Substance Abuse and Mental Health Services Administration

SAMHSA

www.samhsa.gov • 1-877-SAMHSA-7 (1-877-726-4727)

Behavioral Health is Essential To Health

Prevention Works

Treatment is Effective

People Recover

Substance Abuse and Mental Health Services Administration
SAMHSA
www.samhsa.gov • 1-877-SAMHSA-7 (1-877-726-4727)

Schizophrenia: Treating The Whole Person

Jacob S. Ballon, M.D., M.P.H & Douglas L. Noordsy, M.D.

INSPIRE Clinic

PEPPNET Prodrome and Early Psychosis Program NETwork

Stanford University

Department of Psychiatry and Behavioral Sciences

INSPIRE CLINIC

December 15, 2017

CARING FOR EVERY CHILD'S MENTAL HEALTH
Systems of Care

THE TA NETWORK
the national technical assistance network for children's behavioral health

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

This webinar is hosted by PEPPNET - Prodrome and Early Psychosis Program NETwork, *a partner in the National TA Network for Children's Behavioral Health, operated by and coordinated through the University of Maryland.*

This presentation was prepared by the National Technical Assistance Network for Children's Behavioral Health under contract with the U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Contract #HHSS280201500007C.

Substance Abuse and Mental Health Services Administration
SAMHSA

Disclosures

Jacob Ballon:
Research Funding: Otsuka, Alkermes
Consulting: Pear Therapeutics, Alkermes

Doug Noordsy:
Research Funding: Janssen
Consulting: Pear Therapeutics

Outline

- What is Metabolic Dysregulation?
- Prevalence in Early Psychosis Population
- Impacts of Medication
- Guidelines for Testing/Monitoring
- Treatment Strategies

Metabolic Syndrome

Metabolic syndrome occurs when a person has three or more of the following measurements:

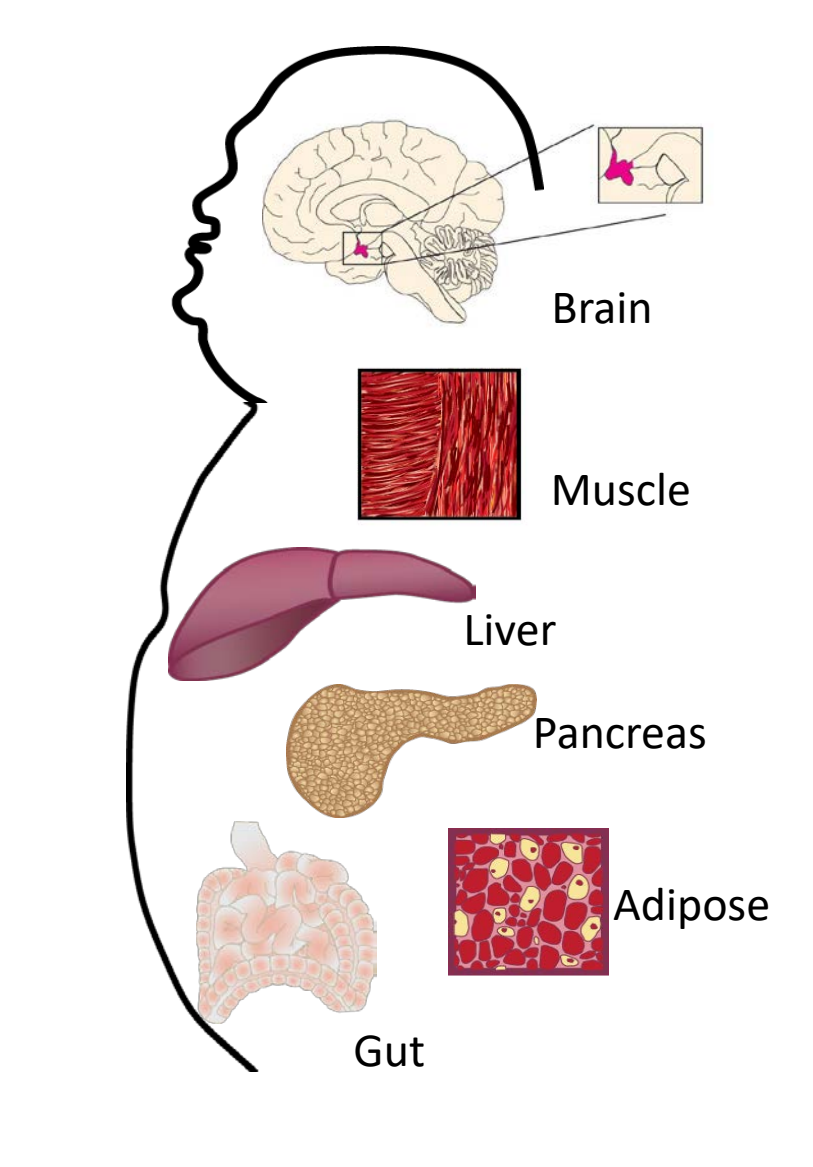
- Abdominal obesity (Waist circumference > 40” in men, > 35” in women)
- Triglycerides >150 mg/dL
- HDL <40 mg/dL in men or <50 mg/dL in women
- Systolic >130mmHg or diastolic >85 mmHg
- Fasting glucose >100 mg/dL

