Atypical Antipsychotics and Diabetes

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Outline

- Atypical antipsychotics (AAPs) cause weight gain and diabetes in some patients
- How can we identify which patients are at risk?
- Are there any interventions which reduce risk?

These are the topics we'll look at this morning.

Diabetes type 1 vs type 2

- DM 1
  - Childhood onset
  - Insulin dependent
  - Auto-immune disorder; destruction of insulin-producing cells in the pancreas
  - Without treatment with insulin:
    - Weight loss
    - Diabetic ketoacidosis
    - death
- DM 2
  - Usually adult onset
  - 90% of cases of DM
  - 90% of DM 2 are obese
  - Insulin resistance
  - Treatments include diet, oral hypoglycemic agents, sometimes insulin
  - Epidemic
  - Complications may be due to too much insulin

Metabolic side effects of atypical antipsychotics

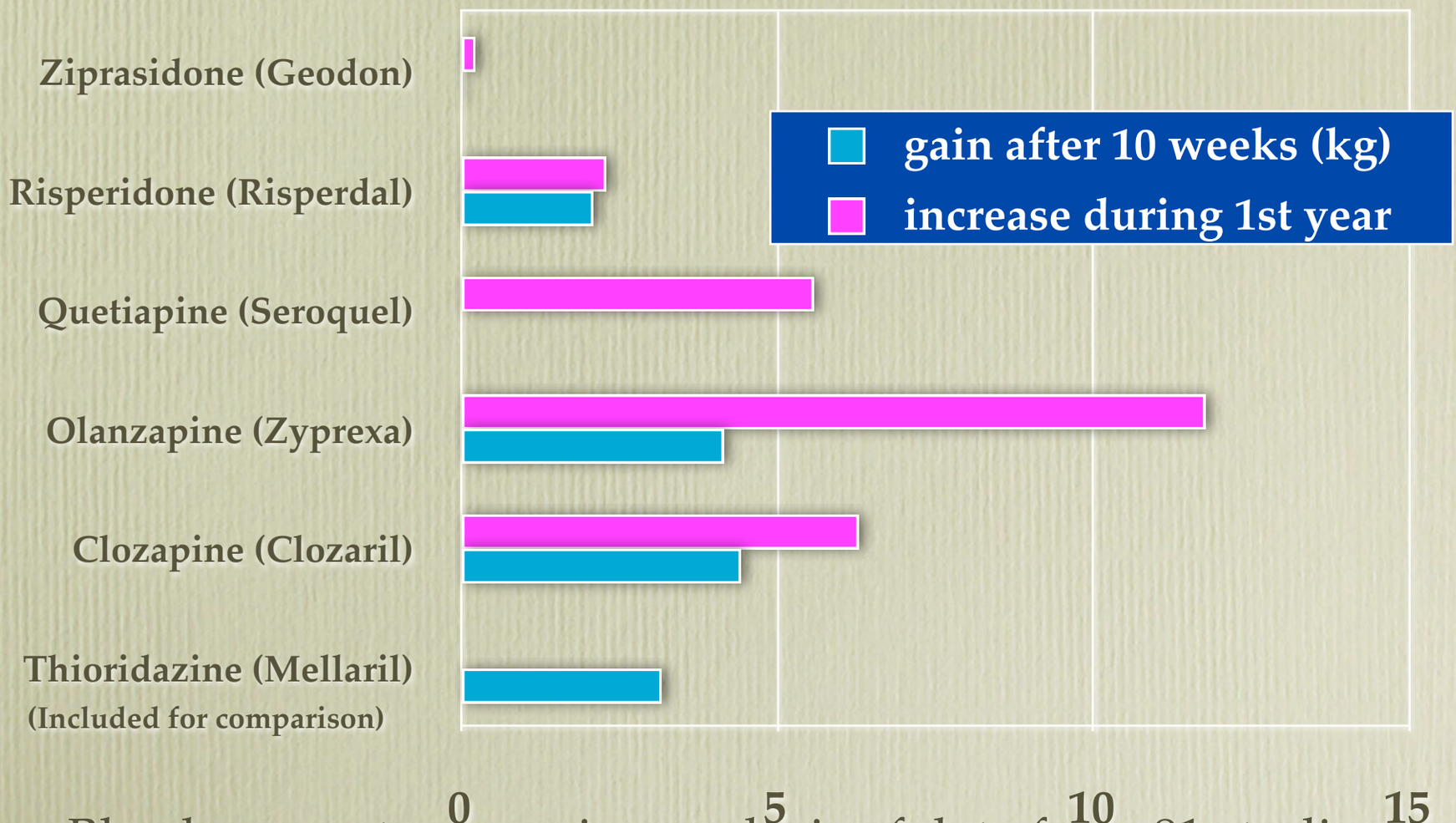
- Weight gain
- Obesity
- Type 2 diabetes
- Sometimes diabetic keto-acidosis (Jin 2002)
  - Younger, female, lower baseline weight

Jin H, Meyer JM, Jeste DV. Phenomenology of and risk factors for new-onset diabetes mellitus and diabetic ketoacidosis associated with atypical antipsychotics: an analysis of 45 published cases. Ann Clin Psychiatry. 2002;14:59-64.

It's not known what causes the diabetic keto-acidosis. It's unusual because ketoacidosis is associated with type 1 diabetes, and can be very serious. People can die from diabetic ketoacidosis.

AAPs and risk of weight gain

(Lebovitz 2003)

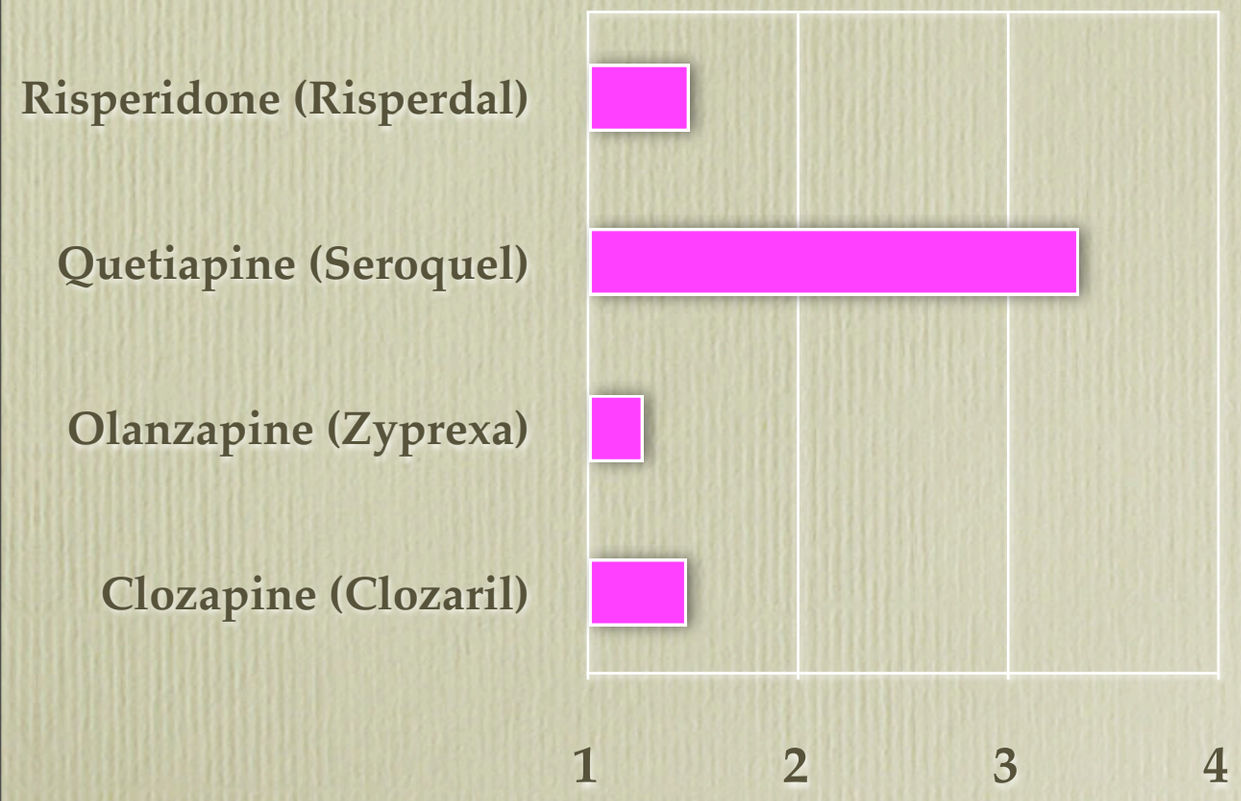


Blue bars: metaregression analysis of data from 81 studies

Lebovitz HE. Metabolic consequences of atypical antipsychotic drugs. Psychiatr Q. 2003;74:277–290.

AAPs and risk of diabetes

(International Conference of Pharmacoepidemiology 2003)



- Veteran's Health Administration study
- 12,235 patients with no prior Dx of diabetes
- 739 cases of diabetes

Abstracts of the 1st International Conference on Therapeutic Risk Management and 19th International Conference on Pharmacoepidemiology. Philadelphia, Pennsylvania, USA. 21-24 August 2003. Pharmacoepidemiol Drug Saf. 2003;12 Suppl 1:S1-198.

Risperidone [Murashita et al, 2007]

	risperidone	controls	P value
body weight	66.3	62.4	ns
% fat	30.7%	23.2%	0.0018
BMI	25.2	22.8	0.015
FBS	98.7	92.8	0.0358
Insulin	6.7	5.5	ns
HbA1c	5.0	4.8	ns

Murashita M, Inoue T, Kusumi I, et al. Glucose and lipid metabolism of long-term risperidone monotherapy in patients with schizophrenia. Psychiatry Clin Neurosci. 2007;61:54-58.

Risperidone has a very low rate of producing diabetes, but it was associated with significantly increased BMI and percent body fat. Fasting blood glucose was also significantly higher in this group of 15 schizophrenic patients, average age 40, on risperidone for an average of 2.5 years. However, the blood glucose was not in the abnormal range.

The Metabolic Syndrome
(NCEP ATP III, JAMA 2001)

- Three or more of:
  - Abdominal obesity: waist circumference > 102 cm (40 in) in men; > 88 cm (35 in) in women
  - Hypertriglyceridemia: ≥ 150 mg/dL (1.69 mmol/L)
  - Low HDL-C: < 40 mg/dL (1.04 mmol/L) in men; < 50 mg/dL (1.29 mmol/L) in women
  - High blood pressure: ≥ 130/85 mm Hg
  - High fasting glucose: ≥ 110 mg/dL (6.1 mmol/L)

Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA. 2001;285:2486-2497.

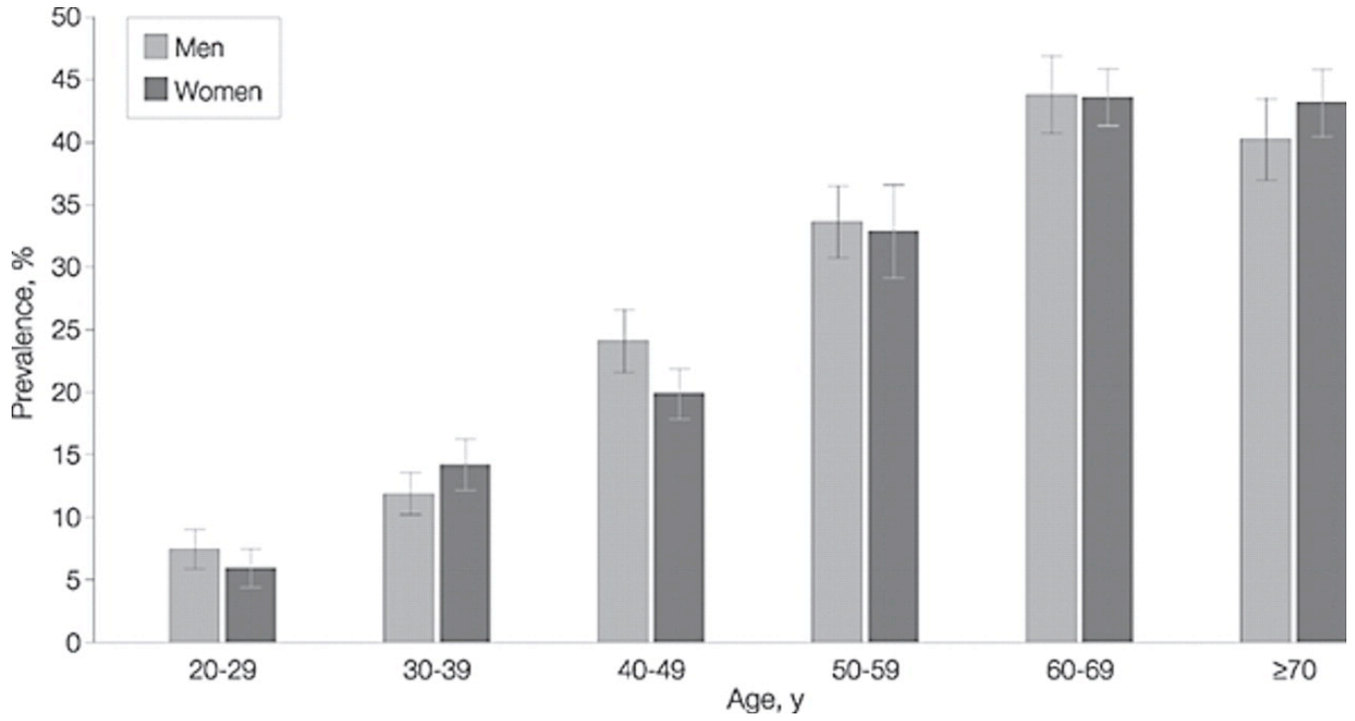
Prevalence - metabolic syndrome

- NHANES III study of 8814 adults age 20 and over [Ford et al, 2002]
  - abdominal obesity most common: 38.6%
  - at least one criterion present: 71.2%
  - three or more criteria present: 23.7%

Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. JAMA. 2002;287:356-359.

Note that this is based on data that was collected from 1988 to 1994. There is every reason to believe that the numbers would be much higher now.

Age-Specific Prevalence of the Metabolic Syndrome Among 8814 US Adults Aged at Least 20 Years, by Sex, National Health and Nutrition Examination Survey III, 1988-1994

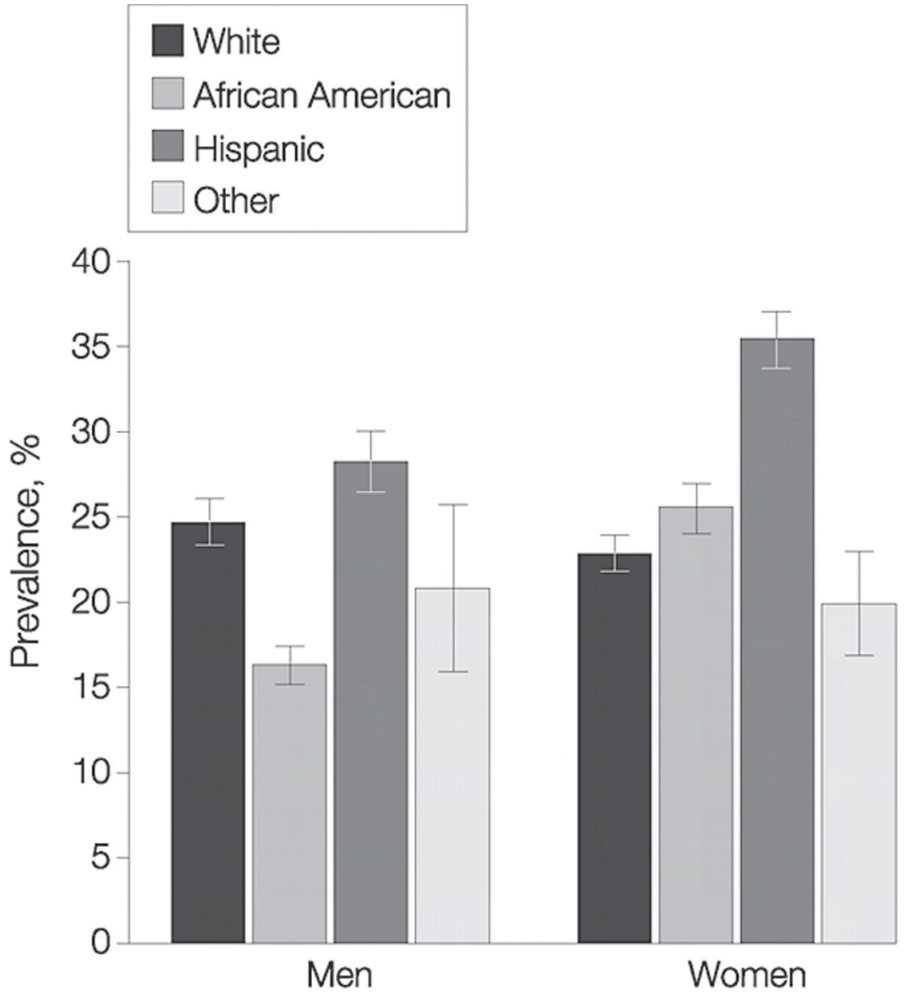


Ford, E. S. et al. JAMA 2002;287:356-359.

JAMA

Note that prevalence increases with age, but then decreases for over 70s. This is likely because people with metabolic syndrome die younger, from heart disease and other complications of diabetes.

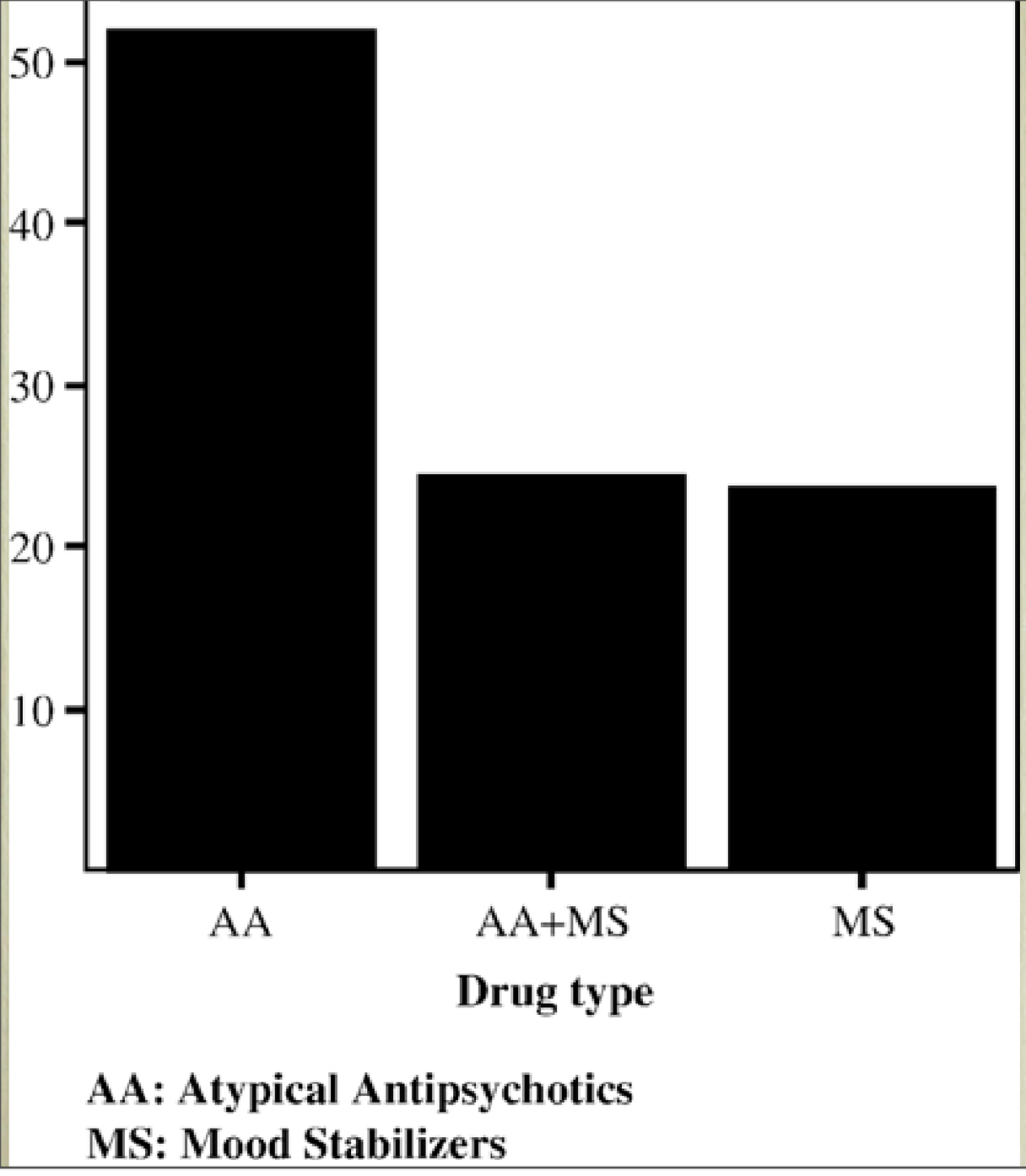
Age-Adjusted Prevalence of the Metabolic Syndrome Among 8814 US Adults Aged at Least 20 Years, by Sex and Race or Ethnicity, National Health and Nutrition Examination Survey III, 1988-1994



Ford, E. S. et al. JAMA 2002;287:356-359.

