Antipsychotics and glucose metabolism: assessing the risks

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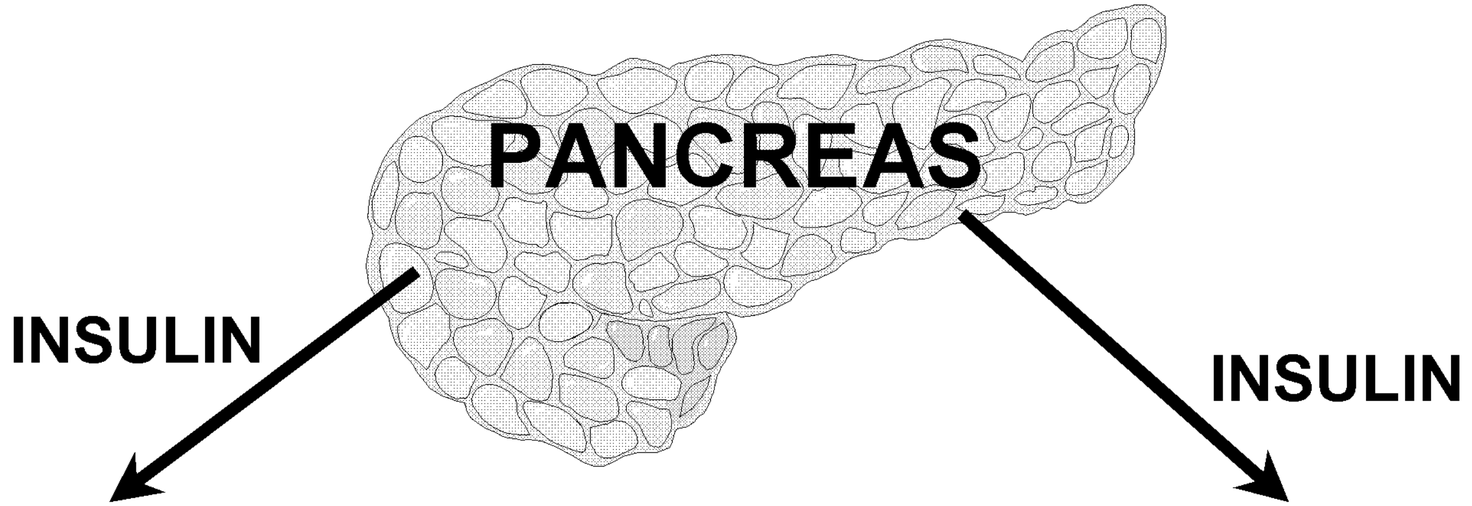
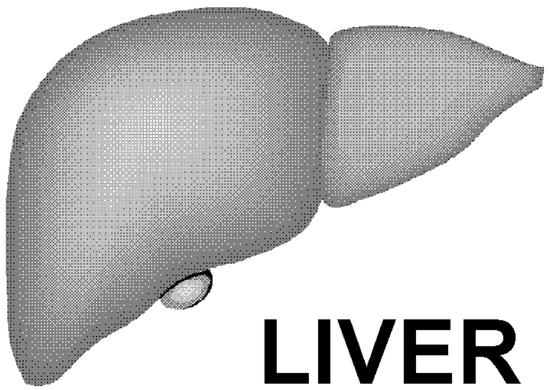
Diabetes mellitus

- A group of metabolic diseases
- Characterised by hyperglycaemia due to defects in insulin secretion, action, or both
- Primary insulin actions occur at
  - skeletal muscle (stimulation of glucose disposal)
  - liver (inhibition of glucose production)
  - adipose tissue (inhibition of lipolysis)

Primary effects of insulin on blood glucose

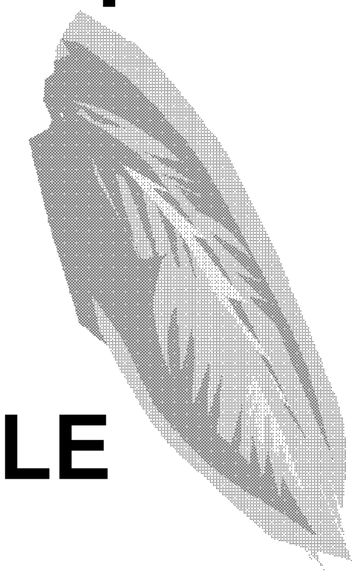


Decrease hepatic glucose production



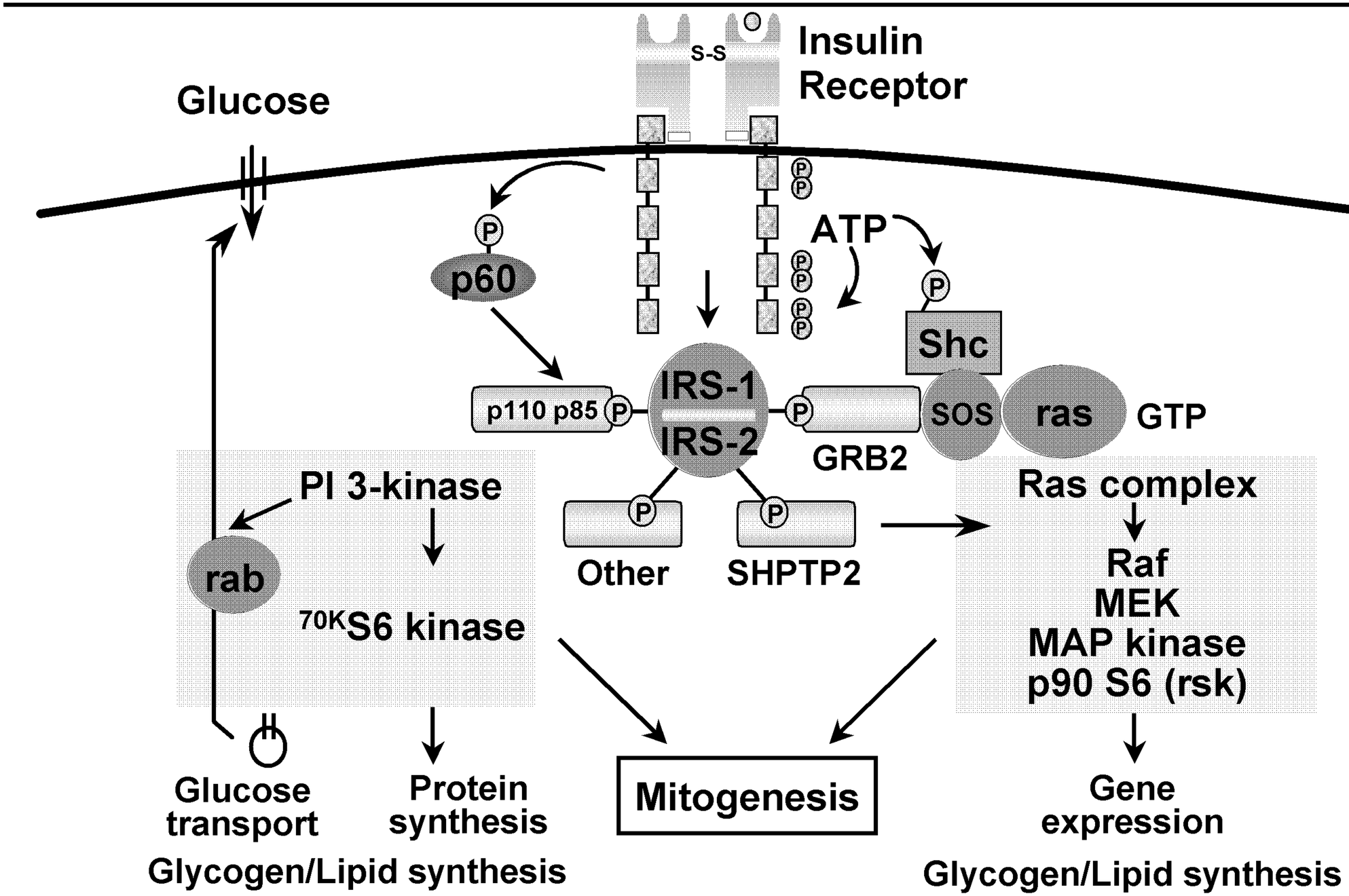
LIVER

Increase peripheral glucose uptake



MUSCLE

Insulin signalling pathways



Type 2 diabetes mellitus

- Disturbances in insulin action lead to abnormalities in glucose and lipid metabolism
- Type 2 is the most prevalent form, resulting from insulin resistance plus an insulin secretory defect
- A serious public health problem with over $100 billion in annual expenditure in the US[1]

[1]Ratner RE. Diabet Med 1998;15:S4–7.

