Antipsychotic Drugs

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I have the following relevant financial relationship with a commercial interest to disclose

- Otsuka- research grant

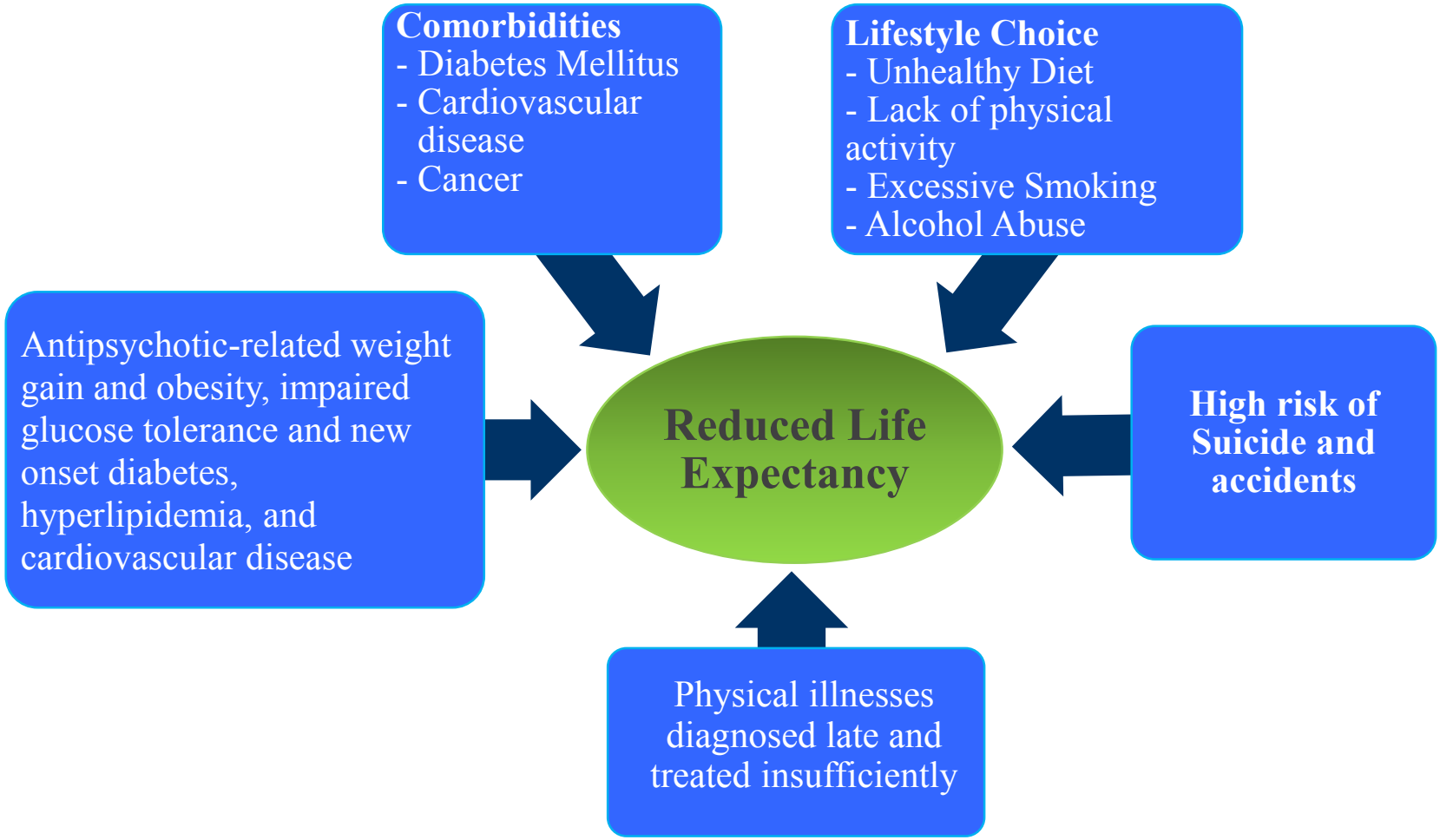
Physical illnesses with increased frequency in SMI patients

Bacterial infections and mycoses	Tuberculosis (+)
Viral diseases	HIV (++), hepatitis B/C (+)
Neoplasms	Obesity-related cancer (+)
Musculoskeletal diseases	Osteoporosis/decreased bone mineral density (+)
Stomatognathic diseases	Poor dental status (+)
Respiratory tract diseases	Impaired lung function (+)
Urological and male genital diseases	Sexual dysfunction (+)
Female genital diseases and pregnancy complications	Obstetric complications (++)
Cardiovascular diseases	Stroke, myocardial Infarction, arterial hypertension, other cardiac and vascular diseases (++)
Nutritional and metabolic diseases	Obesity (++), diabetes mellitus (+), metabolic syndrome (++), hyperlipidemia (++)

(++) very good evidence and (+) good evidence for increased risk

Adapted from Leucht et al. (Acta Psychiatr Scand 2007; 116:317-333).

Mortality in SMI



Estimated prevalence of cardiometabolic modifiable risk factors in patients with schizophrenia

Modifiable risk factors	Estimated prevalence, % (RR)
Obesity	45–55 (1.5–2)*
Smoking	50–80 (2–3)*
Diabetes Mellitus	10–15 (2)*
Hypertension	19–58 (2–3)*
Dyslipidemia	25–69 (≤ 5)*
Metabolic syndrome	37–63 (2–3)*

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Patients with schizophrenia are more likely to be overweight, smoke, and have diabetes, hypertension, dyslipidaemia, or metabolic disorder than were those without schizophrenia (RR, relative risk).

De Hert M et al. *World Psychiatry*. 2009;8:15-22.

*De Hert M et al. *World Psychiatry*. 2009;8:15-22.

Reasons for Increased CVD Mortality in Major Mental Disorders

- Modifiable health risk factors
  - Lipid abnormalities (TC, LDL-C, TG, HDL)
  - Diabetes
  - Hypertension
  - Metabolic syndrome
  - Physical inactivity
  - Smoking
- Access to and/or utilization of medical care
- Adherence with therapies
- Economic capabilities

Newcomer J Hennekens CH. *JAMA* 2007; 298(15):1794-1796

Reasons for Increased CVD Mortality in Major Mental Disorders

- Primary and secondary prevention limitations for mentally ill versus general population
  - Less likely to be screened or treated for dyslipidemia, hyperglycemia, hypertension
  - Less likely to receive angioplasty or CABG
  - Less likely to receive drug therapies of proven benefit (thrombolytics, aspirin, beta-blockers, ACE inhibitors) post-myocardial infarction
  - More likely to have premature mortality post-myocardial infarction

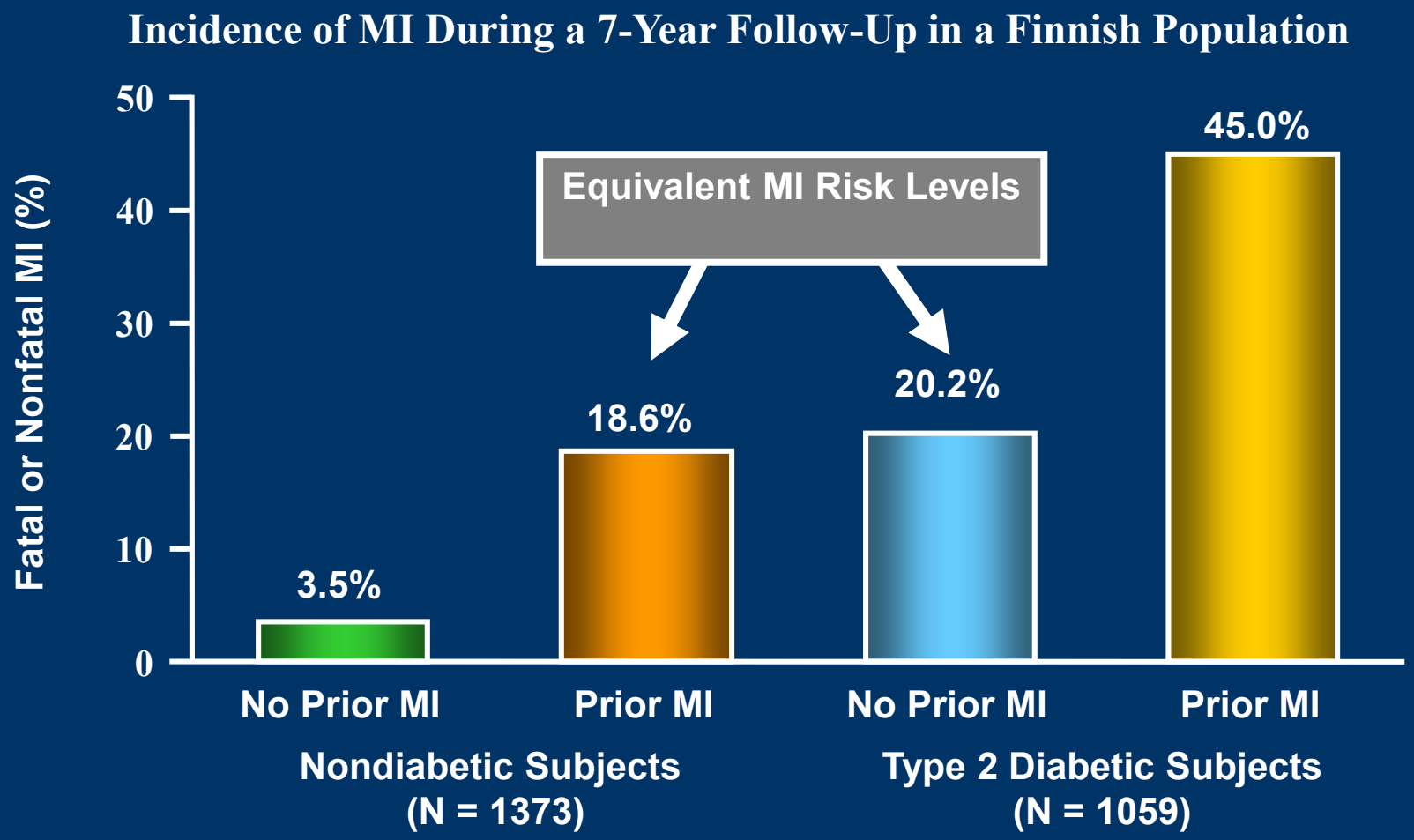
Newcomer J Hennekens CH. *JAMA* 2007; 298(15):1794-1796
Druss BG et al. Arch Gen Psychiatry. 2001;58:565-572.