JAMA

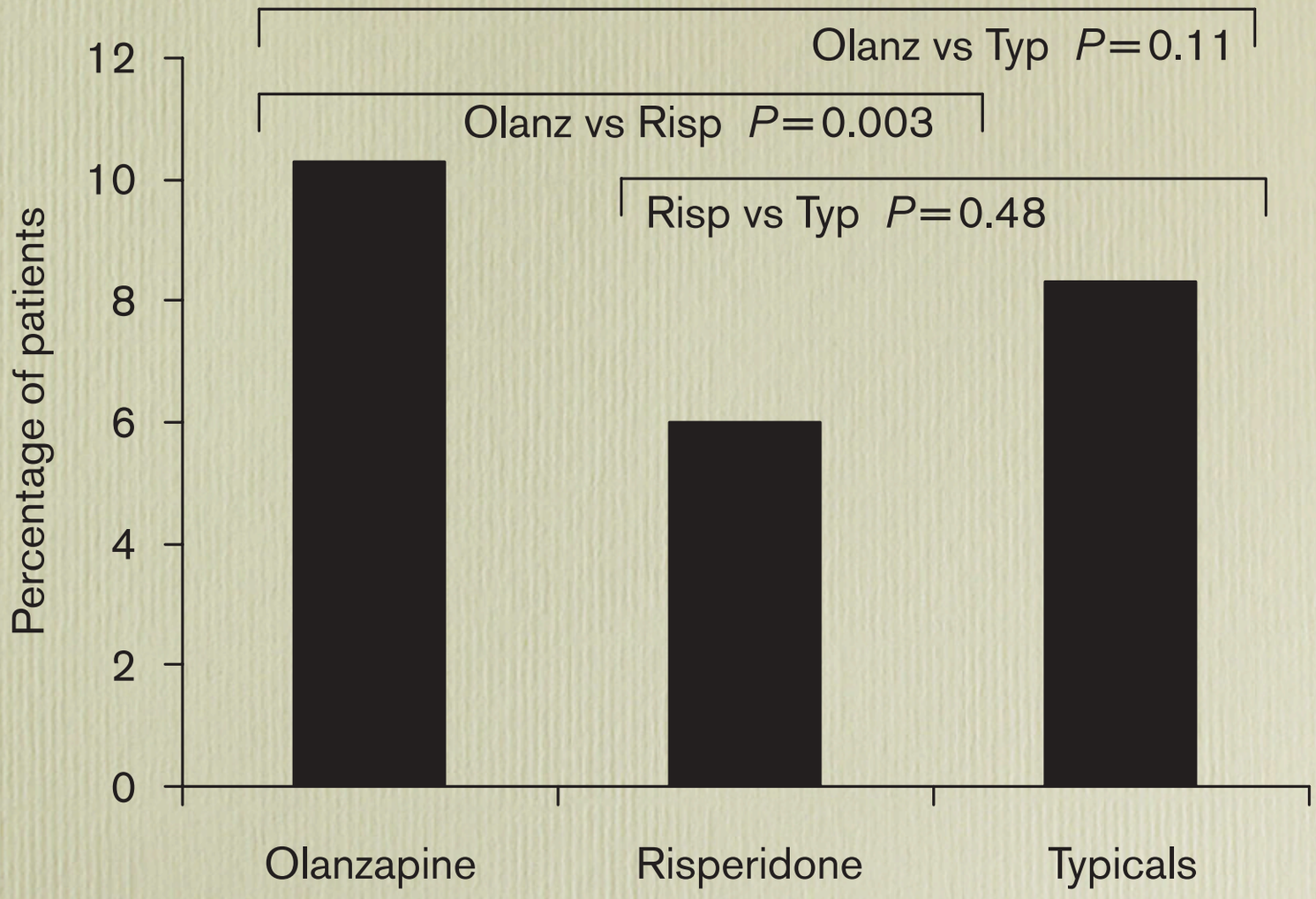
Certain groups, however, are worse off, for example Hispanics, especially Hispanic women.



Percent of patients with metabolic syndrome, according to drug type [Yumru et al, 2007]

Yumru M, Savas HA, Kurt E, et al. Atypical antipsychotics related metabolic syndrome in bipolar patients. J Affect Disord. 2007;98:247-252.

125 bipolar patients, on medication for at least 3 months.
I found it interesting that being on both a mood stabiliser and an atypical antipsychotic greatly reduced the risk.



Percentage of patients without any glucose measurement $\geq$ 160 mg/dl before medication exposure who developed at least one glucose measurement $\geq$ 200 mg/dl during medication exposure. Brackets indicate results of pairwise comparisons between medications.

Duncan E, Dunlop BW, Boshoven W, Woolson SL, Hamer RM, Phillips LS. Relative risk of glucose elevation during antipsychotic exposure in a Veterans Administration population. Int Clin Psychopharmacol. 2007;22:1–11.

This was a retrospective cohort analysis over a five year period involving more than 18,000 U.S. war vets receiving outpatient prescriptions for olanzapine, risperidone, or typical antipsychotics. The graph shows that olanzapine treated patients were more likely to develop random high glucose than risperidone patients.

CLAMORS study [Bobes et al, 2007]

- Spanish study of 1452 outpatients with schizophrenia, schizophreniform or schizoaffective disorder
- evaluated for metabolic syndrome, cardiovascular risk using SCORE & Framingham rating systems
- patients comparable in risk to nonpatients 10 to 15 years older
- lower prevalence of metabolic syndrome than studies in U.S., Canada, and Finland

Bobes J, Arango C, Aranda P, Carmena R, Garcia-Garcia M, Rejas J. Cardiovascular and metabolic risk in outpatients with schizophrenia treated with antipsychotics: Results of the CLAMORS Study. Schizophr Res. 2007;90:162-173.

The lower prevalence for MetS may be due to the long time that Spanish populations have been agrarian, compared to the U.S. and Canada with their mixed populations and Finland with its hunter-gatherer population.

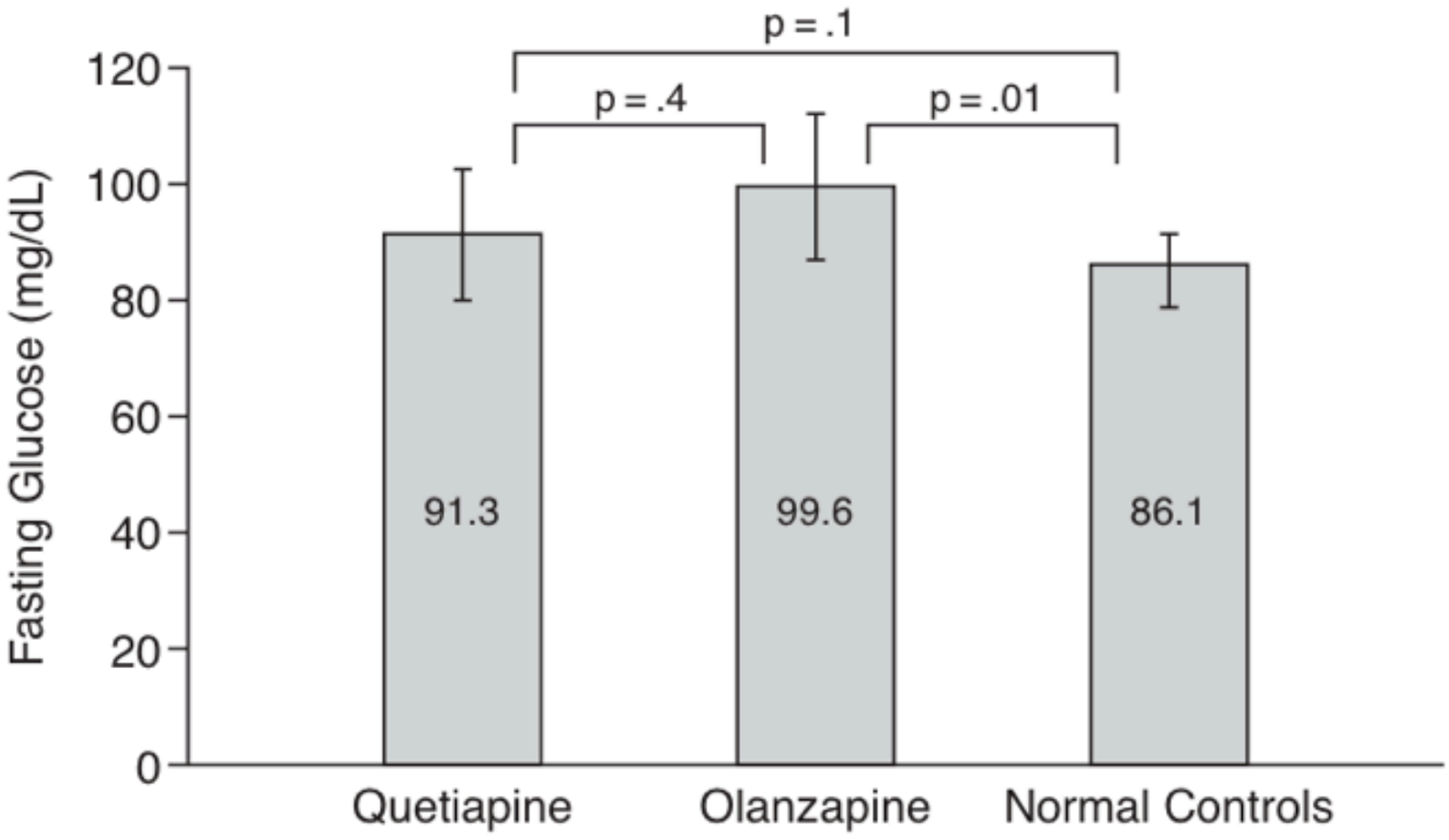
Glucose metabolism

[Henderson et al, 2006]

- 15 non-obese schizophrenia patients compared with 9 normal controls
- frequently sampled glucose tolerance test (38 blood tests for glucose and insulin, over ~3 hours)
- high-carb diet for 3 days before the procedure
- 8 patients on olanzapine for 34 months average
- 7 patients on quetiapine for 24 months average

Henderson DC, Copeland PM, Borba CP, et al. Glucose metabolism in patients with schizophrenia treated with olanzapine or quetiapine: a frequently sampled intravenous glucose tolerance test and minimal model analysis. J Clin Psychiatry. 2006;67:789–797.

Figure 1. Fasting Glucose in Nonobese Schizophrenia Subjects Treated With Olanzapine (N = 8) or Quetiapine (N = 7) and Normal Controls (N = 9)[a]

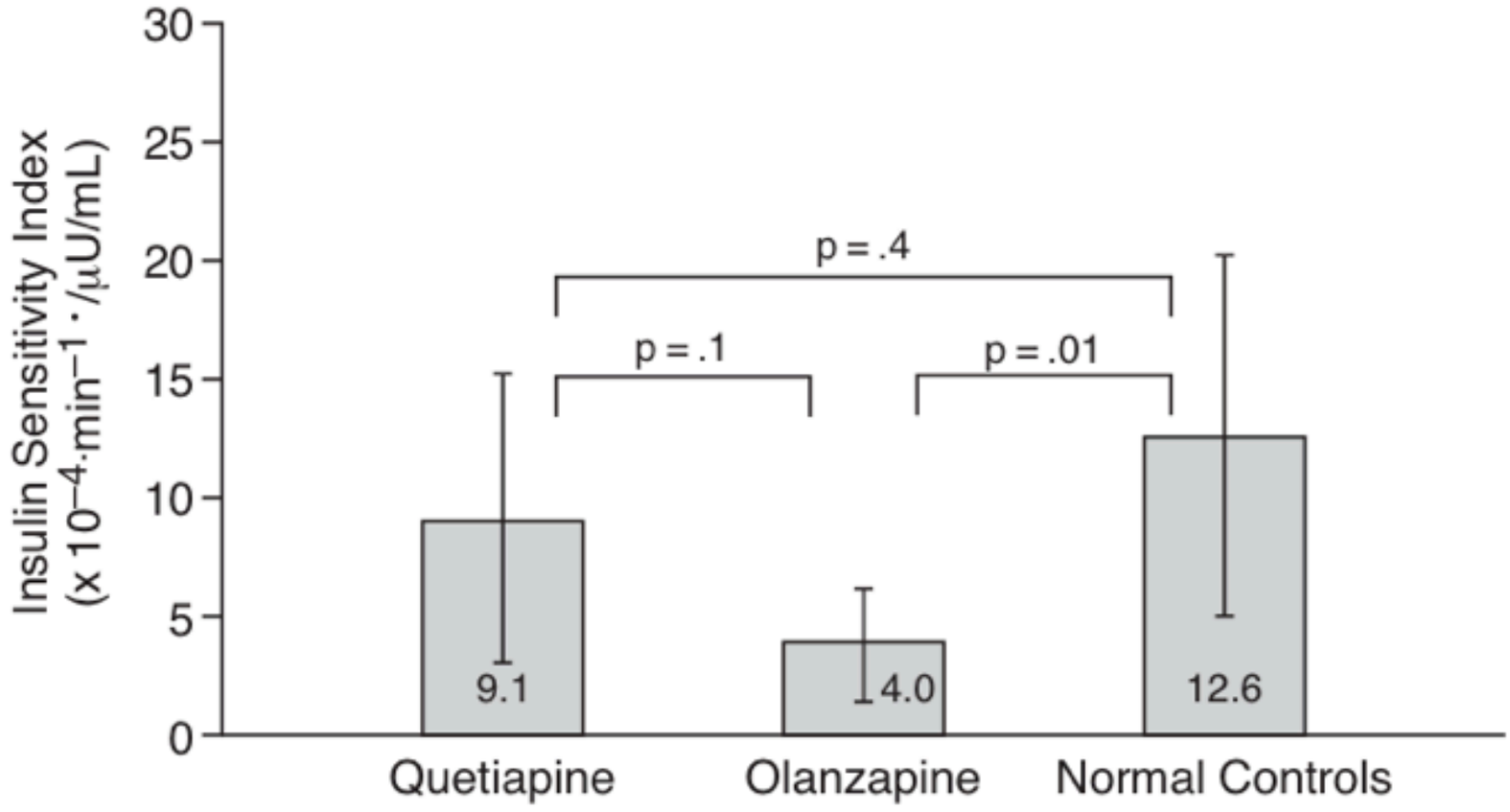


[a]Values expressed as mean ± SD.

[Henderson et al, 2006]

Fasting glucose was significantly higher in the olanzapine group, compared to controls. The other comparisons were not significantly different.

Figure 2. Insulin Sensitivity Index in Nonobese Schizophrenia Subjects Treated With Olanzapine (N = 8) or Quetiapine (N = 7) and Normal Controls (N = 9)[a]



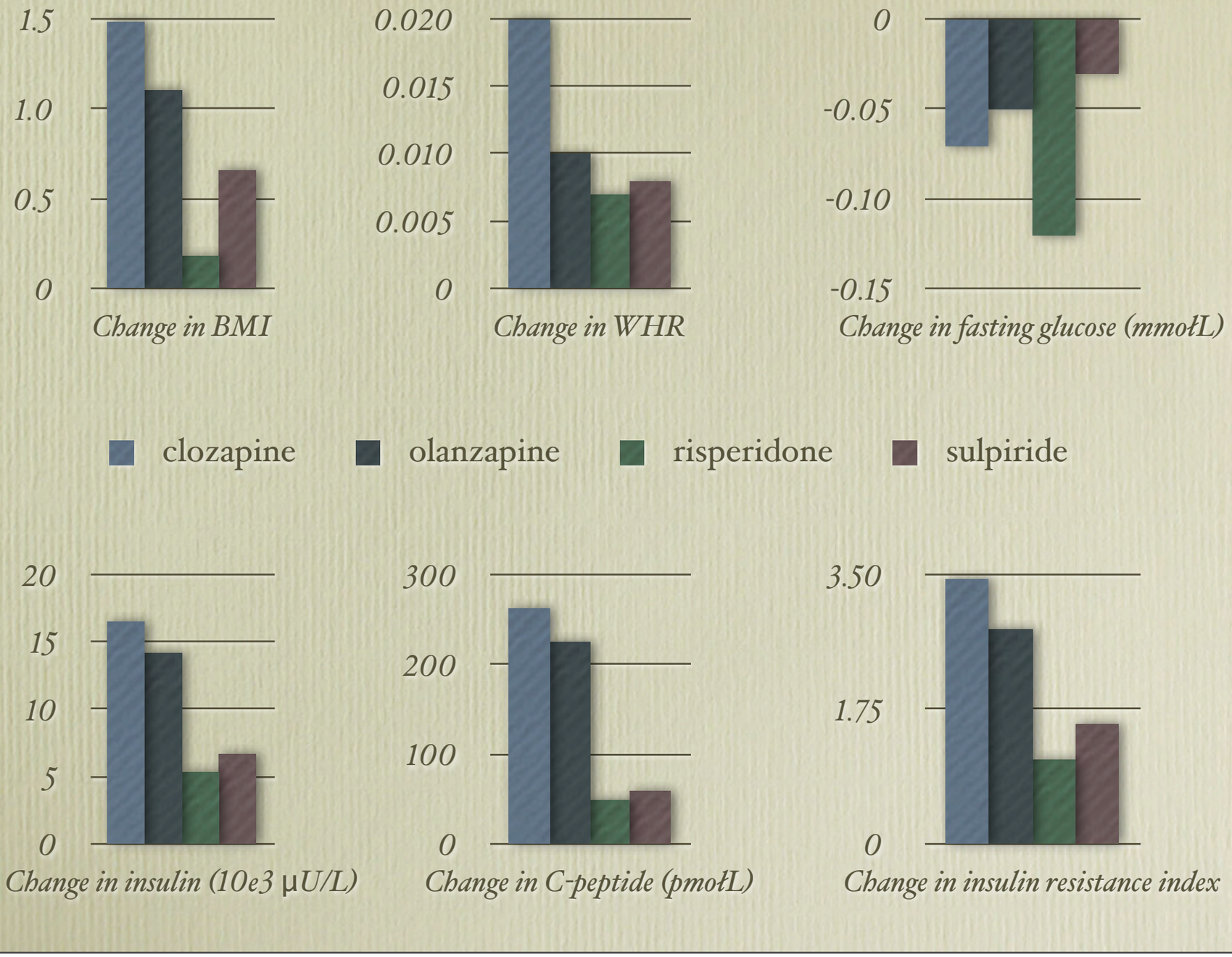
[a]Values expressed as mean ± SD.

Insulin sensitivity, which is the inverse of insulin resistance, was significantly lower in the olanzapine compared to controls. Other comparisons were not significantly different.