(About Metabolic Syndrome, 2016)

Life Span

- 10-25 year shortened life span
  - Lifestyle
    - Smoking
    - Sedentary
  - Medical Comorbidities
    - Cardiovascular disease
    - Diabetes
  - Medication effects
  - Suicide

(Laursen, 2012)



- Hypothalamus
  - Appetite Regulation/Satiety
  - Control of hepatic glucose production
- Liver
  - Hepatic Glucose production
  - De Novo lipogenesis
- Pancreas
  - Insulin/Glucagon secretion
- Gut
  - Insulin/Glucagon regulation
- Muscle
  - Glucose uptake
- Fat
  - Glucose uptake
  - Inflammatory state
  - Adipokine action

Schizophrenia

- Core Symptoms
  - Delusions
  - Hallucinations
  - Negative Symptoms
  - Cognitive Symptoms
  - *Metabolic Symptoms?*

Pre-Antipsychotic Era

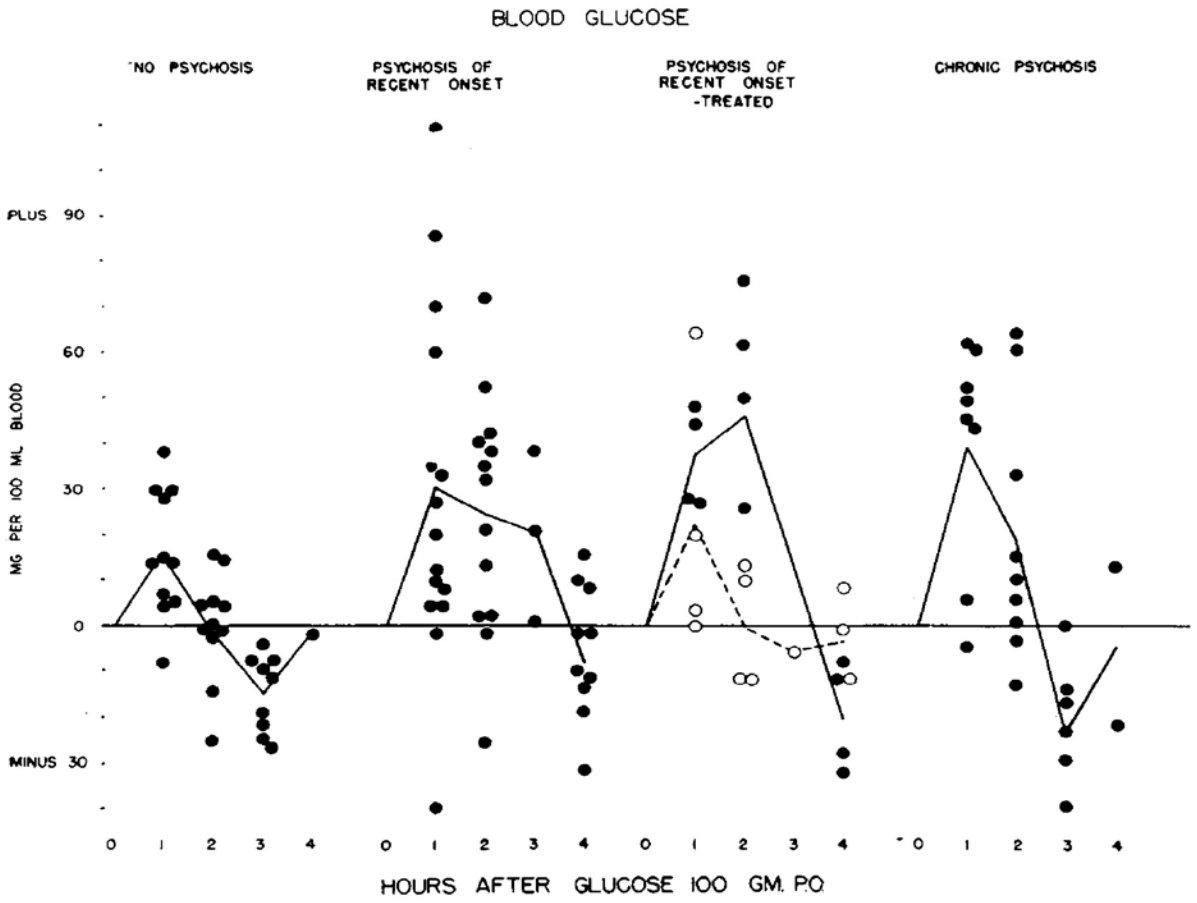


Fig. 1.—Changes in true blood glucose concentration after ingestion of 100 gm. of glucose. Open circles refer to patients improved after treatment. Lines indicate average changes, the broken line indicating average changes in patients improved after treatment.