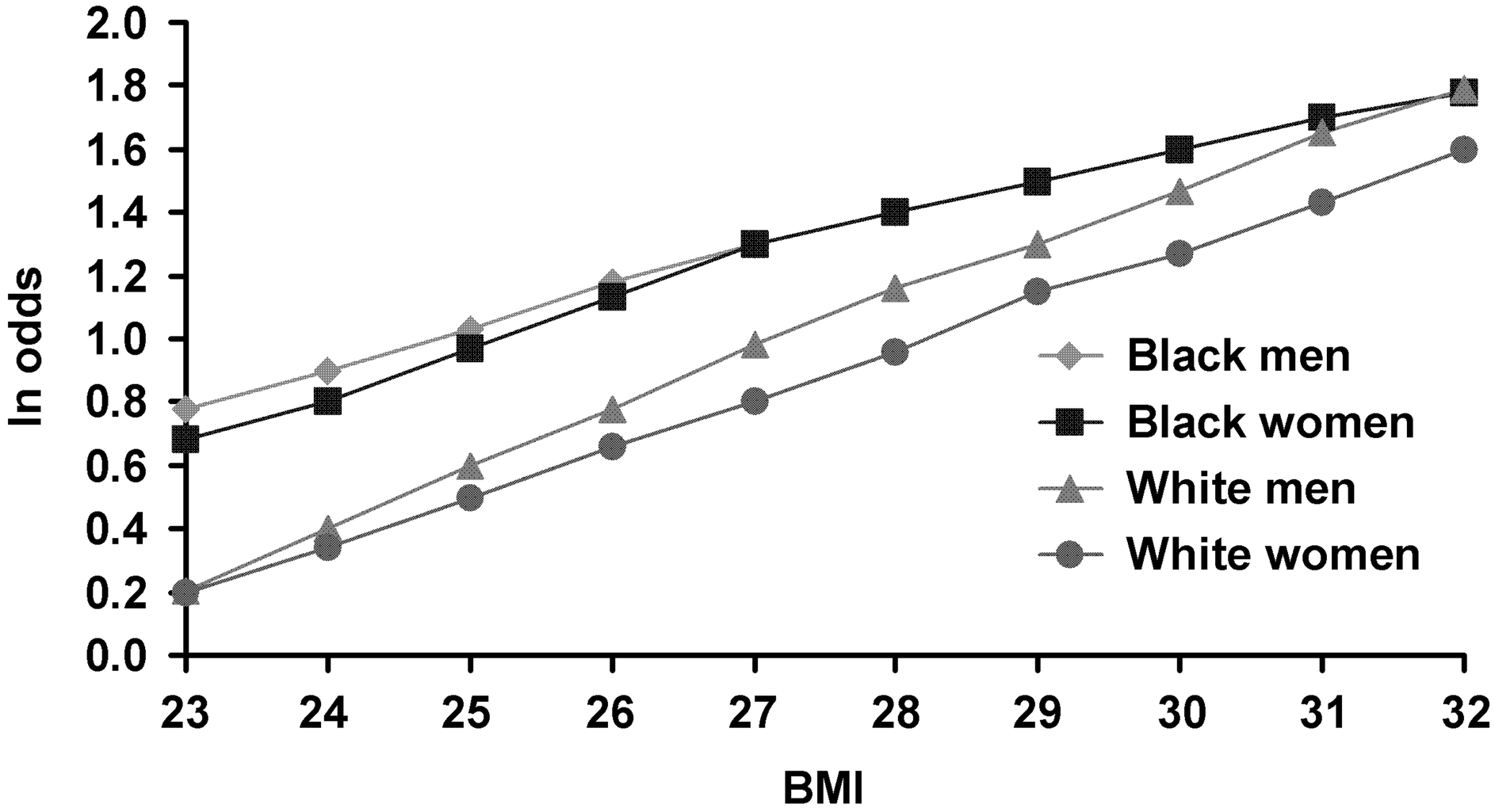
Risk factors for diabetes mellitus

- Abdominal adiposity (fat)
- Increasing age
- Pregnancy (gestational diabetes)
- Ethnicity
- Gender?
- Major psychiatric illnesses
- Medications, including antipsychotics

Diabetes mellitus and gender

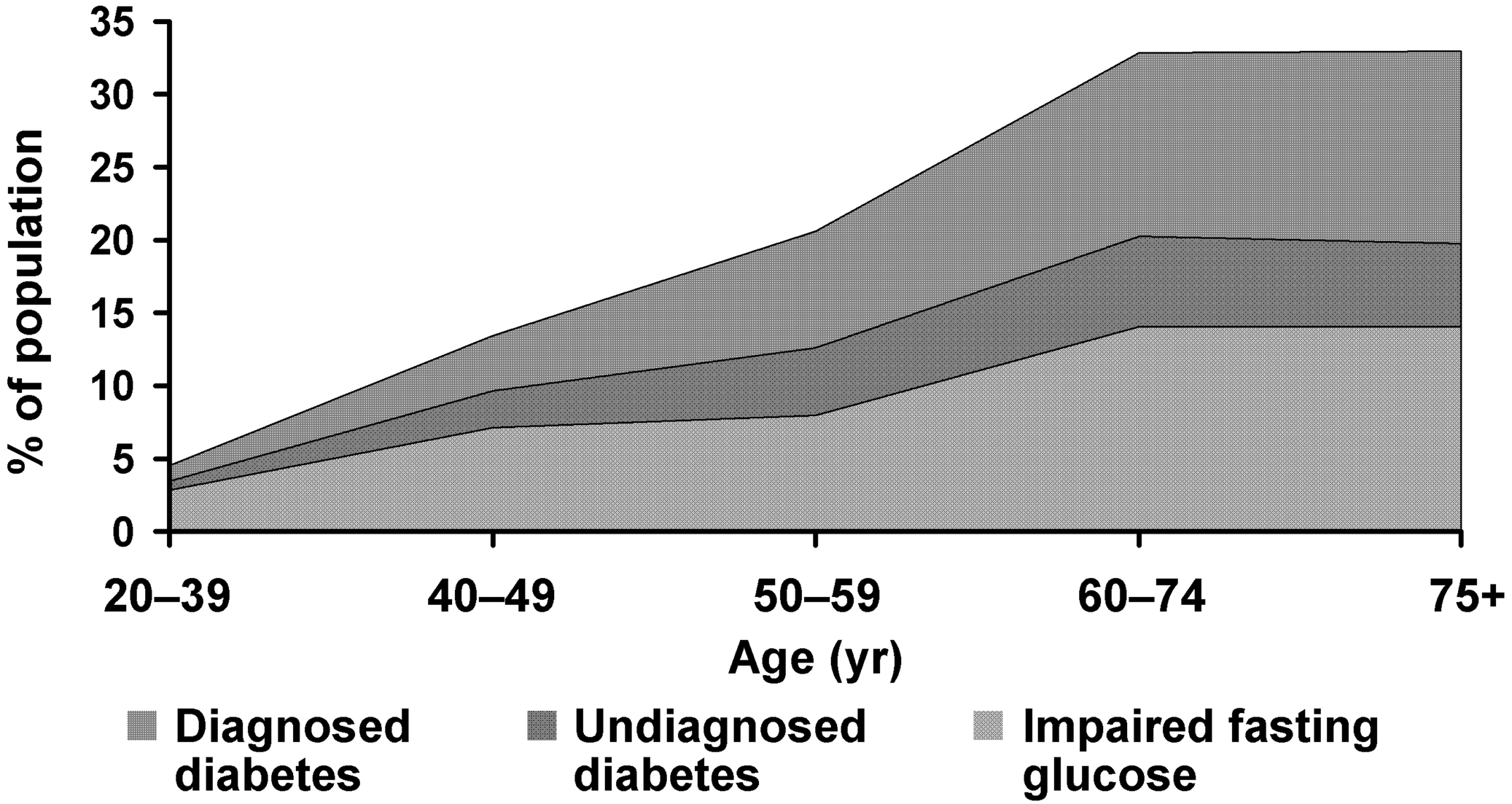
- Women have been reported to have increased risk for diabetes, compared to men
- However, increased risk is related to decreased fitness and increased adiposity
- When women and men are matched for fitness and adiposity, women are reported to have equal or lower risk for diabetes

Diabetes risk related to baseline BMI, gender and race



Resnick HE, et al. Diabetes Care 1998;21:1828–35.

Prevalence of diabetes and impaired fasting glucose (IFG)



Harris MI et al. Diabetes Care 1998;21:518–24.

Neuropsychiatric conditions and glucose regulation

Associations between disturbances in glucose regulation and disease/severity

- Depression
- Bipolar disorder
- Alzheimer's disease
- Schizophrenia

Glucoregulatory abnormalities and diabetes in schizophrenia

- Abnormalities in peripheral glucose regulation and type 2 diabetes can occur more commonly in individuals with schizophrenia than in the general population
- Although first reported prior to the introduction of antipsychotic medications[1], antipsychotics can contribute significantly to abnormalities in glucose regulation

[1]Braceland et al, 1945.

Conventional antipsychotics: effects on glucose regulation and diabetes

- Aggravation of existing diabetes[1]
- New-onset type 2 diabetes[2]
  - introduction of chlorpromazine increased prevalence from 4.2% to 17.2%[3]
- Abnormal glucose regulation[4]
- Association not always found for all drugs[5]

[1]Hiles, 1956; [2]Cooperberg and Eidlow, 1956; Korenyi C, Lowenstein B.Dis Nerv Syst 1968;29:827–8; [3]Thonnard–Neumann E. Am J Psychiatry 1968;124:978–82; [4]Arneson,1964; National Diabetes Data Group. Diabetes 1979;28:1039–57; Erle G et al. Eur J Clin Pharmacol 1977;11:15–8; O'Byrne S, Feely J. Drugs 1990;40:203–19; Pandit MK et al. Ann Intern Med 1993;118:529–39; [5]Keskiner A et al. Psychosomatics 1973;14:176–81; Schwarz L, Munoz R. Am J Psychiatry 1968;125:253–5.