Survival After Myocardial Infarction

- 88,241 Medicare patients ≥65 years of age, hospitalized for MI
- Mortality increased by
  - 19%: any mental disorder
  - 34%: schizophrenia
- Increased mortality explained by measures of quality of care

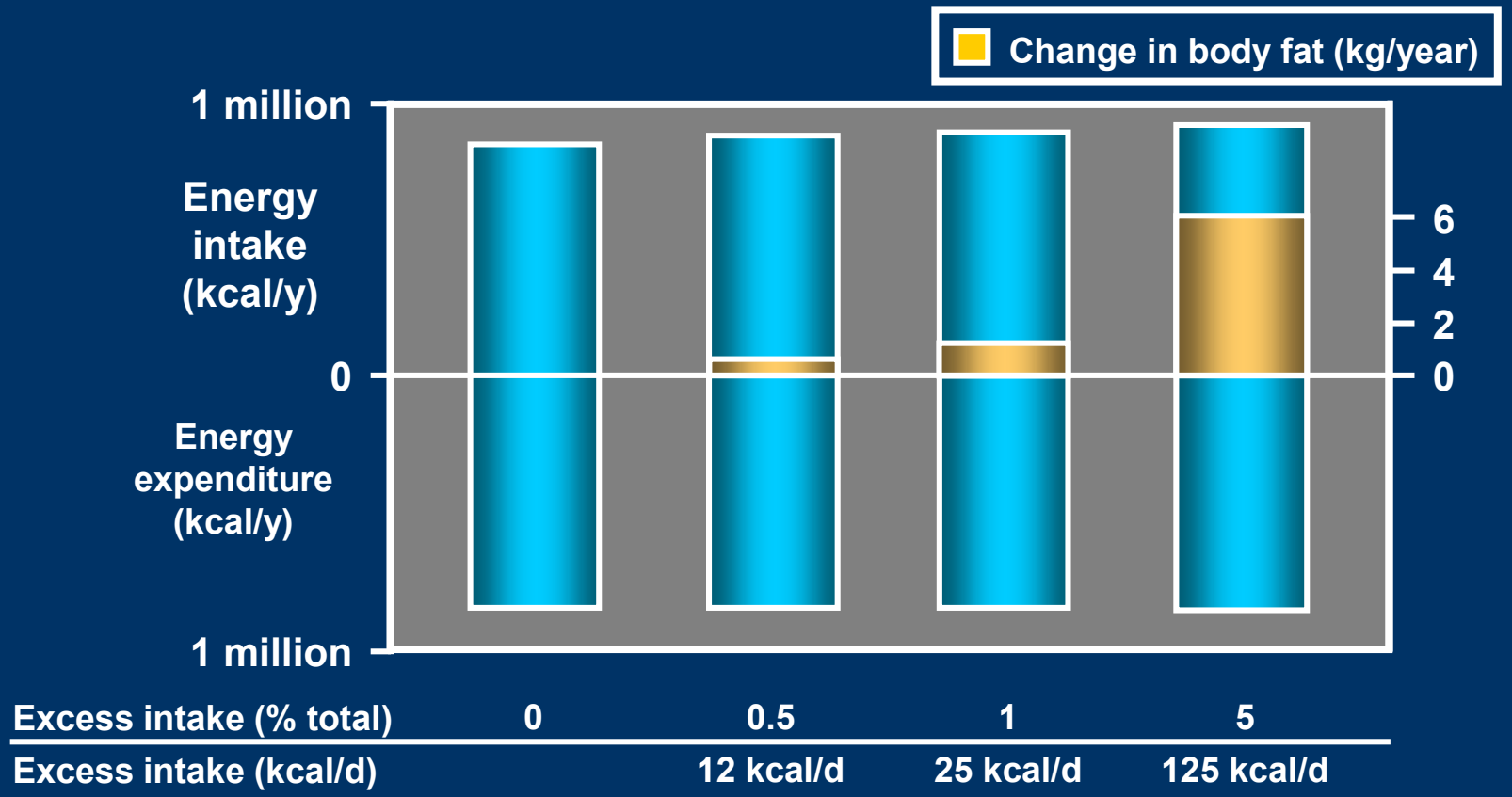
Druss BG et al. *Arch Gen Psychiatry*. 2001;58:565-572.

Diabetes: A Coronary Heart Disease Risk Equivalent



Haffner SM et al. *N Engl J Med*. 1998;339:229-234.

Cumulative Effect of Small Daily Errors in Energy Balance

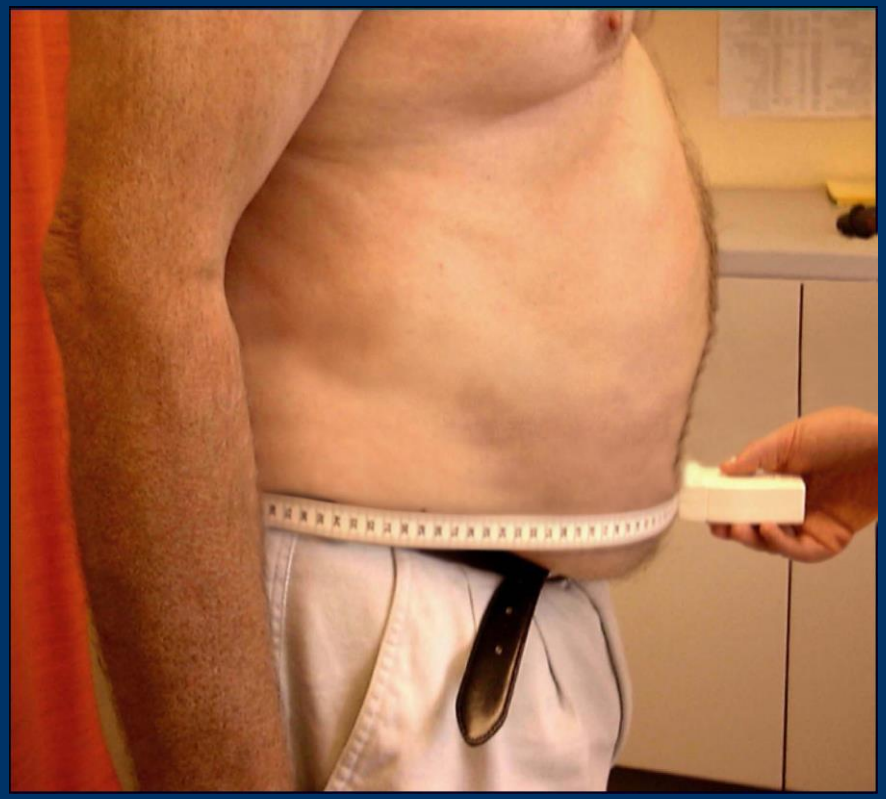


Rosenbaum M et al. *N Engl J Med.* 1997;337:396-407.


Exhibit


24 HOUR
FITNESS

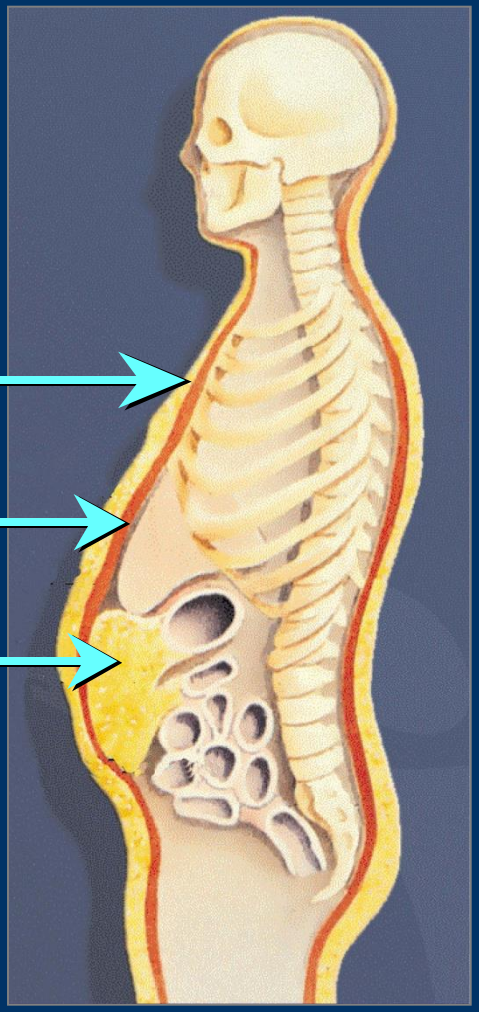
Visceral Adiposity: The Critical Adipose Depot



