Metabolic Syndrome, Diabetes & Psychiatry – An Emerging Problem

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Metabolic Syndrome: IDF 2005

- Central Obesity
  - Defined as waist circumference ≥ 94cm for Europid men and ≥ 80 cm for Europid women
- Plus ANY TWO of the following four factors
  - Raised TG: ≥ 1.7mmol/l or if specific treated
  - Low HDL: < 1.03mmol/l in men or < 1.29 in women or if specific treated
  - Raised BP: Systolic ≥ 130 or diastolic ≥ 85 or treatment of previously diagnosed hypertension
  - Raised fasting plasma glucose ≥ 5.6mmol/l or previously diagnosed type 2 diabetes. (If > 5.6 OGTT strongly recommended)

What is Diabetes?

"A complex metabolic disorder characterised by chronic hyperglycaemia resulting from defects in insulin secretion or insulin action, or both"

First described in 1550 BC

Two Main Types

- Type 1
  - Autoimmune destruction of the β cells of the Islets of Langerhans in the pancreas. This leads to an absolute insulin deficiency. Insulin treatment is therefore mandatory

  - Previously known as IDDM or juvenile onset diabetes

Two Main Types

- Type 2
  - Impaired insulin action (insulin resistance) and eventually, impaired insulin secretion as well
  - Usually treated with oral medication initially, then may move onto insulin
  - Formerly known as NIDDM or maturity onset diabetes

Epidemiology

- Diabetes currently affects approximately 3 to 4% of the population

- 90% of whom have Type 2 diabetes

- Lifetime risk of developing diabetes is about 10%

Why is it Important?

- Poorly controlled diabetes leads to accelerated cardiovascular morbidity and mortality

- A combination of microvascular and macrovascular disease

Thom T et al Circulation 2006;113(6):e85-151

Microvascular Disease

- Diabetic retinopathy – the commonest cause of blindness in the developed world
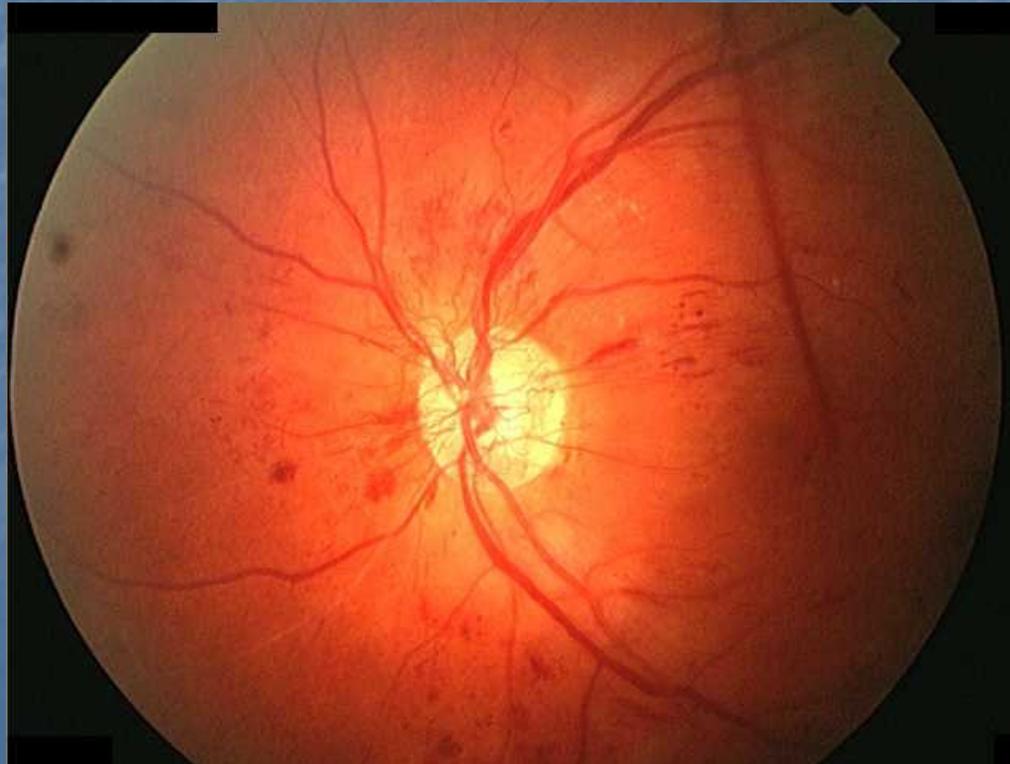
Microvascular Disease

- Neuropathy

Microvascular Disease

- Combinations of neuropathy and ischaemia

Microvascular Disease

- Nephropathy
  - Diabetes is the commonest cause of End Stage Renal Disease in the developed world