Clozapine and olanzapine: effects on glucose regulation and diabetes

- **Abnormal glucose regulation, exacerbation of existing type 2 diabetes, new-onset type 2 diabetes and diabetic ketoacidosis (DKA)**
  - **Clozapine[1]**
    Estimated type 2 incidence: 12–36%
  - **Olanzapine[2]**
    Estimated type 2 incidence: (3.1% [3]) 6– ~30%

- **Effects reported with <u>and without</u> weight gain**

[1]Hagg S et al. J Clin Psychiatry 1998;59:294–9; Popli AP et al. J Clin Psychiatry 1997;58:108–11; Peterson GA, Byrd SL. Am J Psychiatry 1996;153:737–8; Ai D et al. Postgrad Med J 1998;74:493–4; Kostakoglu AE et al. Acta Psychiatr Scand 1996;93:217–8; Koval MS et al. Am J Psychiatry 1994;151:1520–1; Kamran A et al. Am J Psychiatry 1994;151:1395; Mohan D et al. Br J Psychiatry 1999;174:180–1; Wirshing DA et al. Biol Psychiatry 1998;44:778–83; Shiigi Y et al. ACNP 1999:202 (abstract); Melson AK et al. Soc Neurosci abstr 1999;25:2074 (abstract); Wilson DR et al. ACNP 1999:284 (abstract); Colli A et al. Diabetes Care 1999;22:176–7; Henderson DC et al, Am J Psych 2000;157:975–81; [2]Fertig MK et al. J Clin Psychiatry 1998;59:687–9; Ober SK et al. Am J Psychiatry 1999;156:970; Meyer JM. ACNP 1999:211 (abstract); Shiigi Y et al. ACNP abstr 1999:202; Wirshing DA et al. Biol Psychiatry 1998;44:778–83; Wilson DR et al. ACNP 1999:284 (abstract); Newcomer JW et al. ACNP abstr 1999:212 (abstract); [3]Eli Lilly. data on file.

Olanzapine database review

	Placebo n=445	Olanzapine n=4577
Incidence of 160mg/dL≤RG<200mg/dL*	1.57%	2.04%
Incidence of RG≥200mg/dL*	0.89%	1.05%

- 25% more hyperglycaemia on olanzapine than on placebo, but actual incidence is hard to interpret
- Problems:
  - Calculation using ad hoc criteria and RG rather than FBG or OGTT
  - RG>160mg/dl may not be sensitive enough; risk of under-diagnosis
  - Real-world samples using ADA criteria yield higher numbers (e.g. 18%[1])

*Definite/possible/transient: Definite = clear patterns of elevated RGs greater than threshold values, starting during trial and sustained until end of trial; Possible = clear elevations only at the end of trial period and not earlier; Transient = clear elevations during but resolved by the end of the trial period.

[1]Shiigi Y et al. ACNP 1999:202 (abstract).

Quetiapine and risperidone: effects on glucose regulation and diabetes

- Limited observations for quetiapine[1]
- Fewer observations linking risperidone with impaired glucose regulation or diabetes (e.g. in HIV+ male with DKA[2])
  - suggests a less frequent or smaller effect
  - risperidone reportedly used without complications in patients with comorbid diabetes[2]

[1]Wilson DR et al, ACNP 1999:284 (abstract); Bettinger TL et al. Ann Pharmacother 2000;34:865–7; Sobel M et al. J Clin Psychiatry 1999;60:556–7; [2]Croarkin E et al.Psychosomatics 2000;41:369–70; [3]Wirshing DA et al. Biol Psychiatry 1998;44:778–83; Melamed Y, et al. Can J Psychiatry 1998;43:956; Madhusoodanan S et al. J Clin Psychiatry 1995;56:514–8.

Incidence of clinically significant laboratory test abnormalities in ziprasidone phase 2/3

	Ziprasidone		Placebo		Haloperidol		Risperidone	
Lab test	**n**	**n (%)**	**n**	**n (%)**	**n**	**n (%)**	**n**	**n (%)**
Random glucose >1.2xULN	**2362**	**352 (14.9)**	**393**	**48 (12.2)**	**282**	**46 (16.3)**	**134**	**20 (14.9)**

Diabetic ketoacidosis

- Characterised by:
  - hyperglycaemia: glucose usually >300mg/dL
  - ketonaemia: total serum ketones >3mM
  - acidosis: blood pH <7.3 or HCO_3 <15mmol/L
  - mortality rate generally 2–10%, can be higher

- Clinical symptoms
  - polyuria
  - nausea or vomiting
  - shortness of breath
  - fever
  - polydipsia
  - abdominal pain
  - CNS depression
  - infection

Effects of antipsychotics on glucose regulation and diabetes: summary

- For all agents, small increases in glucose levels are more common than large increases, but more quantitative data needed
- Long-term adverse cardiovascular effects of small increases in glucose levels below ‘impaired’/diabetic thresholds are well-established in various populations

Complications of hyperglycaemia include microvascular disease

- Retinopathy with potential loss of vision
- Nephropathy leading to renal failure
- Peripheral neuropathy with risk of foot ulcers, amputation, and Charcot joints
- Autonomic neuropathy causing gastrointestinal, genitourinary, and cardiovascular symptoms and sexual dysfunction

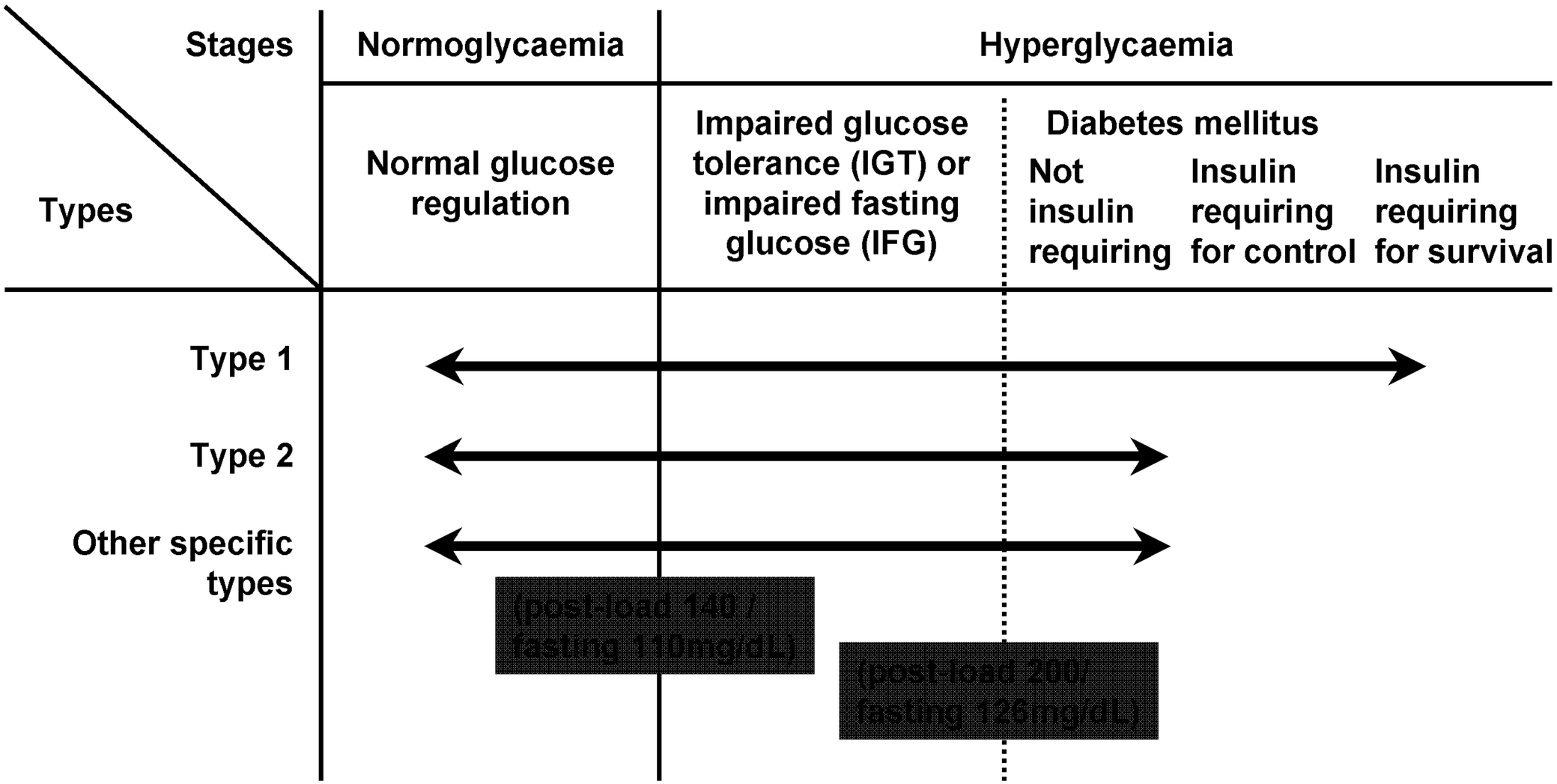
Diabetes Care 2000;23(Suppl 1):S4–S19.

Complications of hyperglycaemia

- Hyperglycemia can also cause or contribute to macrovascular disease (i.e. atherosclerosis)
  - cardiovascular disease
  - peripheral vascular disease
  - cerebrovascular disease
- Insulin resistance syndrome
  - increased incidence of hypertension, dyslipidaemia, and obesity

Klein R. Diabetes Care 1995;18:258–68; Diabetes Care 2000;23(Suppl 1):S4–S19.

Hyperglycaemia: impaired glucose regulation to diabetes mellitus



Diabetes Care 2000;23(Suppl 1):S4–S19.