Subcutaneous Fat

Abdominal Muscle Layer

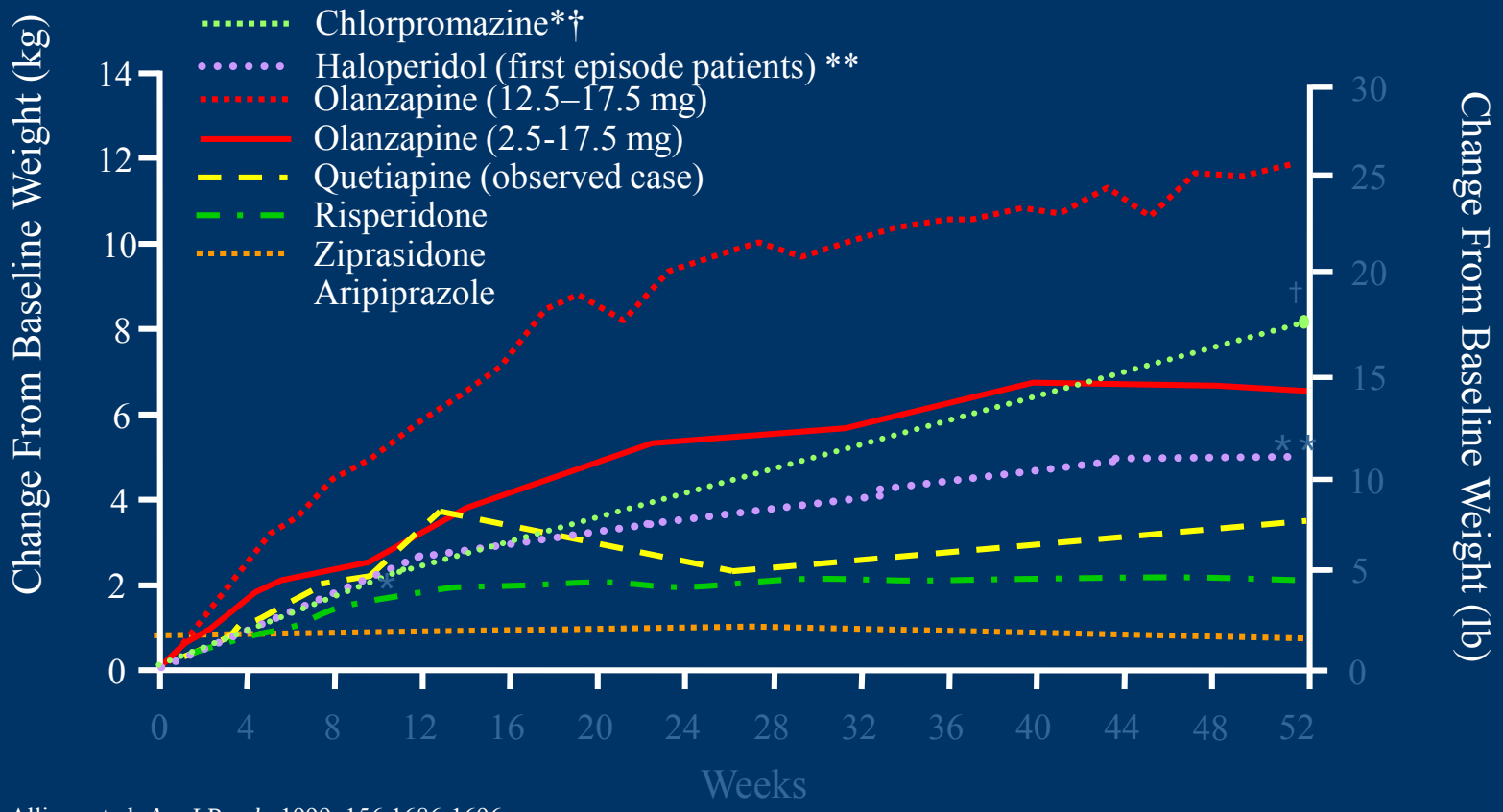
Intra-abdominal Fat



Weight liability of psychotropic agents used in SMI

Drug class	Weight loss	Relatively weight neutral	Weight gain
Antidepressants	Bupropion Fluoxetine	Citalopram Duloxetine Escitalopram Nefazodone Sertraline Venlafaxine	<u>Substantial</u> Amitriptyline Imipramine Mirtazapine <u>Intermediate</u> Nortriptyline Paroxetine
Anticonvulsants/ Mood stabilizers	Topiramate Zonisamide	Lamotrigine Oxcarbazepine	<u>Substantial</u> Lithium Valproate <u>Intermediate</u> Carbamazepine Gabapentin
Antipsychotics	Aripiprazole (in pre-treated individuals) Molindone (in pre-treated individuals) Ziprasidone (in pre-treated individuals)	Amisulpride Aripiprazole Asenapine Fluphenazine Haloperidol Lurasidone Perphenazine Ziprasidone	<u>Substantial</u> Chlorpomazine Clozapine Olanzapine <u>Intermediate</u> Iloperidone Paliperidone Risperidone Quetiapine Sertindole Thioridazine Zotepine

1-Year Weight Gain: Mean Change From Baseline Weight



*(est 10 wks) Allison et al. *Am J Psych*. 1999; 156:1686-1696.

†(median 131 wks drug naïve) Lieberman JA, et al. *Neuropsychopharmacology*. 2003; 28:995-1003.

Nemeroff CB. *J Clin Psychiatry.* 1997;58(suppl 10):45-49; Kinon BJ, et al. *J Clin Psychiatry*. 2001;62:92-100; Brecher M, et al. American College of Neuropsychopharmacology; 2004. Poster 114; Brecher M, et al. *Neuropsychopharmacology*. 2004;29(suppl 1):S109; Geodon® [package insert]. New York, NY: Pfizer Inc; 2005. Risperdal® [package insert]. Titusville, NJ: Janssen Pharmaceutica Products, LP; 2003; Abilify® [package insert]. Princeton NJ: Bristol-Myers Squibb Company and Rockville, MD: Otsuka America Pharmaceutical, Inc.; 2005.
**Zipursky RB, et al. 2005; *British Journal of Psychiatry.* 187:537-543.

Antipsychotics and weight gain (1)

- Almost all antipsychotics show a degree of weight gain after extended use[*]
- Clozapine, olanzapine, quetiapine, and risperidone are associated with an increased risk of obesity, impaired glucose tolerance and new-onset diabetes, hyperlipidaemia, and cardiovascular disease
- Weight gain is more pronounced in antipsychotic naïve patients[*]
- The hypothalamus plays a crucial part in the control of energy balance: it receives and integrates neural signals, hormonal signals including leptin, ghrelin and insulin, and nutrient signals such as glucose, free fatty acids, and aminoacids by modifying the expression of specific neuromodulators, including orexigenic and anorexigenic neuropeptides[^]
- A number of studies examined the association between antipsychotics, appetite, leptin and ghrelin with conflicting results[±]
- Changes in leptin and ghrelin concentration have both been identified as a consequence of second-generation antipsychotics rather than a direct result of food intake[§]

[*]Bak M, *PLoS One* 2014; 9: e94112.;[^]Ferno J, et al. *PloS one* 2011; 6: e20571;[±]Hosojima H, et al. *Journal of psychopharmacology* 2006; 20: 75-9.; Sentissi O, et al. *Schizophrenia bulletin* 2008; 34: 1189-99.; Sugai T, et al. *Journal of clinical psychopharmacology* 2012; 32: 390-3;Haupt DW, et al. *Neuropsychopharmacology* 2004; 30: 184-91.; Togo T, et al. *Psychopharmacology* 2004; 172: 230-2. Murashita M, et al. *Psychoneuroendocrinology* 2005; 30: 106-10;[§]Russell JM, et al. *CNS drugs* 2001; 15: 537-51.; Fountaine RJ, et al. *Obesity* 2010; 18: 1646-51.

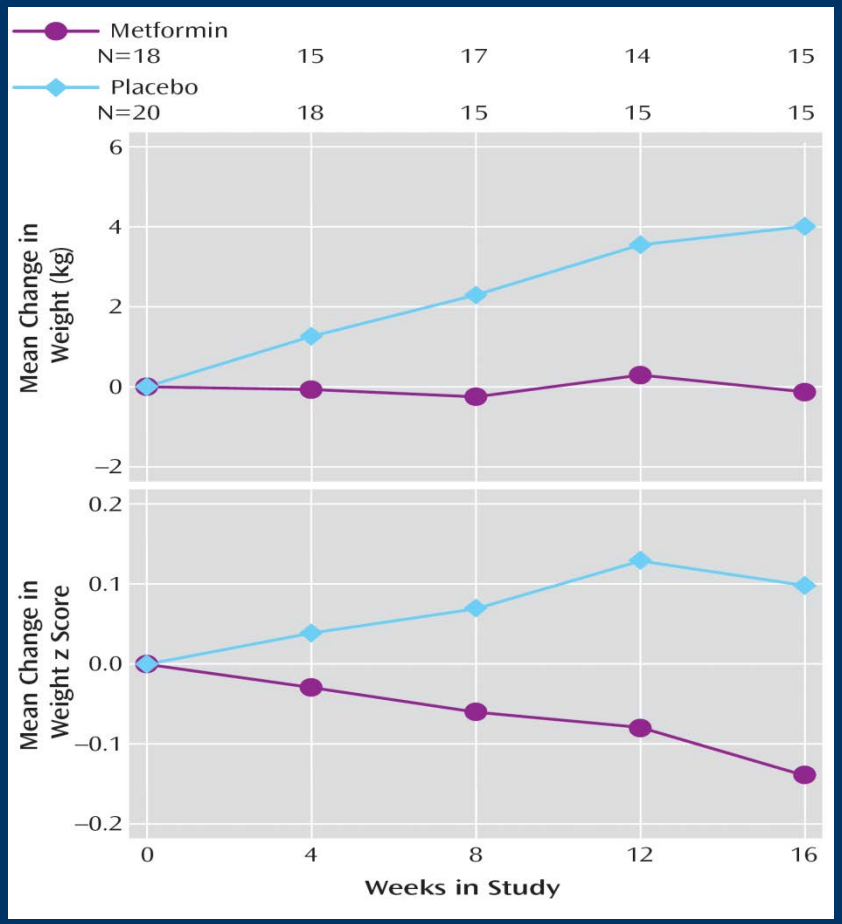
Second-Generation Antipsychotic Agents
Clinical Issues with Weight Gain