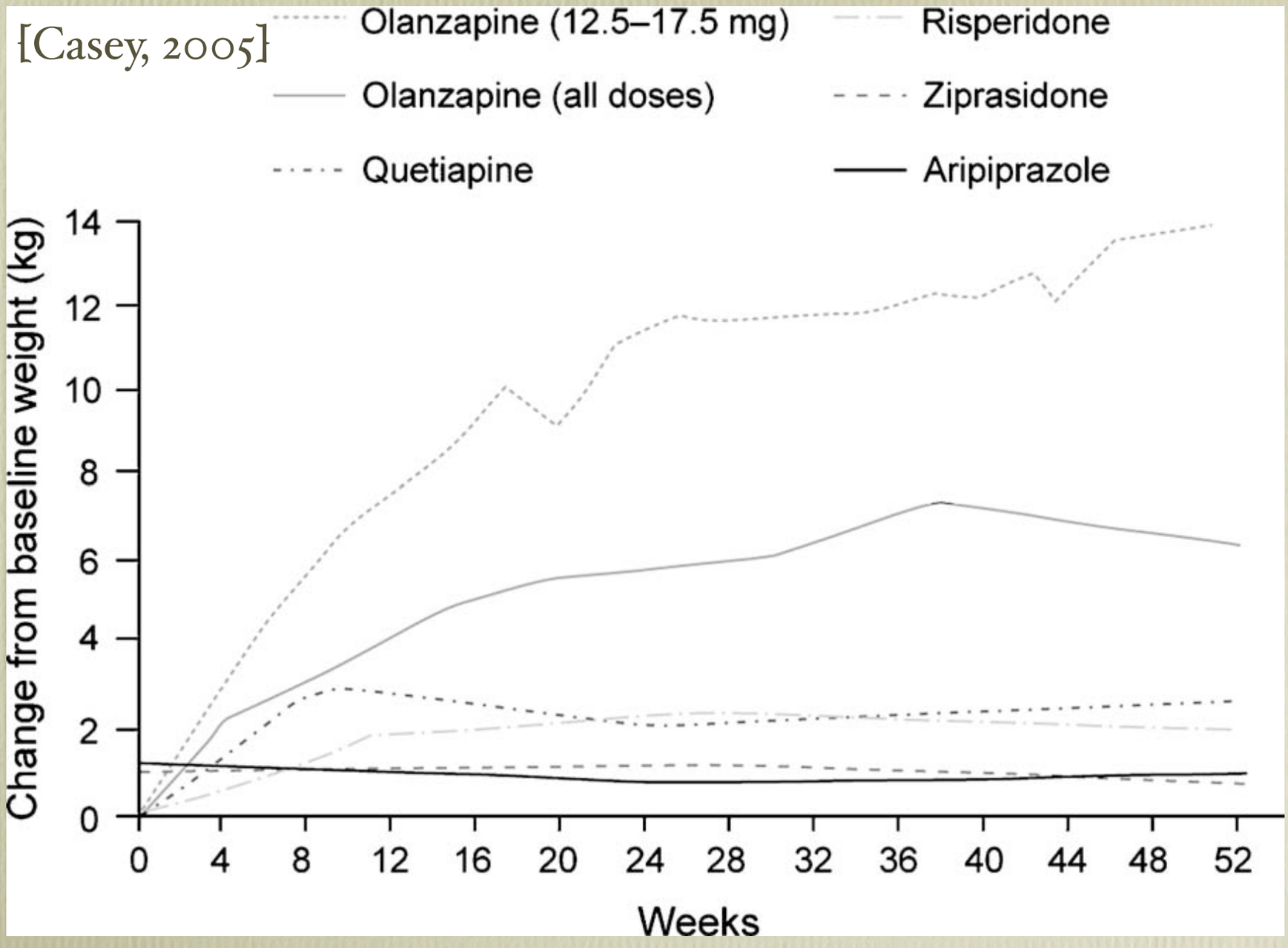
First-episode schizophrenia
[Wu et al, 2006]

- 112 patients with schizophrenia, randomly assigned to receive clozapine, olanzapine, risperidone, or sulpiride for 8 weeks
- first-episode psychosis
- nonblinded study
- inpatients
- on identical diets

Wu RR, Zhao JP, Liu ZN, et al. Effects of typical and atypical antipsychotics on glucose-insulin homeostasis and lipid metabolism in first-episode schizophrenia. Psychopharmacology (Berl). 2006;186:572-578.


1.5
1.0
0.5
0
Change in BMI
0.020
0.015
0.010
0.005
0
Change in WHR
0
-0.05
-0.10
-0.15
Change in fasting glucose (mmoł/L)
clozapine
olanzapine
risperidone
sulpiride
20
15
10
5
0
Change in insulin (10e3 µU/L)
300
200
100
0
Change in C-peptide (pmoł/L)
3.50
1.75
0
Change in insulin resistance index

[Casey, 2005]



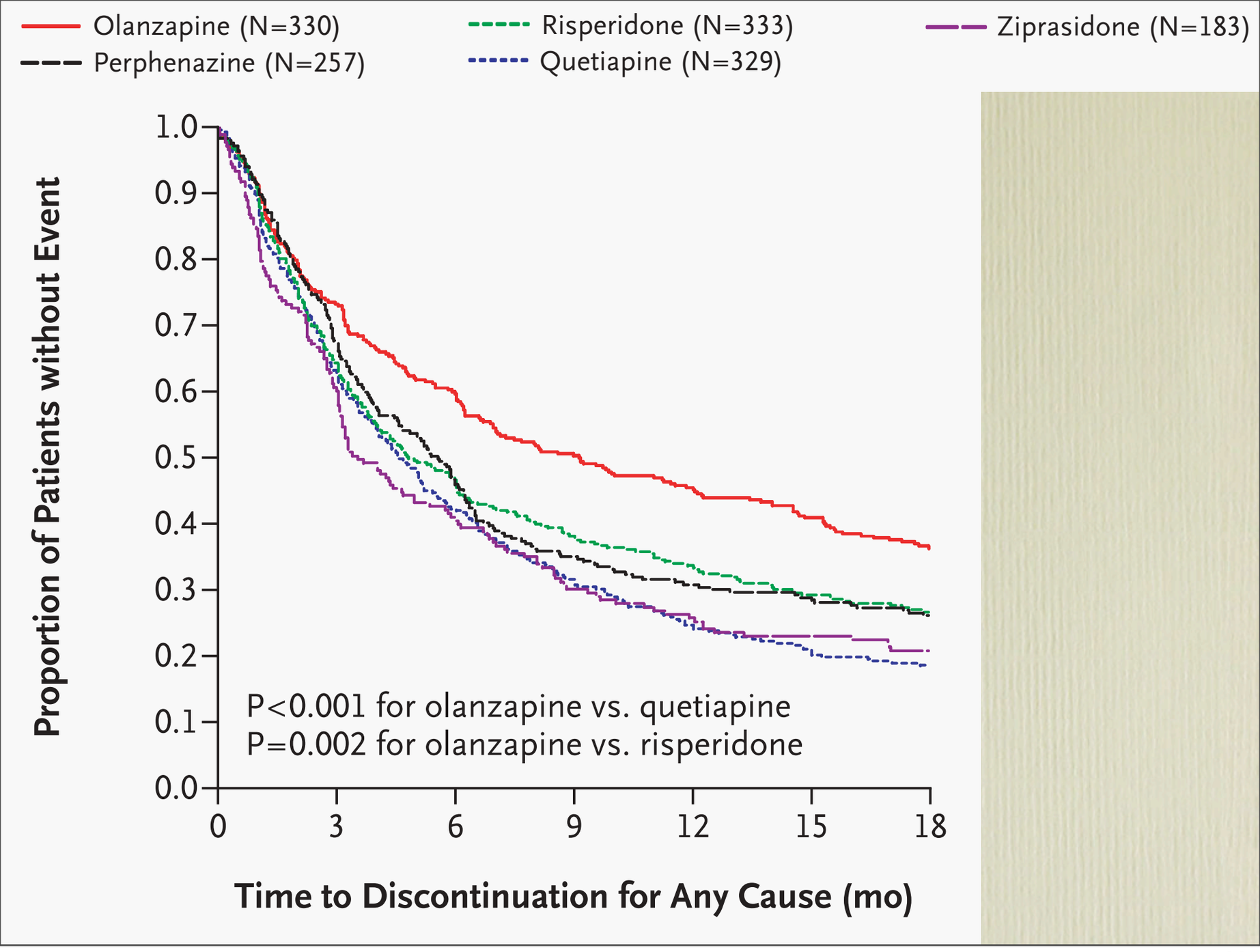
Casey DE. Metabolic issues and cardiovascular disease in patients with psychiatric disorders. Am J Med. 2005;118 Suppl 2:15S–22S.

The CATIE Study

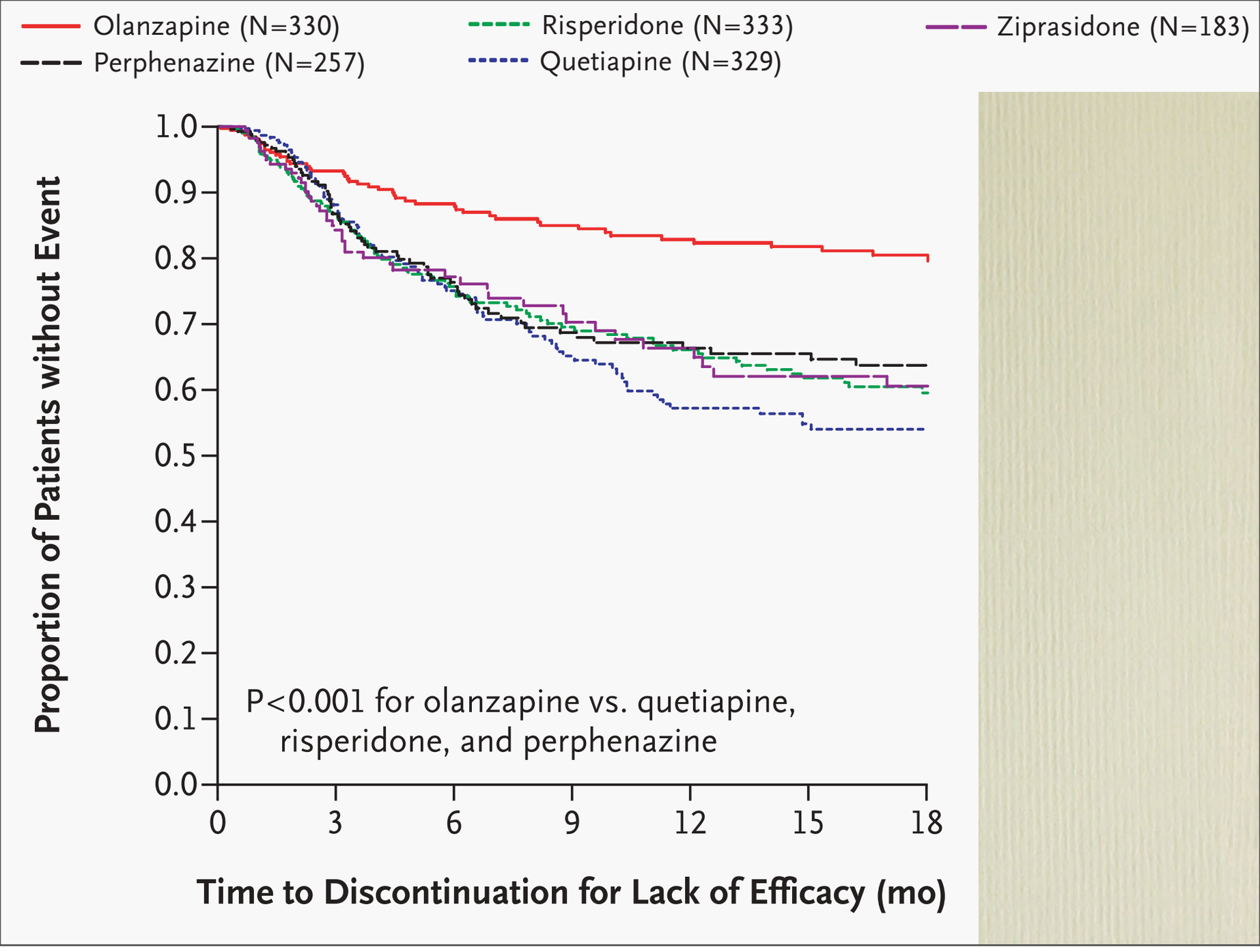
Clinical Antipsychotic Trials of Intervention Effectiveness

- Lieberman et al, 2005
- 1493 patients with schizophrenia
- 57 U.S. sites
- randomized to: olanzapine (7.5-30 mg/day); perphenazine (8-32 mg/day); quetiapine (200-800 mg/day); or risperidone (1.5-6 mg/day) for up to 18 months
- ziprasidone (40-160 mg/day) added after FDA approval

Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med. 2005;353:1209-1223.

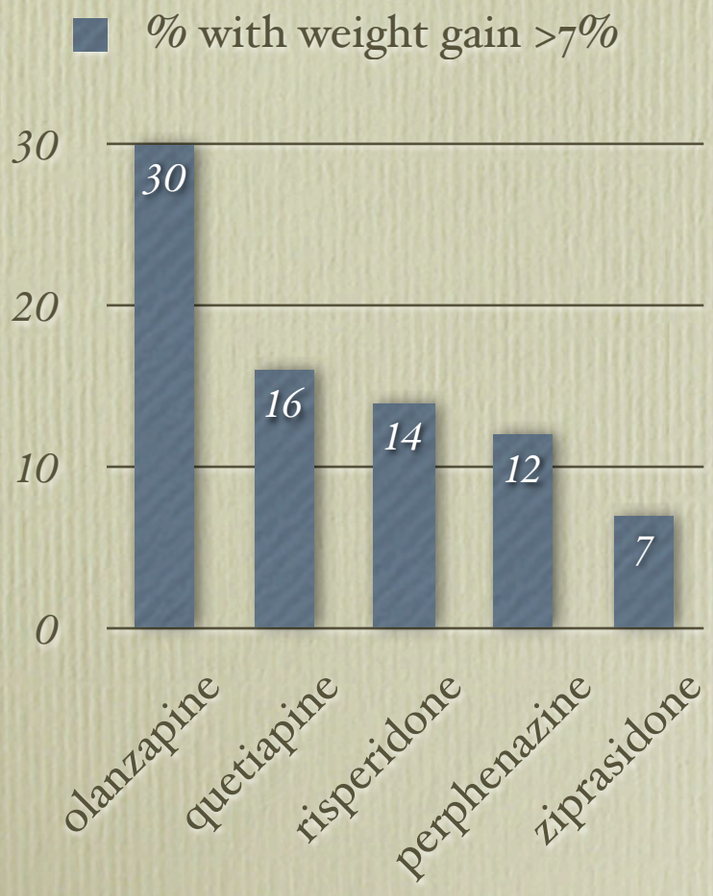


74% of patients discontinued the study medication before 18 months; the time to discontinuation was longest for olanzapine (9.2 mos); this was significantly longer than for quetiapine and risperidone, but not significantly different for perphenazine or ziprasidone after adjusting for multiple comparisons.

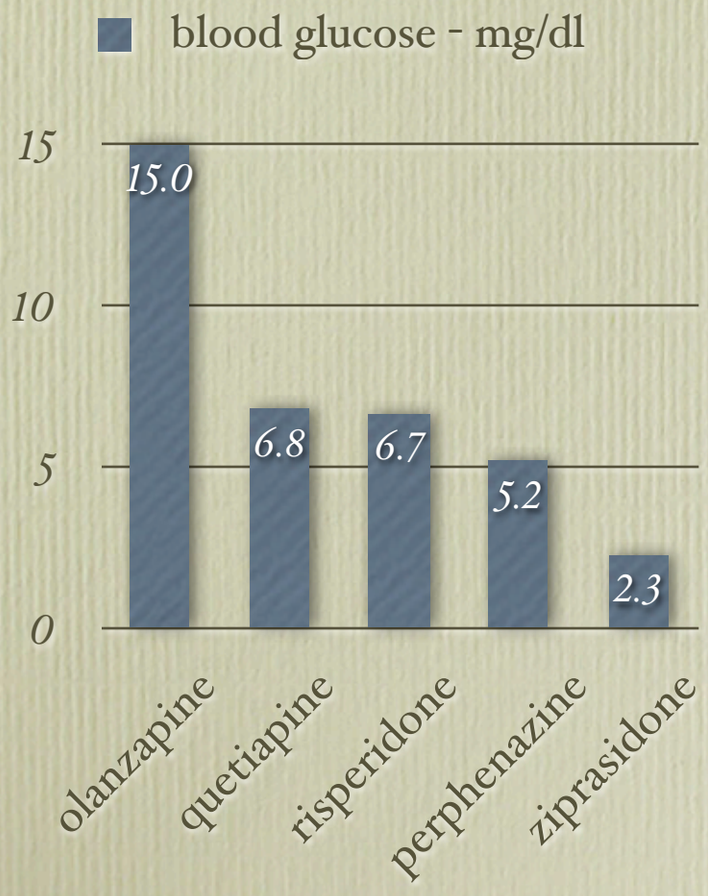


The time to discontinuation of treatment for lack of efficacy was significantly longer in the olanzapine group compared to quetiapine, risperidone, and perphenazine.

Effects on weight

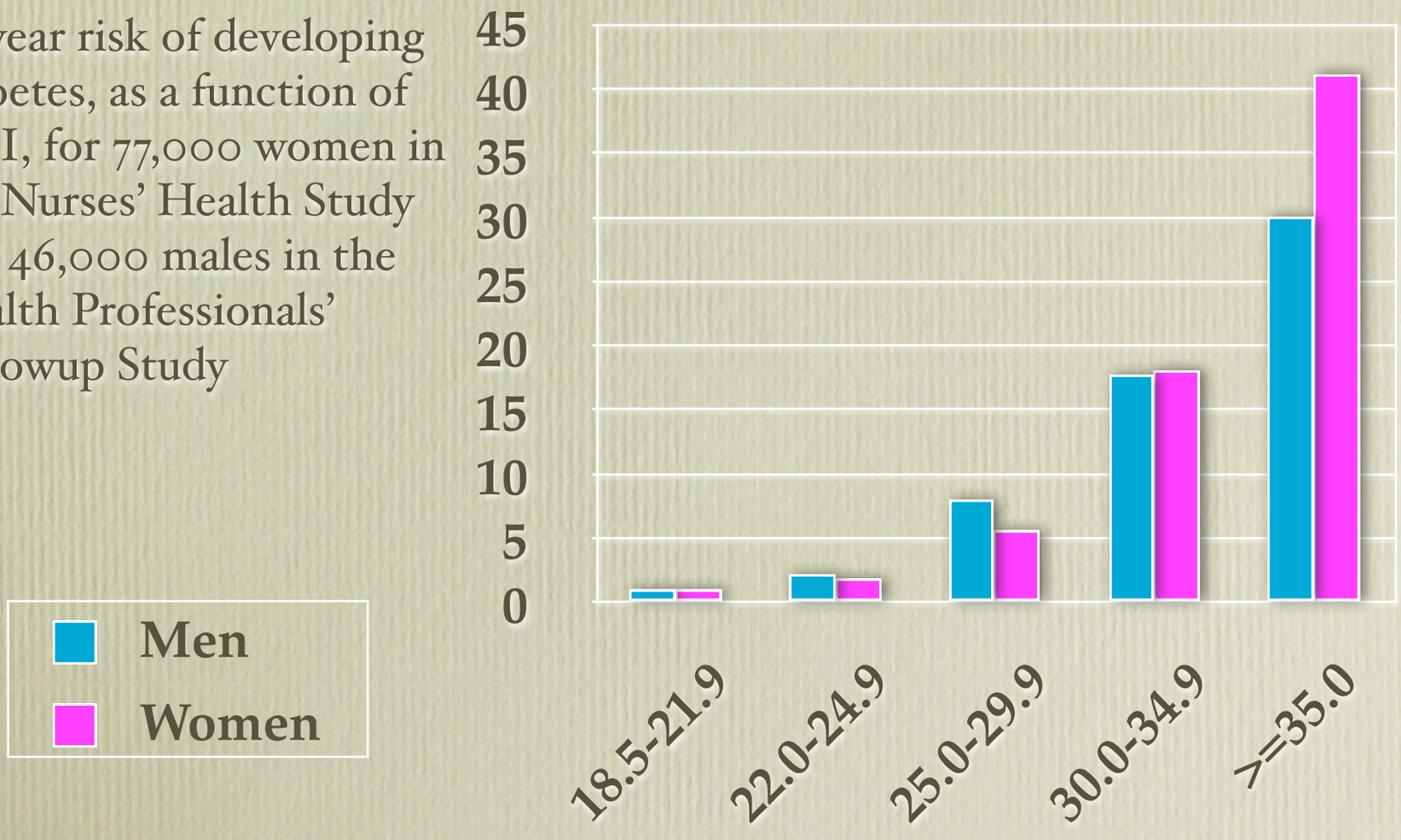


Effects on lab values - changes from baseline



Obesity predisposes to DM 2
(Field 2001)

