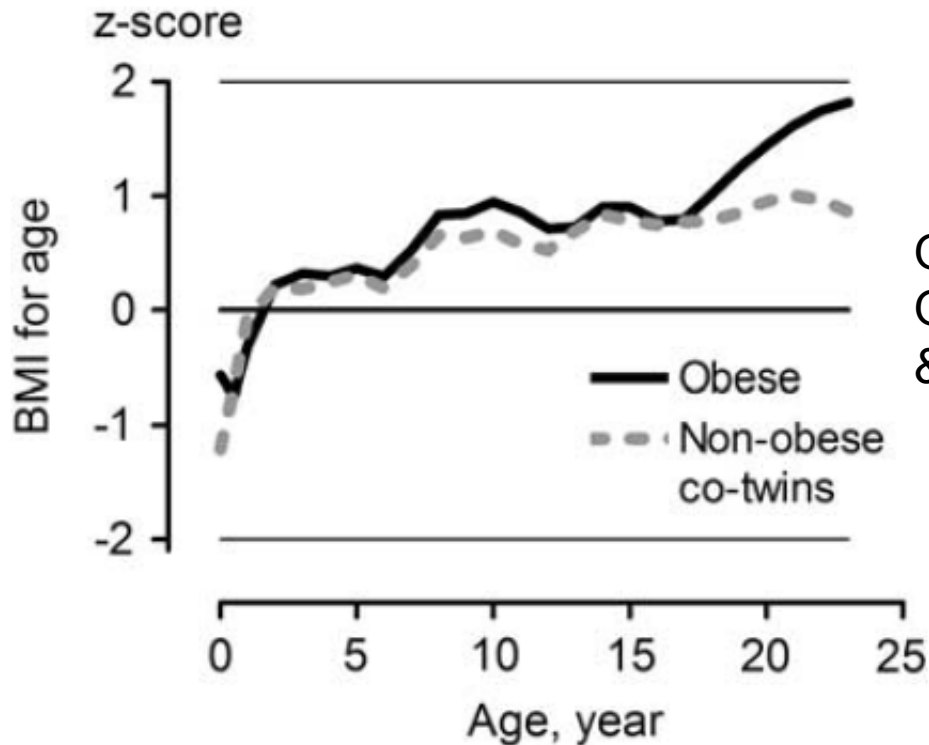
Physical activity:

Mexican Pima 22 to 33 hr/wk

US Pima 2 to 12 hr/wk

Mexican and US Pima
genetically related

Identical twins who are discordant for obesity



Obese twin half as active
Obese twin under-report energy intake
& over-report physical activity

Physical activity reduces the influence of genes on BMI and waist circumference

Summary

- Type 2 diabetes affect 24 million people in the US
- Type 2 diabetes patients have a deficiency in insulin secretion and many also require higher amount of insulin to control their glucose levels (insulin resistance)
- The deficiency in insulin secretion is mostly due to genes
- The need for higher amounts of insulin (resistance) is genetic and environmental
- Obesity is the main environmental factor for resistance
- Reducing obesity rates will reduce rates of diabetes

Prediabetes – the high risk state for diabetes

Prediabetes is defined by test values that are higher than normal but lower than for the diabetes diagnosis

Category	FPG	2hPG	HbA1c
Normal	<100	<140	<5.7
IFG	100-125	---	---
IGT	---	140-199	---
High risk	----	----	5.7 – 6.5
DM	<u>≥</u> 126	<u>≥</u> 200	<u>≥</u> 6.5 %

IFG – impaired fasting glucose; IGT – impaired glucose tolerance

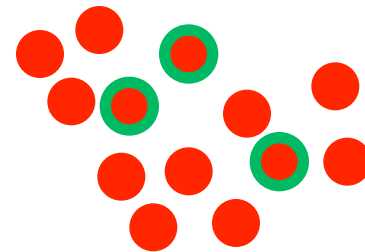
2hPG – 2 hour glucose after 75 grams oral glucose

WHO cutoff for normal fasting plasma glucose is 110 mg/dl (6.1 mmol/l);
& lower cutoff of 6% for HbA1c

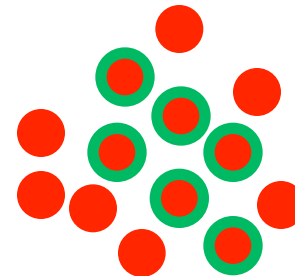
A digression -What is HbA1c?