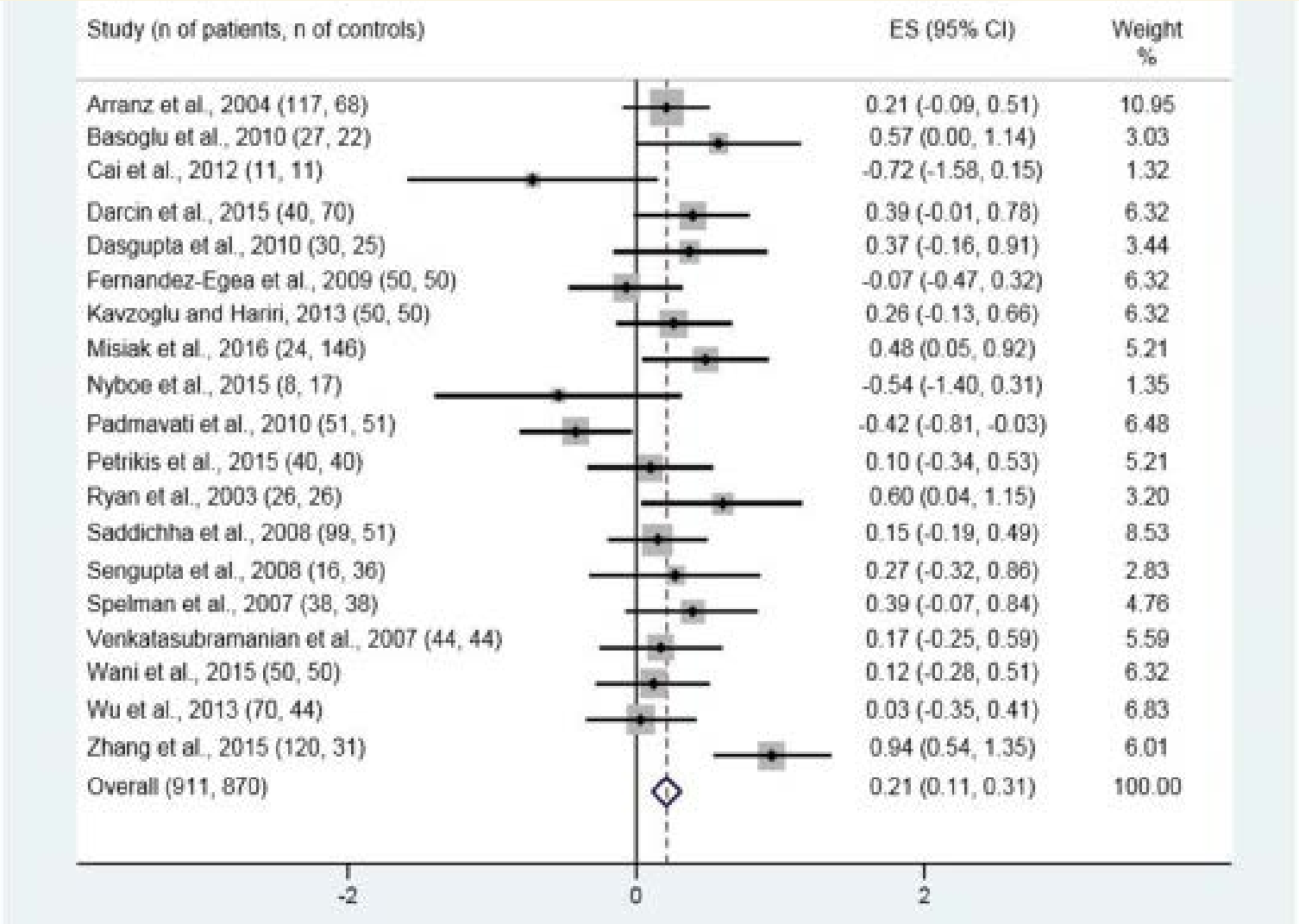
(Henneman, 1954)

Drug-Naive

Clinical Variable	Patients	Control Subjects	Relatives	Significance
Fasting Glucose (mmol/L)	4.7 ± 0.54	4.5 ± 0.48	3.3 ± 0.57	NS
Two-Hour Glucose (mmol/L)	6.0 ± 1.69	4.5 ± 0.81	5.7 ± 1.77	p<0.001
HbA1c (%)	5.3 ± 0.4	5.2 ± 0.3	5.3 ± 0.3	NS
Fasting Insulin (pmol/L)	38.8 ± 20.1	27.3 ± 12.2	40.2 ± 23.9	p<0.01
Two-Hour Insulin (pmol/L)	205.2 ± 124.8	77.5 ± 36.6	160.0 ± 116.2	p<0.001
HOMA-IR	1.15 ± 0.7	0.78 ± 0.3	1.15 ± 0.8	p<0.05
Leptin (nmol/L)	3.7 ± 2.3	3.6 ± 3.2	3.5 ± 1.6	NS