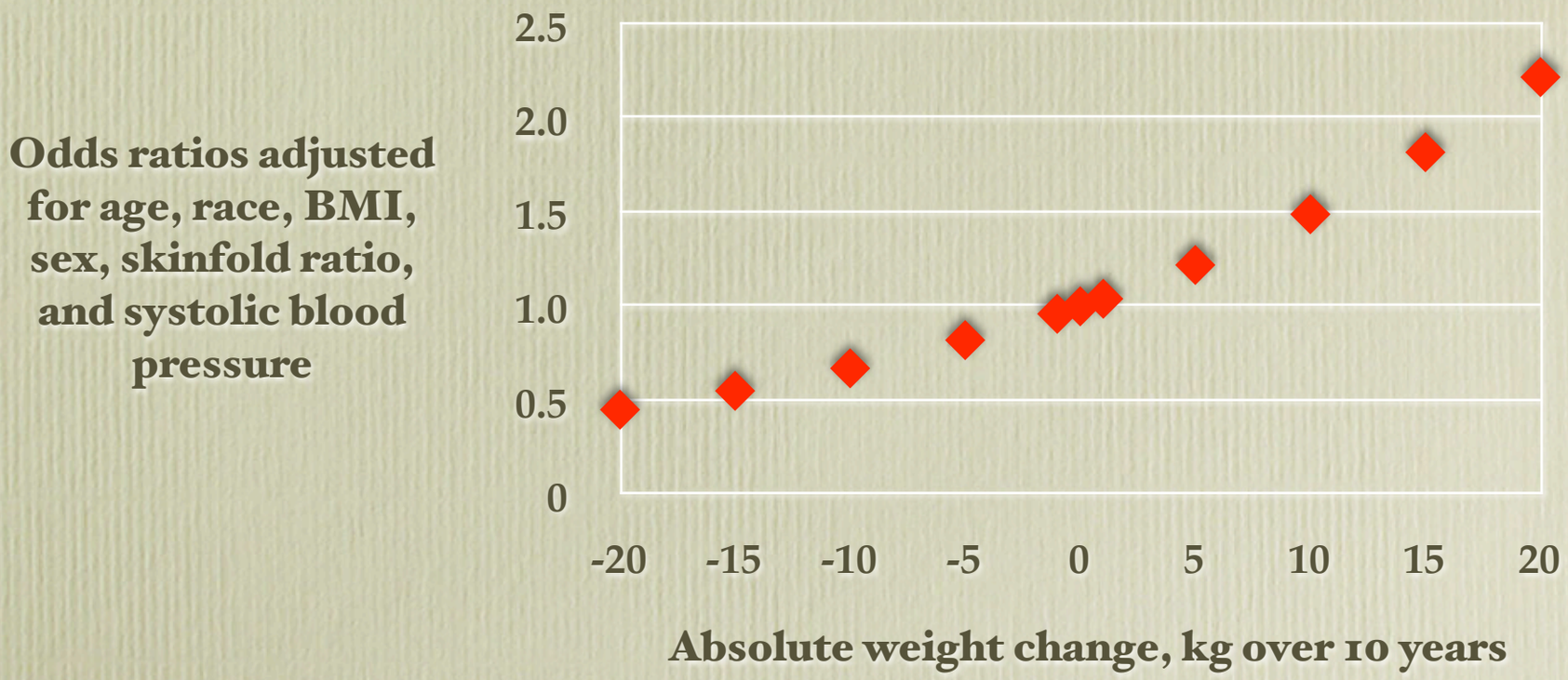
10-year risk of developing diabetes, as a function of BMI, for 77,000 women in the Nurses' Health Study and 46,000 males in the Health Professionals' Followup Study



Field AE, Coakley EH, Must A, et al. Impact of overweight on the risk of developing common chronic diseases during a 10-year period. Arch Intern Med. 2001;161:1581-1586.

10-year risk of developing diabetes, as a function of BMI, for 77,000 women in the Nurses' Health Study and 46,000 males in the Health Professionals' Followup Study.

Weight gain contributes to DM 2
(Resnick 2000)

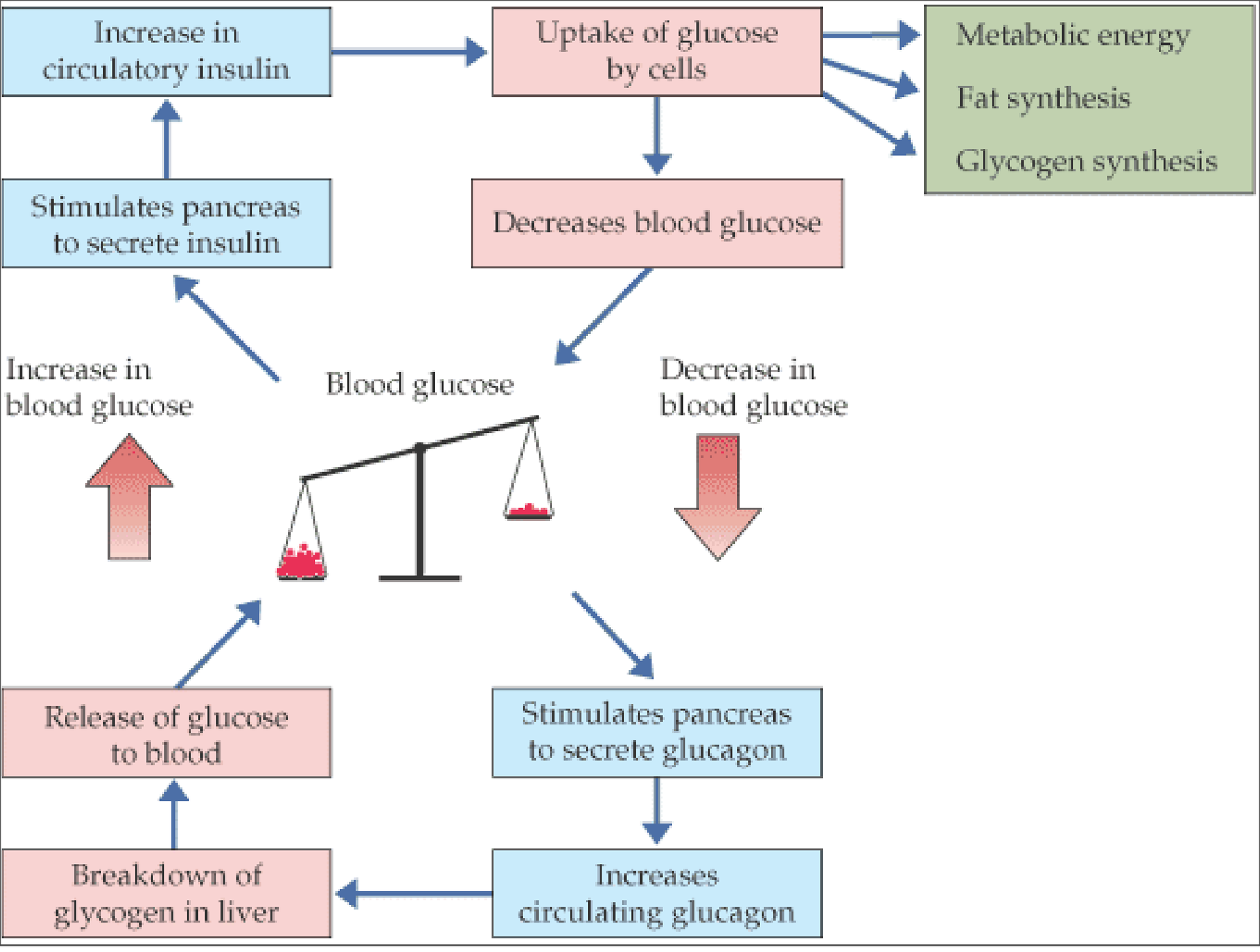


Resnick HE, Valsania P, Halter JB, Lin X. Relation of weight gain and weight loss on subsequent diabetes risk in overweight adults. J Epidemiol Community Health. 2000;54:596–602.

Odds ratios adjusted for age, race, BMI, sex, skinfold ratio, and systolic blood pressure.

How does weight gain occur?

- Action of insulin


Increase in circulatory insulin
Uptake of glucose by cells
Metabolic energy
Fat synthesis
Glycogen synthesis
Stimulates pancreas to secrete insulin
Decreases blood glucose
Increase in blood glucose
Blood glucose
Decrease in blood glucose
Release of glucose to blood
Stimulates pancreas to secrete glucagon
Breakdown of glycogen in liver
Increases circulating glucagon

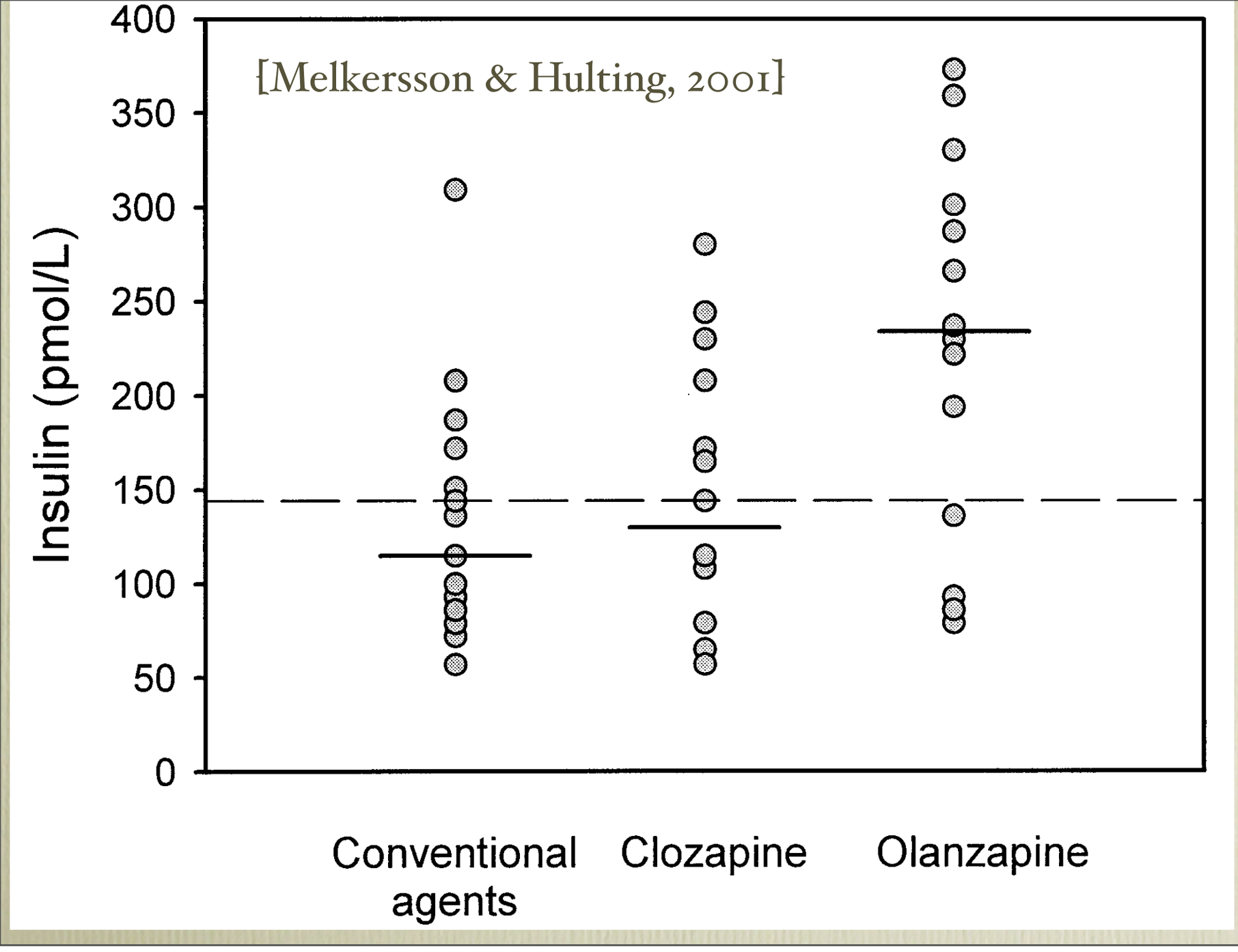
AAPs increase insulin levels

- Hyperinsulinemia in pts on olanzapine
  - 10 / 14 patients (Melkersson 2001)
  - 4 / 11 patients (Cohn 2002)

Melkersson KI, Hulting AL. Insulin and leptin levels in patients with schizophrenia or related psychoses--a comparison between different antipsychotic agents. Psychopharmacology (Berl). 2001;154:205-212.

Cohn TA, Remington G, Kameh H. Hyperinsulinemia in psychiatric patients treated with olanzapine. J Clin Psychiatry. 2002;63:75-76.

The Cohn study only showed elevated fasting insulin levels in 4 out of 11 patients on olanzapine. Why so much lower? Perhaps a baseline difference in the populations under study. The Cohn study was in Toronto, The Melkersson study in Sweden.



Melkersson KI, Hulting AL. Insulin and leptin levels in patients with schizophrenia or related psychoses--a comparison between different antipsychotic agents. Psychopharmacology (Berl). 2001;154:205-212.

Insulin levels were significantly higher in the olanzapine group, compared to the conventional antipsychotic group, even though the BMIs in the two groups were about the same. This suggests that olanzapine induces a rise in insulin even without insulin resistance. Thus, the olanzapine may stimulate weight gain just through its effect on insulin level.

In the clozapine group, insulin levels were correlated with clozapine dose. This is fairly strong evidence that the clozapine was affecting the insulin level, either through increasing insulin secretion or by decreasing the breakdown and elimination of insulin.

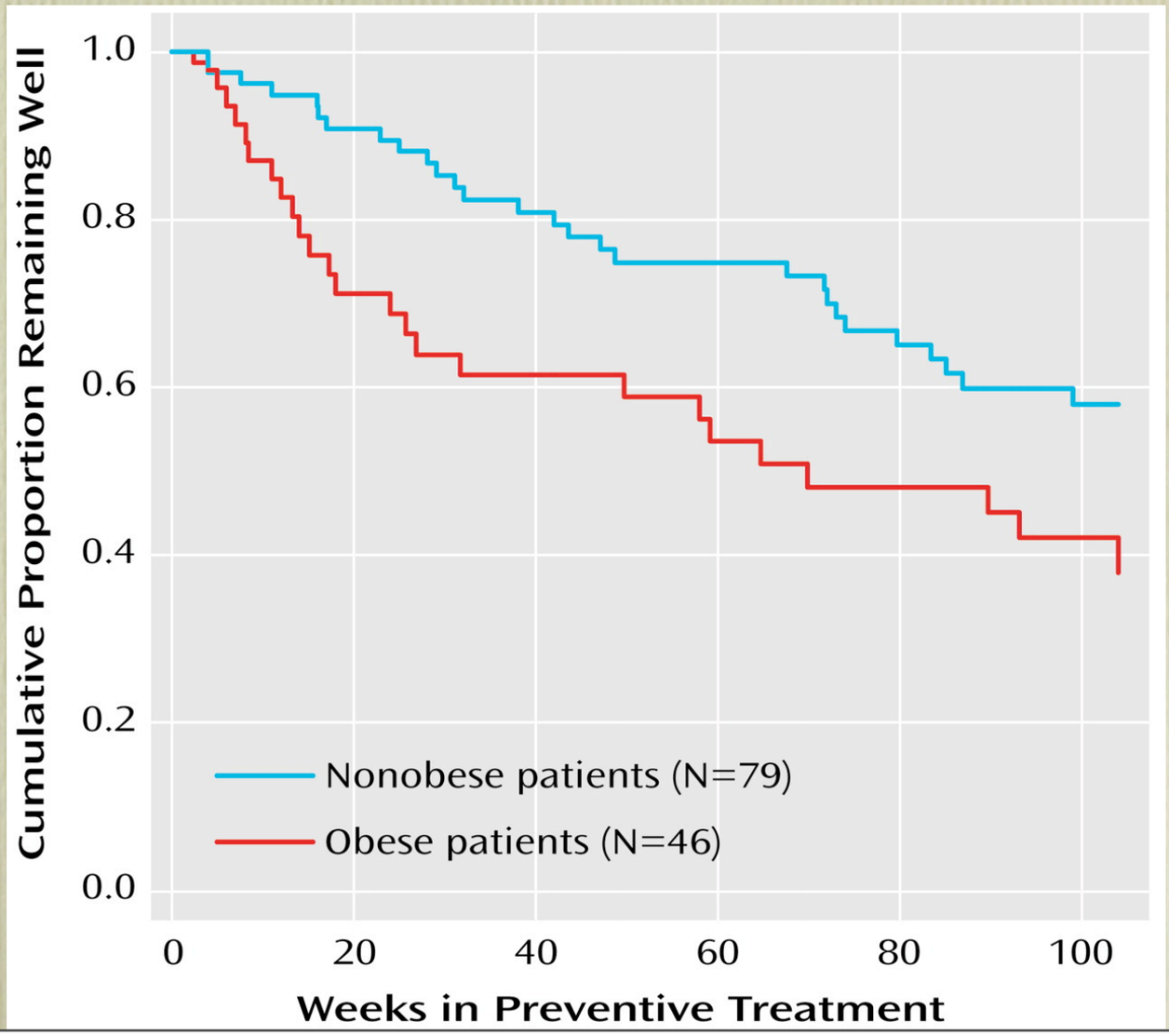
Which patients are most at risk?

- Those who already have high insulin levels (eg, genetics)
  - Due to higher levels of secretion
  - Lower rates of insulin breakdown
  - A combination of the two
- Genetic predisposition
- Bipolar patients are more likely to be obese, especially depressed bipolars
  - 32% of 50 consecutive bipolar I patients had BMI > 30 (Fagiolini 2002)
- Schizophrenic patients are more likely to have DM 2 (2-3 times risk of general population (Lebovitz 2003)

Fagiolini A, Frank E, Houck PR, et al. Prevalence of obesity and weight change during treatment in patients with bipolar I disorder. J Clin Psychiatry. 2002;63:528-533.

Lebovitz HE. Metabolic consequences of atypical antipsychotic drugs. Psychiatr Q. 2003;74:277-290.

Bipolar patients who are obese have a worse course of illness (Fagiolini 2003)



Fagiolini A, Kupfer DJ, Houck PR, Novick DM, Frank E. Obesity as a correlate of outcome in patients with bipolar I disorder. Am J Psychiatry. 2003;160:112–117.