Macrovascular Disease

- CVA
- MI

7 Year Incident Rate of MI

Haffner et al NEJM 1998;339:229-234

Data From 3.3M Danes

Schramm TK et al Circulation 2008;117:1945-1954
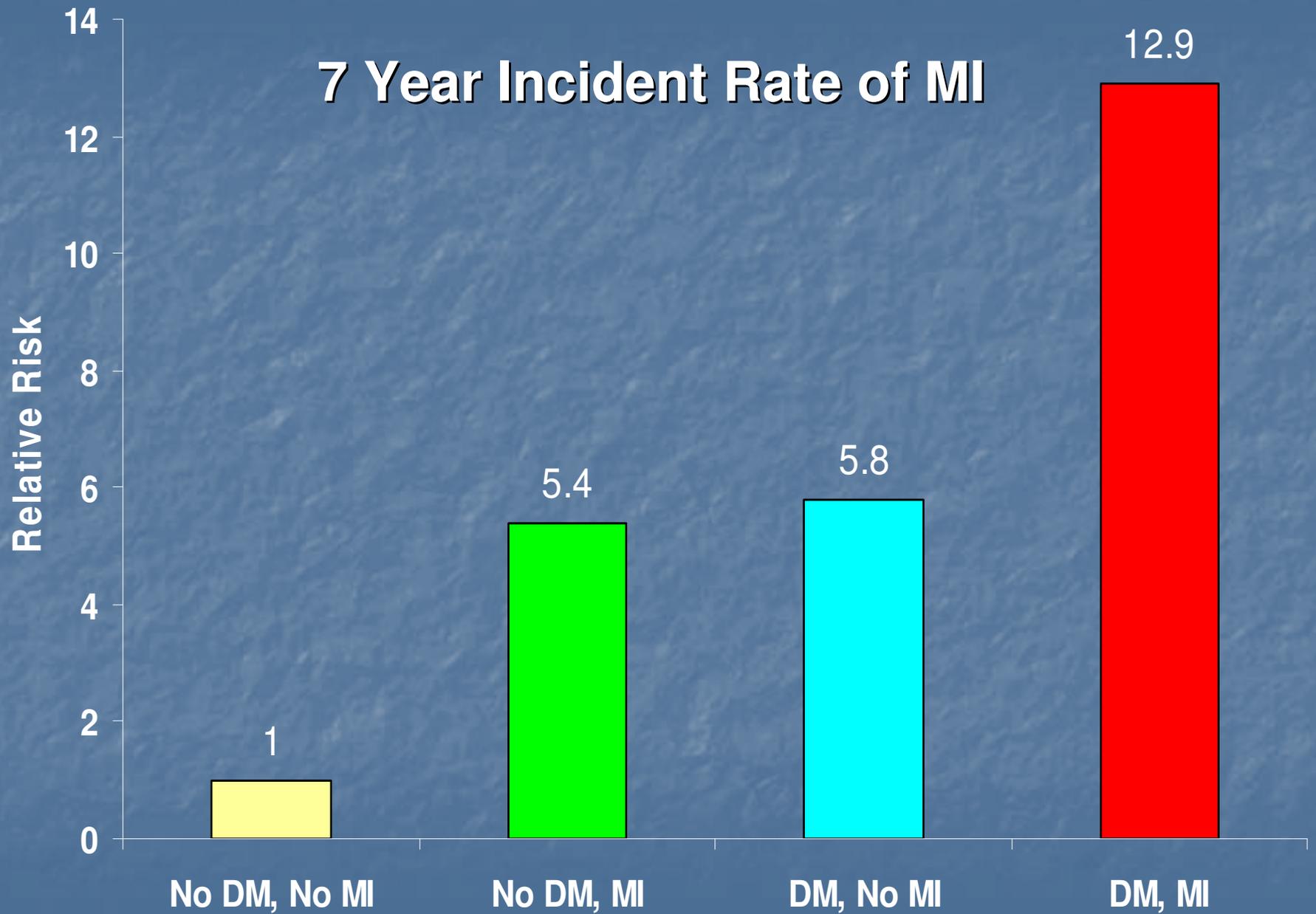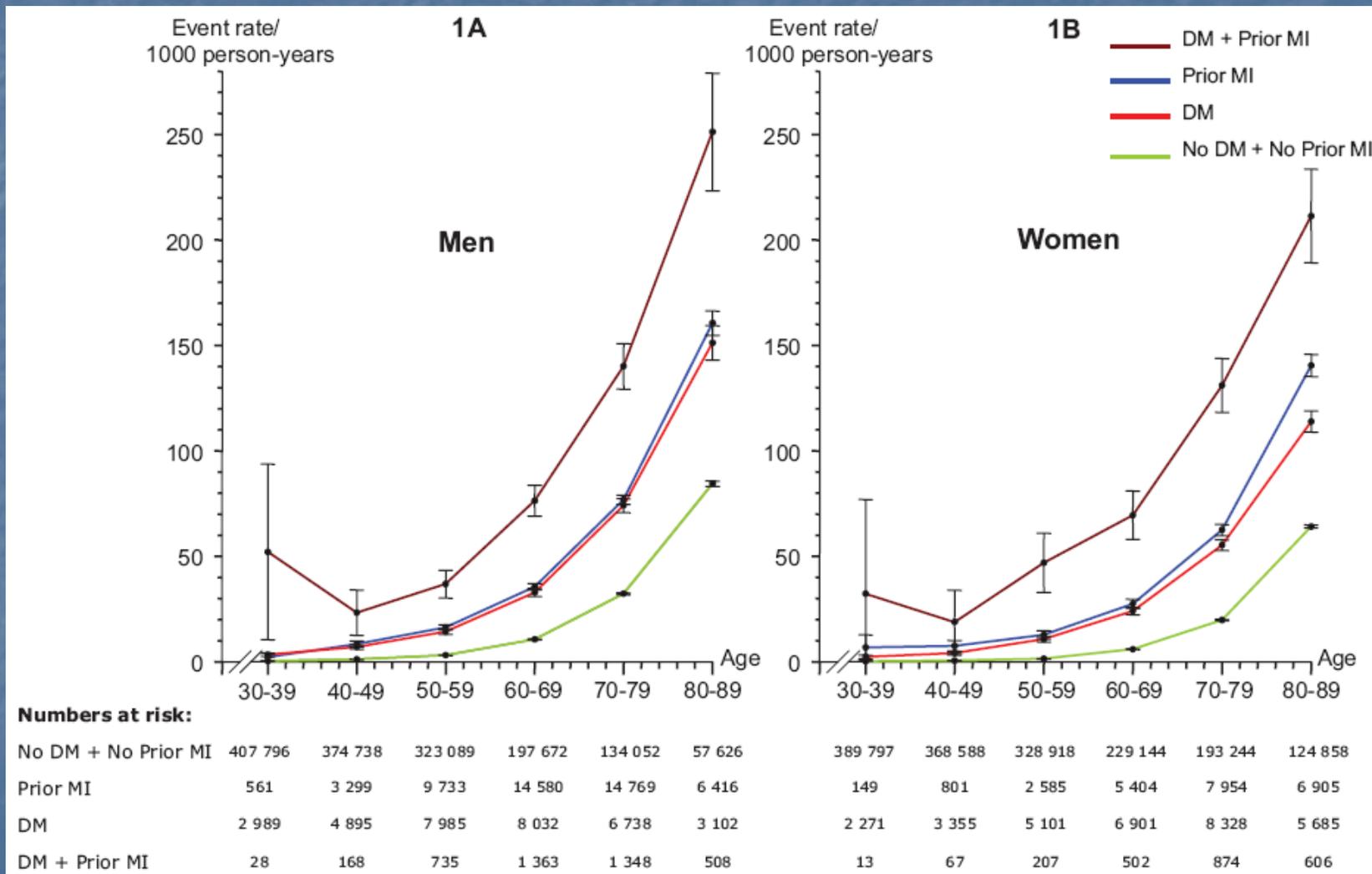
The Global Burden

- Diabetes related healthcare costs account for about 10% of all health expenditure in developed nations

The Incidence Of Type 2 Diabetes Is Rapidly Increasing

3 million in the UK by 2010

Type 1
Type 2

Diabetes prevalence (thousands)

3000
2500
2000
1500
1000
500
0

1995   2000   2010
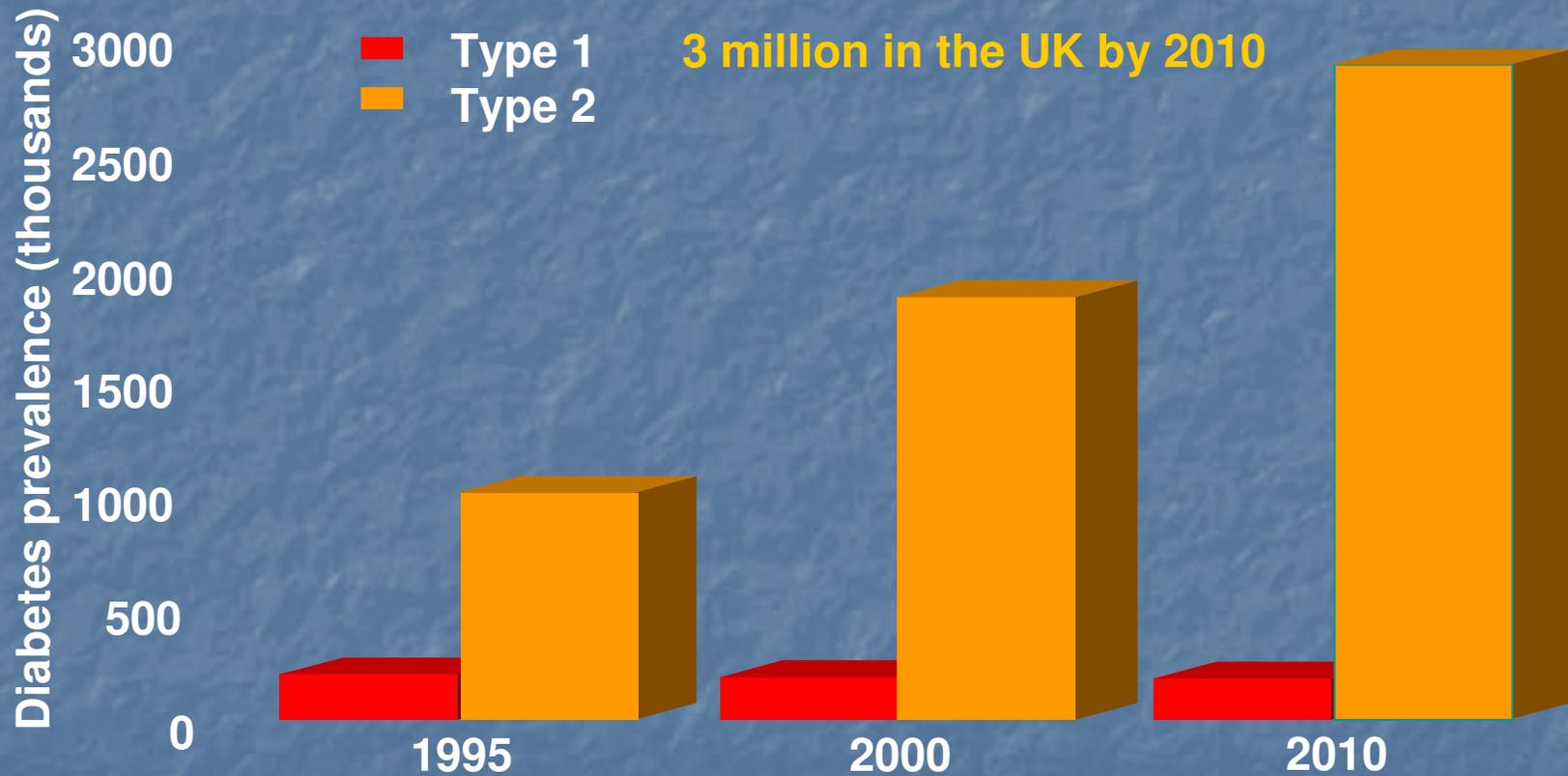
Amos et al Diab Med 1997;14(Suppl 5):S1–S85

'Traditional' Risk Factors for Type 2 Diabetes

GESTATIONAL DIABETES AND PARITY

GENETIC FACTORS
- Ethnicity
- Family history (40%)

CENTRAL OBESITY

PHYSICAL INACTIVITY

INCREASING AGE

Williams G, Pickup JC. Handbook of Diabetes. 2nd Edition, Blackwell Science. 1999.