HbA1c measures the percentage of hemoglobin (the red stuff in your blood) that has an attached glucose molecule

Normal glucose level — 4.3 to 5.6 %
of hemoglobin has attached glucose
— normal HbA1c



High glucose level — higher
percentage of hemoglobin has
attached glucose — higher HbA1c



Some facts about prediabetes

If you use the ADA defined test cutoffs:

- ~ 84 million (33.9%) of US adults; & ~ 48 % adults 65 and older have prediabetes
- ~ 2 % with people with pre-diabetes progress to diabetes every year (conversion rate varies by population characteristics and prediabetes definition)
- Prediabetes can convert back to normal – in one study from England, 86% became normal at 10 years

Diabetes prevention program (DPP) study - 3234 with FPG 95-125 + 2hPG 140-199 + overweight randomized to 7% weight loss + 150 mins exercise/wk or metformin or placebo

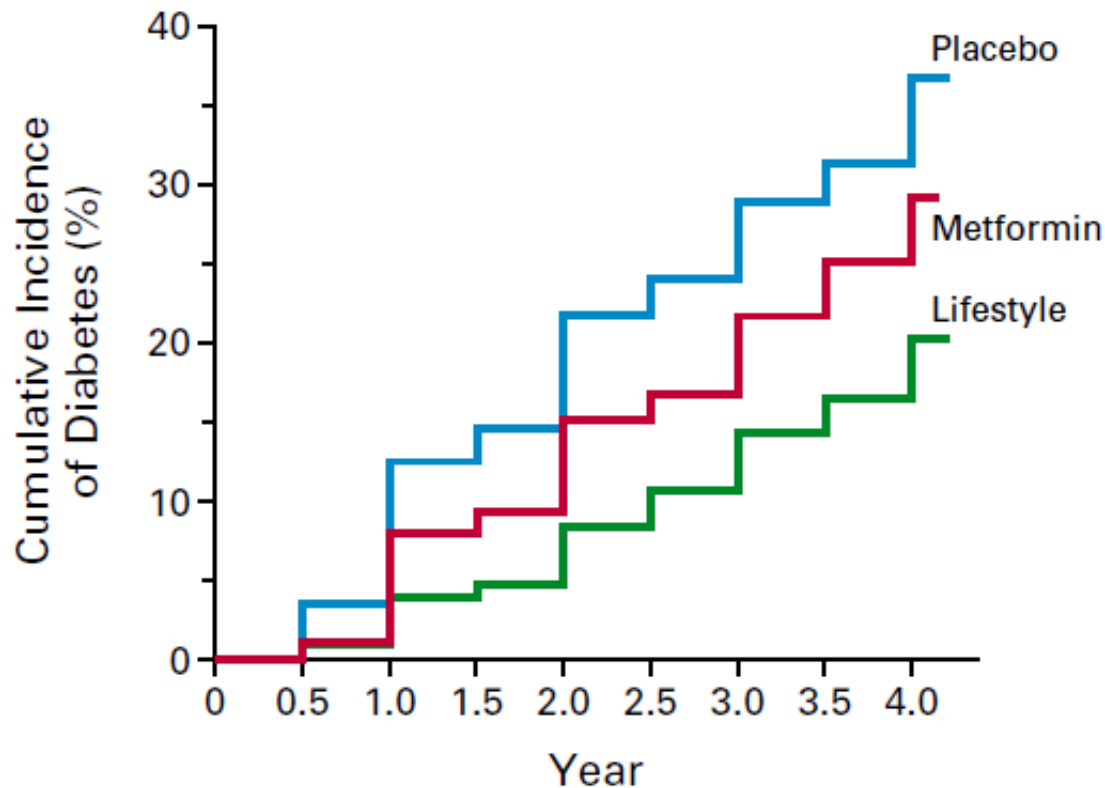


Figure 2. Cumulative Incidence of Diabetes According to Study Group.