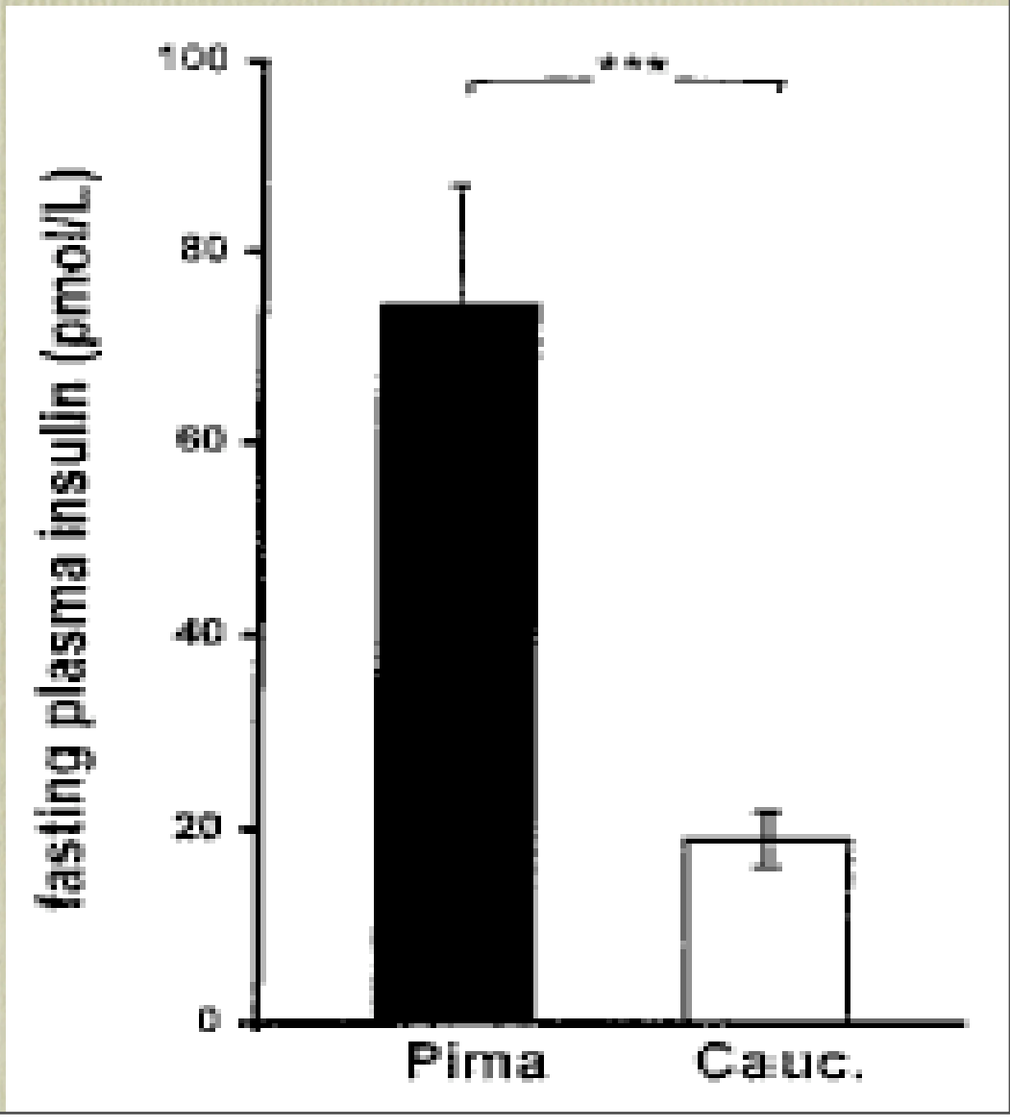
Who has this genetic predisposition to high insulin levels?

- Aboriginals
  - Pima Indian children have higher fasting insulin levels than Caucasian children of similar age and weight (Pettitt 1993)

Pettitt DJ, Moll PP, Knowler WC, et al. Insulinemia in children at low and high risk of NIDDM. Diabetes Care. 1993;16:608-615.

Genetic predisposition

- Another study comparing age and gender-matched Pima Indian & Caucasian children (Weyer 2001)
- Pima children were heavier (BMI 20.1 vs 15.4), but the fasting insulin when controlled for weight was still significantly different.



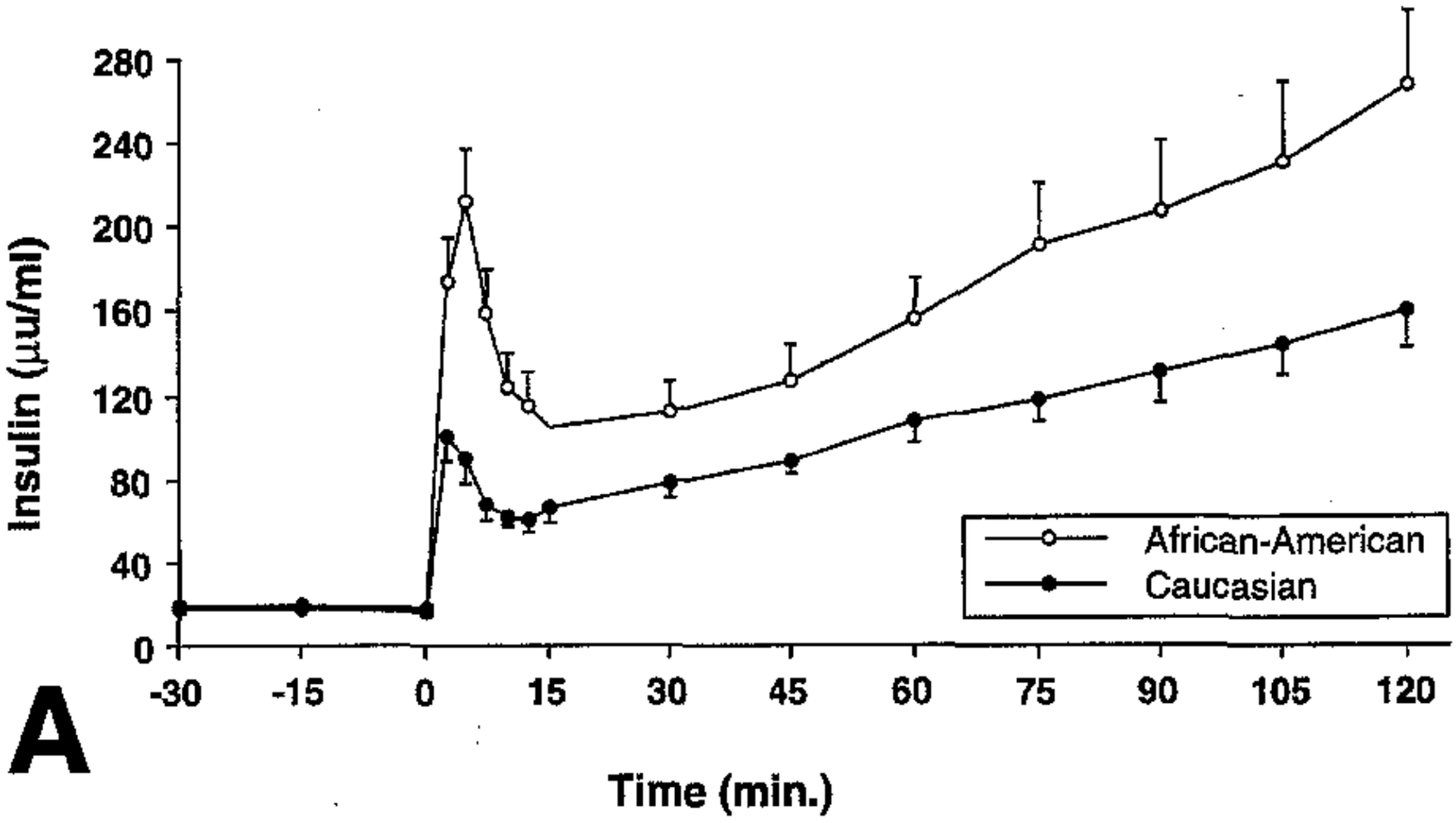
Weyer C, Salbe AD, Lindsay RS, Pratley RE, Bogardus C, Tataranni PA. Exaggerated pancreatic polypeptide secretion in Pima Indians: can an increased parasympathetic drive to the pancreas contribute to hyperinsulinemia, obesity, and diabetes in humans? Metabolism. 2001;50:223-230.

Genetic predisposition

- in African-American children, family history of type 2 diabetes is a risk factor for insulin resistance (Danadian 1999)
- A Canadian study (Katzmarzyk 2000) comparing risks of obesity in spouses and first degree relatives of obese probands showed higher risk for relatives compared to spouses.

Danadian K, Balasekaran G, Lewy V, Meza MP, Robertson R, Arslanian SA. Insulin sensitivity in African-American children with and without family history of type 2 diabetes. Diabetes Care. 1999;22:1325-1329.

Katzmarzyk PT, Perusse L, Rao DC, Bouchard C. Familial risk of overweight and obesity in the Canadian population using the WHO/NIH criteria. Obes Res. 2000;8:194-197.



Arslanian S, Suprasongsin C. Differences in the in vivo insulin secretion and sensitivity of healthy black versus white adolescents. J Pediatr. 1996;129:440-443.

Hyperglycemic clamp experiment: blood glucose level maintained at 12.5 mmol/L for 2 hrs by a variable glucose infusion.

The "Thrifty genotype" hypothesis [Neel, 1962]

- People who are predisposed to diabetes, are initially distinguished by a greater-than-normal availability of effective circulating insulin after food intake
- This helps to prevent loss of sugar in the urine, thus storing a bit more fat for the "lean" periods that characterize the hunter-gatherer lifestyle

NEEL JV. Diabetes mellitus: a "thrifty" genotype rendered detrimental by "progress"? Am J Hum Genet. 1962;14:353-362.

James Neel was a geneticist. He proposed this theory at a time when type 1 and type 2 diabetes had not yet been clearly separated, but it was known that diabetes was particularly common among certain indigenous North American tribes, and it was since learned that type 2 diabetes occurs frequently in a number of developing countries or among minority populations who had formerly a harsh natural environment and a subsequent modernization with changes in nutrition and exercise patterns.

The "thrifty phenotype" hypothesis [Hales & Barker, 1992]

- low birth weight is associated with subsequent type 2 diabetes in an English cohort
- a similar phenomenon has been noted among Nauruans who suffered great nutritional hardship during WW2
- Among Pima Indians, both low and high birth weight are associated with subsequent diabetes, although 90% of adults with diabetes had a normal birth weight [King & Roglic, 1999]

Hales CN, Barker DJ. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. Diabetologia. 1992;35:595-601.

King H, Roglic G. Diabetes and the "thrifty genotype": Commentary. Bulletin of the World Health Organization. 1999;962-.

The thrifty phenotype hypothesis was initially proposed by Hales and Barker as an argument against the thrifty genotype hypothesis of James Neel. But their observation that low birth weight predisposed to diabetes later on, may actually support the thrifty genotype argument. How?

suppose times are very tough during gestation. Very little food is available for the mother, and of course the fetus. Many fetuses will not survive, and will be aborted, or spontaneously resorbed in some species.

The fetuses that do survive may be the ones that are genetically programmed to store that extra little bit of fat efficiently, and thus at higher risk of diabetes if times are continually good.

My extension of the hypothesis

- Typical diet in pre-agrarian days was low in carbohydrates except in autumn
- Weight gain prior to winter had survival value
- Thus, rapid weight gain during periods of high dietary carbohydrates, enhanced survival
- This adaptation was based on high levels of insulin in response to dietary carbohydrates

What do I think? I support the idea of the “thrifty gene” but I think Neel and other scientists have not gone far enough. For one thing, no one ever talks about seasonal variations in available foodstuffs. I guess that comes from living in developed countries where all sorts of food are available fresh all year round, and if not fresh, at least frozen or canned.

But hunter-gatherers do not typically get foods that store well. And even if they did, they would not want to transport large quantities. The only exception is live meat; cattle, reindeer, horses transport themselves quite well,

Not only do high insulin levels result in efficient fat storage, they also prevent breakdown of stored fat. Thus, even if you are not getting enough calories, your fat stores are maintained.

A second effect of high insulin levels is low blood sugar, which prompts eating more carbs.

- The agrarian revolution made carbohydrates available year-round
- The thrifty gene causes obesity with year-round carbohydrates
- Thrifty gene now in only a part of the population
- However, we could say that the thrifty gene represents normalcy

It appears that in many races and cultures, the thrifty gene rules. It hasn't produced diabetes in all the people with the gene, because carbs are available only some of the time, or because total caloric intake is small in relation to caloric expenditure.

The thrifty gene and diabetes

- High-carbohydrate diet leads to high insulin levels
- High insulin = weight gain
  - Especially central adiposity
- Obesity causes insulin resistance [Kahn & Flier, 2000]
  - why: homeostatic mechanism to limit further weight gain
  - the natural history of untreated DM2 is often weight loss

Kahn BB, Flier JS. Obesity and insulin resistance. J Clin Invest. 2000;106:473-481.

This is where we discuss our different view of genesis of type 2 diabetes.

Objections

- It's calories, not carbs, that control weight loss or gain.
- High insulin levels are a response to insulin resistance, which is the primary defect

What happens to type 1 diabetics without insulin, even if they gorge themselves? They lose weight, and then die.

Small amounts of weight loss correct the insulin resistance; this suggests that insulin resistance is not a static phenomenon, but is influenced by things such as the amount of central obesity and the composition of the diet.

The thrifty gene and diabetes (2)

- Insulin resistance reduces further weight gain
- Diabetes contributes to weight loss by calorie loss (Ludwig 2002)
  - Homeostatic mechanism vs pathology
- Weight loss increases insulin sensitivity (Brochu 2003)

Ludwig DS. The glycemic index: physiological mechanisms relating to obesity, diabetes, and cardiovascular disease. JAMA. 2002;287:2414-2423.

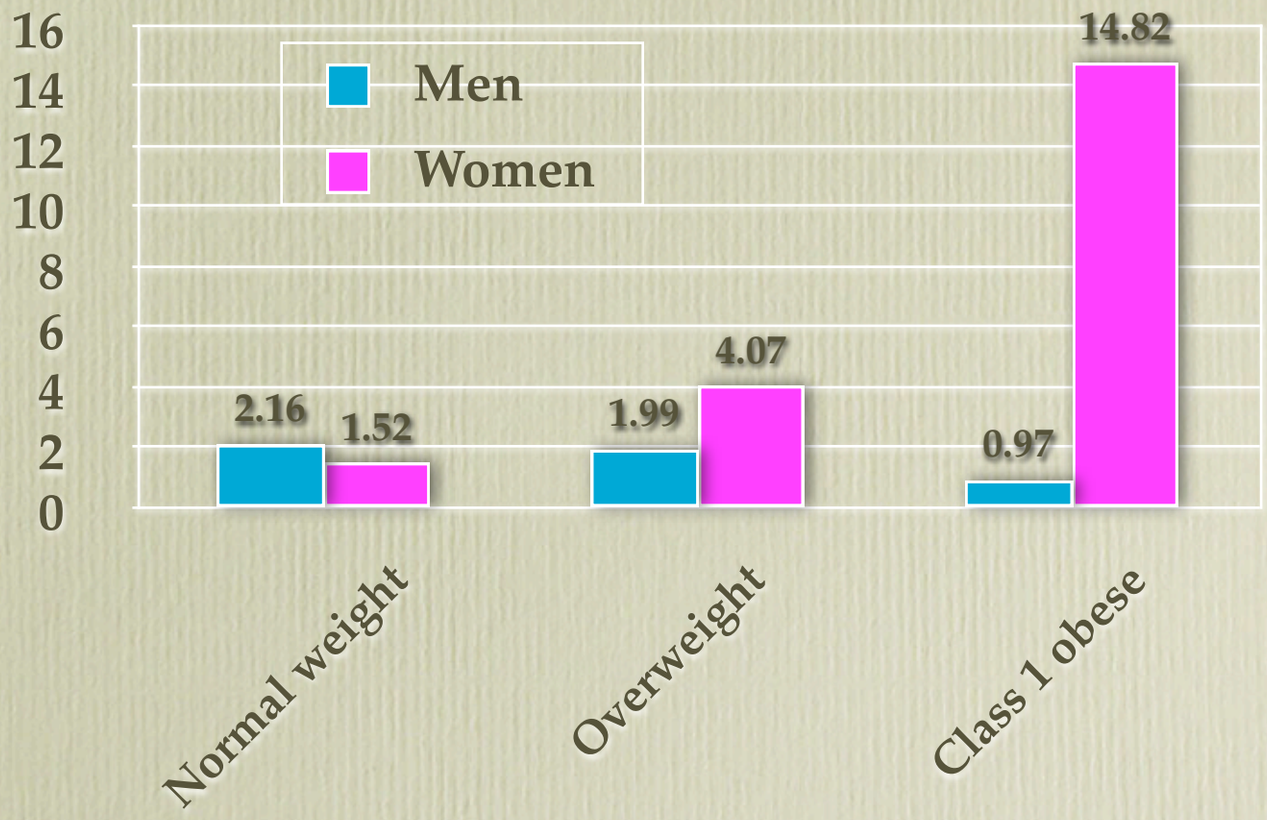
Brochu M, Tchernof A, Turner AN, Ades PA, Poehlman ET. Is there a threshold of visceral fat loss that improves the metabolic profile in obese postmenopausal women? Metabolism. 2003;52:599-604.

Identifying those at risk

- Central obesity (waist circumference) predicts DM 2 (Janssen 2002)

Odds ratio for DM2, high WC vs low WC

Adjusted for age, race, physical activity, smoking, alcohol intake, and the poverty-income ratio

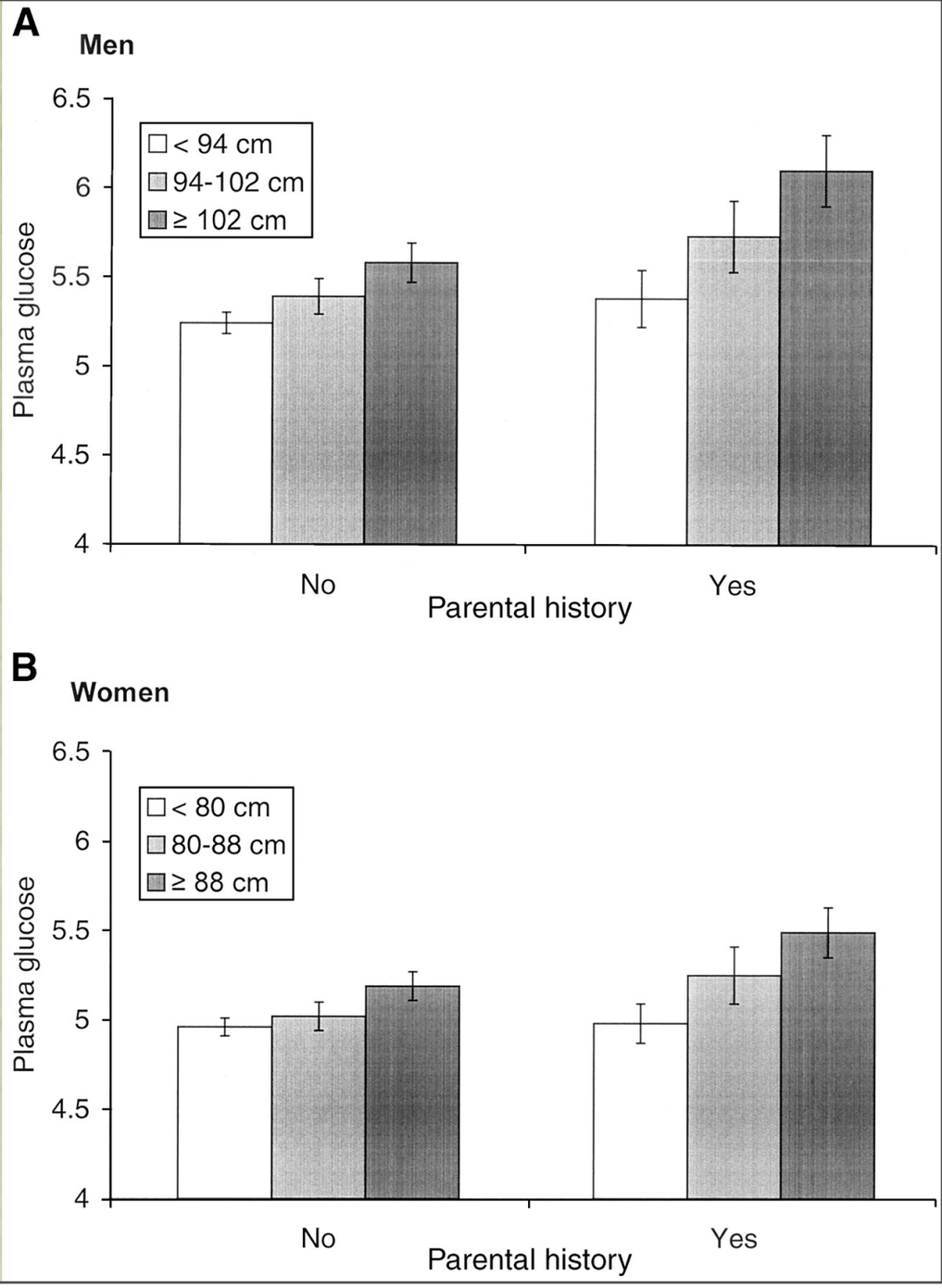


Janssen I, Katzmarzyk PT, Ross R. Body mass index, waist circumference, and health risk: evidence in support of current National Institutes of Health guidelines. Arch Intern Med. 2002;162:2074-2079.

Adjusted for age, race, physical activity, smoking, alcohol intake, and the poverty-income ratio.