Relative Risk of Developing Diabetes
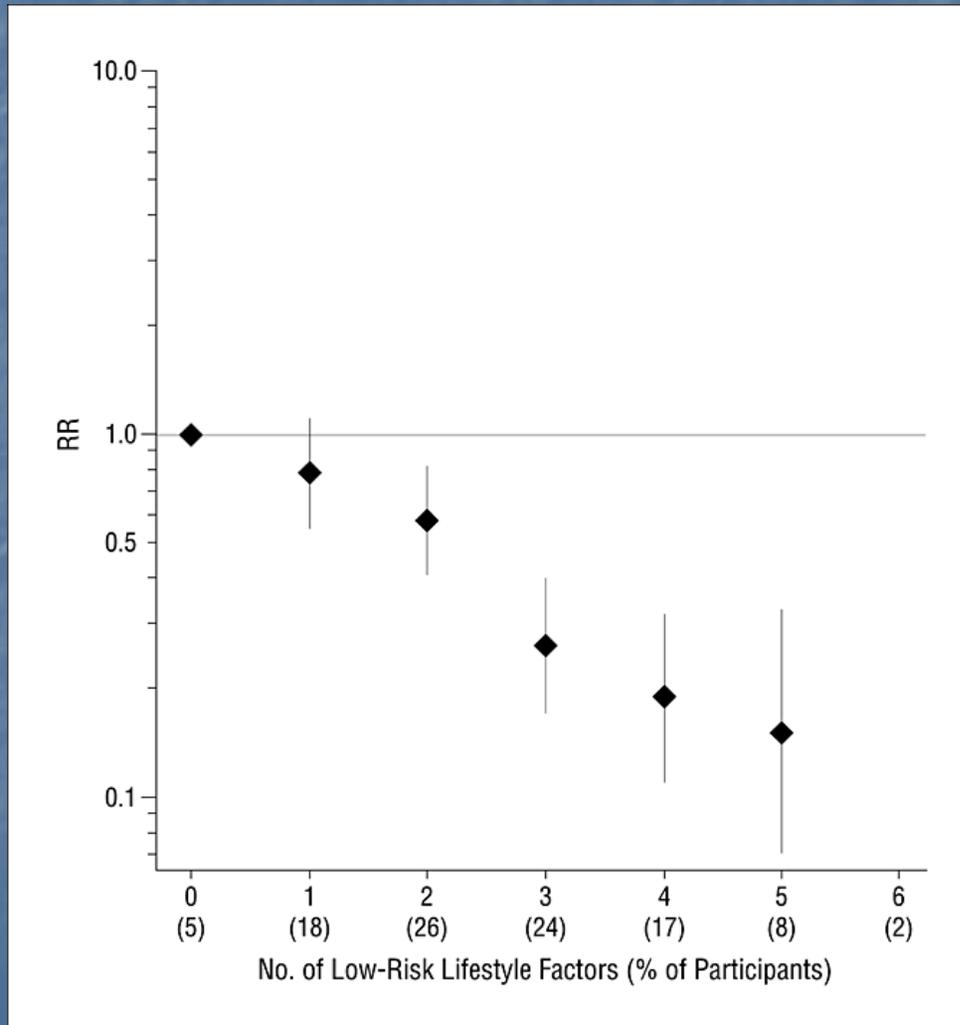
- Lower with more lifestyle factors
    - Moderate physical activity
    - Healthy diet
    - Never smoked
    - Moderate alcohol use
    - BMI<25
    - Waist circumference less than 88 cm for women or 92 cm for men

Mozaffarian D. Arch Intern Med 2009;169(8):798-807

The Main Risk Factor?

Body Weight has been Mirrored by an Increase in Type 2 Diabetes

Mean body weight (kg)

Diabetes prevalence (%)
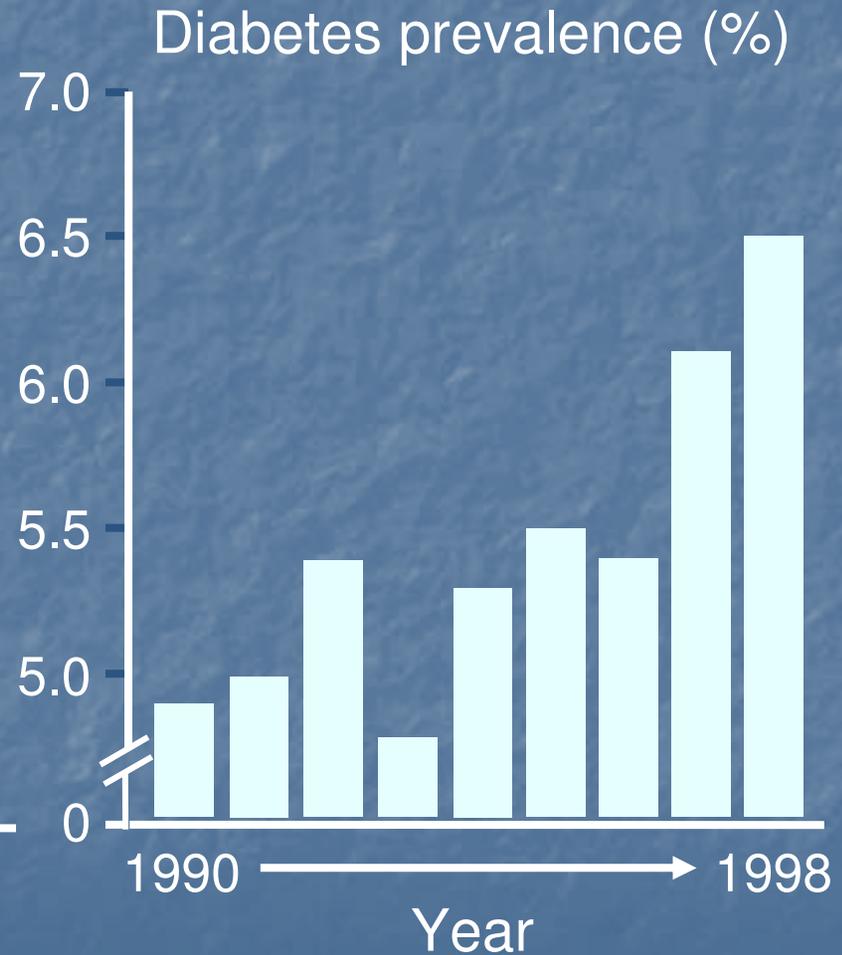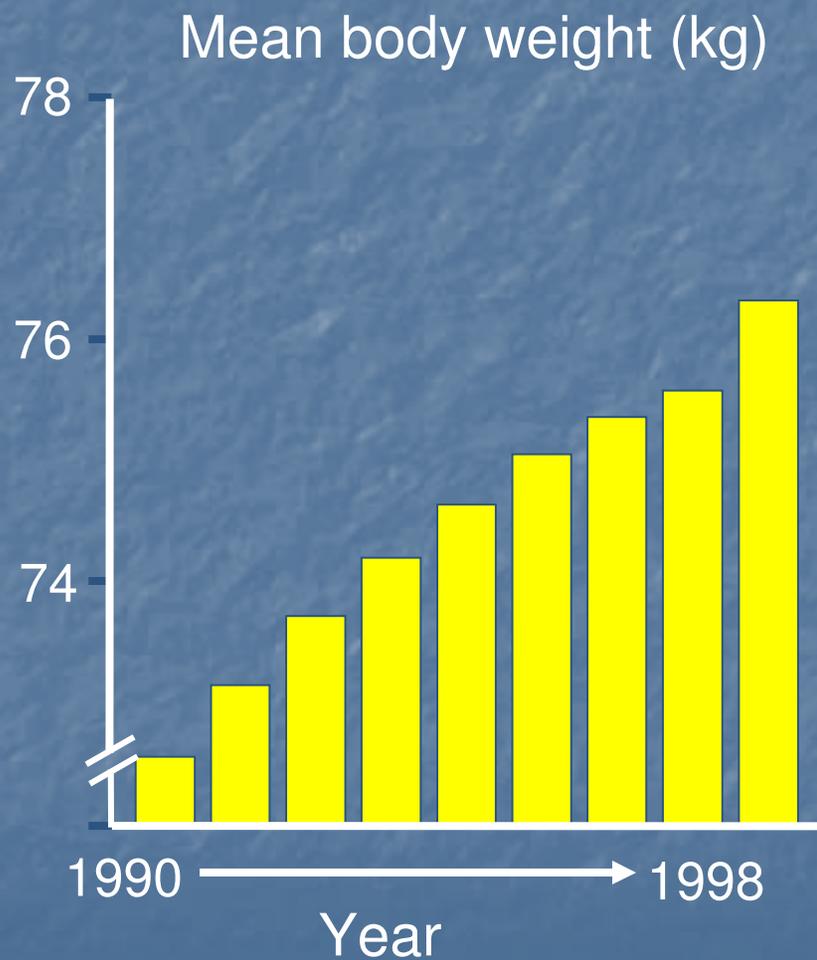
Adapted from Mokdad. Diab Care 2000; 23: 1278-1283