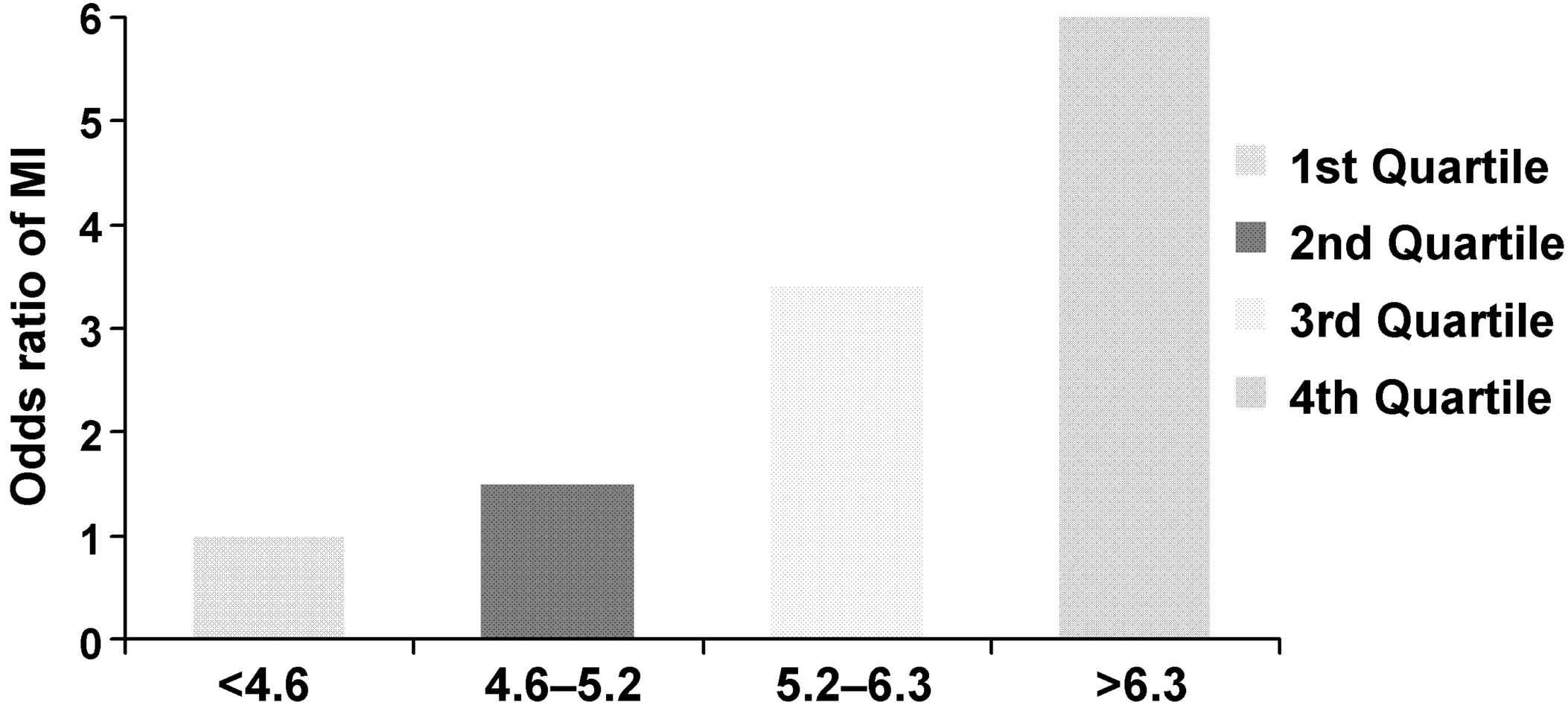
Relationship of hyperglycaemia to cardiovascular disease

- Macrovascular disease risk (e.g. myocardial infarct and stroke) increases continuously with increasing glucose levels
  - no clear threshold

- Progressive relationship between glucose levels and increased cardiovascular risk observed in non-diabetic[1] and diabetic persons[2]

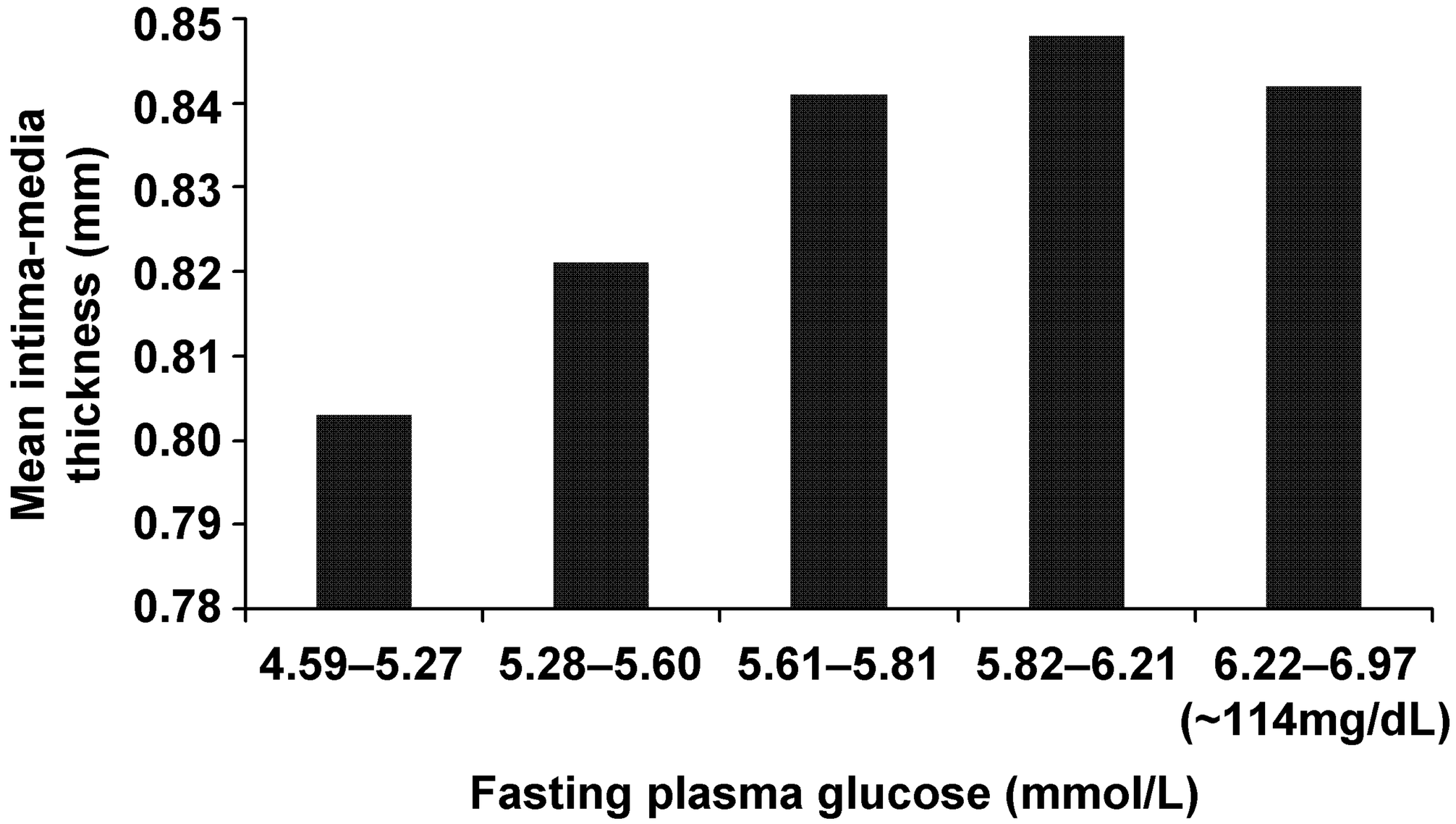
[1]Fuller JH et al. Lancet 1980;1:1373–6; Park S et al. Diabetes Care 1996;19:450–6; Fuller JH et al. Br Med J 1983;287:867–70; Scheidt-Nave C et al. Am J Epidemiol 1991;133:565–76; [2] Moss SE et al. Arch Intern Med 1994;154:2473–9; Andersson DK, Svardsudd K. Diabetes Care 1995;18:1534–43; Kuusisto J et al. Stroke 1994;25:1157–64; McKeigue PM et al. Circulation 1993;87:152–61.