Identifying those at risk

- Family history of DM 2 (van Dam 2001)
- Stronger association between abdominal obesity(waist circumference) and higher plasma glucose in individuals who had a parental history of diabetes than in those who did not



van Dam RM, Boer JM, Feskens EJ, Seidell JC. Parental history of diabetes modifies the association between abdominal adiposity and hyperglycemia. Diabetes Care. 2001;24:1454-1459.

What can be done to reduce the risk of diabetes in patients taking atypical antipsychotics?

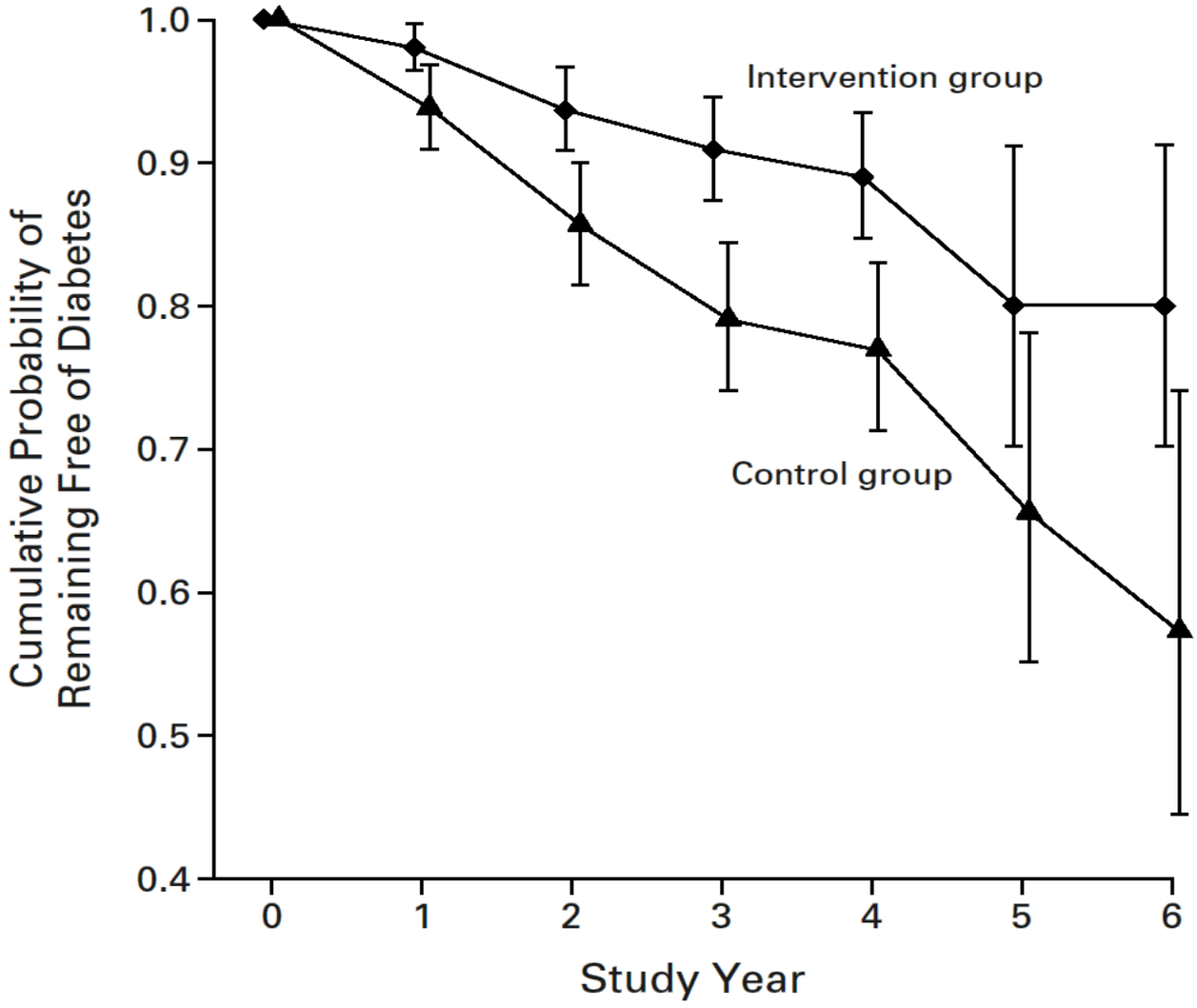
Weight loss can reduce the incidence of diabetes
(Pinkney 2002)

Pinkney J. Prevention and cure of type 2 diabetes. BMJ. 2002;325:232-233.

Example: weight loss (Tuomilehto 2001)

- 522 middle-aged overweight patients with impaired glucose tolerance were randomized
- Intervention group received individualized counseling to:
  - Reduce weight
  - Reduce total fat intake
  - Reduce saturated fat intake
  - Increase dietary fibre
  - Increase physical activity
- After 1 year:
  - weight loss 4.2 kg vs 0.8 kg
  - Waist circumference reduction 4.4 cm vs 1.3 cm

Tuomilehto J, Lindstrom J, Eriksson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med. 2001;344:1343-1350.



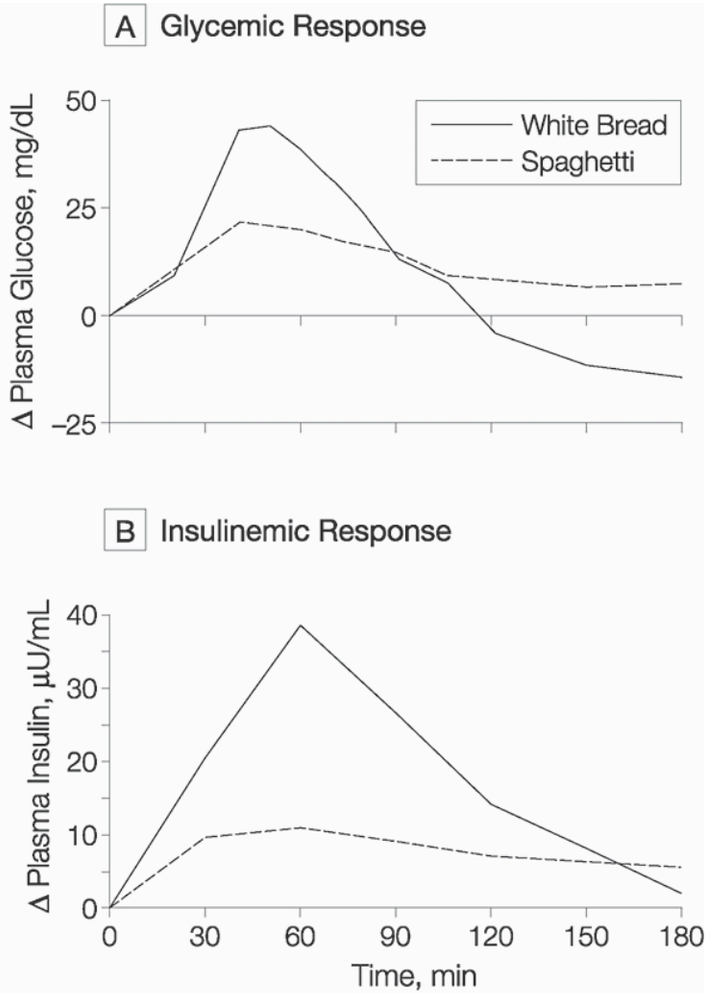
Subjects at Risk						
Total no.	507	471	374	167	53	27
Cumulative no. with diabetes:						
Intervention group	5	15	22	24	27	27
Control group	16	37	51	53	57	59

Glycemic Index

- For comparing different carbohydrate-containing foods
- Defined as the incremental area under the glucose response curve after a standard amount of carbohydrate from a test food relative to that of a control food is consumed.
- Test food: usually white bread or glucose

Who hasn't heard about glycemic index? What does it mean? Basically, it's a way of comparing how different carbohydrate-containing foods affect our metabolism.

Glycemic and Insulinemic Responses After Ingestion of Carbohydrates



Ludwig, D. S. JAMA 2002;287:2414-2423.

JAMA

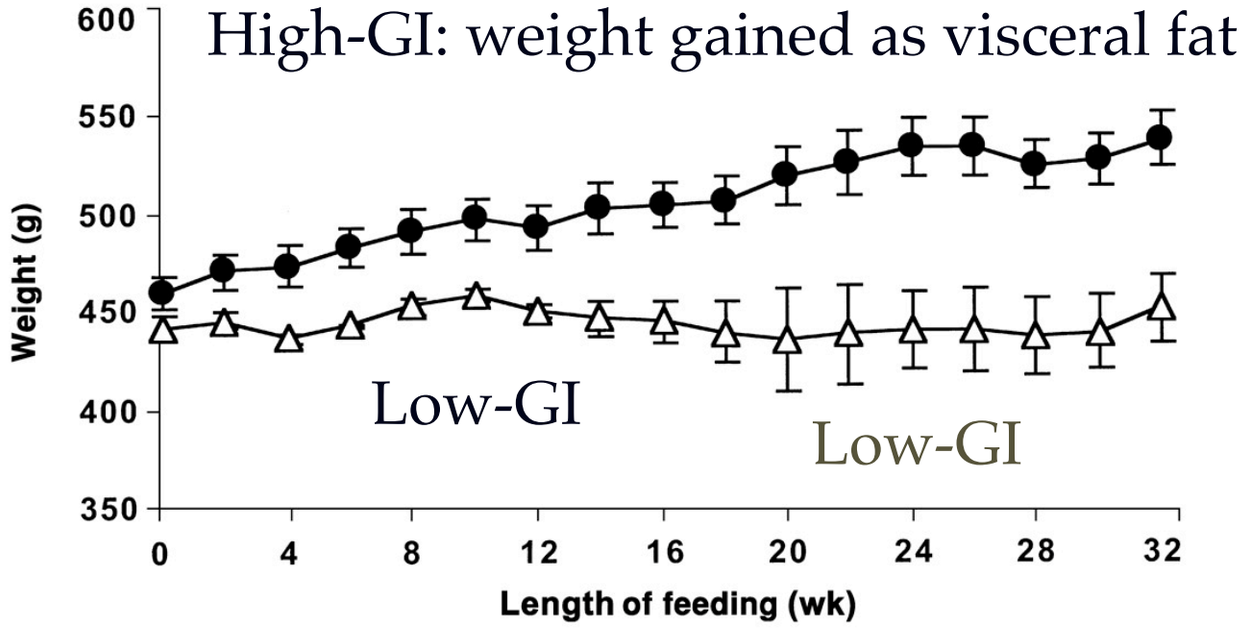
Ludwig DS. The glycemic index: physiological mechanisms relating to obesity, diabetes, and cardiovascular disease. JAMA. 2002;287:2414-2423.

This is an example of two foods, white bread and spaghetti, made from identical ingredients.

I would like you to notice how after the white bread, blood sugar levels go below where they were initially. This may stimulate hunger.

Prevent weight gain: low GI

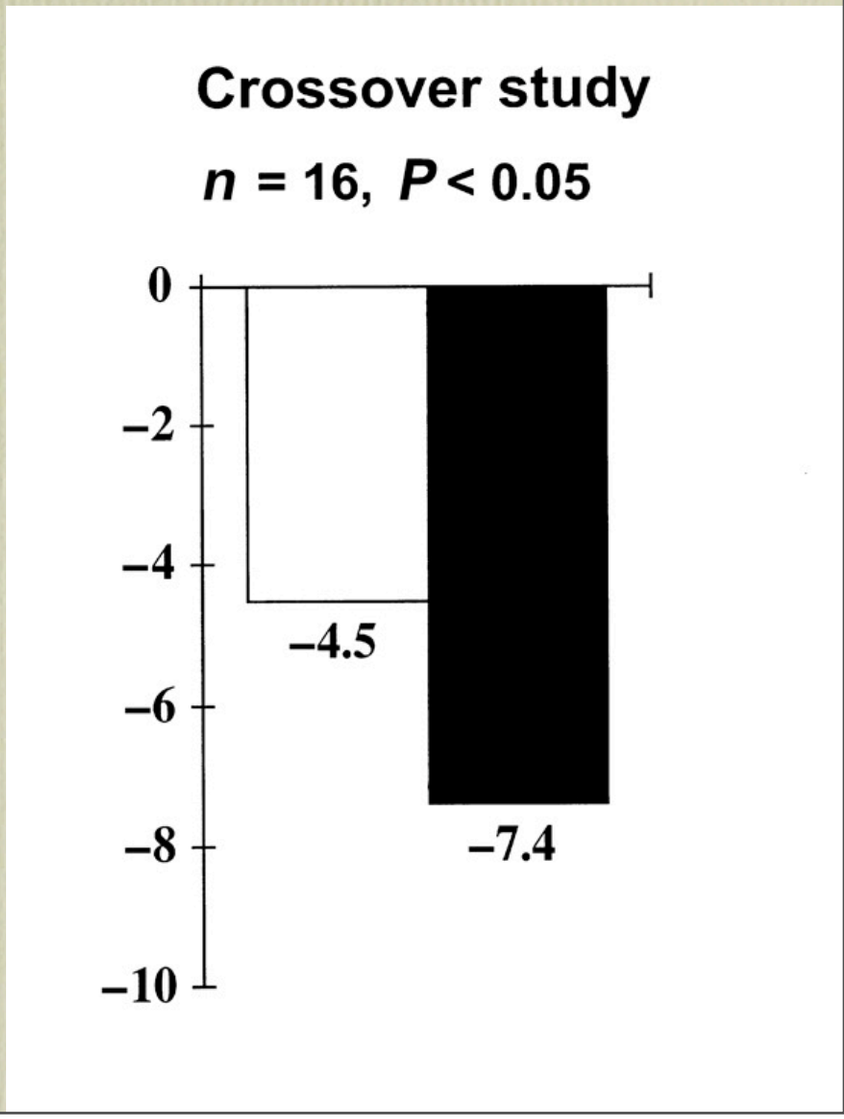
- Low glycemic index meals
  - No weight gain in rats fed isoenergetic low-GI, vs high-GI diet (Brand-Miller 2002)



Brand-Miller JC, Holt SH, Pawlak DB, McMillan J. Glycemic index and obesity. Am J Clin Nutr. 2002;76:281S-285S.

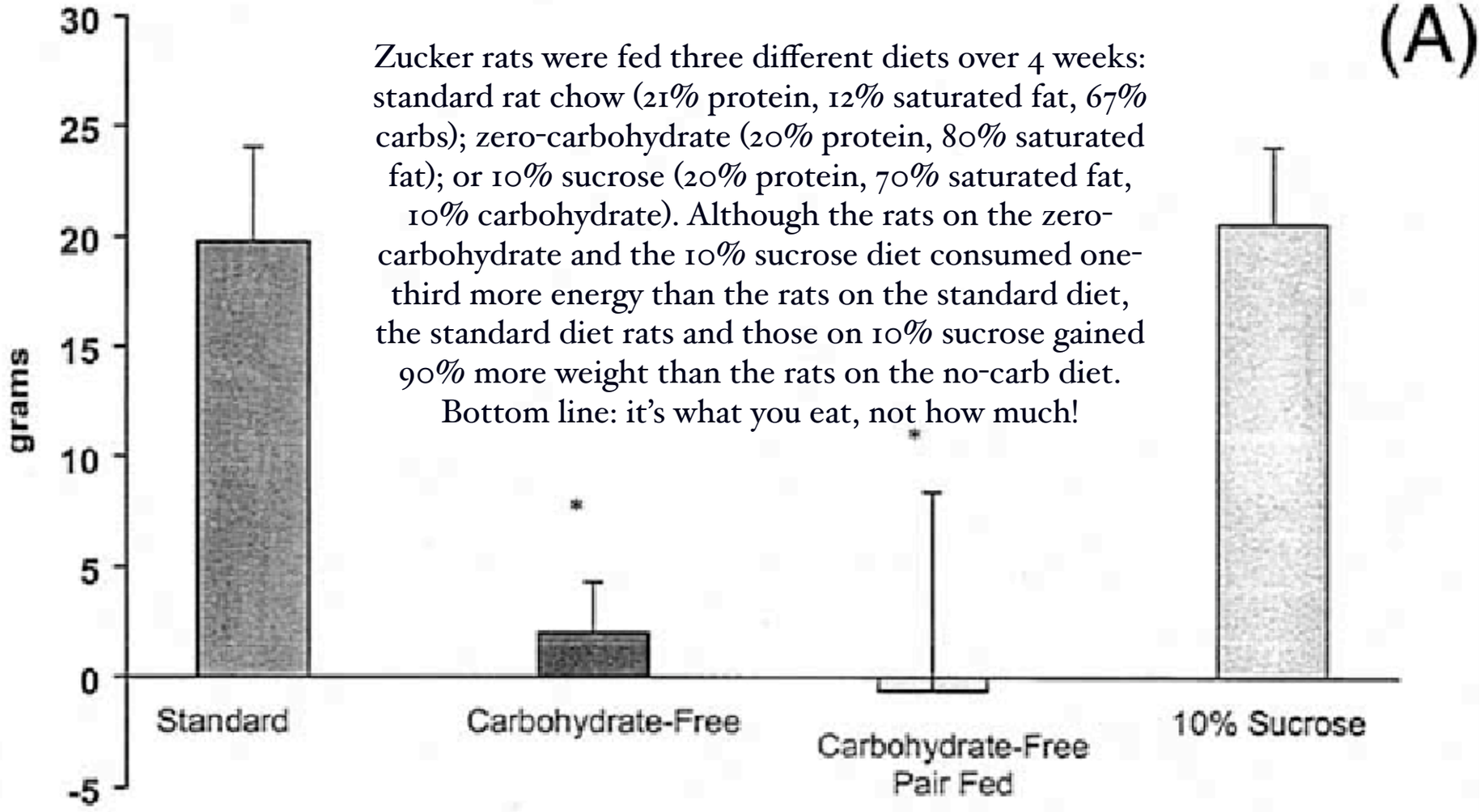
Weight loss with low GI

- Low glycemic index meals
  - Promote weight loss
    - Weight loss in pounds for overweight women randomly assigned to high-glycemic index (white) or low GI diet (black). Diets equal in calories. (Slabber 1994)
  - The Montignac diet is based on low-GI principles



Slabber M, Barnard HC, Kuyl JM, Dannhauser A, Schall R. Effects of a low-insulin-response, energy-restricted diet on weight loss and plasma insulin concentrations in hyperinsulinemic obese females. Am J Clin Nutr. 1994;60:48-53.