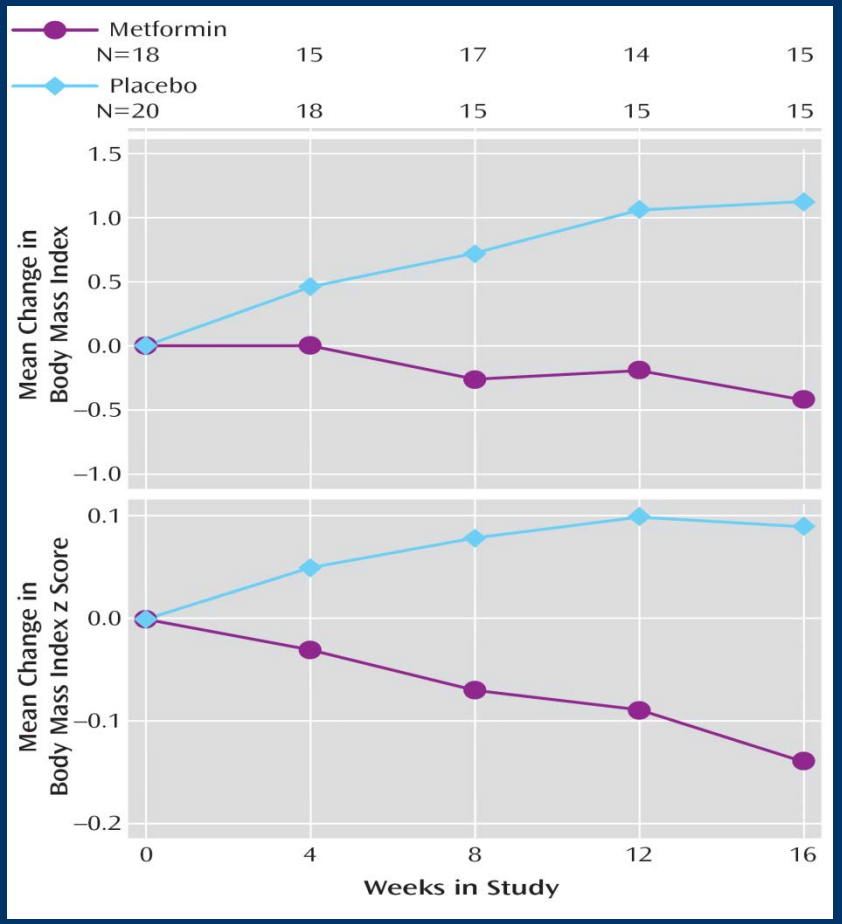
- Not everyone gains weight
- Thought to be associated with clinical response in some studies (not necessary however)
- Difficult to predict who will have weight gain
  - NOT just underweight patients
- Weight gain NOT dose-related
- Weight gain starts early
- Weight gain eventually levels off 3 mo to 1 y (?)
- Weight gained difficult to lose
- Effects on health, self-esteem, compliance

Weight Gain Interventions

- Switch agents
- Education from the onset of treatment
- Diet and nutrition programs
- Exercise programs: walking, etc
- Pharmacologic agents (?): prevention vs. following significant weight gain
  - Sibutramine, orlistat (FDA Approved)
  - Antihistaminic agents (nizatidine)
  - Amantadine, topiramate, bupropion, zonisamide

Change in Weight and BMI in Children Taking SGAs Plus Placebo or Metformin





Klein DJ, et al. *Am J Psychiatry.* 2006;163:2072-2079.

Switching for Side Effects: Important General Findings

- Side-effect differences after switching are very predictable
  - Persistent EPS
  - Persistent sedation
  - Weight gain
  - Dyslipidemia
- Magnitude of improvement = difference in side-effect burden between pre-switch and post-switch medication
- Side-effect improvements continue beyond the short-term period

Leucht S et al. *Lancet*. 2003;361:1581-1589; Leucht S et al. *Schizophr Res*. 1999;35:51-68.

Predicted Long-Term Changes in Weight When Switching Between Newer Antipsychotics

Post-switch →

Pre-switch ↓

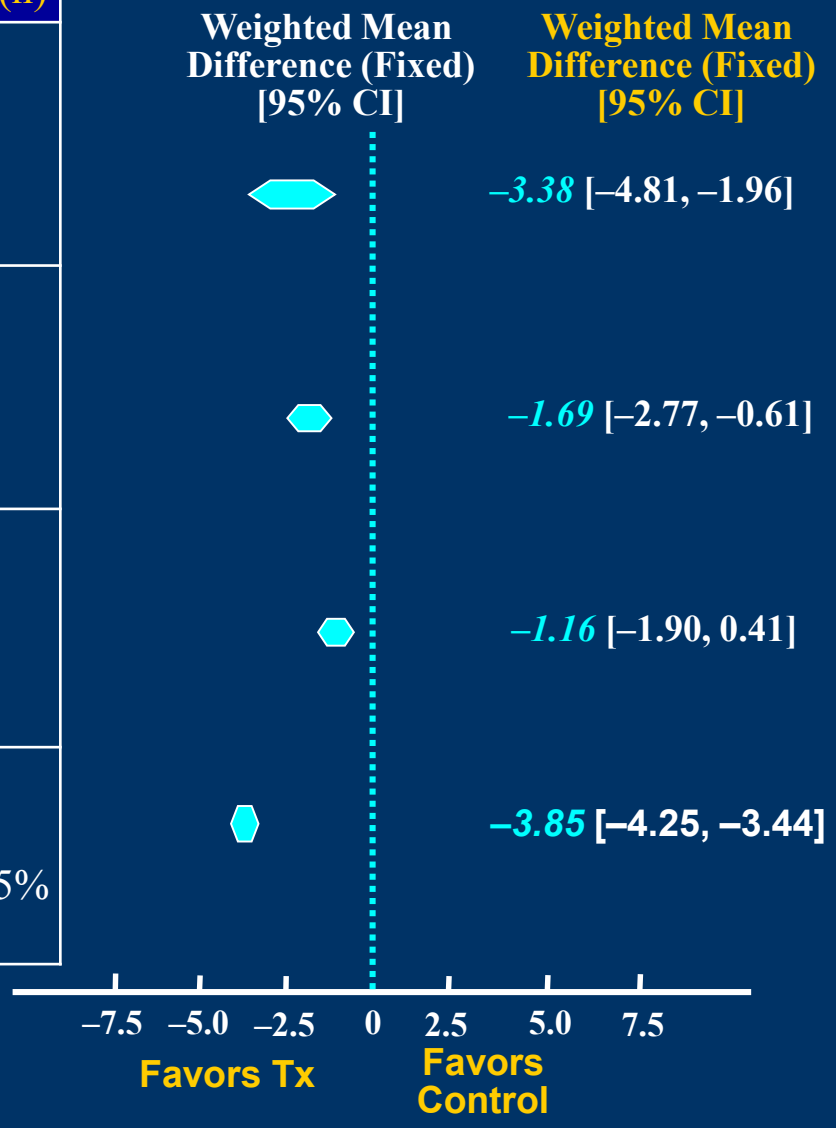
	ARI	OLZ	QUE	RIS	ZIP
ARI		↑↑ weight	↑ weight	↑ weight	≈ weight
OLZ	↓↓ weight		↓ weight	↓ weight	↓↓ weight
QUE	↓ weight	↑ weight		≈ weight	↓ weight
RIS	↓ weight	↑ weight	≈ weight		↓ weight
ZIP	≈ weight	↑↑ weight	↑ weight	↑ weight	

IMPORTANT: Much of the data on weight loss and lipid improvements comes from switch studies with presumably selected patients experiencing mixture of efficacy and tolerability difficulties with prior medication.

Weiden PJ. *Postgrad Med.* 2006 Special Report(September):27-44.

Weight Loss/Maintenance Therapy vs Standard of Care

Study	Tx Group (n)	Control Group (n)
*Cognitive Behavior Weight Gain Prevention Therapy**		
Total	58	46
Test for heterogeneity: chi^2=0.59, *df*=1, *P*=.44, I^2=0.0%		
Test for overall effect: z=4.65, *P*<.00001		
Cognitive Behavior Weight Loss Therapy		
Total	71	58
Test for heterogeneity chi^2=1.76, *df*=2, *P*=.41, I^2=0.0%		
Test for overall effect *z*=4.65, *P*=.002		
Pharmacological Weight Gain Prevention Therapy		
Total	138	136
Test for heterogeneity: chi^2=3.54, *df*=5, *P*=.62, I^2=0.0%		
Test for overall effect: z=3.05, *P*=.002		
Pharmacological Weight Loss Therapy		
Total	146	127
Test for heterogeneity: chi^2=69.64, *df*=8, *P*=<.0001, I^2=88.5%		
Test for overall effect: z=18.59, *P*<.00001		



***Medium-term; In 2 studies lasting 6 months: –4.87 [–7.11, –2.64].**

Faulkner et al. *Cochrane.Database.Syst.Rev.* 2007;1:CD005148.

Identification of the Metabolic Syndrome

≥3 Risk Factors Required for Diagnosis	
Risk Factor	**Defining Level**
Abdominal obesity Men Women	Waist circumference >40 in (>102 cm) (IDF-94 cm) >35 in (>88 cm) ((DF-80 cm)
Triglycerides	>150mg/dL(1.7 mmol/L
HDL cholesterol Men Women	< 40 mg/dL (1.03 mmoI/L) <50 mg/dL(1.29 mmoI/L)
Blood pressure	≥130/85 mm Hg
Fasting blood glucose	>100 (5.6 mmoI/L)

HDL = high-density lipoprotein.