Conclusions from the DPP

- After an average of 2.8 yrs, lifestyle reduced incidence of diabetes by 58%
- On average, lifestyle intervention delayed the onset of diabetes by 3-4 years
- After 15 yrs follow-up, the cumulative incidence of diabetes was 55% in the lifestyle group; 56 % metformin group; 62% placebo group

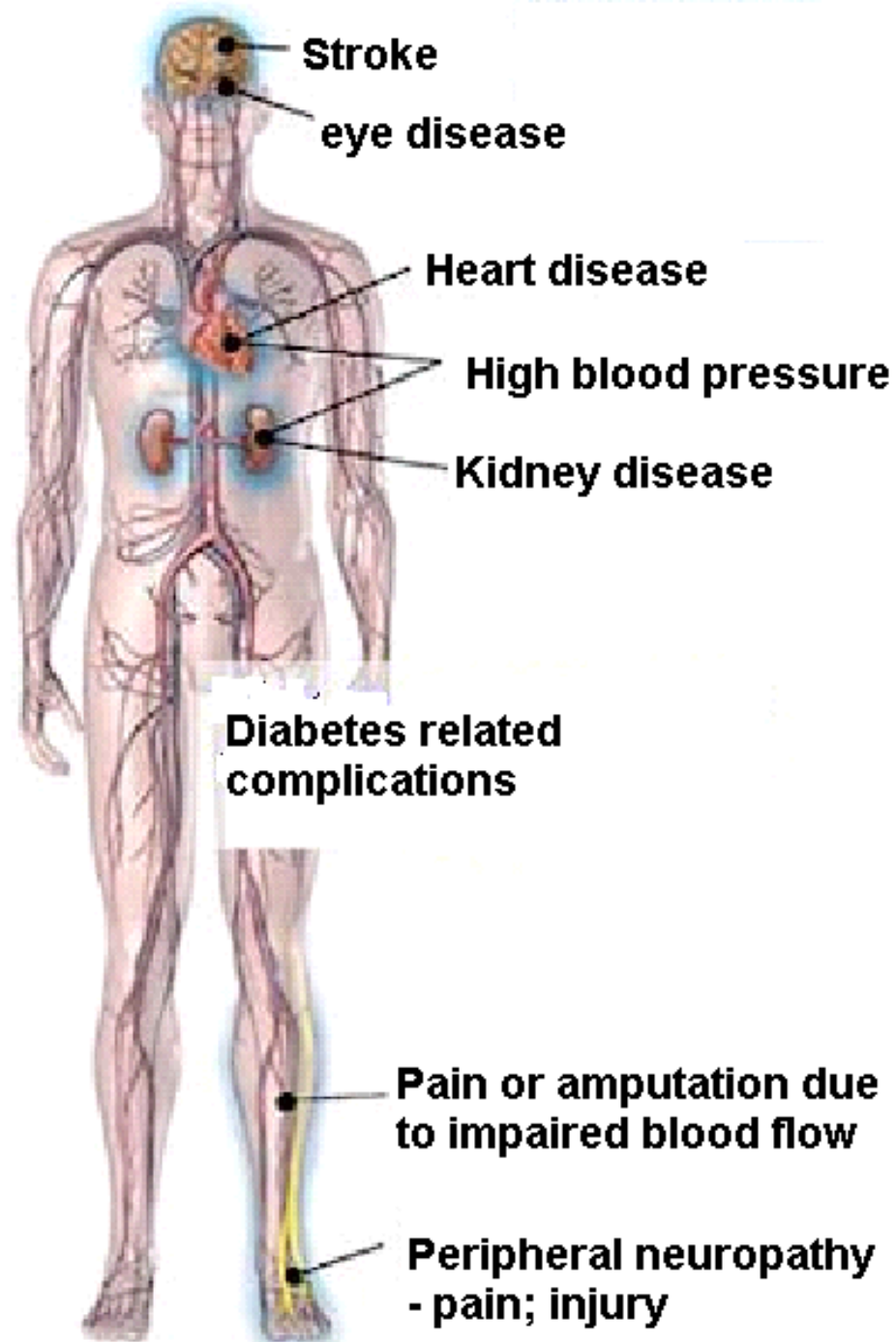
Before you embrace the prediabetes diagnosis

- You are labelling 1/3 of the adult US population as having an illness
- The DPP study used a high risk group (IGTT + IFG + overweight group). The benefits of intervention may not be as great in the general population
- Lack of evidence that prediabetes diagnosis prevents diabetes complications or premature death