BMI is Directly Related to Risk of Development of the Metabolic Syndrome
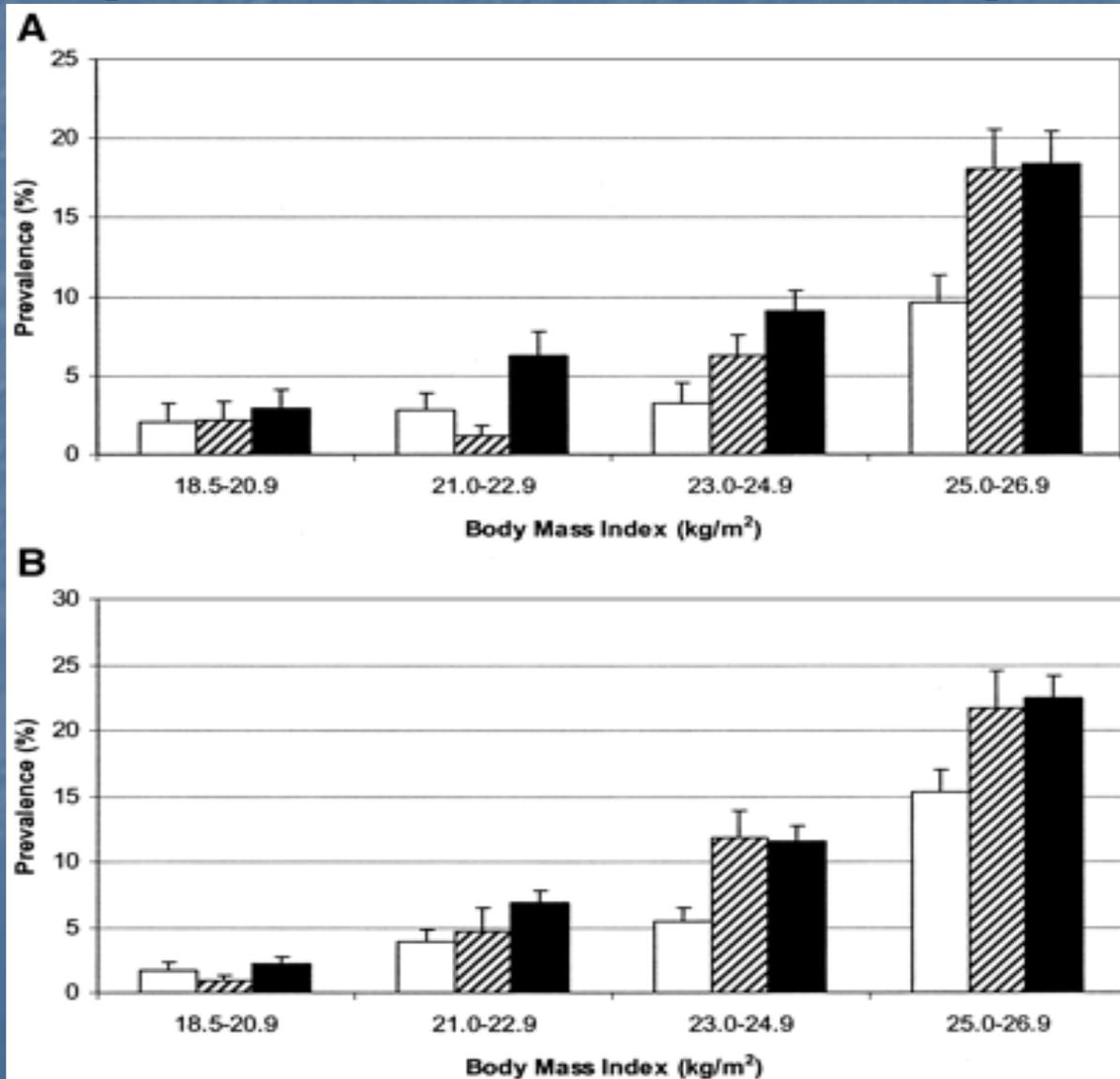
A = Men

B = Women

■ = Blacks

▨ = Hispanics

□ = Whites

St Onge MP et al Diabetes Care 2004;27(9):2222-2228

BMI and Diabetes
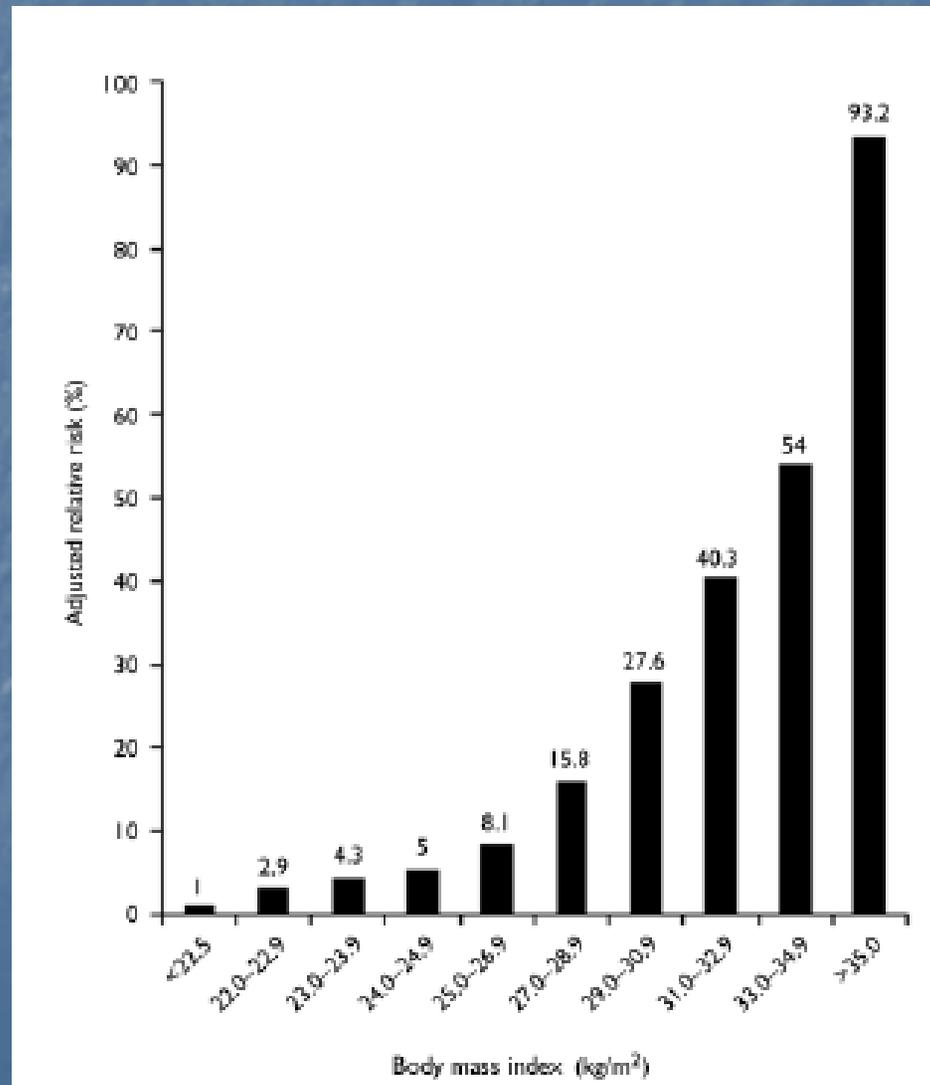
Colditz et al Ann Internal Med 1995; 122:481-486