Reduce carbohydrates (Morris 2003)

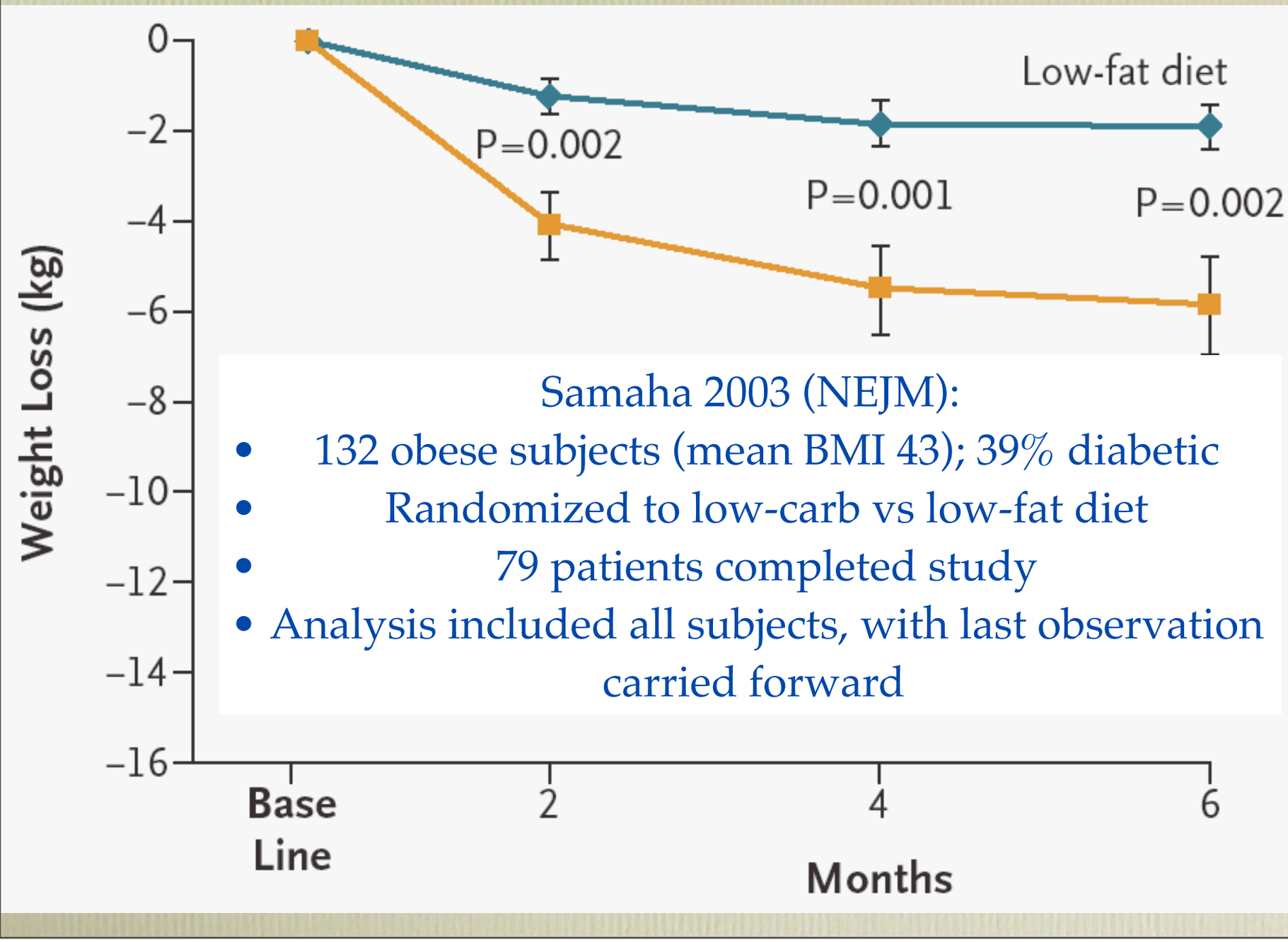


Zucker rats were fed three different diets over 4 weeks: standard rat chow (21% protein, 12% saturated fat, 67% carbs); zero-carbohydrate (20% protein, 80% saturated fat); or 10% sucrose (20% protein, 70% saturated fat, 10% carbohydrate). Although the rats on the zero-carbohydrate and the 10% sucrose diet consumed one-third more energy than the rats on the standard diet, the standard diet rats and those on 10% sucrose gained 90% more weight than the rats on the no-carb diet. Bottom line: it's what you eat, not how much!

22.4 kJ | 30.5 kJ | 22.7 kJ | 29.5 kJ

Morris KL, Namey TC, Zemel MB. Effects of dietary carbohydrate on the development of obesity in heterozygous Zucker rats. J Nutr Biochem. 2003;14:32–39.

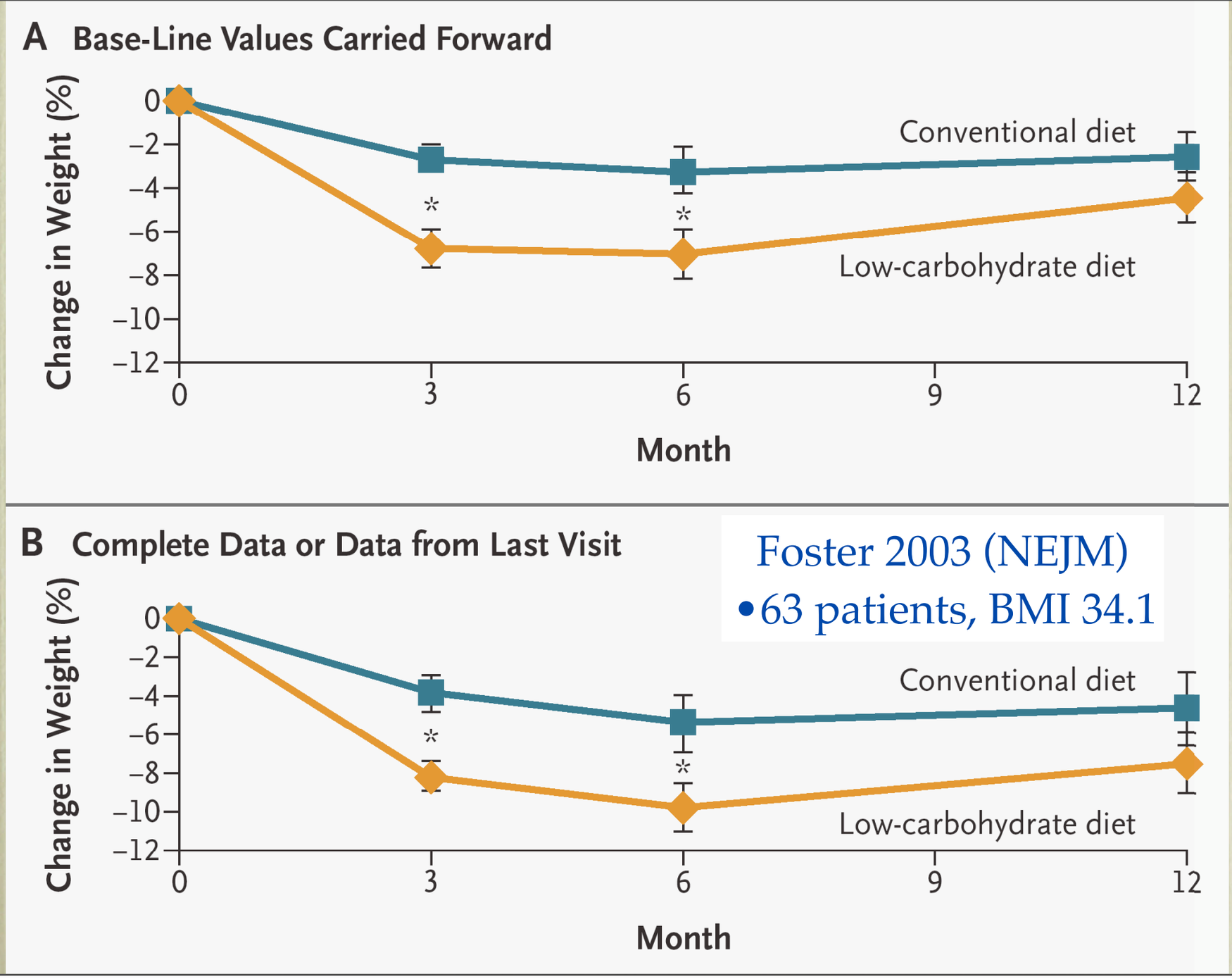
Low-carb (Dr. Atkins) diet



Samaha 2003 (NEJM):

- 132 obese subjects (mean BMI 43); 39% diabetic
- Randomized to low-carb vs low-fat diet
- 79 patients completed study
- Analysis included all subjects, with last observation carried forward

Samaha FF, Iqbal N, Seshadri P, et al. A low-carbohydrate as compared with a low-fat diet in severe obesity. N Engl J Med. 2003;348:2074-2081.



Foster 2003 (NEJM)

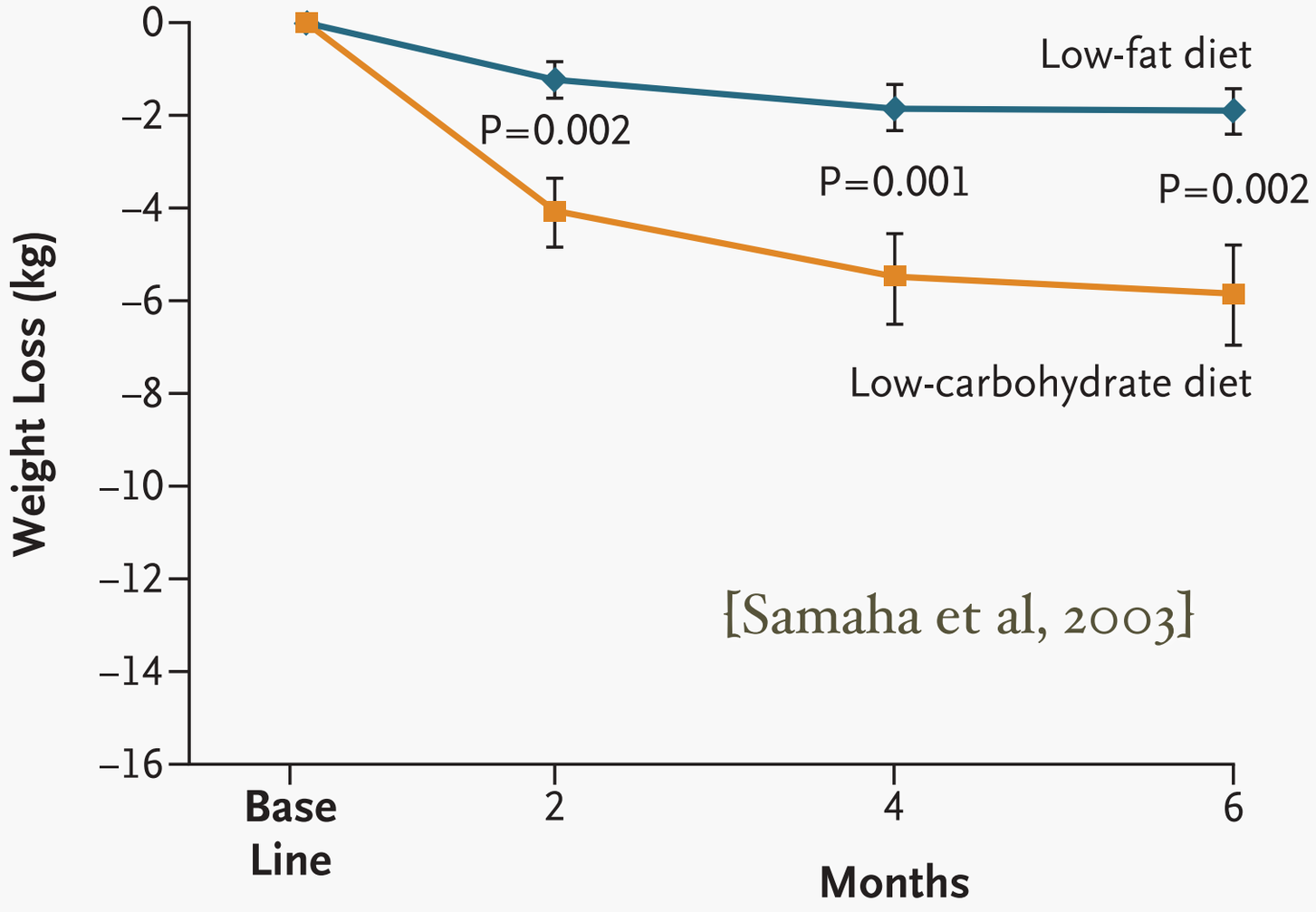
- 63 patients, BMI 34.1

Foster GD, Wyatt HR, Hill JO, et al. A randomized trial of a low-carbohydrate diet for obesity. N Engl J Med. 2003;348:2082-2090.

Low-carb vs low-fat in severe obesity [Samaha et al, 2003]

- 132 patients, average BMI 43, 39% diabetic, 43% metabolic syndrome
- randomized to low-carb or low-fat:
  - low-carb: prot 22%, carb 37%, fat 41%
  - low-fat: prot 16%, carb 51%, fat 33%
- analysis used all patients, with LOC for dropouts (47% low-fat; 33% low-carb, difference ns)

Patients in both groups met in weekly diet counseling sessions for 4 weeks, followed by monthly sessions. Participants in the low-carb group were instructed only to reduce carb intake to less than 30g per day. Participants in the low-fat diet were instructed to reduce caloric intake by 500 calories per day, with less than 30% of calories derived from fat.

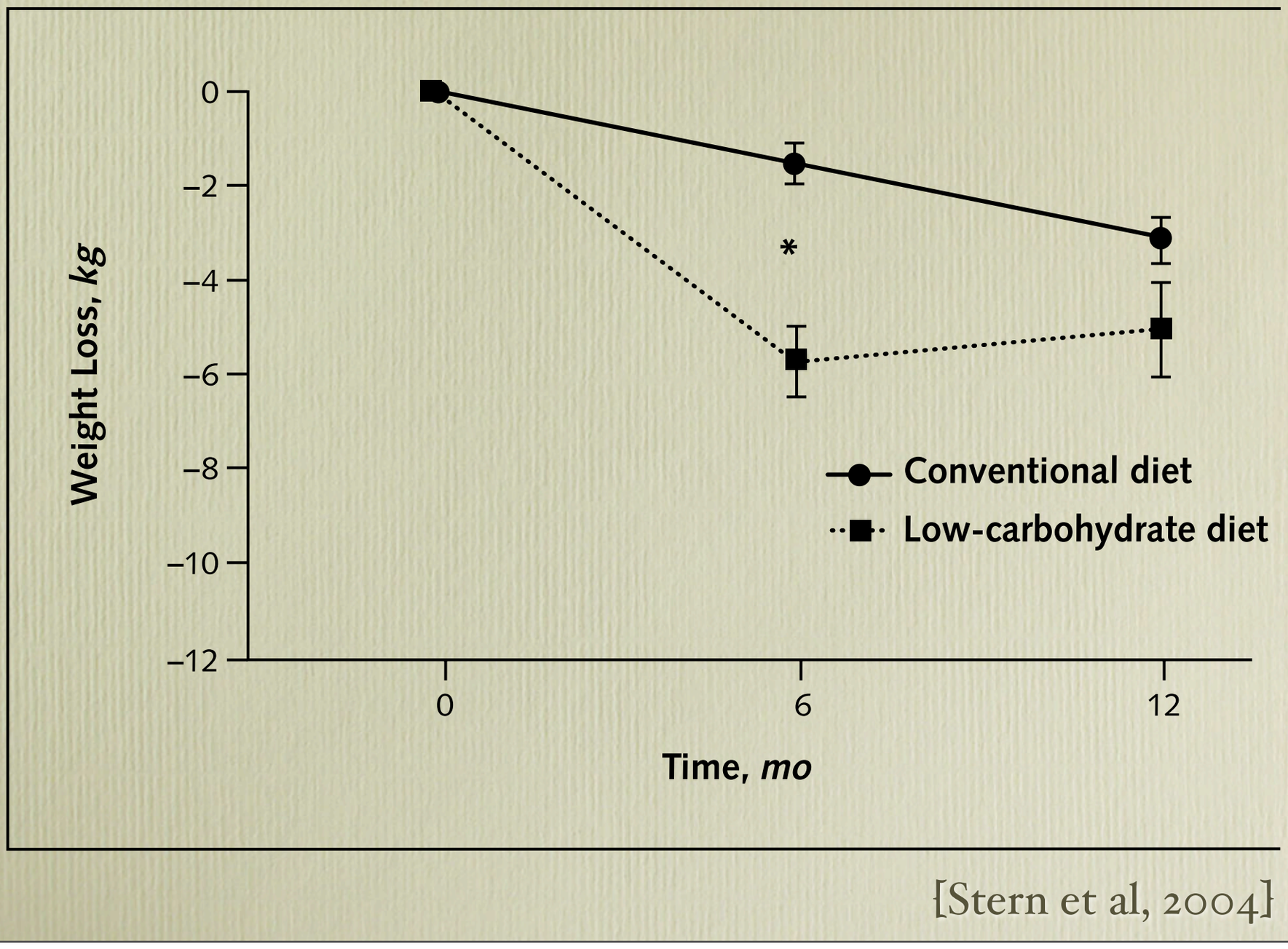


No. Analyzed				
Low-fat diet	68	68 (38)	68 (47)	68 (32)
Low-carbohydrate diet	64	64 (26)	64 (36)	64 (21)

Samaha FF, Iqbal N, Seshadri P, et al. A low-carbohydrate as compared with a low-fat diet in severe obesity. N Engl J Med. 2003;348:2074-2081.

	low-fat	low-carb	P value
triglycerides, mg/dL	-7	-38	0.001
insulin sensitivity	-0.01	+0.02	0.01
glucose, mg/dL	-2	-11	0.017
glucose in diabetic patients	-5	-26	0.01
insulin level, without diabetes meds, μU/mL	1	-6	0.008
glycosylated hemoglobin in diabetic patients, %	0	-0.6	0.06 ns

Total cholesterol, HDL and LDL cholesterol, glucose level in nondiabetic subjects, and insulin level for those taking diabetes medication, did not differ significantly between the two diets.



[Stern et al, 2004]

Stern L, Iqbal N, Seshadri P, et al. The effects of low-carbohydrate versus conventional weight loss diets in severely obese adults: one-year follow-up of a randomized trial. Ann Intern Med. 2004;140:778-785.

This is the same group, reporting results after one year. At this point, the low-carb group had reduced their daily carb intake to 120 g on average, certainly not the 30 g that they were aiming for. However, this was still about half of the carb grams for the low-fat group.

After one year, the difference in weight loss was no longer statistically significant.

HbA1c values for those with diabetes, fell by 0.1% for the low-fat group, and by 0.7% for the low-carb group, statistically significant at 0.019 after adjusting for weight loss differences. This suggests a direct effect of the low-carb diet on glycemic control.

High-protein low-carbs for DM2

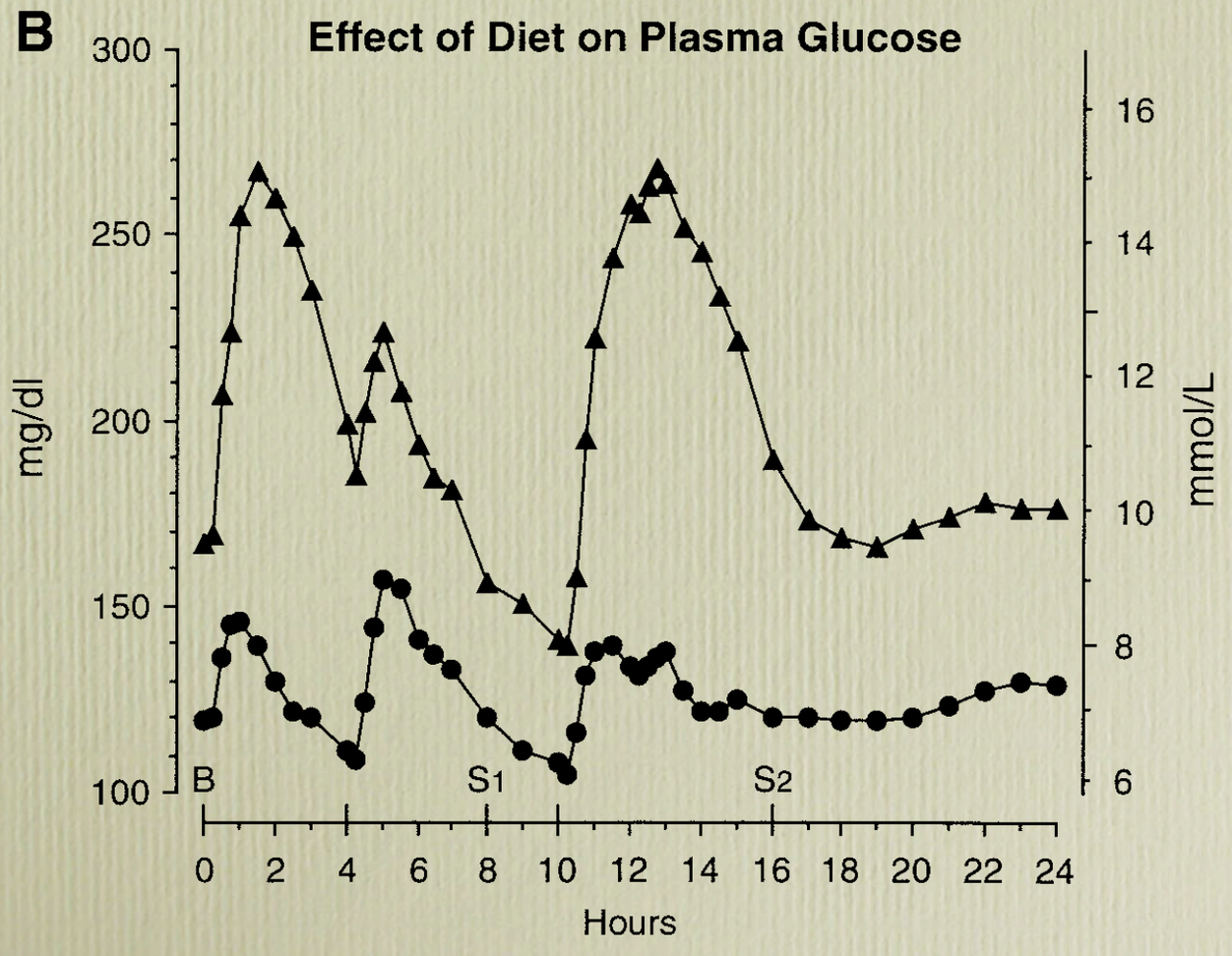
[Gannon & Nuttall, 2004]

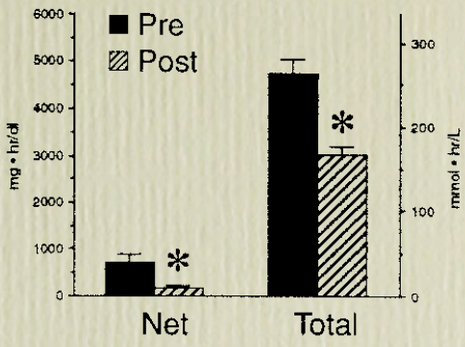
- This was a randomized, 5-week, crossover study
- 8 men with mild, untreated DM2 completed the trial
- Diets were provided by the researchers
- control diet: carb:prot:fat 55:15:30 by weight, ie 388 g carbs
- test diet: 20:30:50, ie 142 g carbs

Gannon MC, Nuttall FQ. Effect of a high-protein, low-carbohydrate diet on blood glucose control in people with type 2 diabetes. Diabetes. 2004;53:2375-2382.