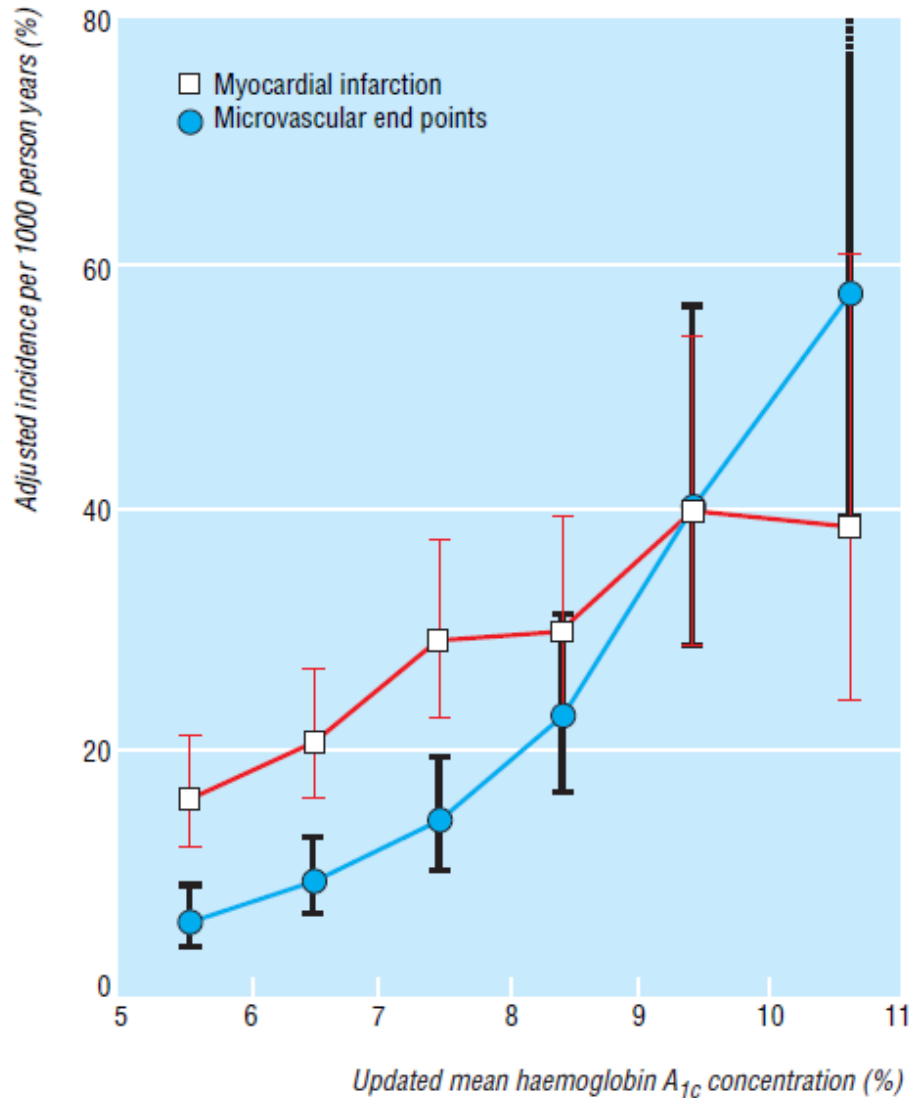
Summary

- Prediabetes is defined by tests values that are higher than normal but lower than for the diabetes diagnosis
- What test and cutoffs you use can greatly affect who gets the diagnosis
- If you have prediabetes, weight loss and exercise can delay the onset of diabetes
- It is unclear that having the prediabetes label leads to better health