Lipid metabolism dysregulation (1)

- Dyslipidemia represents one of the most important risk factors for cardiovascular morbidity and mortality
- Patients with schizophrenia treated with second–generation antipsychotics showed increased levels of LDL cholesterol and triglycerides and decreased levels of HDL cholesterol*,^
- Olanzapine is associated with nearly a five-fold increased odds of developing hyperlipidemia compared to no-antipsychotic exposure±
- Antipsychotics differ in their weight gain potential, suggesting that the effects on lipid levels seen during antipsychotic therapy may be related to their effect on body weight and adiposity§

*Cohn T,et al.*Canadian journal of psychiatry Revue canadienne de psychiatrie* 2004; 49: 753-60;^Henderson DC,et al. *Am J Psychiatry* 2000; 157: 975-81;±Koro CE, et al. *Archives of general psychiatry* 2002; 59: 1021-6;§Hasnain M. *Postgraduate medicine* 2012; 124: 154-67.§§Subramanian S, et al. *Biochimica et biophysica acta* 2012; 1821: 819-25.

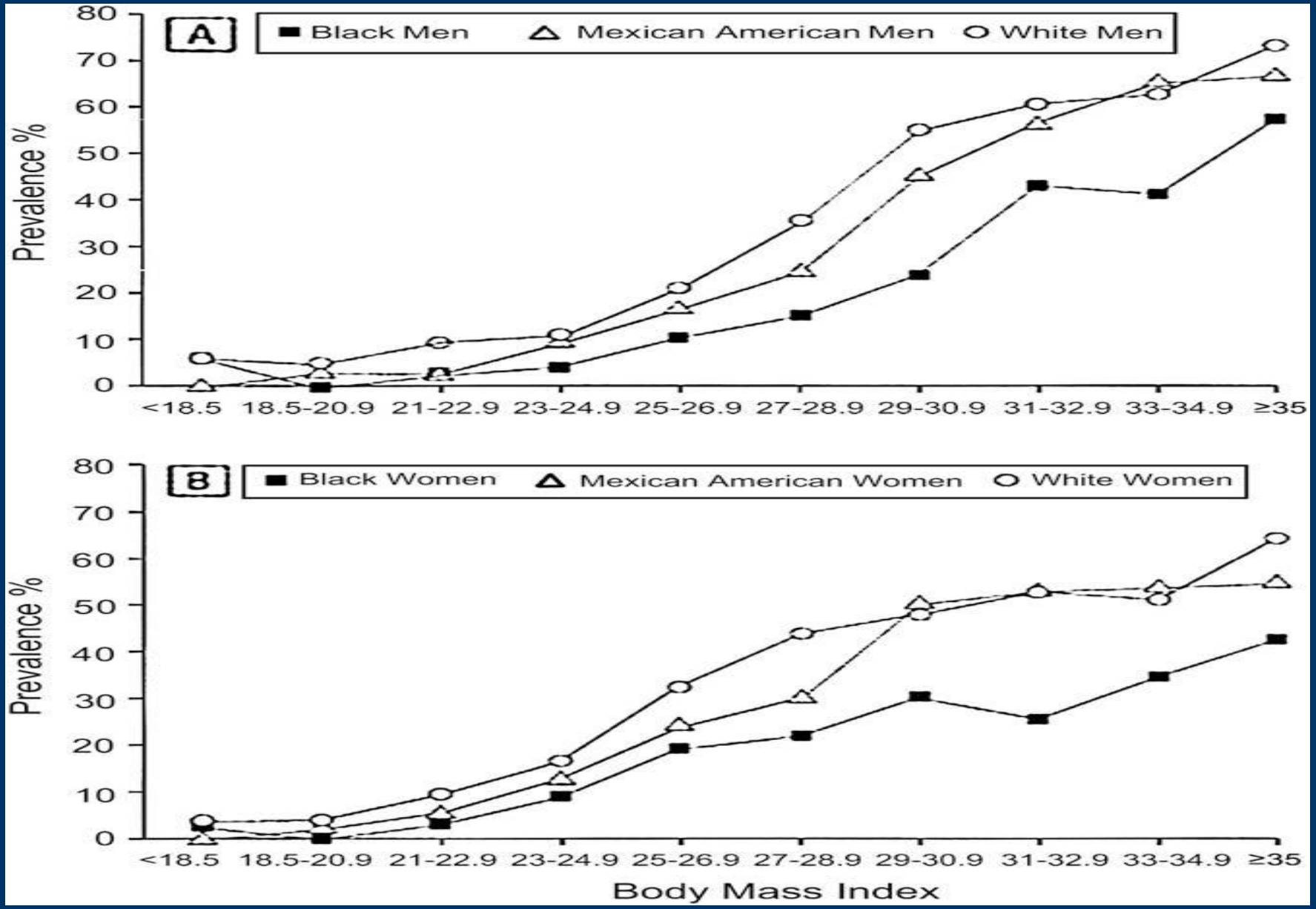
Lipid metabolism dysregulation

- Insulin resistance, commonly associated to obesity, may also play a role in the development of treatment-associated dyslipidemia§§
- The lack of insulin sensitivity stimulates compensatory insulin secretion, which leads to hypersecretion of VLDL and triglycerides§§
- Insulin resistance increased intracellular hydrolysis of triglycerides and release of FFAs into the circulation form the adipose tissue§§

Lipid metabolism dysregulation(2)

- As Antipsychotics can cause substantial elevations in triglyceride levels with only modest weight gain* they may directly affect lipids metabolism or levels with some unclear mechanisms
- Olanzapine-treated rats have hypertrophic adipocytes± which may be more prone to rupture and increase the risk of dyslipidemia by releasing their content (triglycerides) into the circulation^
- Antipsychotic agents can directly increase lipogenesis and decrease lipolysis in the visceral tissue of mature rats in order to facilitate adipocyte lipid storage±
- Antipsychotics stimulate sterol regulatory element-binding proteins (SREBP) as well as VLDL gene leading to hyperlipidemia in peripheral adipose tissue and in the circulation^,^^
- The SREBPs are the most important transcriptional regulators of cellular lipid and cholesterol synthesis§ : due to antipsychotic treatment side effects, LDL-derived cholesterol accumulates within the cells±±

*Meyer JM. *The Journal of clinical psychiatry* 2000; **62**: 27-34; discussion 40-1.; ^Goncalves P,et al. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology* 2015; **25**: 1-16.; ±Minet-Ringuet J, et al. *Molecular psychiatry* 2007; **12**: 562-71.;^^Shimano H. *The FEBS journal* 2009; **276**: 616-21.;§Horton JD, et al. *J Clin Invest* 2002; **109**: 1125-31; ±±Kristiana I,et al. *The pharmacogenomics journal* 2010; **10**: 396-407.



Prevalence of the metabolic syndrome in adults: NHANES III. Arch Intern Med 2003;163:427-436.

Ethnic Differences in Triglyceride Levels and HDL-Cholesterol

- Black adults and children have a better lipid profile- lower triglyceride and higher HDL
- The effects of insulin resistance on lipid profile were the same in whites and blacks, TG should be higher and HDL lower
- Differences in diet do not account for this
- Lipoprotein lipase (LPL) are higher and hepatic lipase are lower in blacks
- Insulin resistance (IR) does not seem to impair LPL in blacks so can clear triglyceride with IR
- May explain the lower rates of metabolic syndrome and criteria not set to identify high risk for DM and cardiovascular disease.

Sumner AE: J Pediatri 2009; 155:S7.e7-11; Gaillard et al. Ethn Dis 2009 Spring:19:S2-1-7

Glucose metabolism dysregulation(1)

- Patients with schizophrenia have a higher prevalence of glucose metabolism abnormalities, insulin resistance, diabetes mellitus type 2 and metabolic syndrome compared to the general population*
- The prevalence of glucose metabolism abnormalities is higher in patients treated with second-generation antipsychotics compared to typical antipsychotics^
- Second-generation antipsychotics may also have acute hyperglycemic effects, occasionally leading to diabetic ketoacidosis (DKA), coma, and death±
- Antipsychotic agents may affect glucose metabolism with different mechanisms increasing the risk of insulin resistance, diabetes mellitus type 2 and metabolic syndrome
- Some patients may experience glucose metabolism dysregulation regardless weight or adiposity changes§

*Henderson DC et al. *Archives of general psychiatry* 2005; 62: 19-28.; ^Henderson DC et al. *Am J Psychiatry* 2000; 157: 975-81.; 87;± Koller EA et al. *Pharmacotherapy* 2003; 23: 735-44.; Koller EA et al. *J Clin Psychiatry* 2004; 65: 857-63; Kohen I et al. *The Annals of pharmacotherapy* 2008; 42: 588-91; Makhzoumi ZH et al. *Pharmacotherapy* 2008; 28: 1198-202; § Reynolds GP et al. *Pharmacology & therapeutics* 2010; 125: 169-79.