β Cell Failure

Holman et al Diab Res Clin Pract 1998;40:S21-S25
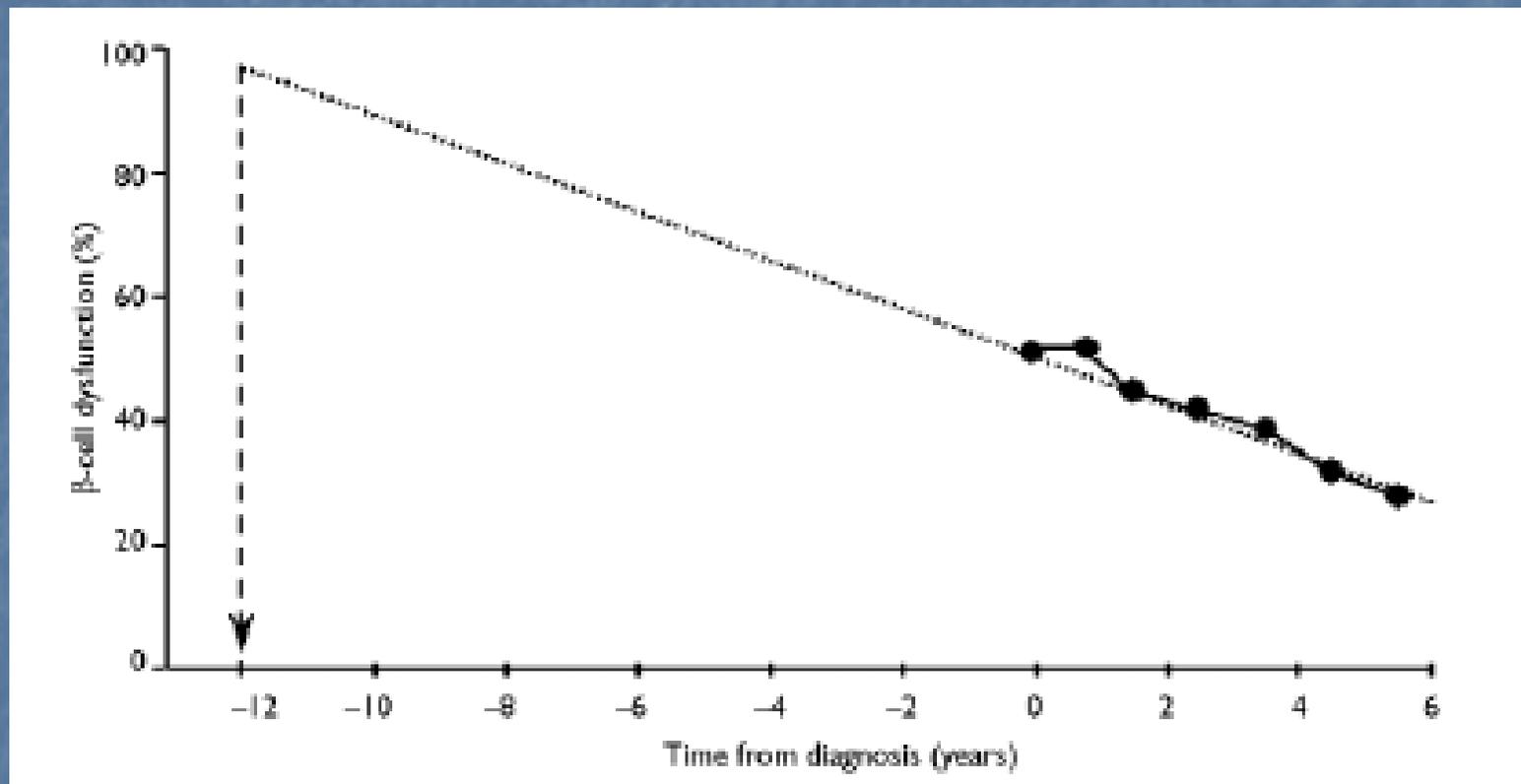
β Cell Failure
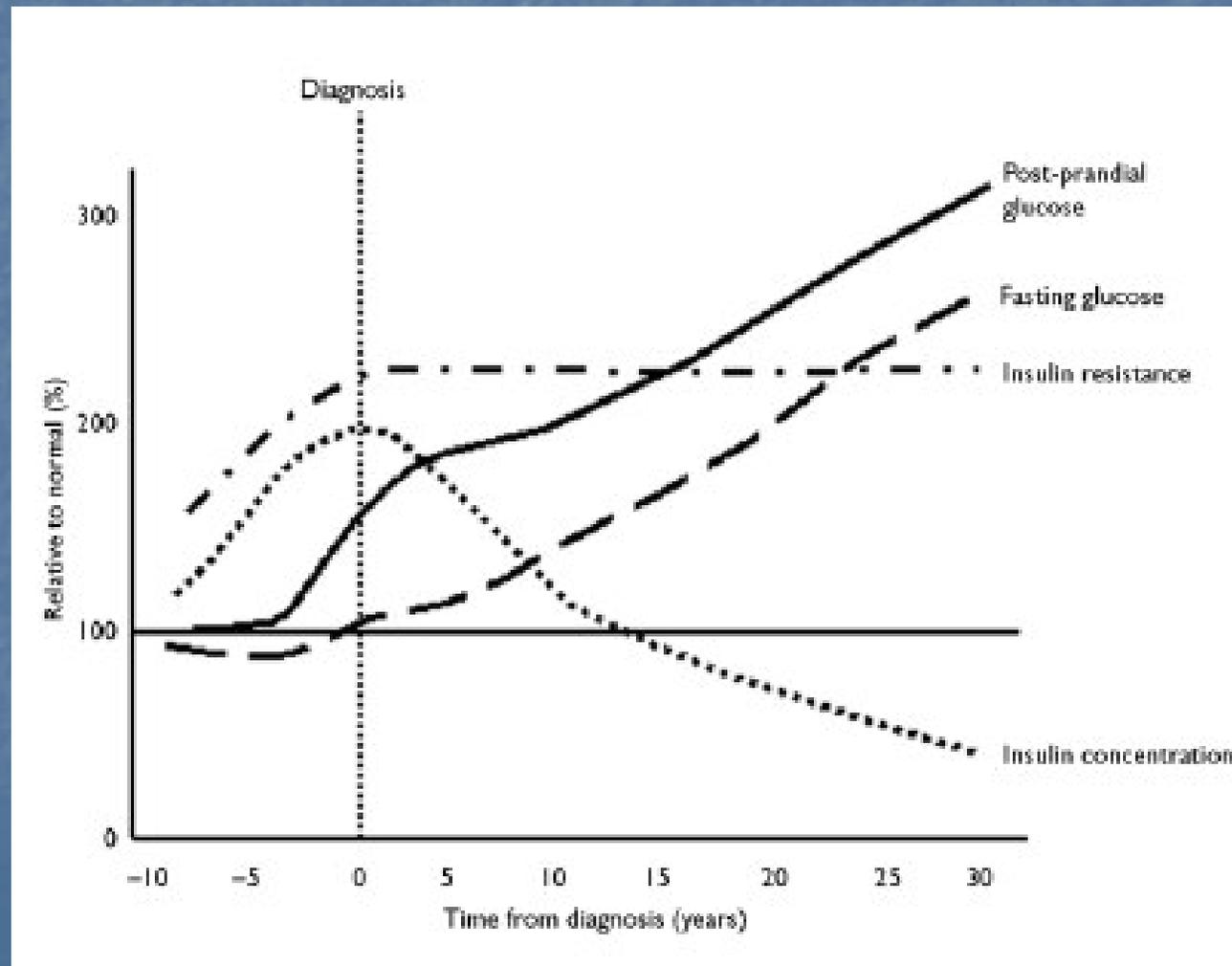
How Does Type 2 Diabetes Usually Present?