Odds ratio of MI as a function of fasting blood glucose



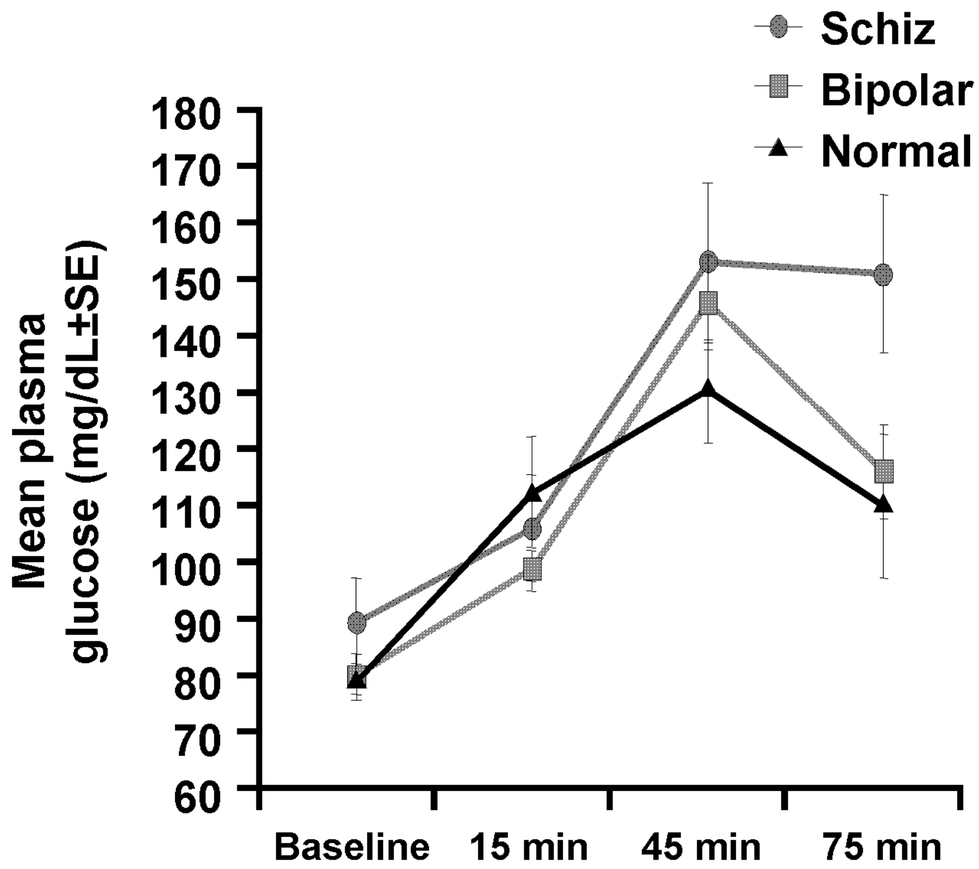
Gerstein HC et al. J Am Coll Cardiol 1999;33:612–19.

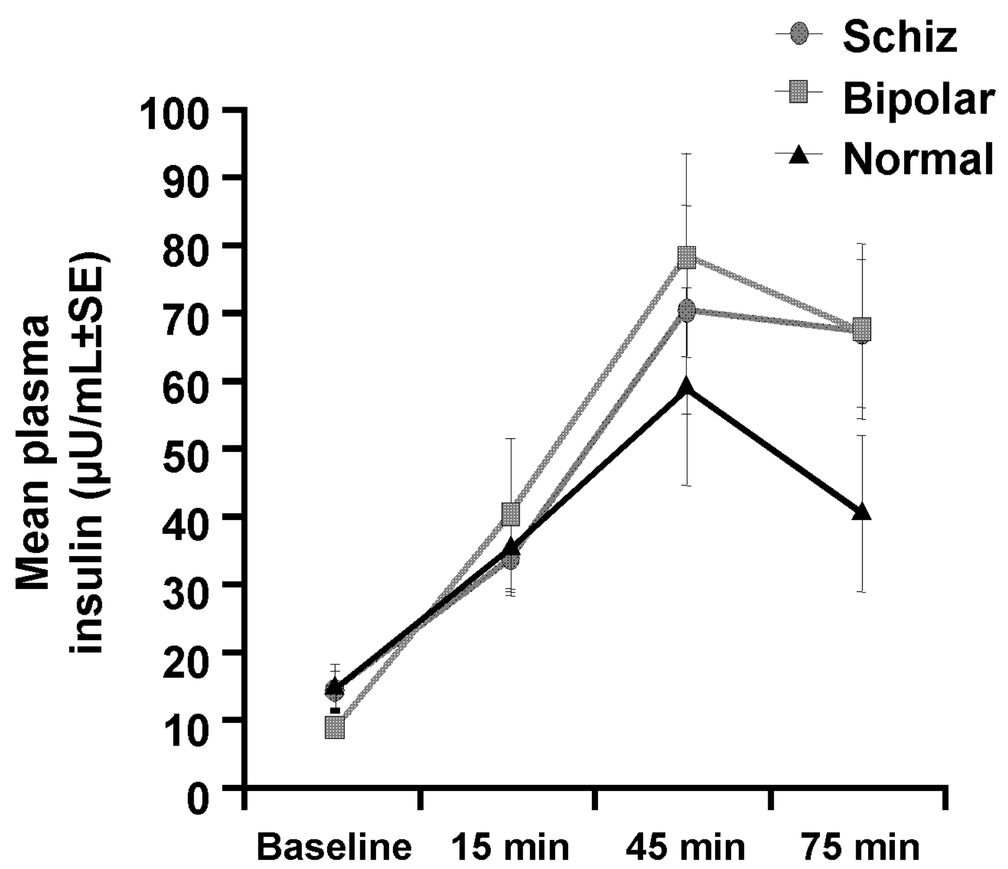
Carotid intima-media thickness as a function of FPG



Hanefeld M et al. Atherosclerosis 1999;144:222–35.

Schizophrenia-related abnormalities in glucose regulation

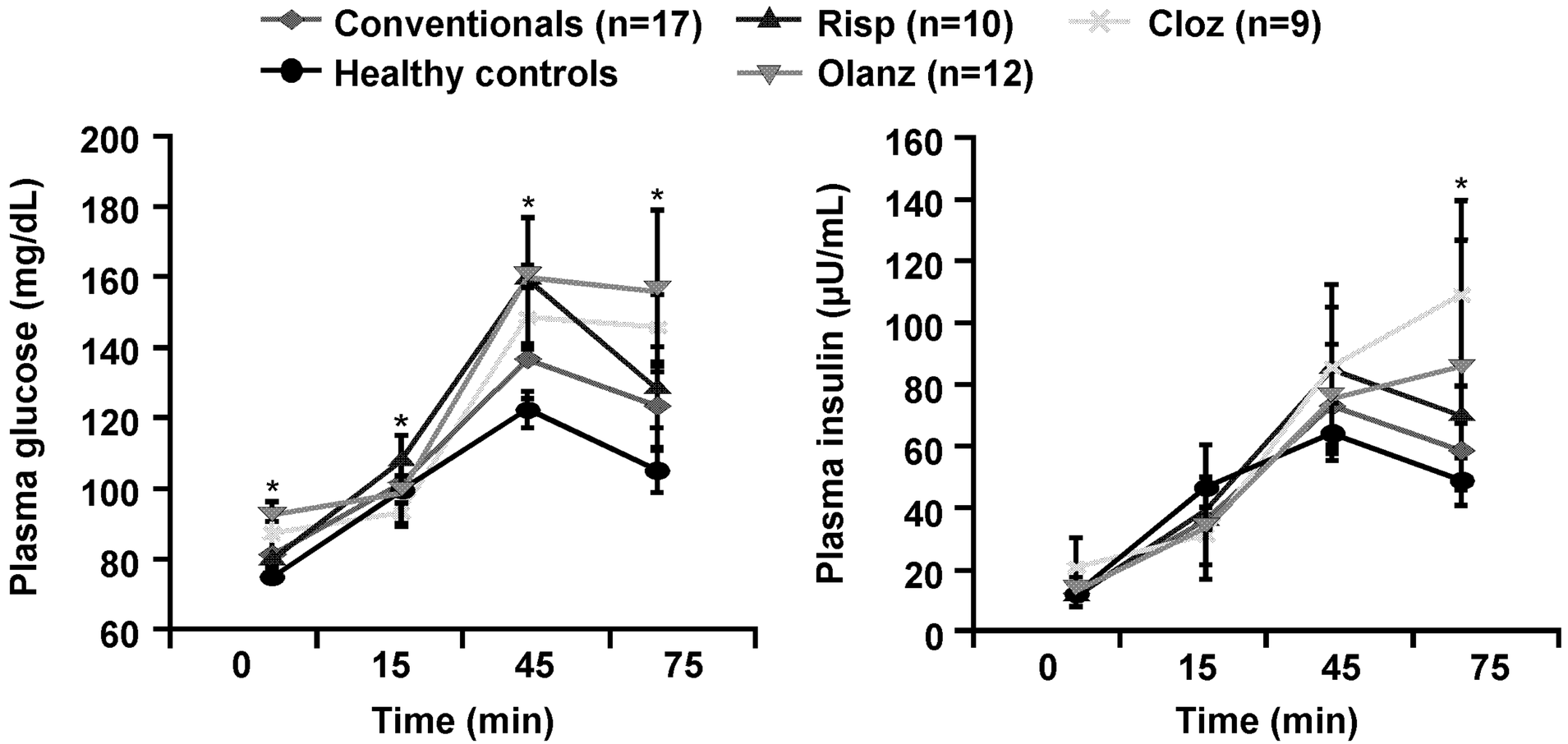




Mean plasma glucose (mg/dL±SE) and insulin (mU/mL±SE) before and after 50g oral dextrose in patients with schizophrenia (n=10) and bipolar affective disorder (n=10), and normal healthy controls (n=10)

Newcomer JW et al. Schizophr Bull 1999;25:321–35.