Treatment



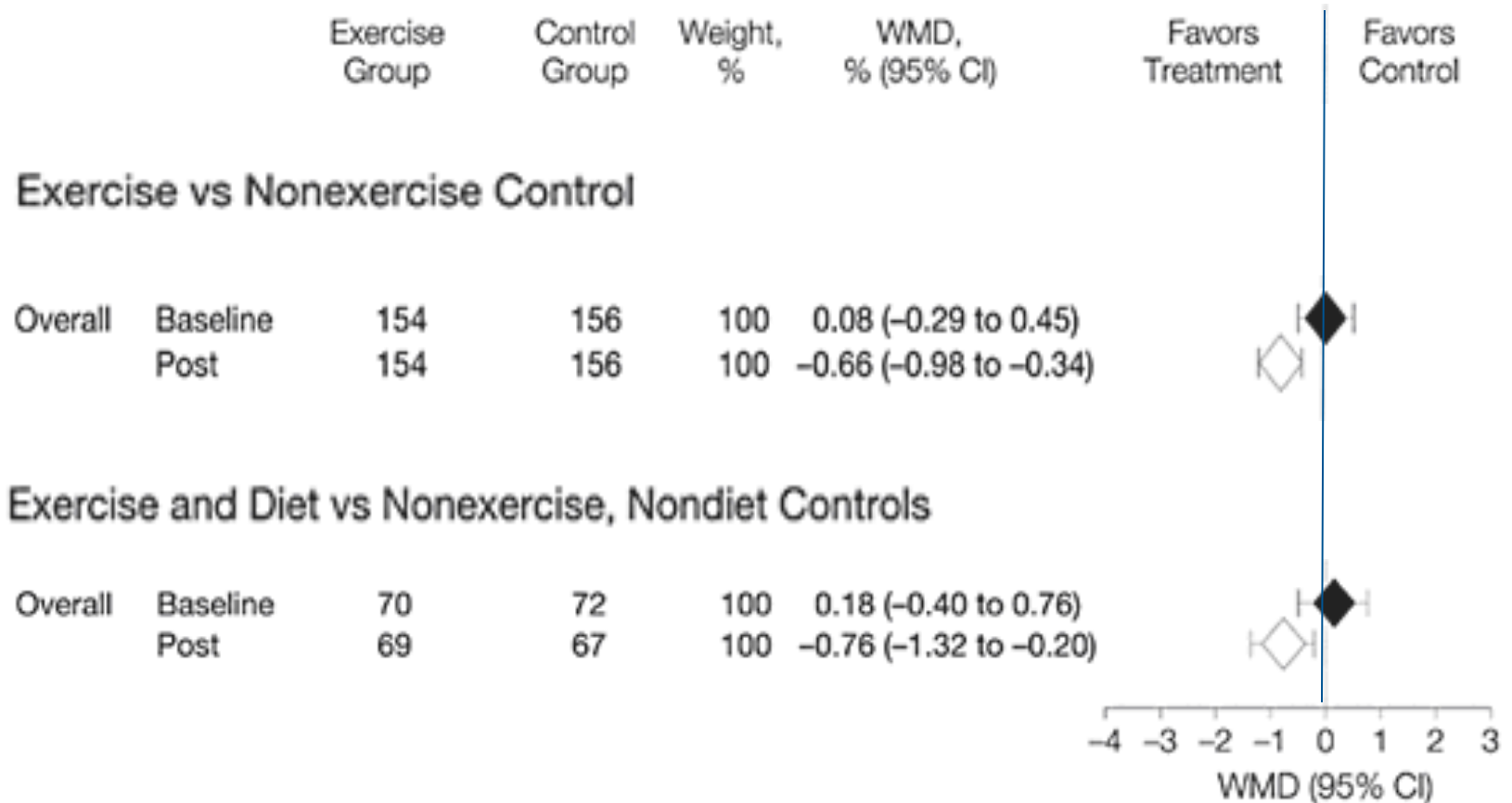
UKPDS study



Per 1 % reduction in HbA_{1c}:

- 37 % decrease in microvascular complications
- 14 % decrease in fatal & non-fatal MI