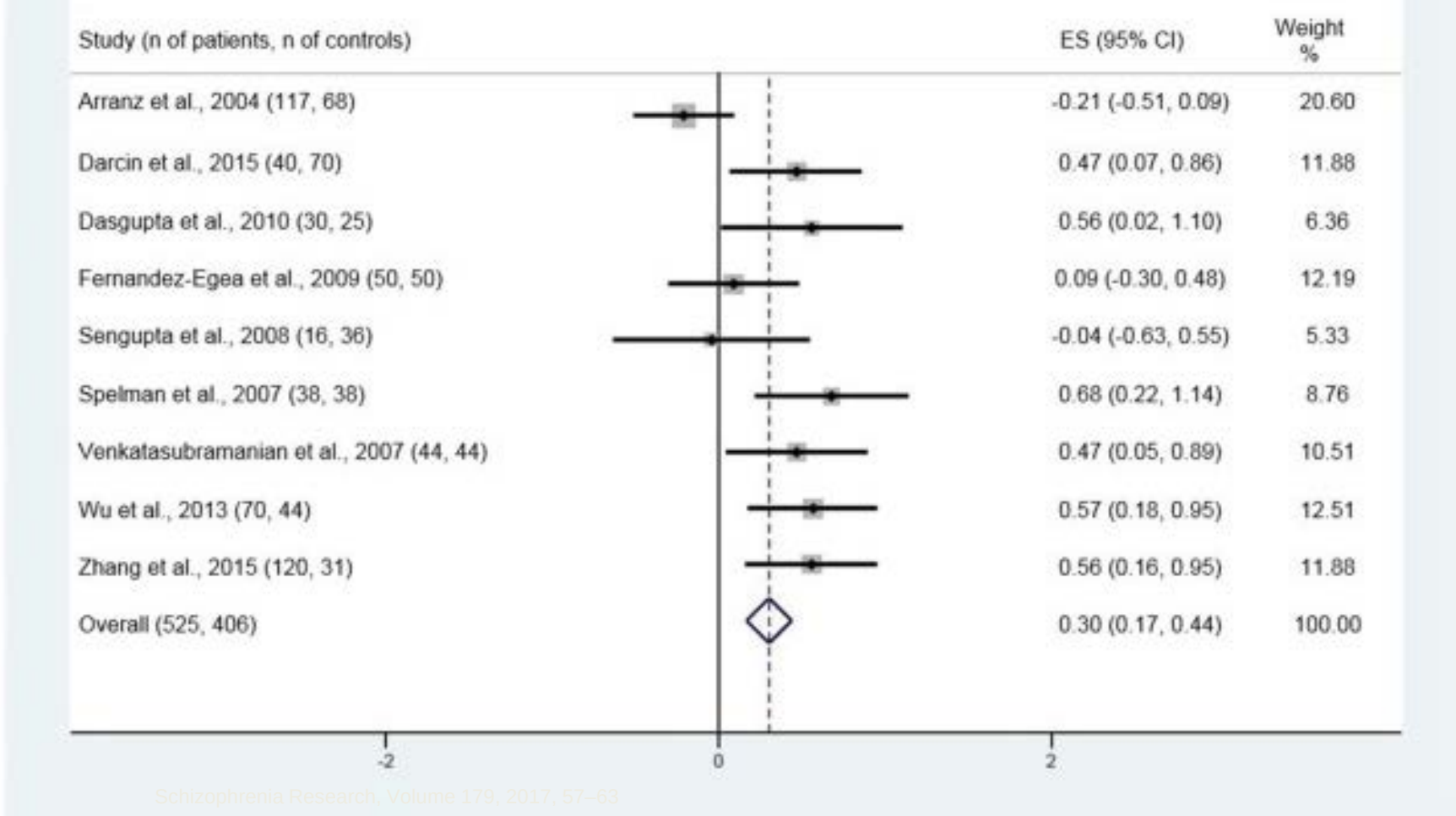
(Spelman, 2006)

Meta-Analysis – Fasting Glucose



(Schizophrenia Research, 2017)

Meta-Analysis – Insulin Resistance



Schizophrenia Research, Volume 179, 2017, 57–63

(Schizophrenia Research, 2017)

Danish Cohort

TABLE 2. Age-Specific Incidence Rates of Diabetes Mellitus in People With and Without Schizophrenia in a Population Cohort

Group and Age	Person-Years	Incident Diabetes	Incidence Rate[a]		Difference From People Without Schizophrenia
People without schizophrenia (N=2,727,565)	Person-Years (millions)	N	Rate	95% CI	
0–9 years	23.66	3,449	0.15	0.14–0.15	
10–14 years	9.16	2,654	0.29	0.28–0.30	
15–19 years	7.34	2,462	0.33	0.32–0.35	
20–24 years	5.15	1,776	0.35	0.33–0.36	
25–29 years	2.98	2,100	0.70	0.67–0.75	
30–36 years	1.24	1,474	1.18	1.12–1.25	
0–36 years	49.53	13,915	0.28	0.28–0.29	
People with schizophrenia (N=8,945)	Person-Years	N	Rate	95%CI	Mid-p[b]
0–9 years	29.12	0	0.00	—	0.99
10–14 years	269.44	0	0.00	—	0.93
15–19 years	4,824.17	13	2.69	1.56–4.64	<0.001
20–24 years	16,263.53	59	3.63	2.81–4.68	<0.001
25–29 years	16,941.88	75	4.43	3.53–5.55	<0.001
30–36 years	8,987.59	56	6.23	4.80–8.10	<0.001
0–36 years	47,315.73	203	4.29	3.74–4.92	<0.001

[a] Incidence rate of diabetes mellitus per 1,000 person-years.
[b] Two-sided exact test.