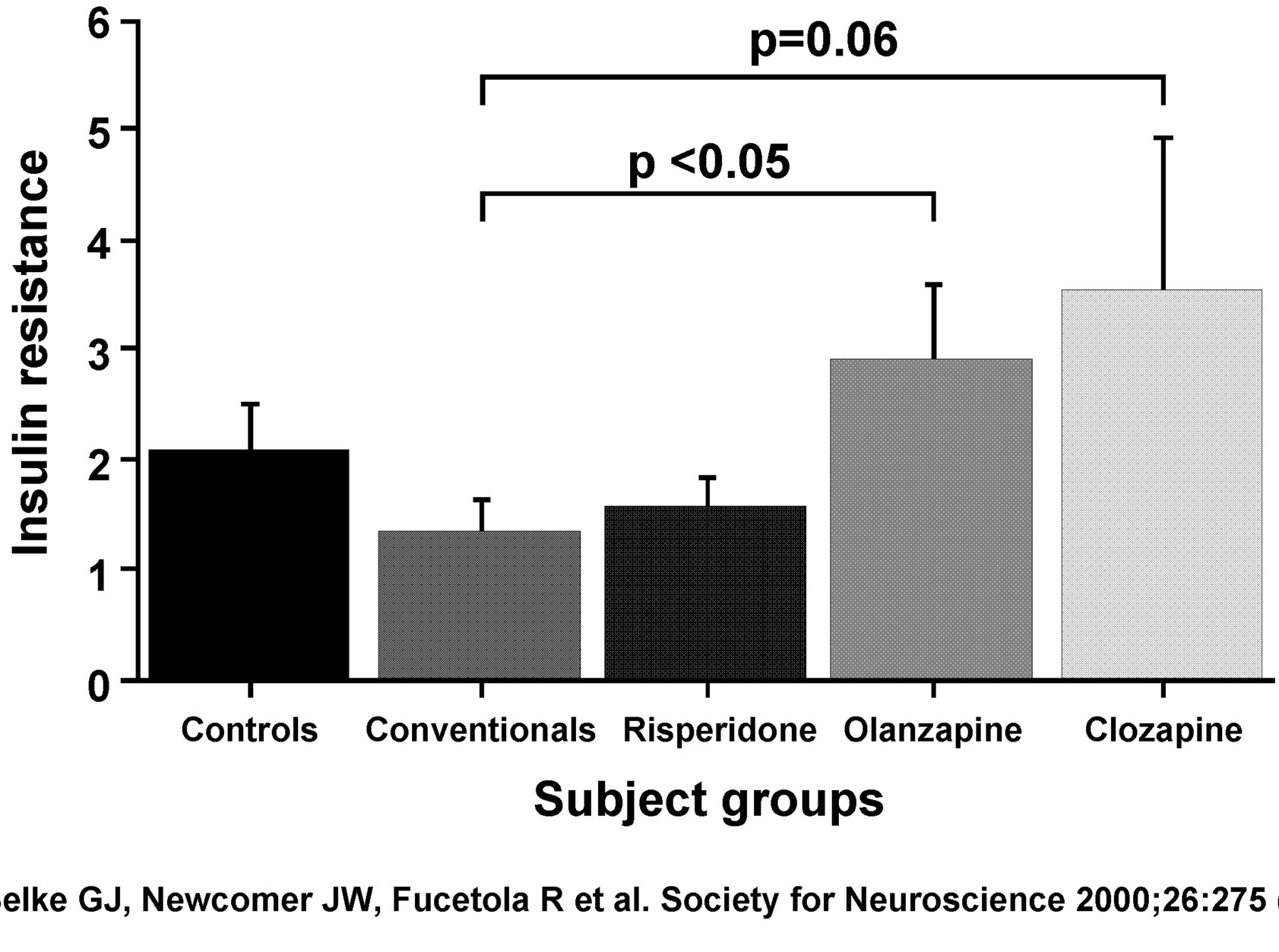
Medication-related abnormalities in glucose regulation in schizophrenia



Oral 50g dextrose challenge in patients with schizophrenia (n=48) and healthy controls (n=31), with treatment groups matched for age and body mass index (BMI).
***Significant effect of treatment condition, $p<0.05$**

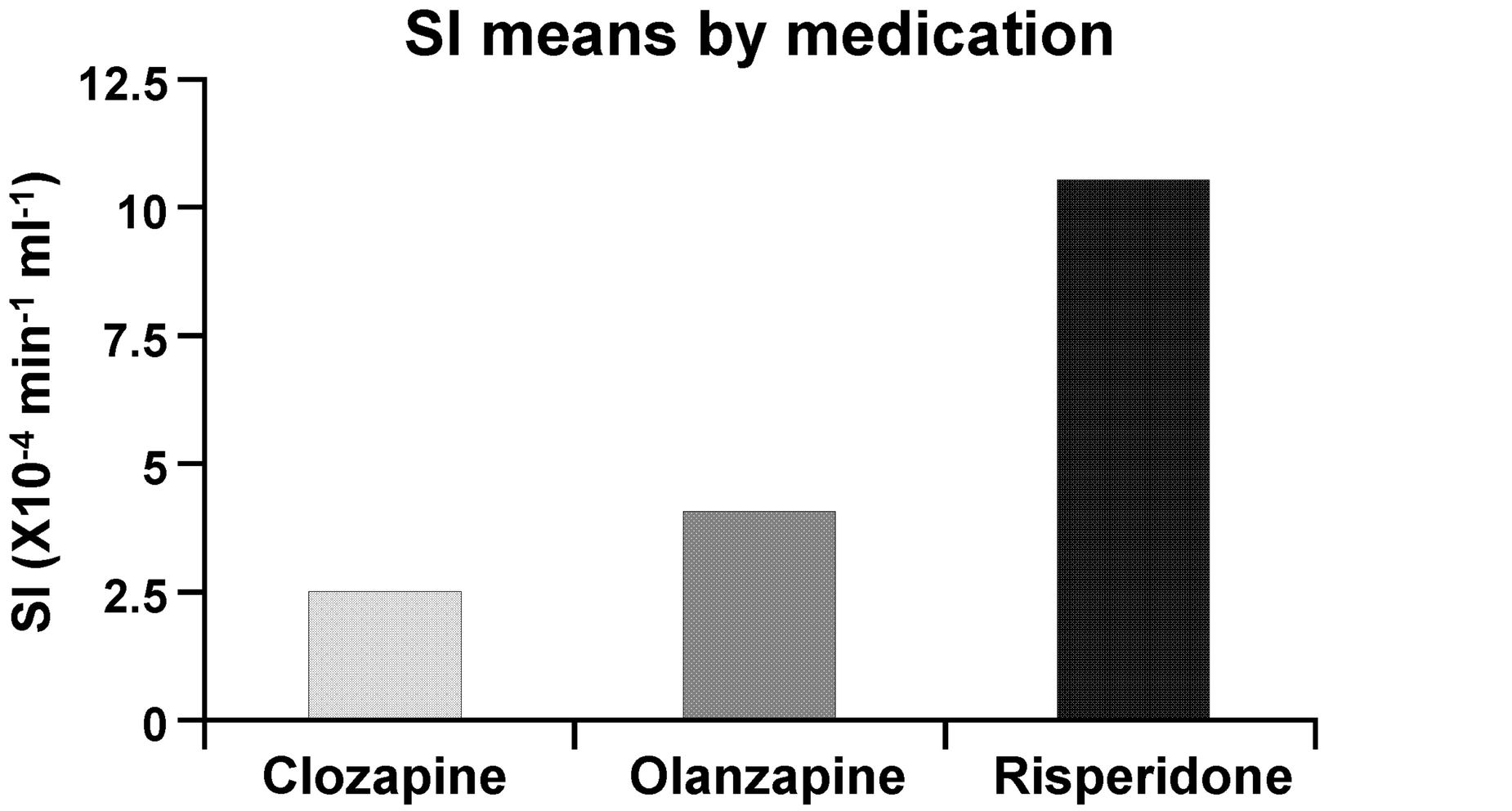
Selke GJ, Newcomer JW, Fucetola R et al. Society for Neuroscience 2000;26:275 (abstract).

HOMA insulin resistance in treated patients with schizophrenia



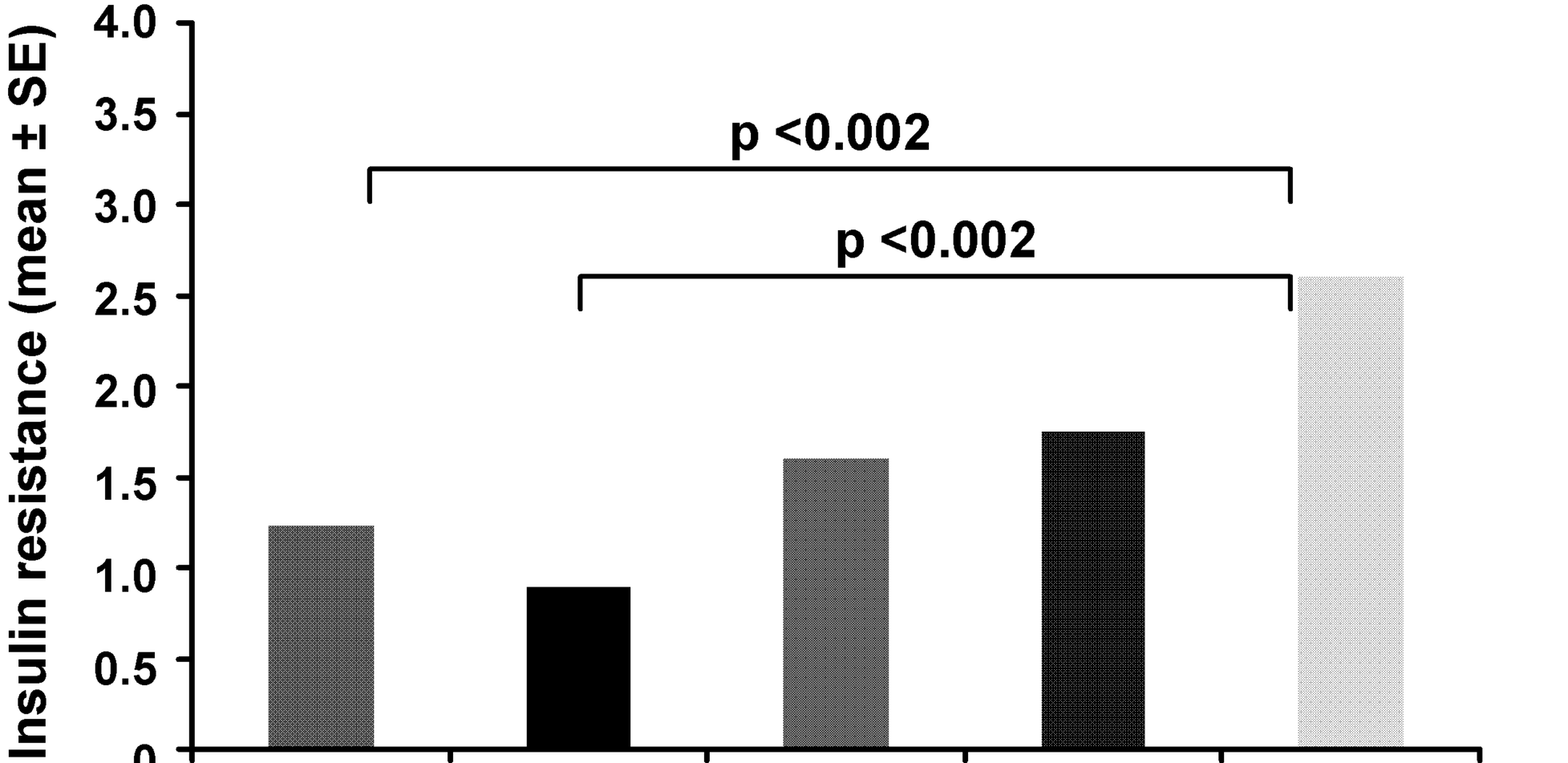
Selke GJ, Newcomer JW, Fucetola R et al. Society for Neuroscience 2000;26:275 (abstract).