Glucose metabolism dysregulation(2)

- Clozapine and olanzapine may directly affect glucose regulation by limiting the capacity of pancreatic β-cells function to secrete appropriate amount of insulin*
- Antipsychotics may decrease glucose entry from the circulation^
- Some SGAs may decrease the insulin sensitivity GLUT or decrease the recruitment of GLUT-4 to plasma membrane±
- Olanzapine may affect insulin production and resistance by blocking M3R signaling pathways in the brain§
- Increased HOMA-IR induced by chronic treatment with SGAs has been correlated with weight gain and adiposity&

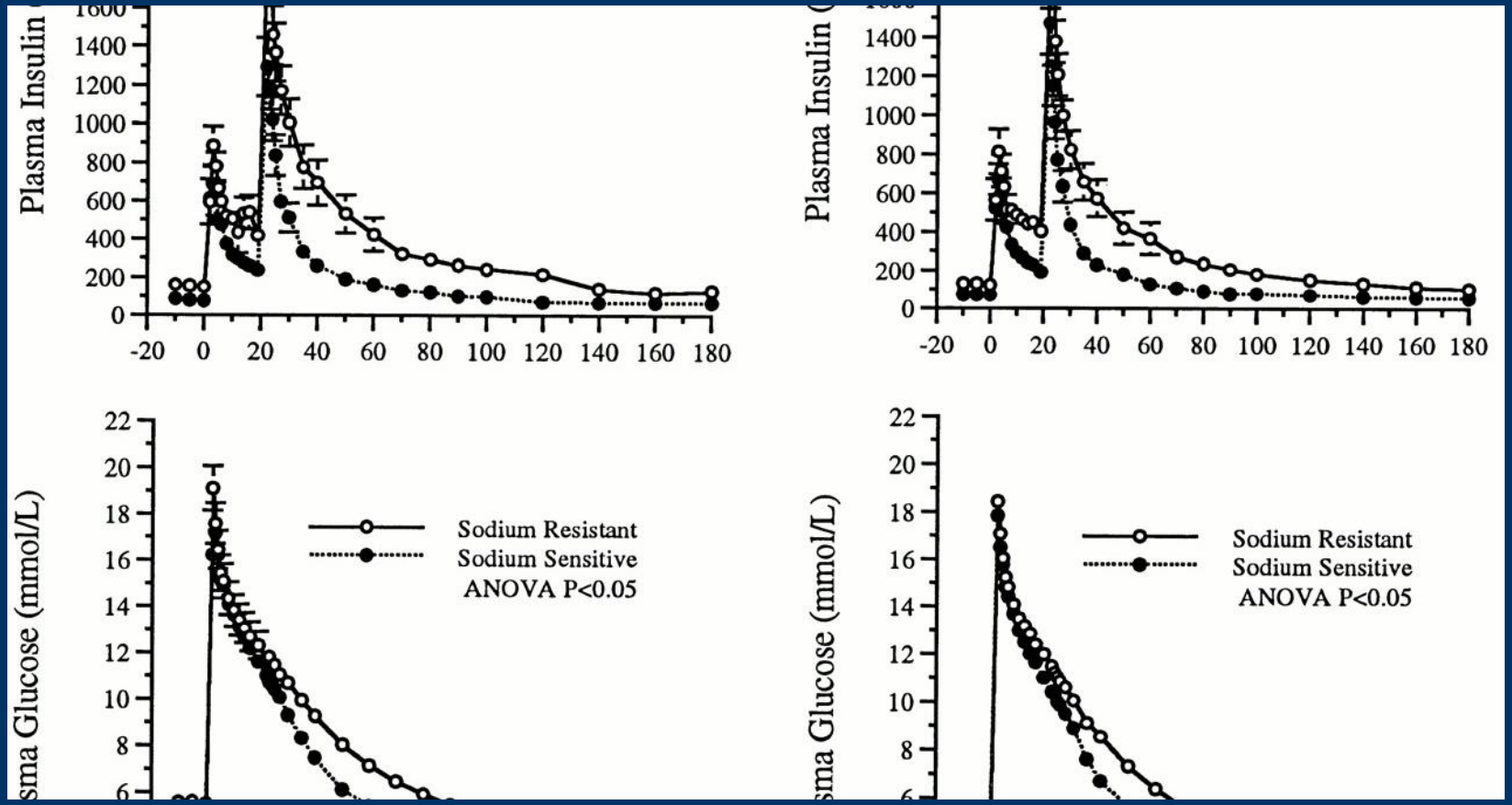
*Bergman RN, et al. *J Clin Psychiatry* 2005; 66: 504-14;^Saltiel AR et al. *Nature* 2001; 414: 799-806;±Henderson DC, et al. *J Clin Psychiatry* 2006; 67: 789-97.;§Weston-Green K.et al. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology* 2012; 22: 364-73; &Hardy TA,et al. *Diabetes, obesity & metabolism* 2011; 13: 726-35; ^^Henderson DC,et al. *Acta psychiatrica Scandinavica* 2006; 113: 121-5; ^^^Girault EM et al. *Naunyn-Schmiedeberg's archives of pharmacology* 2014; 387: 185-95.; ±±Baig MR et al. *Journal of psychiatric practice* 2010; 16: 325-33.

Glucose metabolism dysregulation (3)

- Homocysteine levels are significantly higher in subjects with impaired fasting glucose than in those with normal fasting glucose level^^
- The increased hepatic glucose output associated with a reduction in active glucagon-like peptide 1 concentrations and high glucagon levels may likely play a part in glucose metabolism defects^^^
- Antipsychotics also negatively affect mitochondrial function within the cells altering electron transport during oxidative phosphorylation thereby decreasing glucose metabolism±±

FSIVGTT

FSIVGTT


Plasma Insulin
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Plasma Insulin
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sma Glucose (mmol/L)
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Sodium Resistant
Sodium Sensitive
ANOVA P<0.05
sma Glucose (mmol/L)
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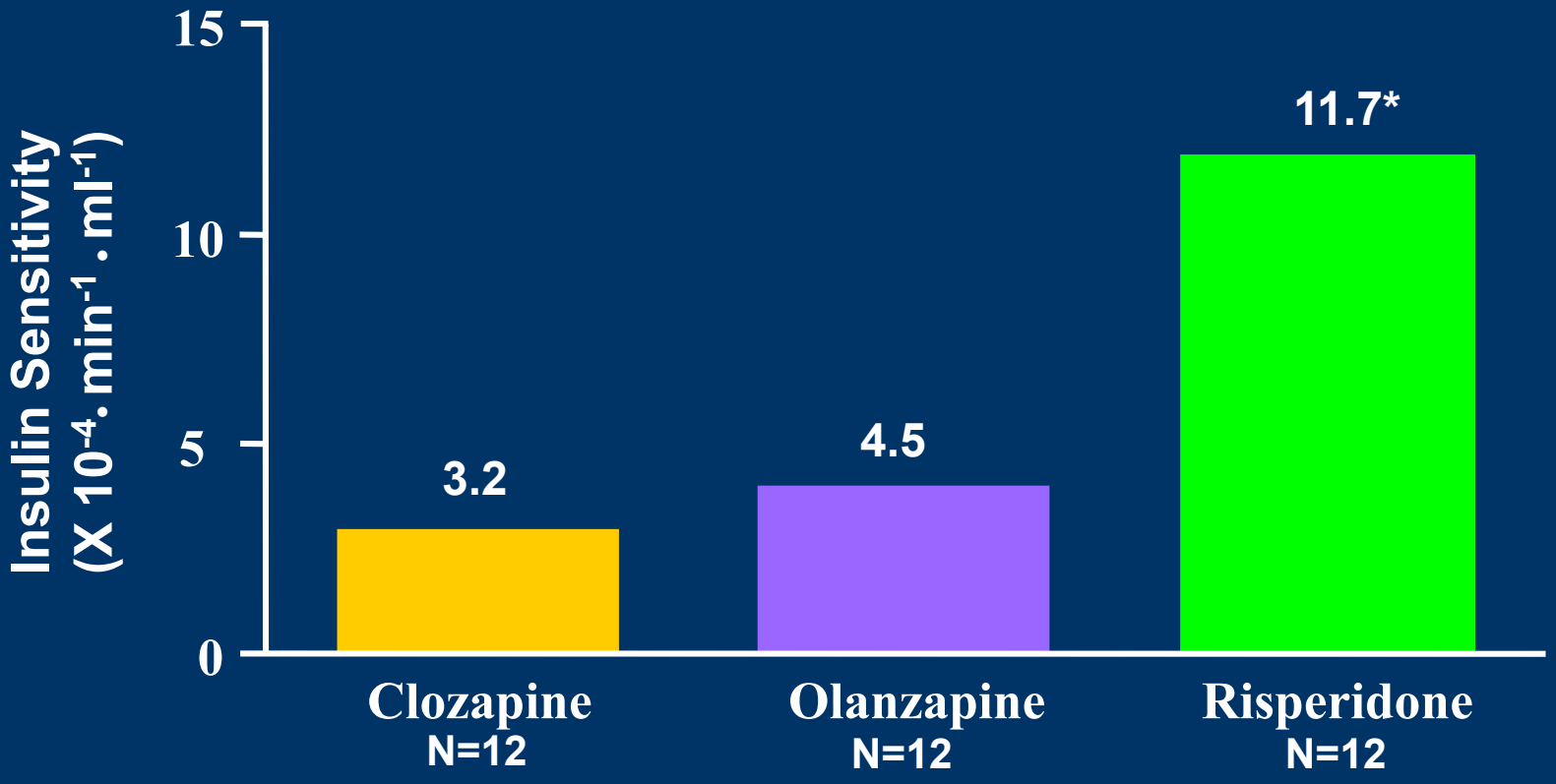
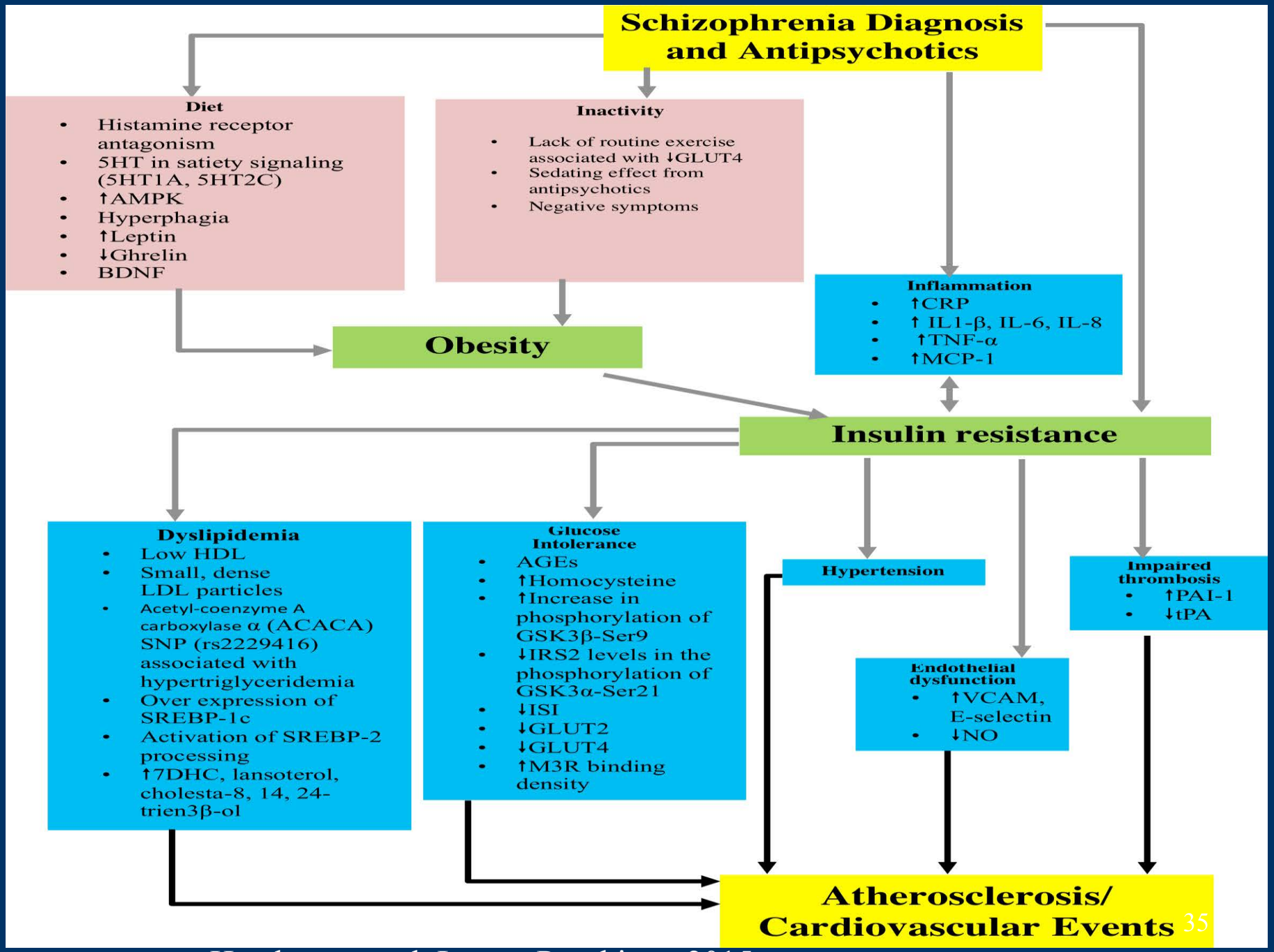
Insulin Sensitivity by Medication IVGTT With Minimal Model Analysis