Danish Cohort (cont.)

TABLE 3. Endogenous Risk for Diabetes Mellitus in Antipsychotic-Naive People With Schizophrenia in a Population Cohort

Group	Incidence Rate[a]	95% CI[a]	Adjusted Hazard Ratio	95% CI	Number Needed to Harm[b]	95% CI[b]	p
Follow-up censored at first antipsychotic prescription[c]							
People without schizophrenia (N=2,736,510)[d]	0.27	0.27–0.28	1.00[e]		–	–	–
People with schizophrenia (N=4,322)	1.84	1.05–5.15					
Model 1[f]			2.92	1.66–5.15	1,931	894–5,614	<0.001
Model 2[g]			3.07	1.71–5.41	1,791	841–5,219	<0.001
No use of antipsychotics during the entire follow-up[h]							
People without schizophrenia (N=2,673,114)	0.27	0.27–0.28	1.00[e]		–	–	–
People with schizophrenia (N=1,154)	2.18	1.09–4.36					
Model 1[f]			3.18	1.59–6.36	1,700	692–6,280	0.001
Model 2[g]			2.98	1.49–5.95	1,872	749–7,562	0.002

[a] Incidence rate of diabetes mellitus per 1,000

American Journal of Psychiatry; Published online ahead of print (January 20, 2017)

Microbiome in Early Psychosis

- Higher rates of antibiotic treatment prior to onset

- Gut bacterial colonies differ from general population

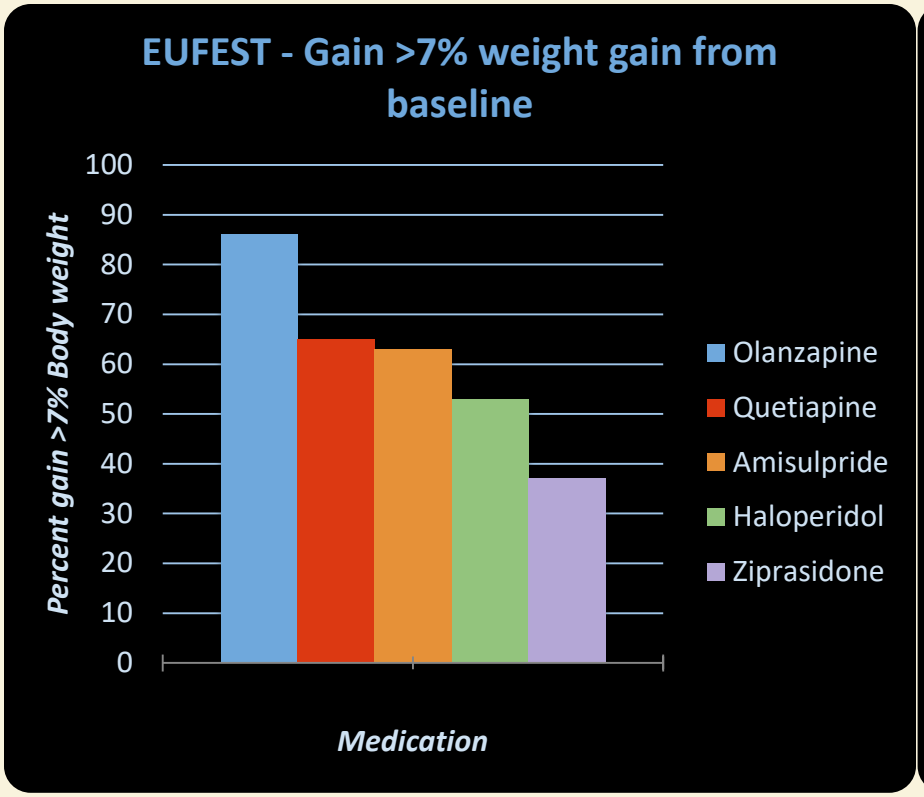
Challenges for Studying Medication Impact