IVGTT with MinMod Analysis: antipsychotic-associated differences in insulin sensitivity



Henderson DC et al. Am J Psych 2000;157:975–81.

Insulin resistance in treated patients with schizophrenia



Newcomer JW et al, unpublished data.

Cardiovascular mortality in schizophrenia

- Increased in some, but not all, earlier studies
- Cardiovascular disease takes years (e.g. some pre-antipsychotic) and involves multiple factors (e.g. dyslipidemia, smoking, obesity)
- Danish Psychiatric Case Registry (1970–1987; n = 9,156 with schizophrenia, n = 1,081 with death and cause) indicates standardised mortality rates increased for combined cardiovascular and cerebrovascular disease in both men (3.33 higher than control) and women (2.42 higher than control) with schizophrenia[1]

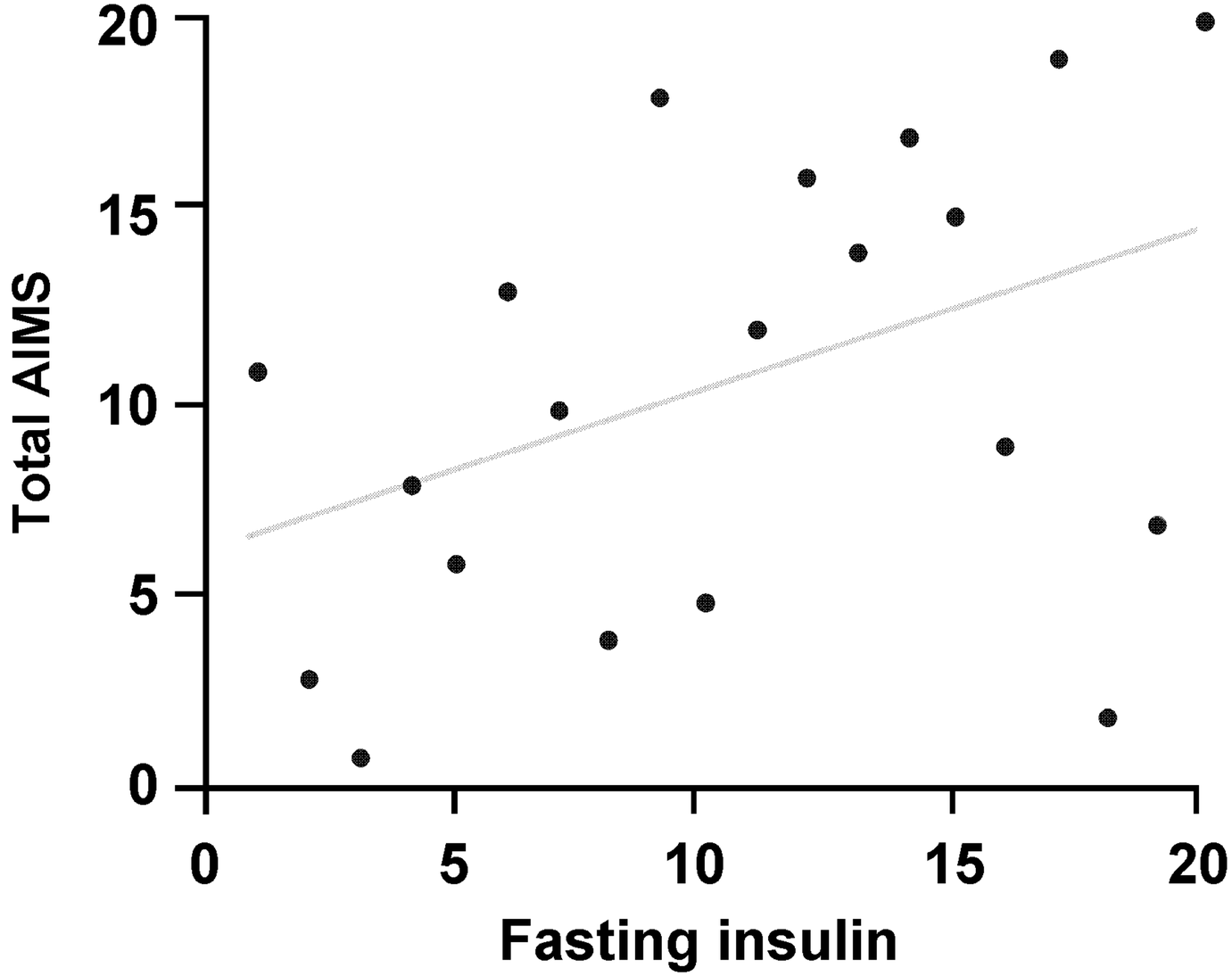
[1]Mortensen B, Juel K. Br J Psychiatry 1993;163:183–9.

Risks hypothesised to be associated with abnormal glucose regulation

- TD severity or risk may increase with increasing glucose dysregulation[1]
- Glucose dysregulation and comorbid diabetes associated with worse clinical status[2]
- Altering glucose or insulin levels can alter cognitive performance[3]

[1]Ganzini L et al, Arch Gen Psychiatr 1991;48:259–63; Mukherjee S et al. Arch Gen Psychiatry 1986;43:342–6; Mukherjee S et al. Psychiatry Res 1989;29:17–27; Schultz SK et al. Am J Psychiatry 1999;156:640–2; Lozovsky DB et al. Science 1981;214:1031–3; Lozovsky DB et al. Brain Res 1985;343:190–3; Mouret J et al. Eur Neurol 1991;31:199–203; [2]Schimmelbusch WH et al. Br J Psychiatry 1971;118:429–36; Surridge DH et al. Br J Psychiatry 1984;145:269–76; [3]Newcomer JW et al. Schizophr Bull 1999;25:321–35; Fucetola R et al. Psychiatry Res 1999;88:1–13; Craft S et al. Arch Gen Psychiatry 1999;56:1135-40.

Abnormal movements and glucose and insulin plasma levels in treated schizophrenia



Eight of 21 patients met criteria for IGT, none for diabetes

($r=^{-}0.48$, df=16, $p<0.04$)

AIMS = Abnormal Involuntary Movement Scale

Schultz SK et al. Am J Psychiatry 1999;156:640–2.