High-protein low-carbs for DM2

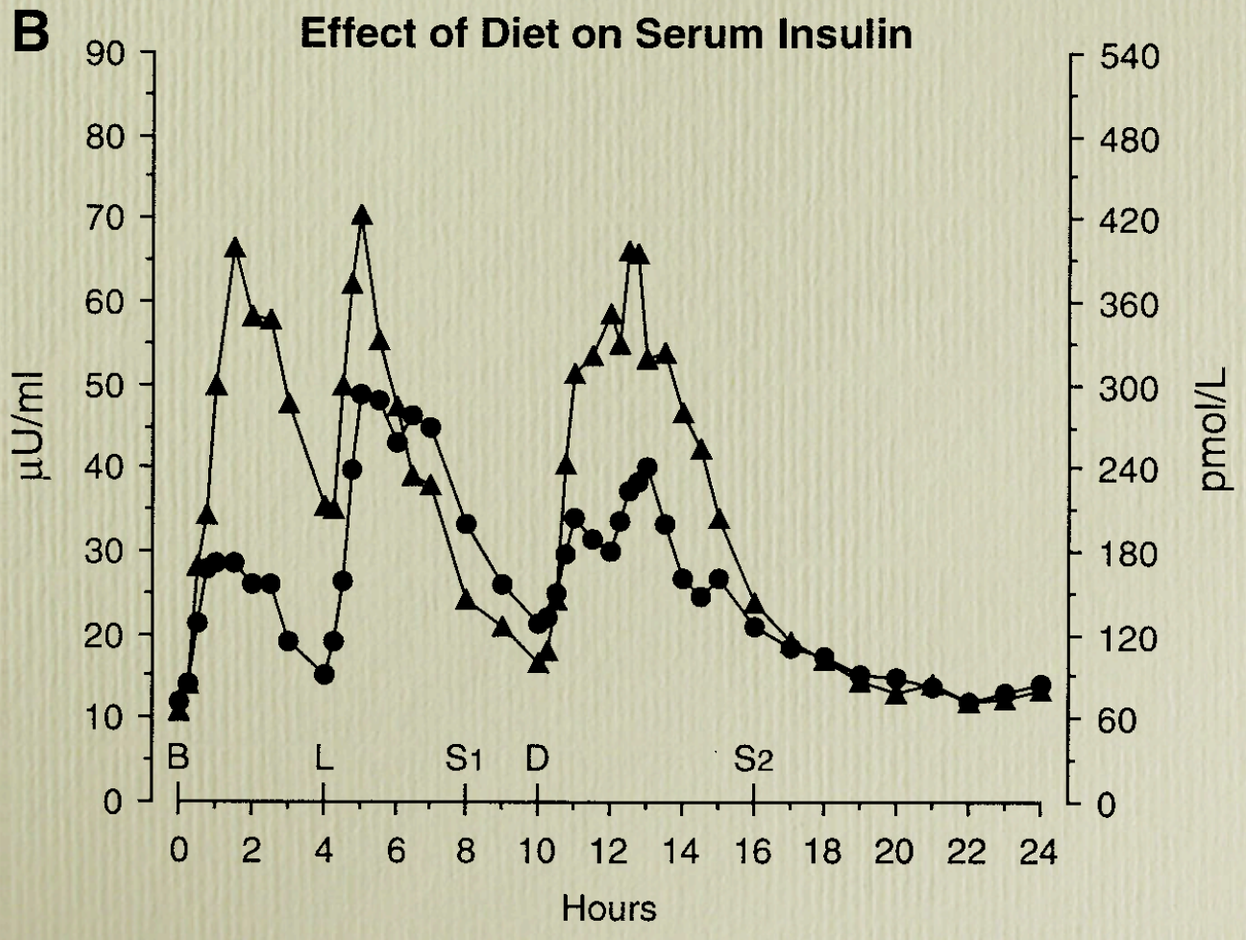
[Gannon & Nuttall, 2004]

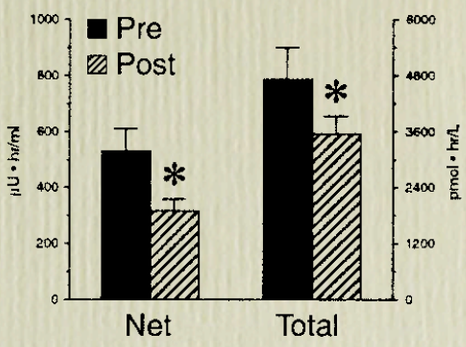




High-protein low-carbs for DM2

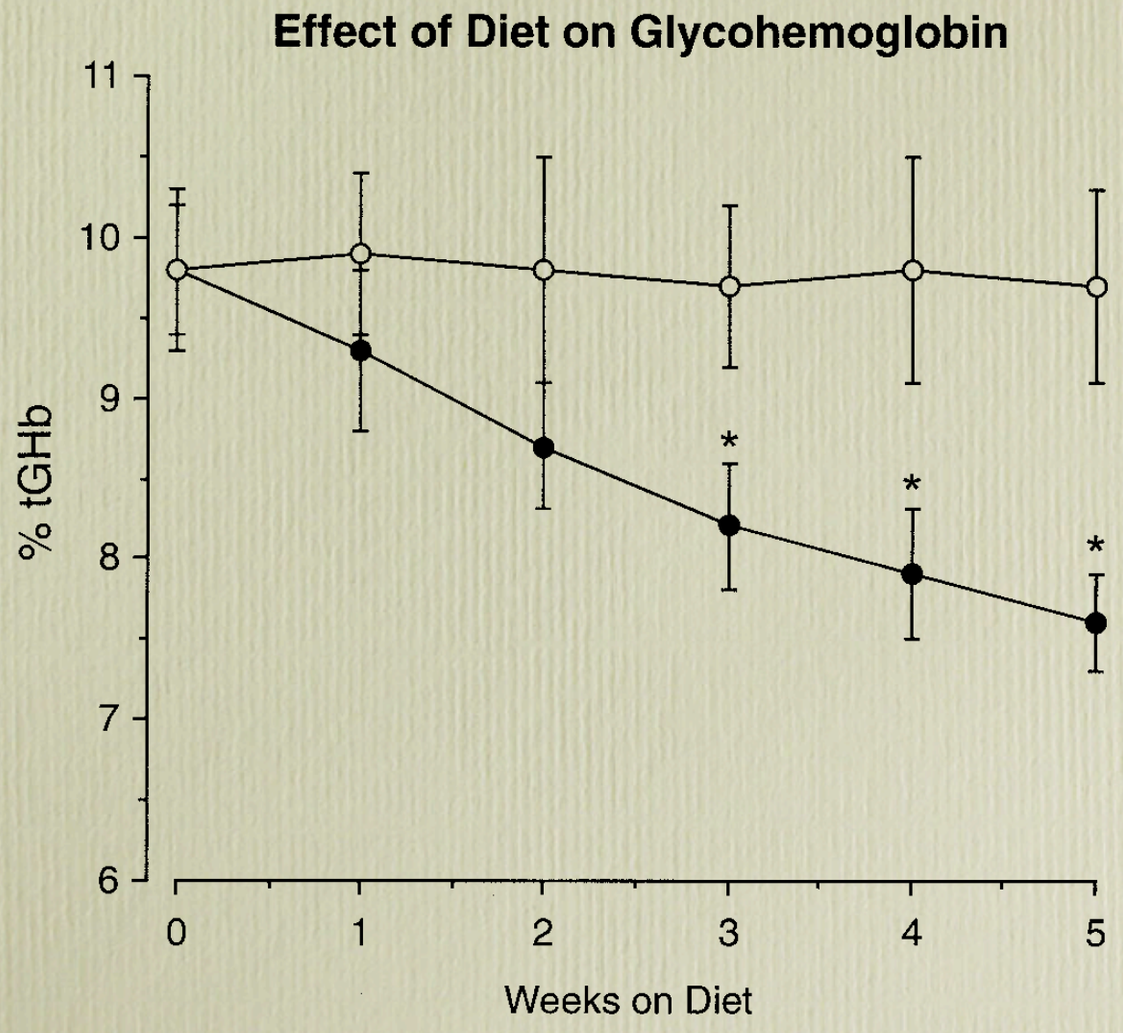
[Gannon & Nuttall, 2004]





High-protein low-carbs for DM2

[Gannon & Nuttall, 2004]



The control diet left the glycohemoglobin unchanged, while there were drops on the test diet, with the differences being significant at weeks 3, 4, and 5.

Low calorie diets in DM2
[Miyashita et al, 2004]

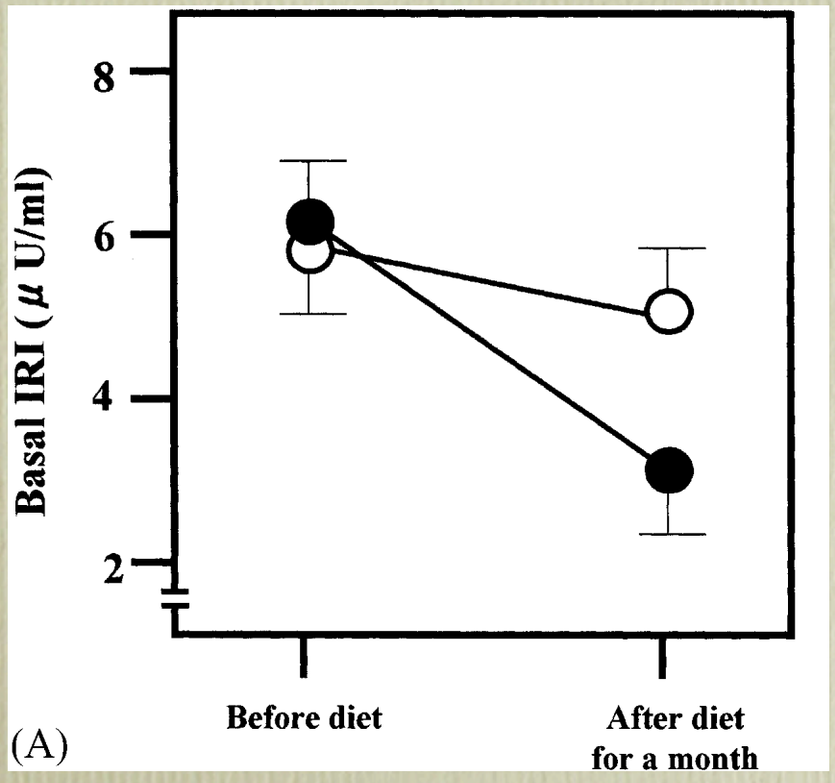
- Obese subjects with DM2, randomly assigned to:
  - low cal low carb diet: 1000 kCal per day, prot:carb:fat 25:40:35 ie 100 g carbs per day
  - low cal high carb diet: 1000 kCal per day, prot:carb:fat 25:65:10 ie 163 g carbs per day
- inpatient treatment for 4 weeks
- exercise: walking 30 min twice daily

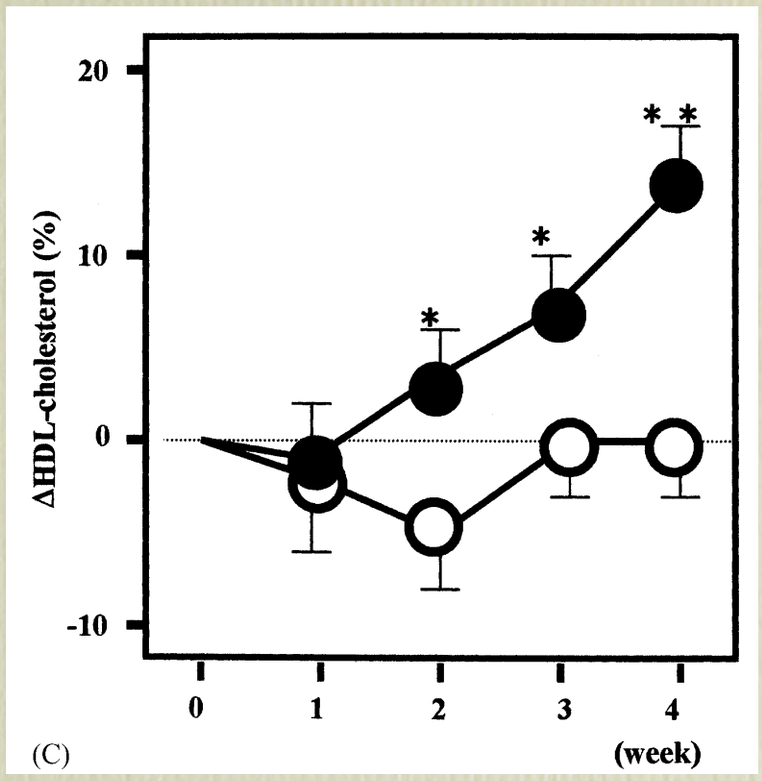
Miyashita Y, Koide N, Ohtsuka M, et al. Beneficial effect of low carbohydrate in low calorie diets on visceral fat reduction in type 2 diabetic patients with obesity. Diabetes Res Clin Pract. 2004;65:235–241.

This is very severe calorie restriction.

Low calorie diets in DM2

[Miyashita et al, 2004]





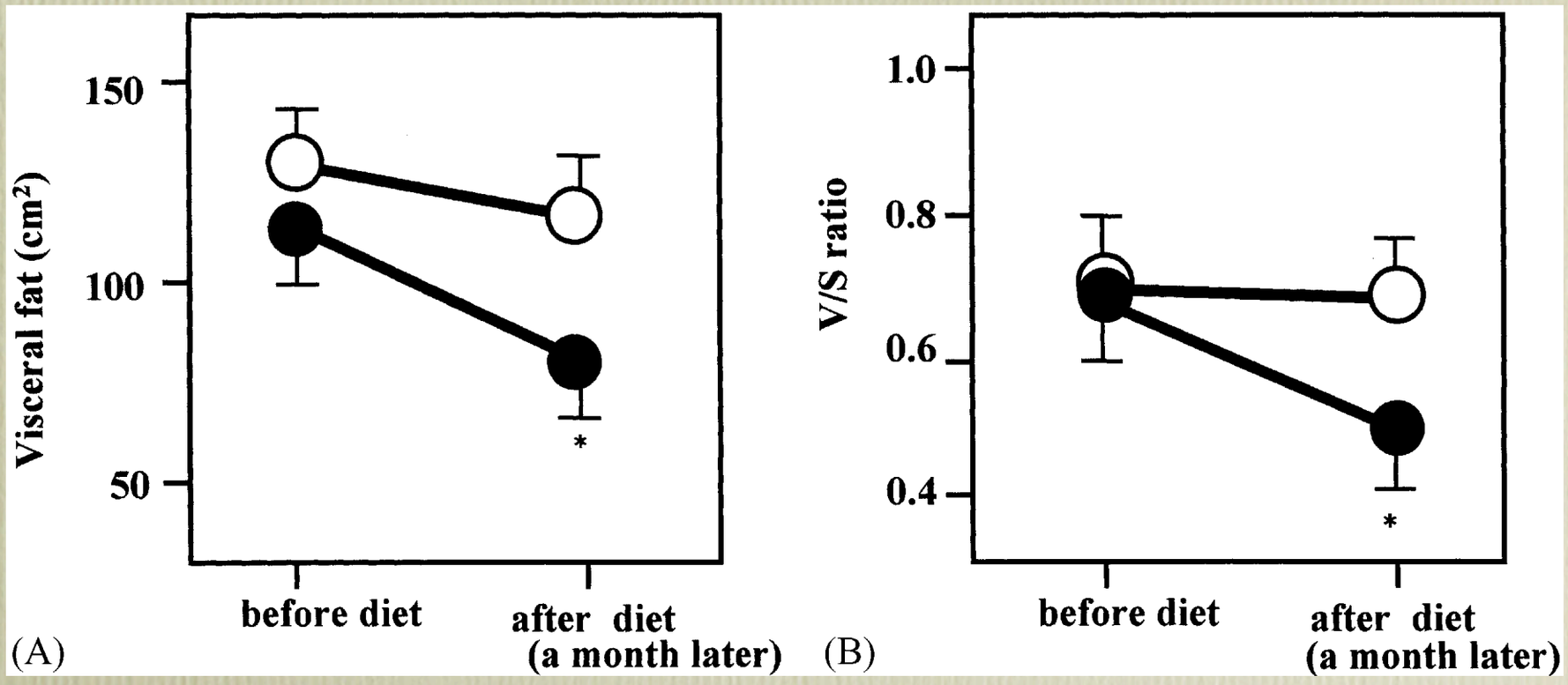
Similar decreases in body weight and serum glucose levels were seen in the two groups.

Fasting serum insulin levels were significantly lower in the low carb group.

HDL cholesterol increased in the low-carb group, but not in the high carb group.

Low calorie diets in DM2

[Miyashita et al, 2004]



The amount of visceral fat and subcutaneous fat was measured by CT scan. Visceral fat dropped significantly more on the low carb diet than on the high carb. The ratio of visceral fat to subcutaneous fat did not change in the high carb group, but dropped significantly in the low carb group.

Low carb ketogenic diet in DM2

[Yancy et al, 2005]

- 28 overweight participants with DM2 recruited from an outpatient clinic
- 16 week trial, single arm
- counselling provided every two weeks with an initial goal of < 20 g/day of carbs
- 21 completed the study: 20 men; 13 white, 8 A-A
- mean age 56 years; mean BMI 42.2

Yancy WS, Jr., Foy M, Chalecki AM, Vernon MC, Westman EC. A low-carbohydrate, ketogenic diet to treat type 2 diabetes. Nutr Metab (Lond). 2005;2:34.

Low carb ketogenic diet in DM2

[Yancy et al, 2005]

- Over 16 weeks:
  - HgA1c dropped from 7.5 to 6.3% (16% decrease, $P < 0.001$)
  - diabetes medications were discontinued in 7, reduced in 10, and left unchanged in 4 participants
  - Mean body weight dropped from 131.4 kg to 122.7 kg (6.6% decrease, $P < 0.001$)
  - Fasting serum triglyceride levels dropped from 2.69 mmol/L to 1.57 (42% decrease, $P = 0.001$)

Other serum lipid measurements did not change significantly.

Attempts to ban Atkins diet

- Norfolk and Norwich Hospital in Britain has banned Atkins diet from its menus, citing safety concerns
- Physicians Committee for Responsible Medicine in the U.S. is urging hospitals, eg Johns Hopkins & Mayo Clinic, to adopt a similar ban

Summary

- Atypical antipsychotics are associated with weight gain and diabetes
- Individuals with central obesity, family history of diabetes, and metabolic syndrome appear to be at greatest risk
- Risk reduction:
  - weight loss
  - low glycemic index diets
  - low carbohydrate diets