- Aged over 40
- Usually found serendipitously on screening or admission for other conditions
- Symptoms otherwise include
  - Weight loss
  - Polyuria and polydipsia
  - Fatigue and listlessness
  - Oral or genital thrush

Vascular Complications Of Type 2 Diabetes At The Time Of Diagnosis

Retinopathy — 21%

Nephropathy — 18%

Erectile dysfunction — 20%

Ischaemic skin changes (foot) — 6%

Abnormal vibration threshold (foot) — 7%

7% — **Cerebrovascular disease**

18% — **Abnormal ECG**

35% — **Hypertension**

4.5% — **Intermittent claudication**

13% — **Absent foot pulses**
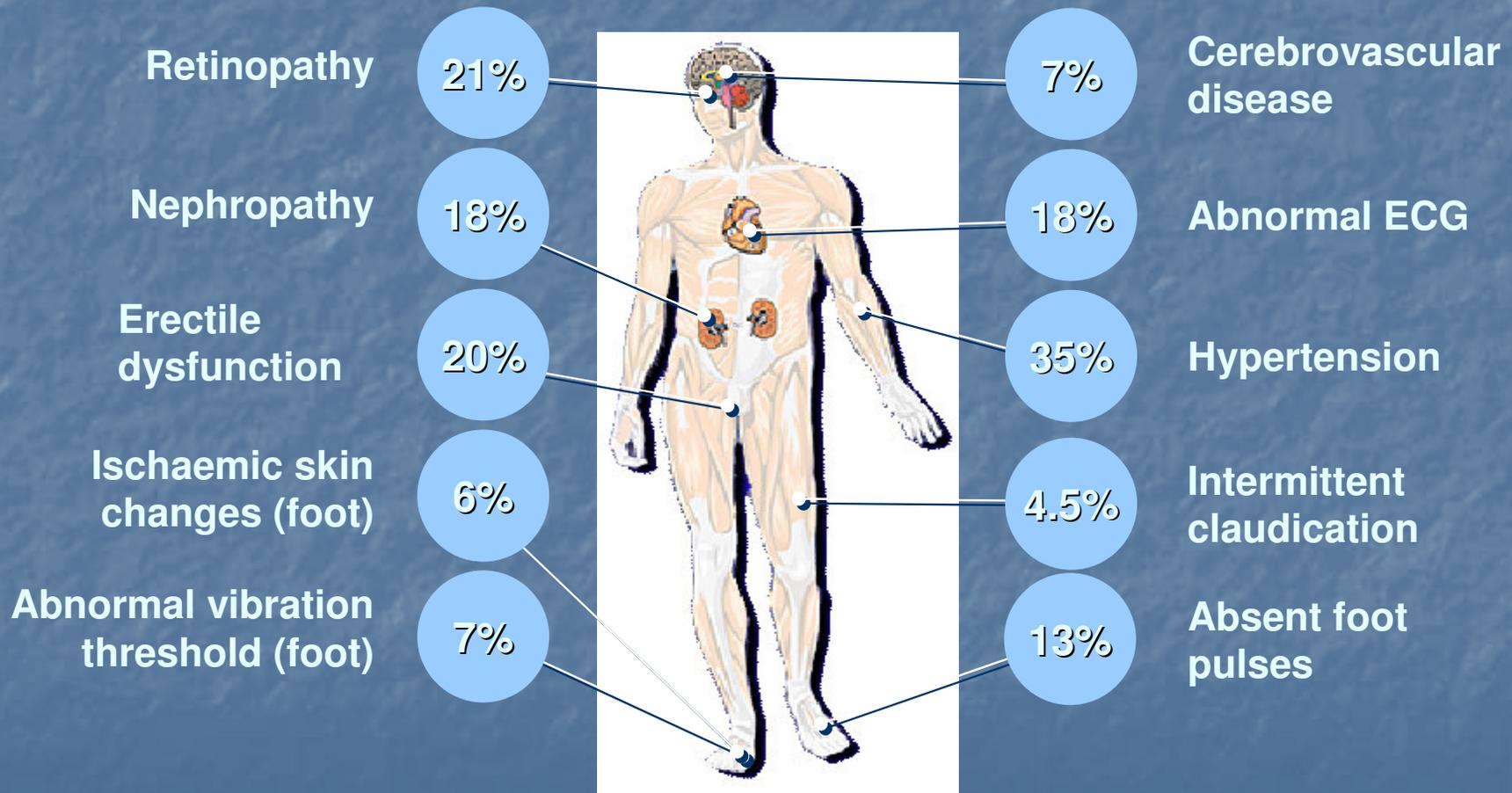
What Should be Done to Confirm the Diagnosis?

Plasma glucose concentration 2 h following a 75 g oral glucose test (mmol/l)	Fasting plasma glucose concentration (mmol/l)		
	< 6.1	≥6.1–6.9	≥7.0
<7.8	Normal	Impaired fasting glycaemia	Diabetes
≥7.8–11.0	Impaired glucose tolerance	Impaired glucose tolerance	Diabetes
≥11.1	Diabetes	Diabetes	Diabetes

Diabetes and Psychiatry

" Diabetes is a disease which often shows itself in families in which insanity prevails"

Sir Henry Maudsley, 1879

Diabetes and Psychiatry

- Schizophrenia is associated with 2-3 times higher levels of diabetes than the rest of the population – a relationship first described in 1922

- This may be related to lifestyle – poor nutrition, lack of exercise, etc

- Recent finger pointing at conventional and 'atypical' antipsychotics

Meduna F et al *Arch Neurol Psychiatry* 1942;47:38–52
Braceland F et al *Am J Psychiatry* 1945;102:108–110
Barnett AH et al *J Psychopharm* 2007;21:357-373

Diabetes and Schizophrenia

- Some aspects of the metabolic syndrome are more prevalent in schizophrenia, such as visceral obesity and glucose intolerance (1.5 to 2 fold)

- Others are not – e.g. hypertension and detrimental lipid profile

Mechanisms Linking Diabetes with Schizophrenia

Bushe C & Holt R Br J Psych 2004;184(Suppl 47):s67-71
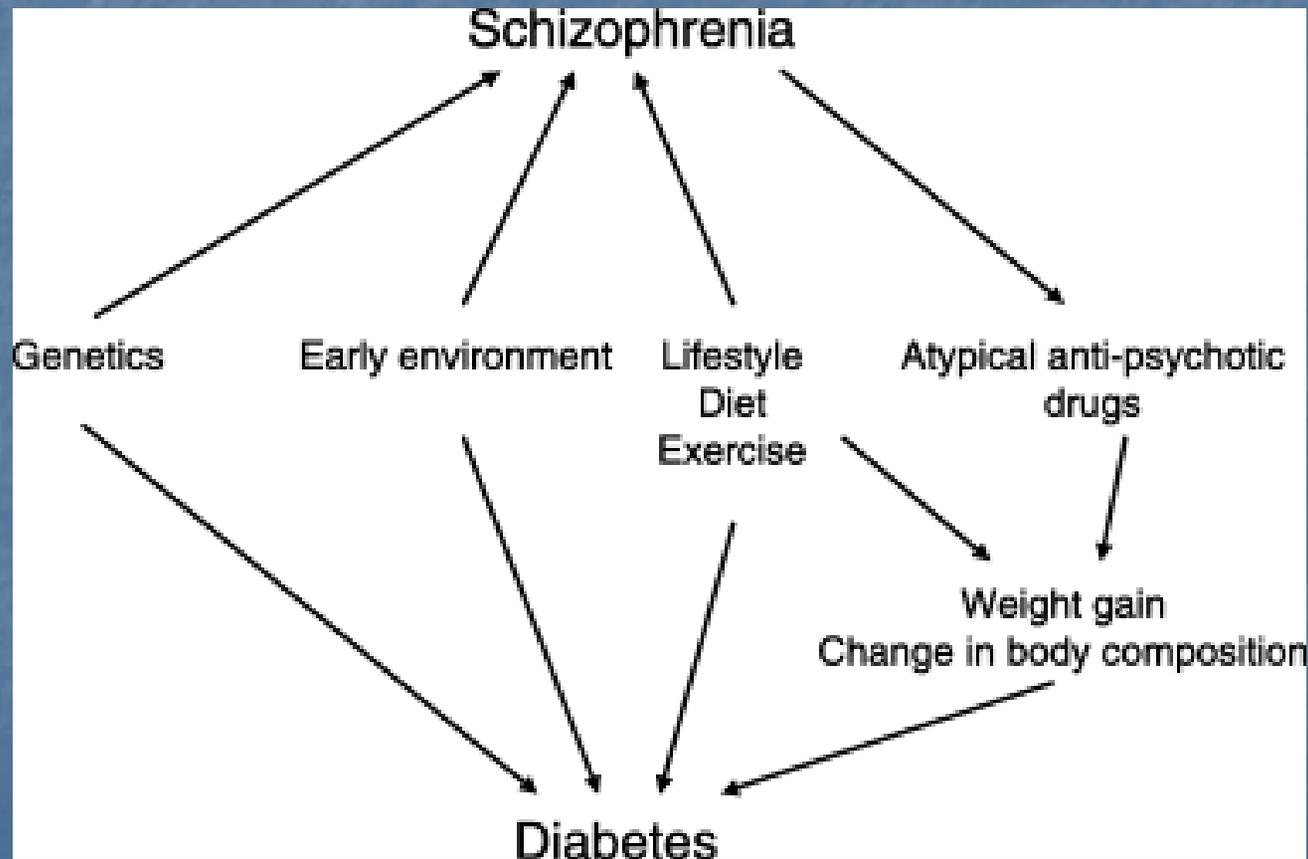
Genetics