Antipsychotic-induced weight gain

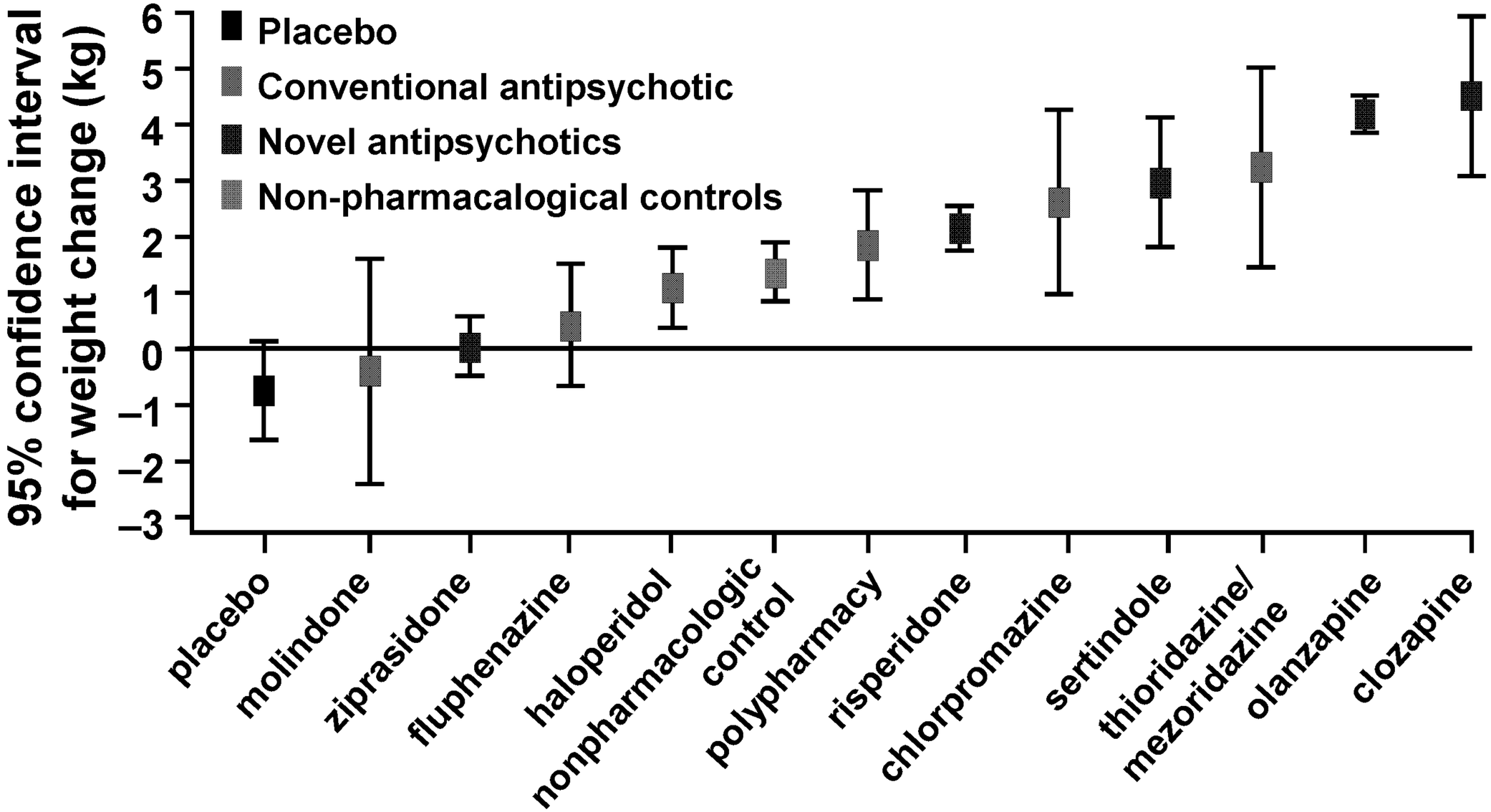
- Complications of obesity include hyperglycaemia and type 2 diabetes (insulin resistance), hypertension, cardiovascular disease, and dyslipidaemias

- Complications of obesity can add to risk for cardiovascular disease (variable BMI threshold)

- First reported as an effect of conventional agents, some atypical antipsychotic agents can induce significant weight gain, e.g. clozapine and olanzapine[1]

[1]Leadbetter R et al. Am J Psychiatry 1992;149:68–72; Lamberti JS et al. Am J Psychiatry 1992;149:689–90; Cohen S et al. Am J Psychiatry 1990;147:503–4; Collaborative Working Group on Clinical Trial Evaluations. J Clin Psychiatry 1998;59:17–22; Kraus T et al. Am J Psychiatry 1999;156:312–4; Gupta S et al. Ann Clin Psychiatry 1998;10:39.

Weight change after 10 weeks on standard drug doses, estimated from a random effects model



Allison DB et al. Am J Psychiatry 1999;156:1686–96.

Diabetes screening criteria (1)

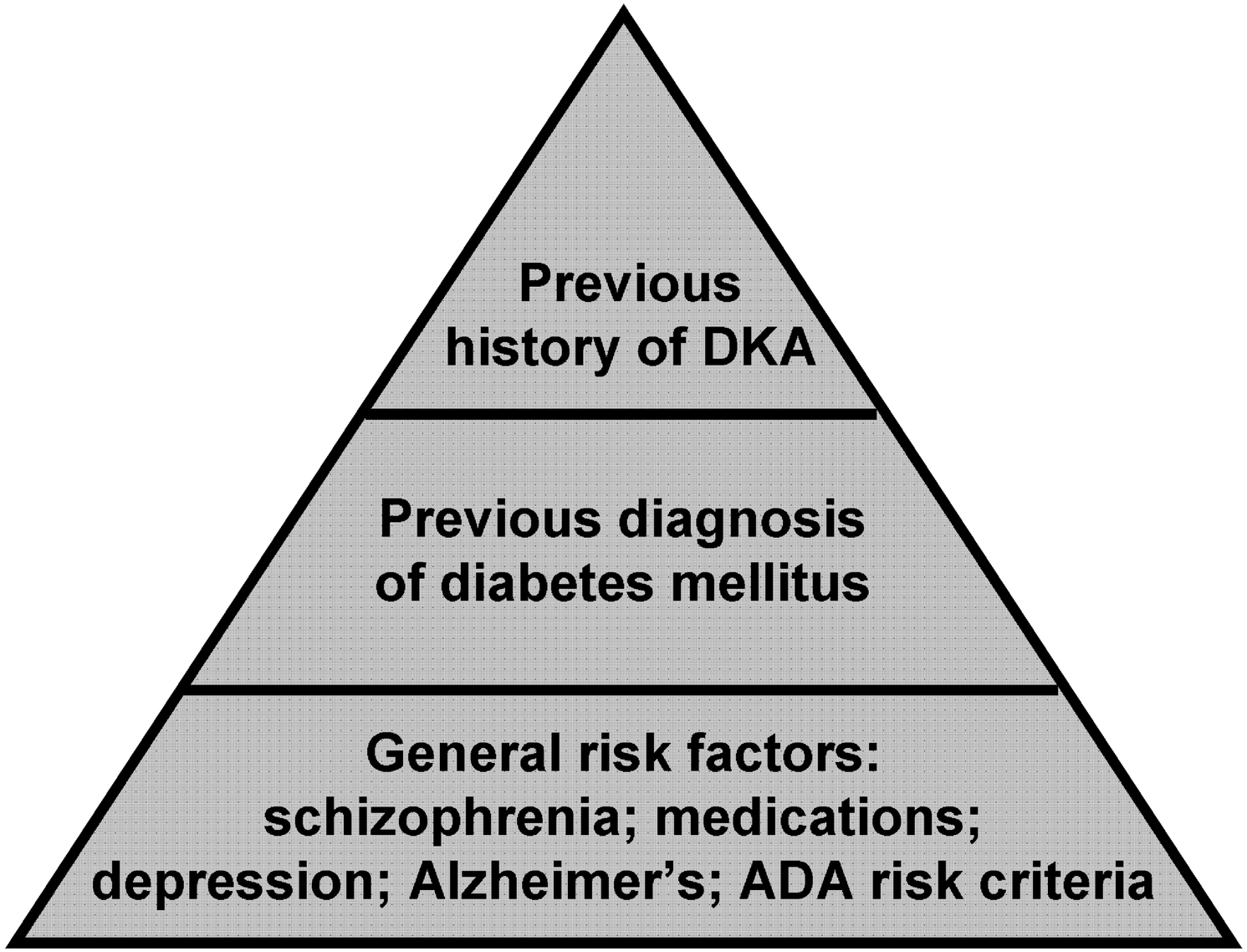
- Testing is considered for everyone ≥45 years
  - if normal, repeat at 3-year intervals
- Testing is considered at a younger age or done more frequently in individuals who
  - are obese (≥120% ideal weight or BMI>27kg/m^2)
  - have first-degree relative with diabetes
  - are members of a high-risk ethnic population (e.g. African American, Hispanic American, Native American, Asian American, Pacific Islander)

Diabetes screening criteria (2)

- Have delivered a baby weighing >9lb or have been diagnosed with gestational diabetes
- Are hypertensive (≥140/90)
- Have a high-density lipoprotein cholesterol level ≤35mg/dL and/or a triglyceride level ≥250mg/dL
- Had IGT or IFG on previous testing

  (FBG testing preferred over OGTT because of ease of administration, convenience, acceptability and cost)

Recommendations: risk level determines level of monitoring



Recommendations: monitoring for hyperglycaemia in schizophrenia

- Annual maintenance screen (e.g. FPG)
- Screen high risk patients more frequently and carefully (e.g. OGTT)
- Baseline measurement prior to new treatment
- Serial measurement during treatment initiation and dose titration (frequency determined by level of risk)
  - FPG – more convenient
  - OGTT – more sensitive

Conclusions (1)

- **Antipsychotic treatment in schizophrenia is associated with changes in glucose regulation, potentially interacting with a disease-related abnormality in glucose regulation**
- **Could lead to acute and long-term complications, including increased risk for DKA and cardiovascular events (e.g. MI and stroke)**

Conclusions (2)

- **Treatment-associated changes in glucose regulation may interact with treatment-induced weight gain to further disturb glucose regulation**
- **Treatment-associated changes in glucose regulation may interact with treatment-associated changes in triglyceride levels and treatment-induced weight gain to further increase risk for cardiovascular disease**

Conclusions (3)

- **Patients taking antipsychotics should undergo regular monitoring for hyperglycaemia, dyslipidaemia and weight gain**
- **Education, in addition to monitoring, will be required to reduce the risk of diabetic ketoacidosis**
- **Collaboration between the psychiatrist and either an endocrinologist, internist or interested family practice physician is required**

Conclusions (4)

- Clinicians should individualise treatment decisions:
  - consider potential antipsychotic medication effects on glucose regulation and weight in the context of any pre-existing risk factors (obesity, smoking, hypertension, race/ethnicity, family history, or pre-existing hyperglycaemia)

- Future research is needed to guide treatment decisions and optimise long-term outcomes