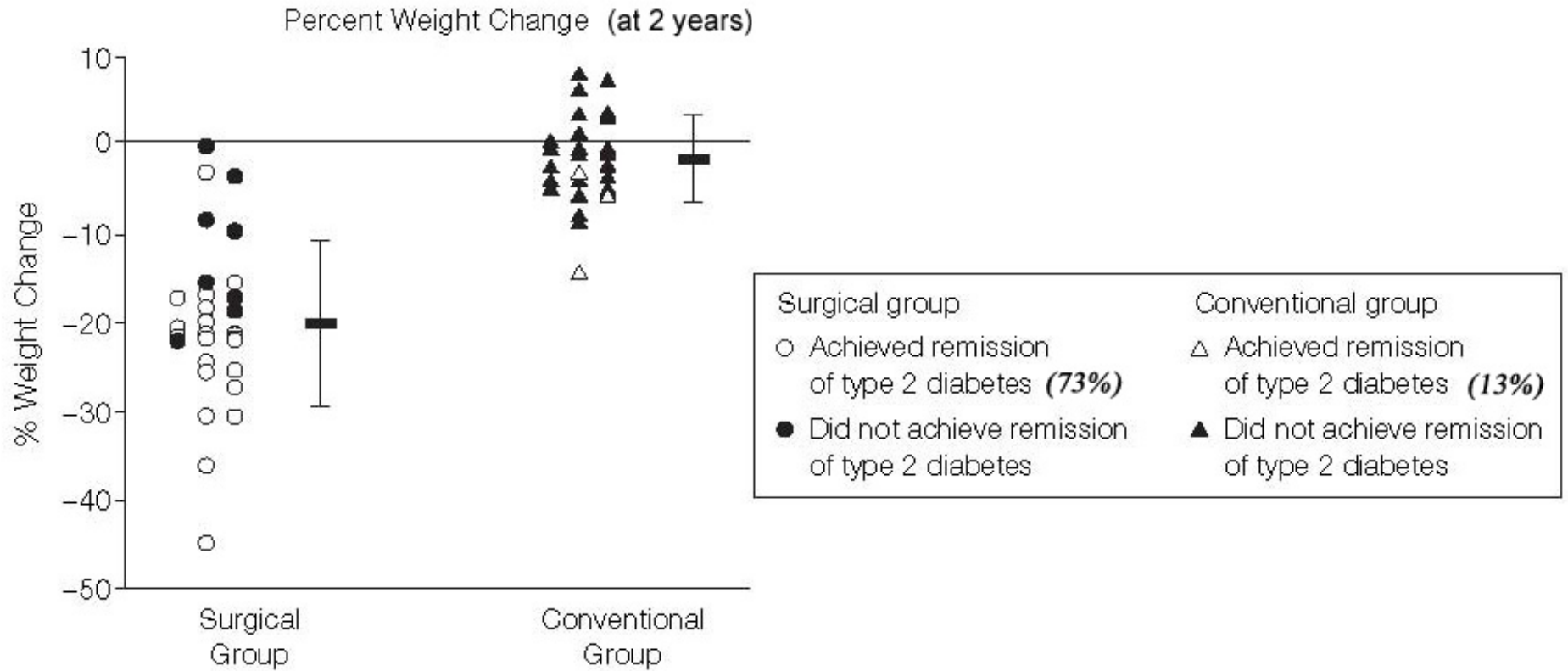
Meta-analysis of 14 clinical trials of effects of exercise intervention (>8 wks) on HbA1c in type 2 DM



HbA1c 7.65% vs 8.31%; weighted mean difference (WMD) -0.66%; $P < .001$).

No sig. difference in weight or BMI

Randomized controlled study of gastric banding vs lifestyle weight loss in 60 obese patients (BMI 30 to 40) with DM for less than 2 years



Evidence based nutrition principles

- The total amount of carbohydrate in meals and snacks is more important than the source or the type.
- Replacing carbohydrates with monounsaturated fat reduces postprandial glucose spikes & triglycerides
- You have to eat very large amounts of fiber to get the metabolic benefits
- Limit saturated fats -- less than 10 % of energy intake
- Dietary cholesterol intake – less than 300 mg/day

1. Secretagogues (e.g. sulfonylureas)
2. Metformin
3. Alpha glucosidase inhibitors
4. Thiazolidinediones
5. GLP-1 receptor agonists
6. DPP-4 inhibitors
7. SGLT2 inhibitors
8. Pramlintide
9. Insulin
10. (Bromocriptine; colesevelam)

ADA/EASD algorithm 2015

6 classes of drugs:

Metformin

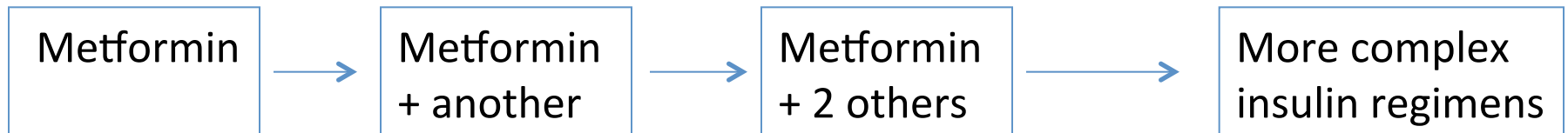
GLP1 receptor agonists/DPP 4 inhibitors

Sulfonylureas (+other secretagogues)