- Up to 30% of people with schizophrenia have a family history of diabetes

- There is overlap between the genes thought to be responsible for the development of both conditions

Mukherjee S et al 1989 *Lancet*, i, 495

Early Environment

- Links now established between low birth weight and the increased risk of developing diabetes

- Low birth weight is also associated with neurological or psychological problems

Lifestyle and Diet

- Poverty and poor access to good nutrition are associated with Type 2 diabetes

- Individuals take in fewer calories, but they take in a higher proportion of fat with less fruit and vegetables, and less minerals and vitamins

- Little exercise, with high smoking rates

- This is a pattern seen in schizophrenia

Brown et al. *Psychol Med.* 1999;29:697–701
Newcomer. *CNS Drugs.* 2005;19(Suppl 1):1–93

Obesity is More Common With Mental Health Disorders

- Globally, DSM-IV mental disorders (anxiety disorders, depressive disorders, alcohol use disorders) are modestly associated with obesity

Scott et al *International Journal of Obesity* (2008) **32,** 192–200

Lifestyle and Diet

- In one study 15% of newly diagnosed drug naïve patients with schizophrenia have impaired fasting glucose compared to healthy volunteers

Ryan et al Am J Psychiatry 2003;160(2):284-289

Drugs and Diabetes

- Drugs directly toxic to the Islets
  - Ciclosporin, Pentamidine
- Drugs increasing insulin resistance
  - Glucocorticoids

Antipsychotics and Diabetes

- Phenothiazine use increased the prevalence of diabetes from 4.2% in 1956 to 17.2% in 1968

- Ketoacidosis was reported with clozapine and olanzapine use, with glucose metabolism normalising after drug withdrawal

Antipsychotics and Diabetes

Drug	Weight gain	Risk for diabetes	Worsening lipid profile
Clozapine	+++	+	+
Olanzapine	+++	+	+
Risperidone	++	D	D
Quetiapine	++	D	D
Aripiprazole*	+/−	−	−
Ziprasidone*	+/−	−	−

+ = increase effect; − = no effect; D = discrepant results. *Newer drugs with limited long-term data.

Weight Gain and Antipsychotics

	Number of studies	Number of participants	Mean weight-gain difference (kg; 95% CI)	p value
SGA versus haloperidol				
Amisulpride	2	373	0·9 (0·2 to 1·6)	0·012
Aripiprazole	2	1598	0·6 (−0·1 to 1·2)	0·071
Clozapine	3	170	3·4 (2·0 to 4·9)	<0·0001
Olanzapine	9	2952	3·3 (2·2 to 4·4)	<0·0001
Quetiapine	3	945	1·4 (0·7 to 2·1)	<0·0001
Risperidone	9	1366	1·7 (0·9 to 2·4)	<0·0001
Sertindole	2	779	3·3 (0·2 to 6·4)	0·040
Ziprasidone	1	301	0·1 (−1·2 to 1·3)	0·887
Zotepine	3	321	2·7 (1·7 to 3·7)	<0·0001
SGA versus low-potency FGA				
Amisulpride	1	30	0·3 (−3·6 to 4·2)	0·881
Aripiprazole	..	..	..	..
Clozapine	3	232	0·3 (−1·6 to 2·2)	0·753
Olanzapine	..	..	..	..
Quetiapine	1	201	0·5 (−1·0 to 2·0)	0·518
Risperidone	..	..	..	..
Sertindole	..	..	..	..
Ziprasidone	1	307	−1·1 (−2·3 to 0·2)	0·087
Zotepine	1	106	1·0 (−0·9 to 2·9)	0·306

FGA=first-generation antipsychotic drug. SGA=second-generation antipsychotic drug.

Leucht S et al Lancet 2009;373(9657):31-41

It's Not Limited to Adults

Treatment	Weight gain over 12 weeks (Kg) [95% CI]
Olanzapine	8.5 [7.4, 9.7]
Quetiapine	6.1 [4.9, 7.2]
Risperidone	5.3 [4.8, 5.9]
Aripiprazole	4.4 [3.7, 5.2]

205 children aged 5 to 19

But People With Schizophrenia Are Already at Increased Risk

- In drug naïve people with schizophrenia evidence shows that they start with an increased risk of developing diabetes

- Increased hepatic insulin resistance
  - Unrelated to intra abdominal fat mass or other known factors associated with hepatic insulin resistance

Van Nimwegen et al JCEM 2008;93(2):572-577

Antipsychotics and Diabetes

- Conflicting results from epidemiological and observational studies

- Results vary from no increase in incidence in diabetes to up to 34% increased risk of developing diabetes with antipsychotic use

Antipsychotics and Diabetes

- BUT major methodological differences in data collection, inclusion criteria, demographic details, activity levels, polypharmacy, race, alcohol intake, etc, etc

Austin Bradford Hill Criteria

- Strength
- Consistency
- Specificity
- Temporality
- Biological gradient
- Plausibility
- Coherence
- Experimental evidence
- Analogy

1897 - 1991

What Do The SPC's Say?

- Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotic agents

What Do The SPC's Say?

- Incidence for hyperglycaemia is very rare (<0.01%) for the following
    - Olanzapine
    - Risperidone
    - Quetiapine
    - Clozapine (rare <0.01 - <0.1%)
    - Aripiprazole (very rare <0.0001%)

Risk Attributable to AAPD v FGAs
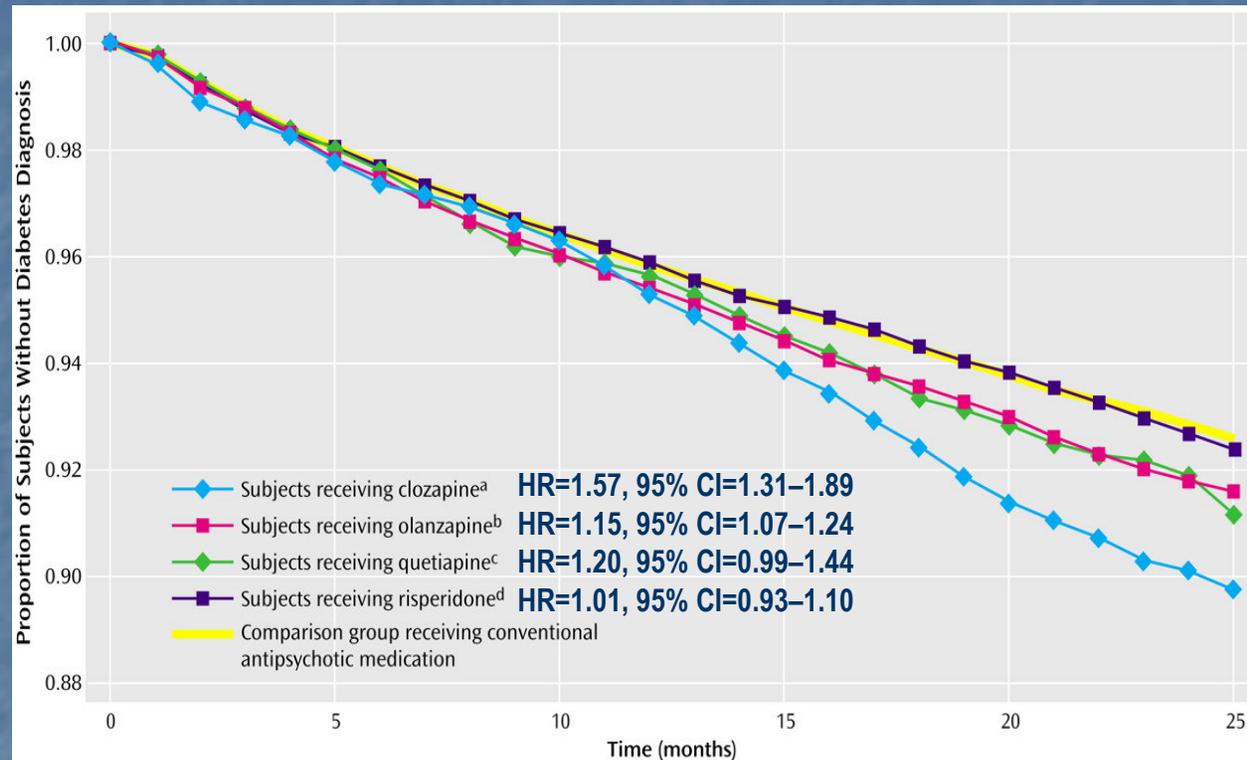
- 60,000 Veterans Administration patients
- The attributable risk was highest for clozapine (2.03%), followed by quetiapine (0.80%), olanzapine (0.63%), & risperidone (0.05%)