*p<0.001; IVGTT = intravenous glucose tolerance test; Nonobese patients with schizophrenia, matched on BMI (p=0.81), but not leptin (p<0.001); Hip-waist ratio (p=0.04) or subscapular skinfold (p=0.049); Henderson DC et al. (2005), Arch Gen Psychiatry 62(1):19-28



Henderson et al. Lancet Psychiatry 2015

ADA Consensus on Antipsychotic Drugs and Obesity and Diabetes

Drug	Weight Gain	Diabetes Risk	Dyslipidemia
Clozapine	+ + +	+	+
Olanzapine	+ + +	+	+
Risperidone	+ +	0	0
Quetiapine	+ +	0	0
Aripiprazole*	+/-	-	-
Ziprasidone*	+/-	-	-

+ = increased effect; - = no effect; 0 = discrepant results.

*Newer drugs with limited long-term data.

Consensus Statement on Antipsychotic Drugs, Obesity, and Diabetes: Monitoring Protocol for Patients on 2nd-Generation Antipsychotics*

	Short-Term				Long-Term		
	Baseline	4 wk	8 wk	12 wk	Quarterly	Annually*	Every 5 y
Personal/family history	X					X	
Weight (BMI)	X	X	X	X	X		
Waist circumference	X					X	
Blood pressure	X			X		X	
Fasting plasma glucose	X			X		X	
Fasting lipid profile	X			X		X	[X]

*More frequent assessments may be warranted based on clinical status.

Wellness Programs

Education and Activity + **Nutrition and Exercise** + **≥ 3 Months' Duration** = **Success**

Note: Programs that are less likely to be successful include briefer duration interventions, general wellness or health promotion or education-only programs, non-intensive, unstructured, or non-manualized interventions and programs limited to nutrition only or exercise only (as opposed to combined nutrition and exercise).

Bartels S et al. *Health Promotion Programs for People with Serious Mental Illness*. Wash DC SAMHSA-HRSA Center for Integrated Health Solutions. Jan 2012. Available at: http://www.integration.samhsa.gov/Health_Promotion_White_Paper_Bartels_Final_Document.pdf. Accessed July 22, 2014.

Wellness Programs

Program	Description	Results
Canadian Study[1]	Outpatient program: One 90-minute educational session (dietary and physical activity counseling) at beginning of study; twice-weekly, 60-minute exercise sessions for 18 months Active treatment: N = 59	Significant improvement in BMI, weight, waist circumference, triglycerides, total cholesterol, HDL, LDL, glucose, HA_{1c} No significant improvement in prolactin or thyrotropin-stimulating hormone
Healthy Living[2]	Day treatment program 12-week intensive weight control program (including basic nutrition principles, principles of physical fitness and behavioral management), followed by a 12-week step-down program and a 6-month maintenance program Active treatment: N = 31	Significant improvement in BMI, weight, waist circumference, $HA_{1c,}$ SBP, DBP No significant improvement in total cholesterol, HDL, LDL, or triglycerides

BMI, body mass index; DBP, diastolic blood pressure; HA_{1c}, glycosylated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.

1. Poulin MJ et al. *Aust NZ J Psychiatry*. 2007;41:980-989; 2. Menza M et al. *J Clin Psychiatry*. 2004;65:471-477.

Wellness Programs (cont'd)

Program	Description	Results
Southlake Regional Health Centre[1]	Outpatient program Weekly group sessions for 12 weeks (exercise component for 1 hour and healthy eating and lifestyle teaching for 1 hour N = 6	Improvement in fitness level, weight, BMI, waist circumference, percent body fat No significant improvement in fasting blood glucose, cholesterol, HDL, LDL
IN SHAPE[2]	Community-integrated program Individual weekly sessions (45–60 minutes) for up to 9 months; weekly sessions included review of progress, individualized exercise instruction, and education about healthy eating N = 76	Significant improvement in hours/week exercising, Overall Activity Index (YPAS), Vigorous Activity Index (YPAS), Leisurely Walking Index (YPAS), waist circumference No significant improvement in weight, BMI, SBP, or DBP

BMI, body mass index; DBP, diastolic blood pressure; HA_{1c}, glycosylated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; YPAS, Yale Physical Activity Scale.

1. Cappuccio P et al. *A Schizophrenia Wellness Program: Reducing Gaps & Improving Linkages Across the Continuum*. Presented Dec 2, 2010. Available at: http://www.docstoc.com/docs/83517595/A-Schizophrenia-Wellness-Program-Reducing-Gaps-Improving. Accessed July 22, 2014; 2. Van Citters AD et al. *Community Ment Health J*. 2010;46:540-552. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3163497/pdf/nihms-175473.pdf. Accessed July 22, 2014.

Wellness Programs (cont'd)

Program	Description	Results
Solutions for Wellness/Team Solutions[1]	Psychiatric inpatient setting 4 hours per day, 5 days/week, for 36 weeks Solutions for Wellness program: tips on nutrition and fitness, with an exercise component Team Solutions program: patients learned about symptoms of mental illness, promotion of recovery, and prevention of relapse N = 275	Significant improvement in BMI, weight, glucose, triglycerides, blood pressure (% of patients with SBP ≥ 140 mmHg or DBP ≥ 90 mmHg) No significant improvement in cholesterol, HDL, LDL, HA_{1c}

BMI, body mass index; DBP, diastolic blood pressure; HA_{1c}, glycosylated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.

1. Lindenmayer J-P et al. *J Clin Psychiatry*. 2009;70:1385-1396.

Wellness Programs (cont'd)

Program	Description[2]	Results[1]
STRIDE[1,2]	Community outpatient settings 12-month program including usual care or a weight loss and lifestyle intervention program consisting of weekly group participation for 6 months covering topics on nutrition, physical activity and lifestyle changes + monthly group participation for an additional 6-month maintenance period + individual monthly contacts from intervention group facilitators during the second 6-month phase N = 200	Intervention participants lost 4.4 kg more than control participants from baseline to 6 months and 2.6 kg more than controls from baseline to 12 months At 12 months, fasting glucose levels had increased in the control group (from 106.0 mg/dL to 109.5 mg/dL) and decreased in the intervention group (from 106.3 mg/dL to 100.4 mg/dL) Medical hospitalizations were lower in the intervention group vs control group (6.7% vs 18.8%)

BMI, body mass index; DBP, diastolic blood pressure; HA_{1c}, glycosylated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.