Pioglitazone

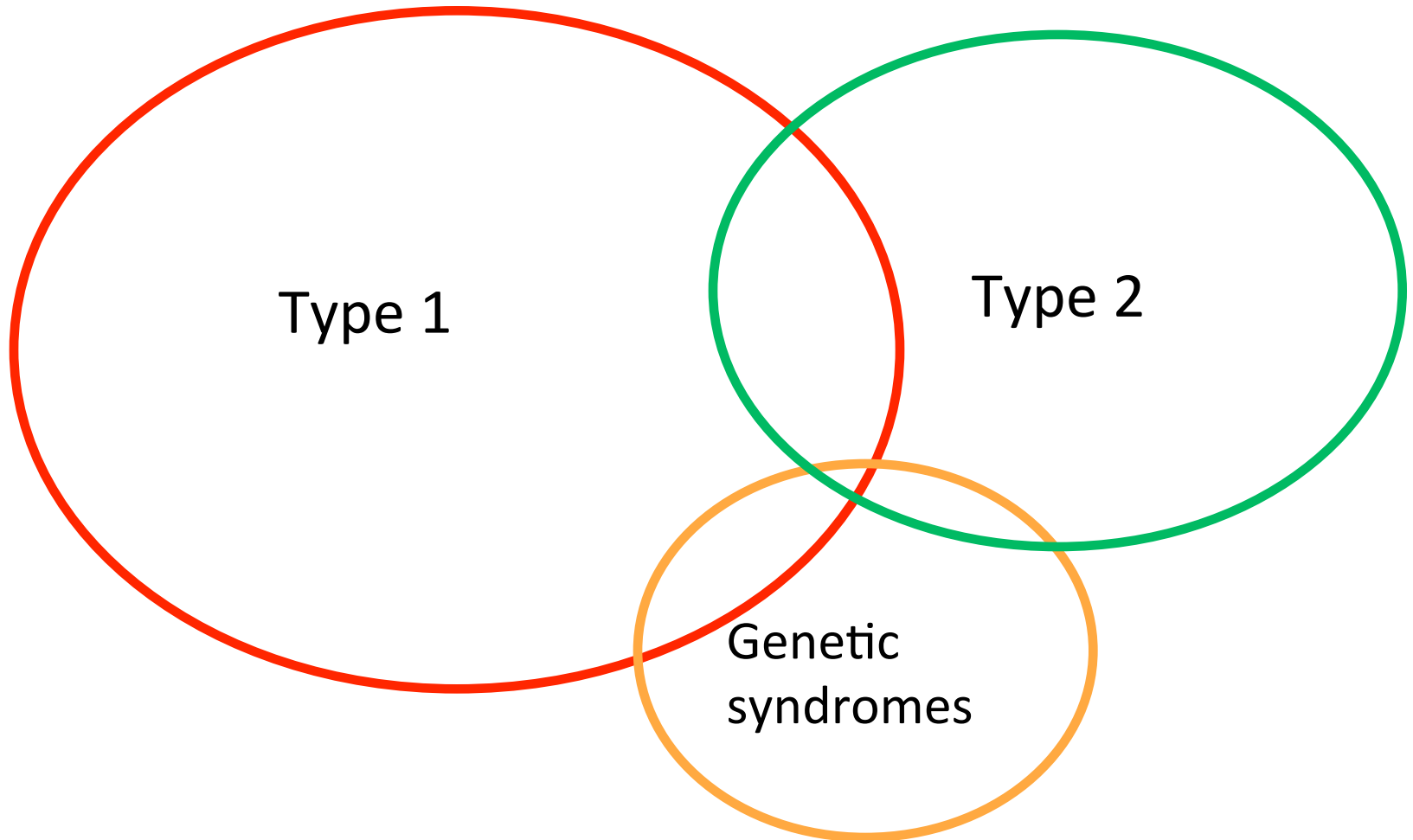
SGLT2 inhibitors

Insulin



In making therapeutic decision take into account efficacy; hypoglycemia risk; effect on weight; major side effects; cost

Overlap of phenotypes





- 80 YO Hispanic woman
- Diagnosed 4 yrs ago routine testing
- HbA1c deteriorated from 7.4 % to 13 % within a year

On Metformin 1 gm BID Glyburide 5 mg daily

- GAD Ab >30 (1 or < U/mL)
- ICA 512 Ab 3.7 (<0.8 U/mL)