Leslie & Rosenheck 2004

Antipsychotics and Diabetes

- On further analysis of the data
  - Most individuals who do go on to develop diabetes do so within the first 3 – 4 months of starting the drug
  - Most were male
  - Most were overweight prior to starting the drug
  - Most had a family history of type 2 diabetes

Antipsychotics and Diabetes

- These drugs are not directly islet cell toxic but are often associated with weight gain, thus may indirectly cause increased insulin resistance

- Clozapine and olanzapine are associated with most weight gain, with olanzapine causing higher lipid levels. Ziprasidone was associated with the least weight gain

Lieberman et al NEJM 2005;353(12):1209-1223

Antipsychotics and Diabetes

- The mechanism for the weight gain is unknown but is thought to involve alterations in hypothalamic neurotransmitter levels involved in food finding behaviour and satiety

Degree of Additional Risk with Newer Atypicals?

? Additional possible small risk associated with some atypicals over typicals 0.05 – 2.03%

Additional 2 to 4 fold risk associated with mental illness

Established Risk Factors e.g. age, ethnicity, family history, weight, etc.

Problems with Trials

- Most of the trials looking at this issue are sponsored by the drug companies

- When they are comparator trials – it is always the 'other guy' who has more diabetes than the sponsor's drug

- Independently conducted trials indicate that newly emergent glucose intolerance is independent of antipsychotic treatment

What Does All This Mean to You, the Practicing Psychiatrist?

- There are artificial boundaries in the NHS between physical illness and mental illness

- This means that there is often no 'seamless' care for these individuals between specialties

Implications

- NICE in 2002 recommended 'atypical' antipsychotics as first line to prevent extra-pyramidal side effects, but this was updated in March 2009 (CG 82) to say in "newly diagnosed schizophrenia offer oral antipsychotic medication"

- "Provide information and discuss the benefits and side-effect profile of each drug with the service user."

- This suggests that the incidence of type 2 diabetes is likely to keep rising

- This may be asymptomatic

- Thus these individuals need to be regularly screened for diabetes

Screened How?

- A fasting or random blood glucose is the best method

- Ideally within 3 months of starting the drug and then at least once a year

- Also measure their BMI and BP prior to starting the drugs

How Do You Treat Them?

- The best combination to prevent weight gain (and the subsequent risk of developing diabetes)
  - Lifestyle intervention with diet and exercise
  - Metformin

Wu et al JAMA 2008;299(2):185-193

Follow Up

- BMI should be measured every 3 months

- BP should be measured after 3 months and then annually

- If the patient gains excessive weight, consider switching to an alternative antipsychotic agent

Does this Happen?

- In February 2004, the ADA / APA / AACE published a consensus statement that said that anyone on second generation antipsychotics have baseline and ongoing assessment for fasting glucose and lipids

No

Trends in baseline serum glucose (A) and lipids (B) laboratory testing in SGA-treated adults
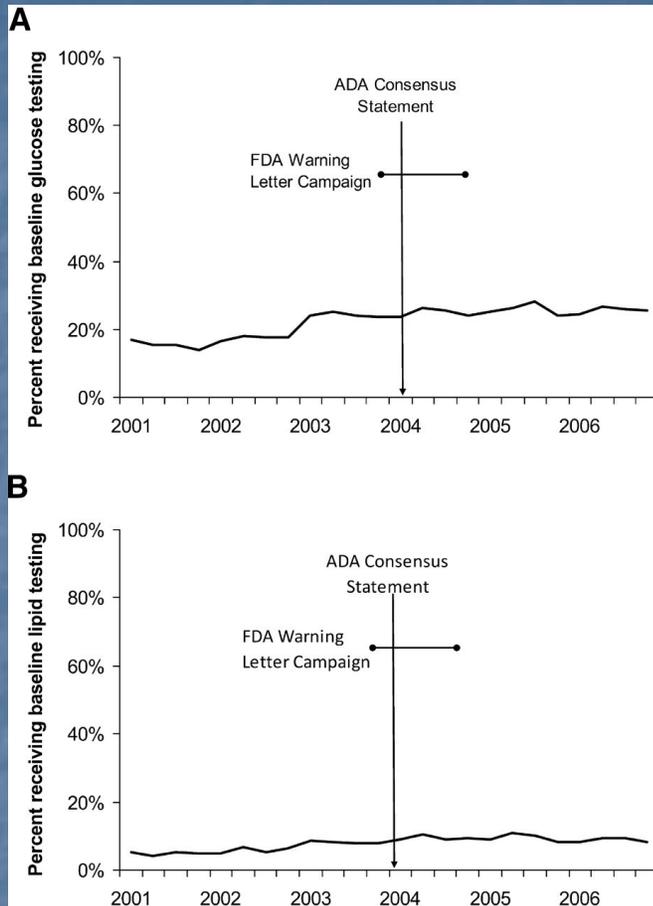
n = 18,876 adults initiating SGA drug therapy
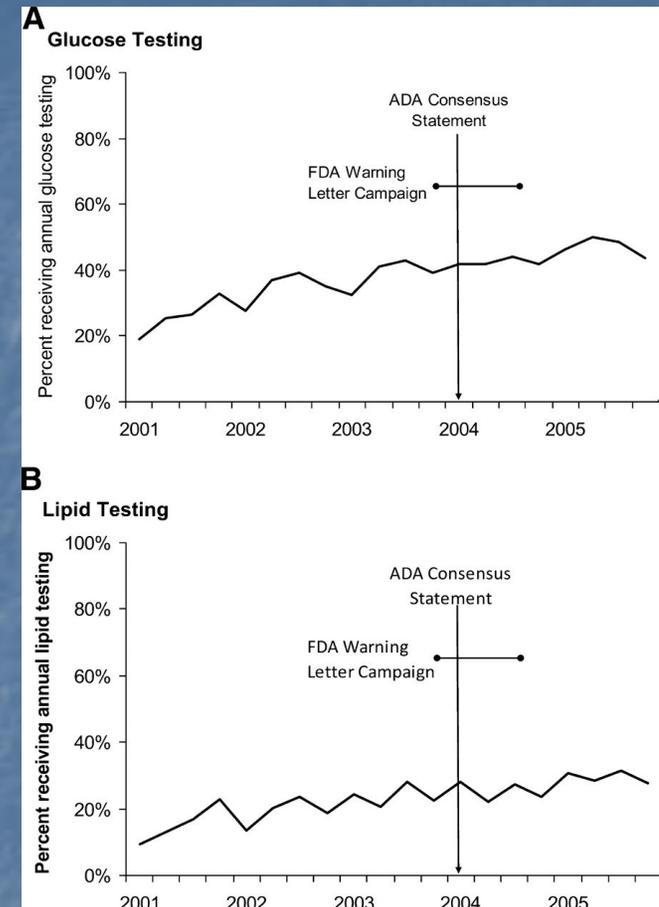
n = 3,140 adults initiating SGA drug therapy who were therapy persistent for 1 year

Diabetes Care 2009;32(6):1037-1042

What Can You Do?

- If your patient is diagnosed with diabetes
  - Ensure that that GP knows
  - Put the patient on aspirin 75 mg once a day after food
  - Put the patient on a statin at 40 mg at night
  - Try and get the BP down to less than 140/80 using an ACE inhibitor

What Can You Do?

- Behavioural therapy is useful
  - 35 patients with a BMI > 30 Kg/m^2 were enrolled
  - 12-week group behavioural weight control program
  - Mean weight loss over 12 weeks = 2.5 Kg
  - A further 3 months after treatment, mean weight loss was 3.2 Kg

Kalarachian et al *J Clin Psychiatry* 2005;66:1058-1063

Potential Difficulties

- Compliance – family and care givers need to be 'in the loop'

- Care in the Community with the burden on the GP

- Lack of appropriate training for nursing staff looking after psychiatric inpatients

- Who takes responsibility for these patients?

Thank you for your attention