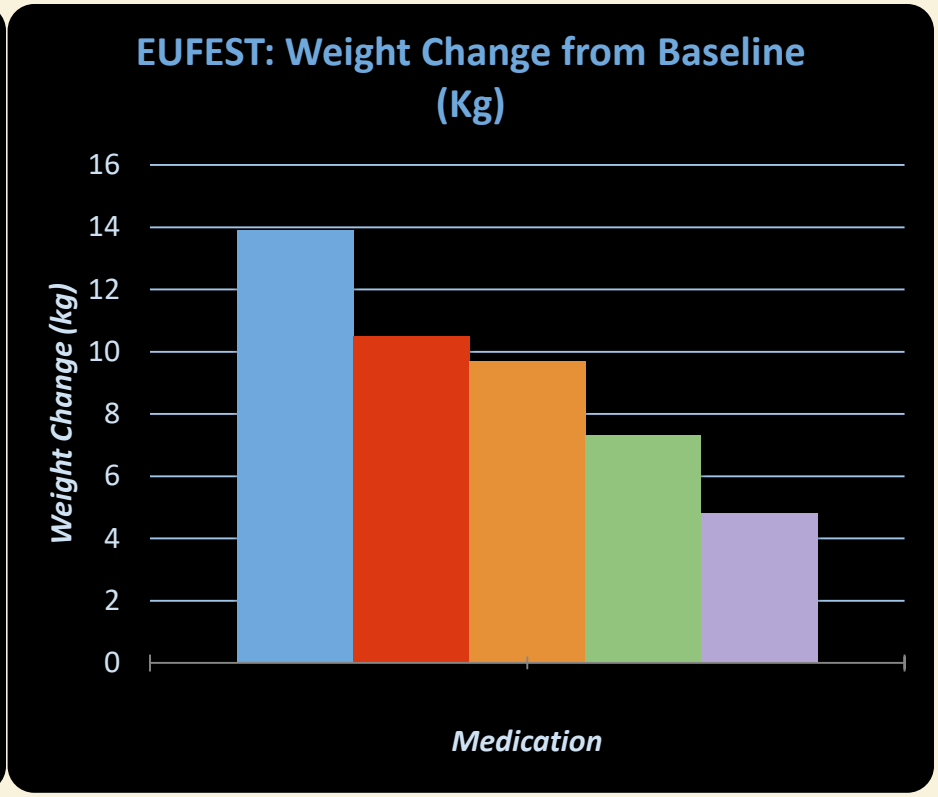
- First exposure is fleeting
  - Changes occur rapidly
- Diagnostic Imprecision
  - Heterogeneity of APD effects
  - Heterogeneity of schizophrenia
- Comorbidities
  - Lifestyle factors
  - Substances
  - Previous exposures

Findings: Animals

- Hypothalamic changes from olanzapine
  - Primary effect on gene expression
- Increased food intake
  - Slowed metabolism
- Hyperglycemia within one hour of 1st dose
  - Marked hepatic insulin resistance

EUFEST



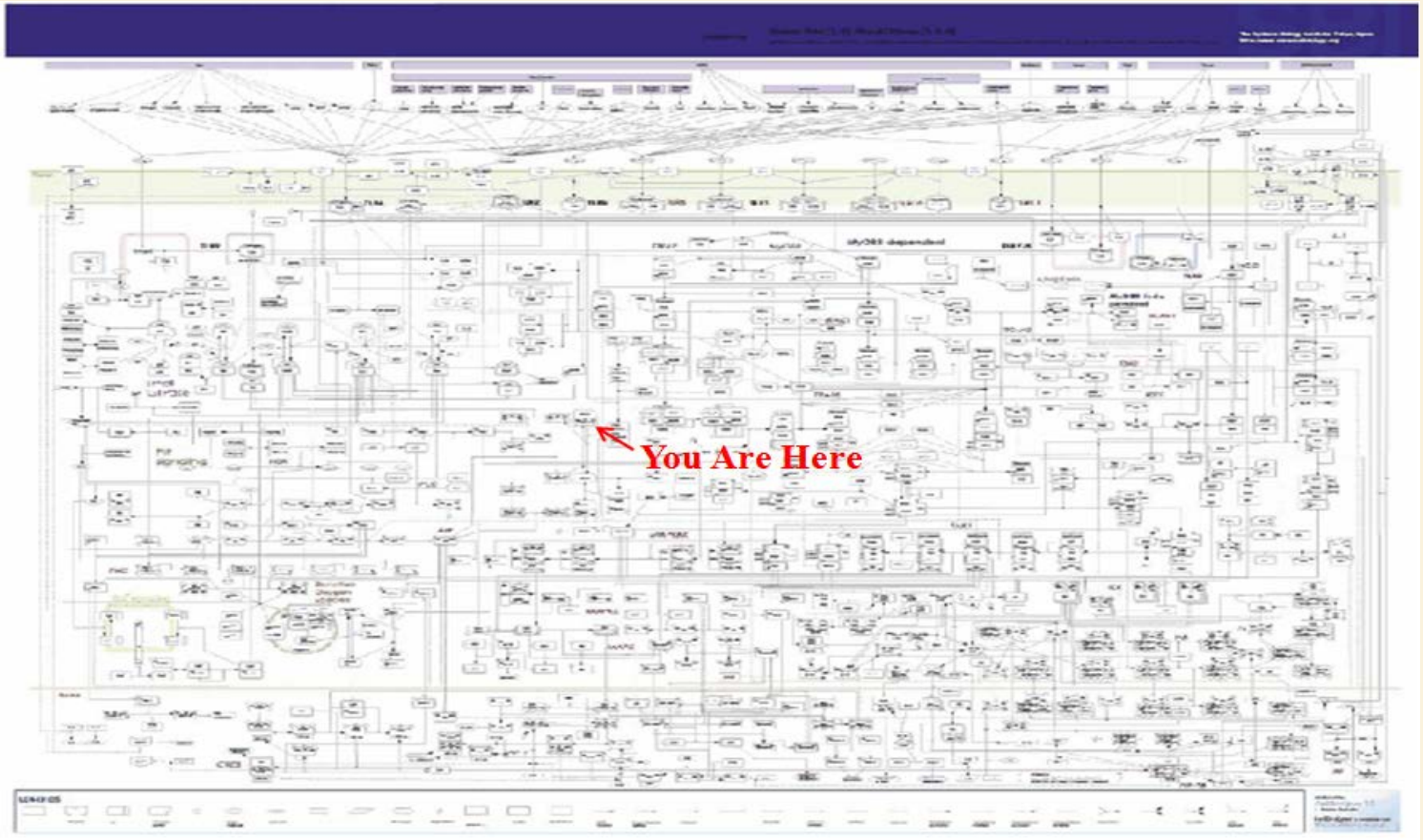


(Fleischhacker, 2013)