1. Green CA et al. *Am J Psychiatry*. 2014;Sep 15. doi: 10.1176/appi.ajp.2014.14020173. [Epub ahead of print]; 2. Yarborough BJH et al. *BMC Psychiatry*. 2013;13:238.

Wellness Programs (cont'd)

Program	Description	Results
Wellbeing Suport[1]	Outpatient setting Healthy living education In addition, patients could participate in a group for weight management or physical activity Minimum of 6 consultations over 2 years N = 966	Significant improvement in cigarette smoking, alcohol use, physical activity, diet No significant improvement in BMI, DBP, SBP

BMI, body mass index; DBP, diastolic blood pressure; HA_{1c}, glycosylated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.

1. Smith S et al. *Eur Psychiatry*. 2007;22:413-418.

http://professional.diabetes.org/ResourcesForProfessionals.aspx?cid=77219

DIABETES AND OBESITY
TIP SHEET #1

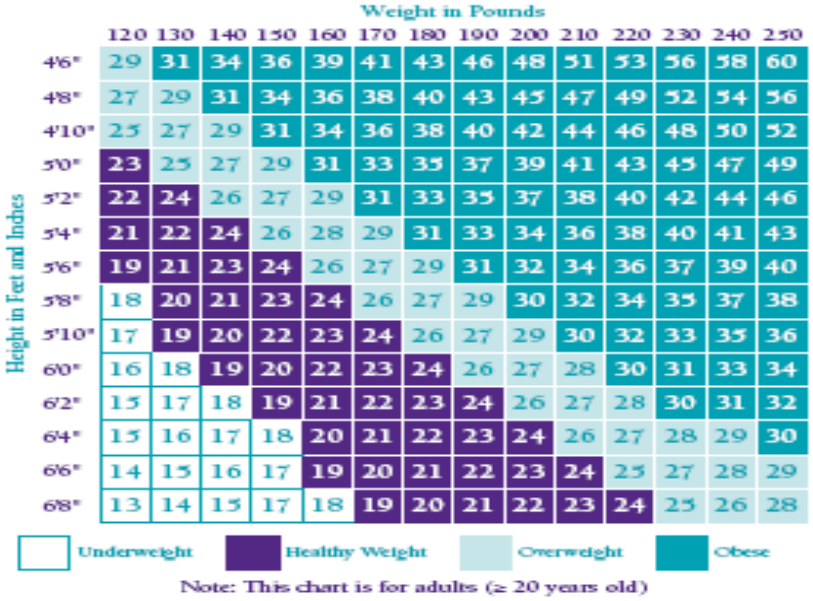
American Diabetes Association.
Cure • Care • Commitment®

Getting Started

What is the link between diabetes and obesity?

Being overweight or obese is a leading risk factor for type 2 diabetes. The body gets its energy from a type of sugar called glucose. Insulin, which is produced in the pancreas, is required to help your body use glucose. Type 2 diabetes develops when your body can no longer use insulin effectively, or when the pancreas cannot make enough insulin to keep blood glucose levels normal.

A healthy weight is determined by body mass index (BMI), which you can calculate by using the chart below. Overweight is defined as a BMI greater than/equal to 25; obesity is defined as a BMI greater than/equal to 30.



Note: This chart is for adults (≥ 20 years old)

Losing Weight

- Begin a weight-loss program with the help of your health care team.
- Ask for a referral to a dietitian who can help you find a diet you can use every day.
- Don't try to do everything at once. Take one step at a time and make changes you can stick with.

If diet and exercise are not enough to reduce your weight, your health care provider may prescribe medications that can help.

Physical Activity

Exercise and other forms of physical activity can help you lose weight by burning calories and building muscle. Results can take time, but each activity will become easier as you get more fit. Becoming physically active can:

- Help you burn extra calories and naturally increase your glucose uptake by increasing your metabolism and muscle mass.
- Improve the body's response to insulin
- Help reduce or even eliminate your need for diabetes medication by lowering blood glucose levels if you have type 2 diabetes
- Reduce your risk for heart disease and stroke, the leading causes of death for people with diabetes

Here are some ideas to help you get started:

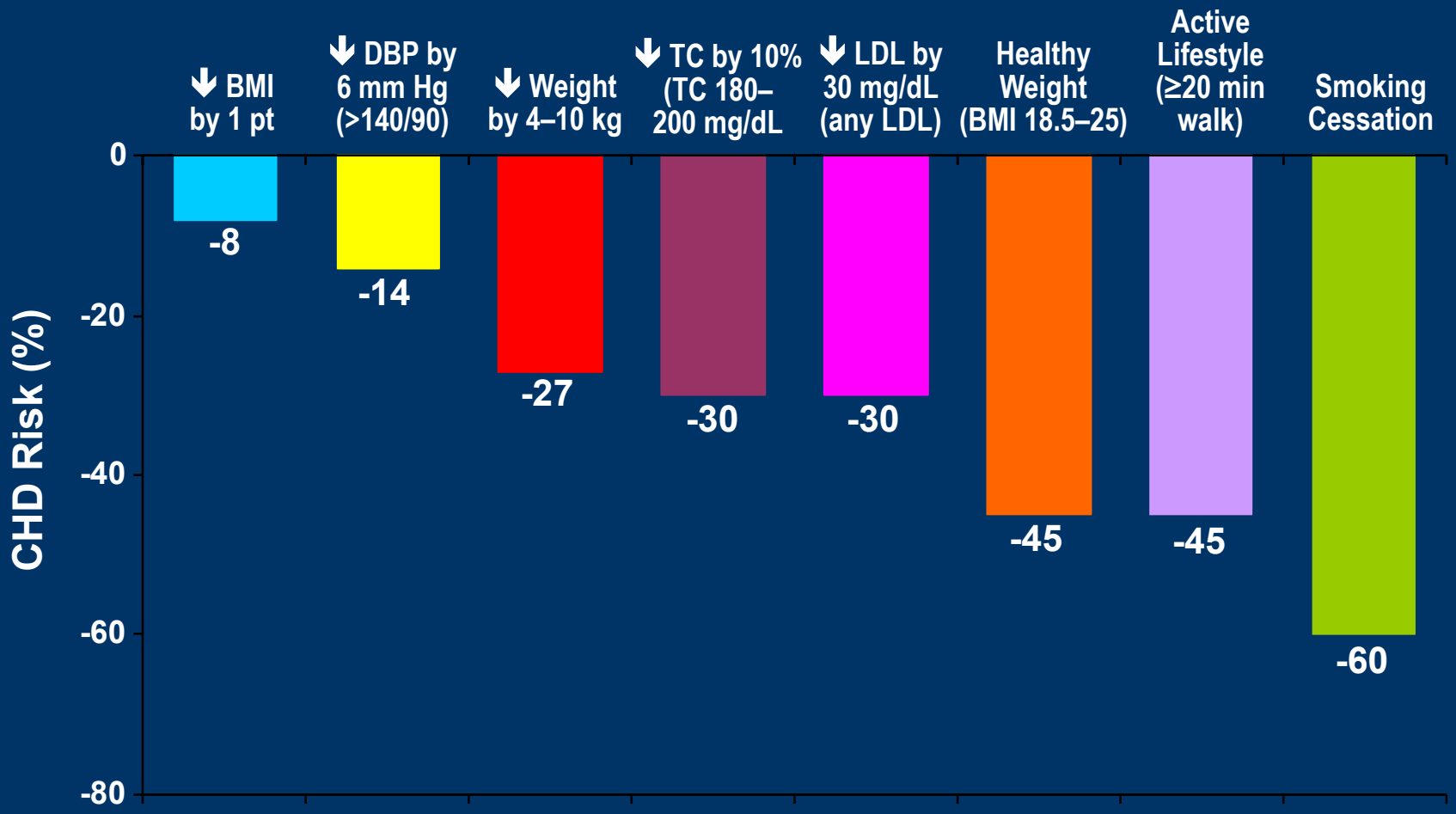
- Walk the dog
- Take the stairs instead of the elevator
- Find a friend you can exercise with

12-Step Healthy Lifestyle Program

Do's	Do Not's
• Replace sugar-containing drinks with water • Eat 4 to <6 meals, with <2 meals in the evening or night • Serve small meal portions • Eat slowly, drink water, take seconds only after delay • Eat food with a low glycemic index (<55) • Consume >25–30 grams of soluble fiber per day • Snack only when hungry and use fruit or vegetables • Perform moderate physical activity for >30–60 min/day	• Skip breakfast • Consume fast food >1 per wk • Consume saturated or processed fat-free food • Watch TV, play computer games ≥2 hours/day

Correll CU, Carlson HE. *J Am Acad Child Adolesc Psychiatry.* 2006;45: 771-791.

Effect of Interventions to Reduce CHD Risk



Li TY et al. *Circulation.* 2006;113:499-506; Hennekens CH. *Circulation.* 1998;97:1095-1102; Rich-Edwards JW et al. *N Engl J Med.* 1995;332:1758-1766; Bassuk SS, Manson JE. *J Appl Physiol.* 2005;99:1193-1204; Grundy SM. *Circulation.* 2004;110:227-239; Critchley JA, Capewell S. *JAMA.* 2003;290:86-97..

Conclusions

- Individuals with mental health disorders are at significantly elevated risk for premature mortality, especially CVD-related
- Modifiable cardiometabolic risk factors are prevalent in this population
- Individual psychotropics are associated with different levels of risk for adverse effects on weight, lipids and plasma glucose
- Clinicians can beneficially modify patient risk through the use of monitoring and interventions, including appropriate PCP and specialty referrals, and use of medications with lower potential for adverse metabolic effects

Thank You!

"You must be the change you want to see in the world."

Mahatma Gandhi