Findings in Schizophrenia

- Clinical Conundrum
- Obesity and Impaired Glucose Metabolism
  - 1. Which comes first?
  - 2. Separate mechanisms?
  - 3. Central or peripheral?

Antipsychotic Signaling Pathway(s)



Substance Abuse and Mental Health Services Administration
SAMHSA

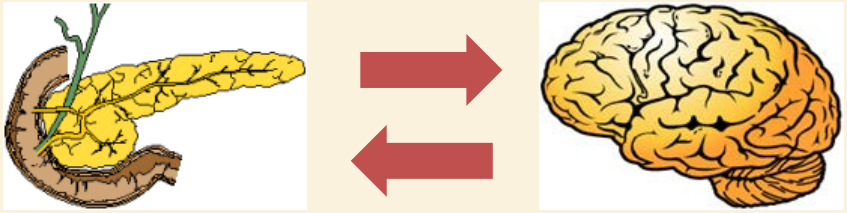
Dopamine Receptors

- Best studied in the CNS
  - Putative target of APD therapy

  However...
- Dopamine receptors are also expressed outside the CNS
  - Pancreas
  -
    - D_1R-D_5R expressed in insulin-secreting beta cells

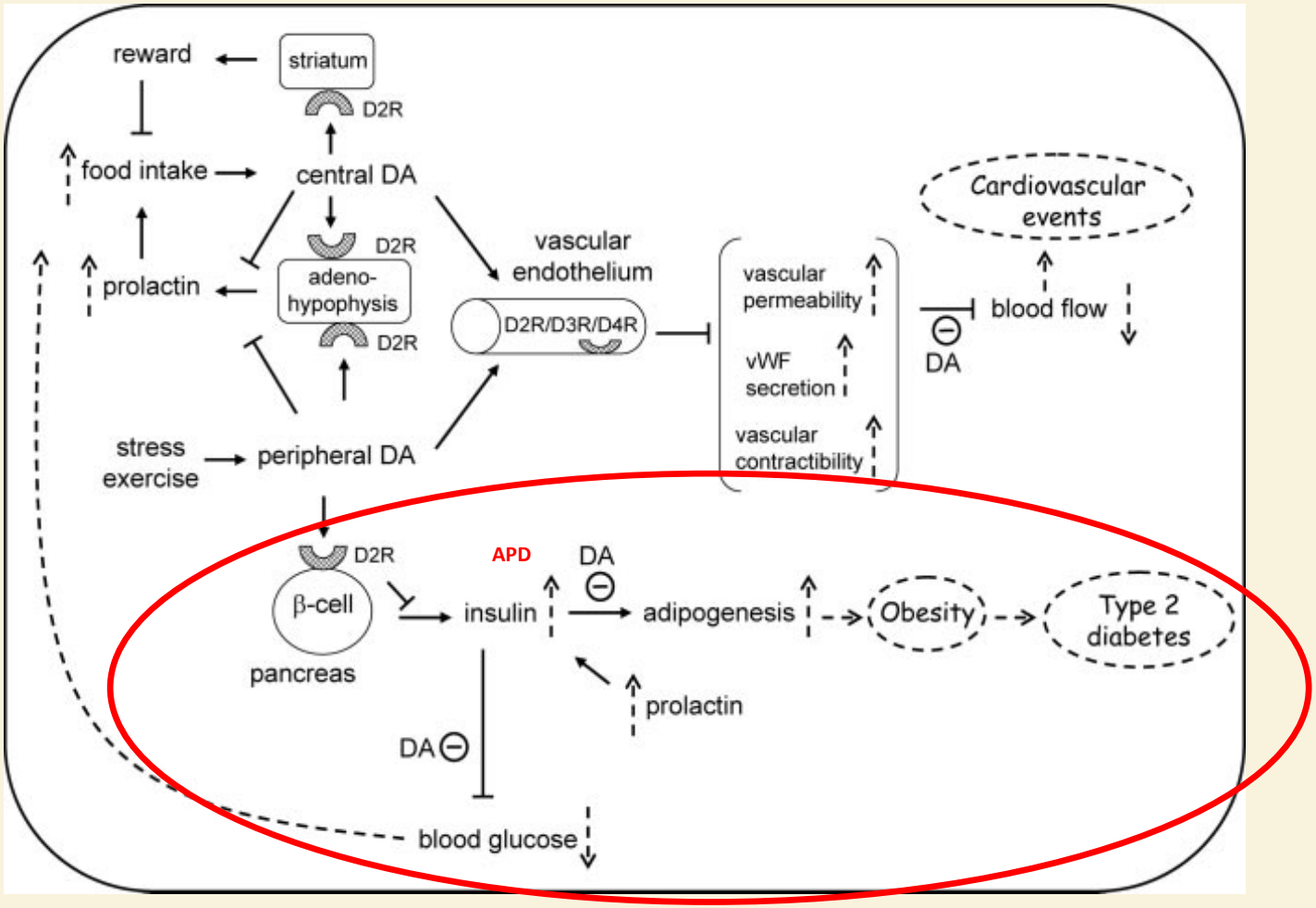
Dopamine's Role in the Pancreas?

- L-DOPA triggers hyperglycemia
- Dopamine inhibits glucose-stimulated insulin release
  - D_2R-dependent



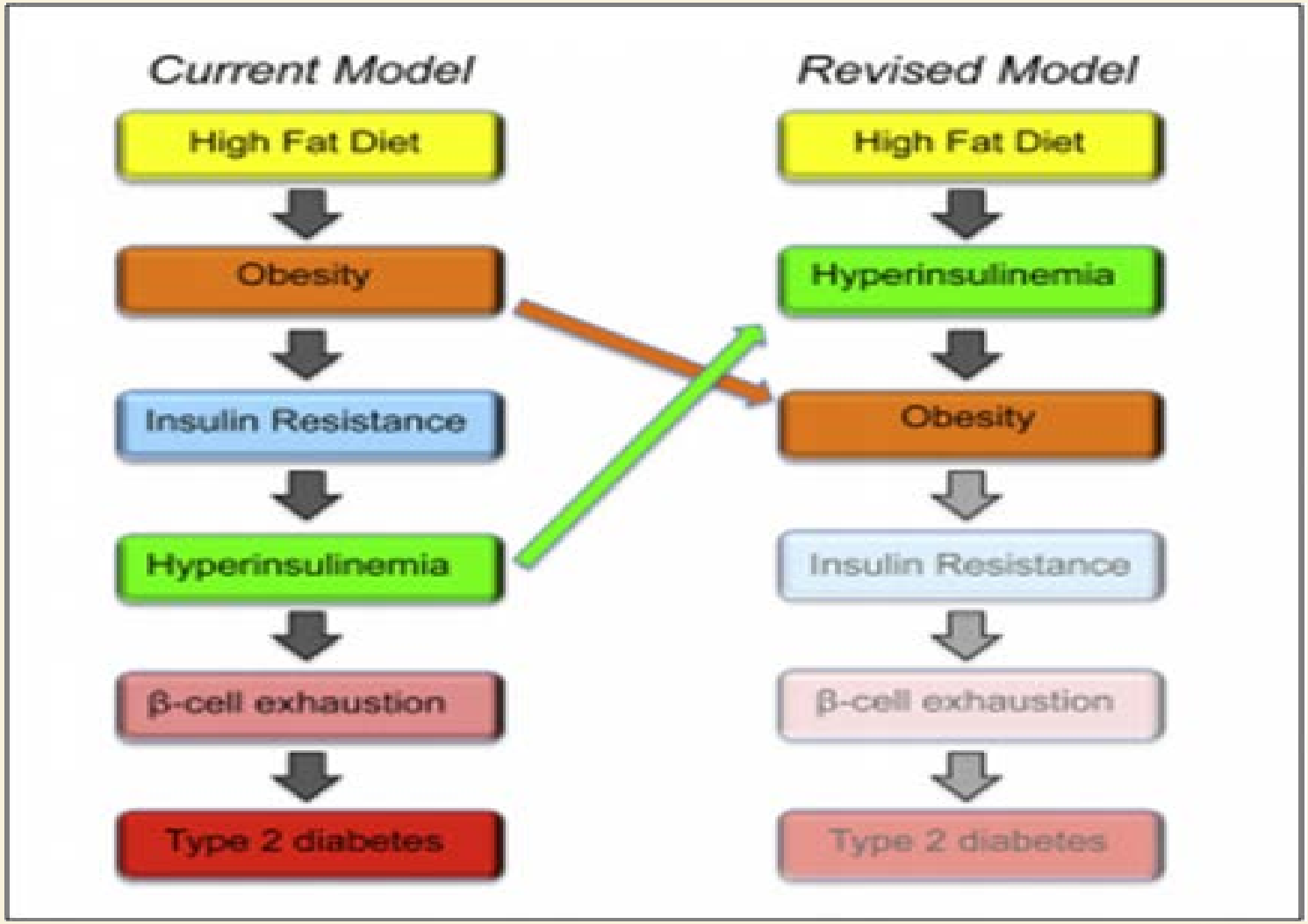
- Unclear if these effects are primarily modulated in the pancreas, CNS or both

What Role(s) APDs Play in the Pancreas?



(Rubí & Maechler, 2010)

Clinical Relevance: Hyperinsulinemia



(Mehran *et al.*, 2012)

Take Home - Pancreas

- Pancreatic beta cells express DA signaling machinery.

- Glucose stimulation increases beta cell DA secretion.

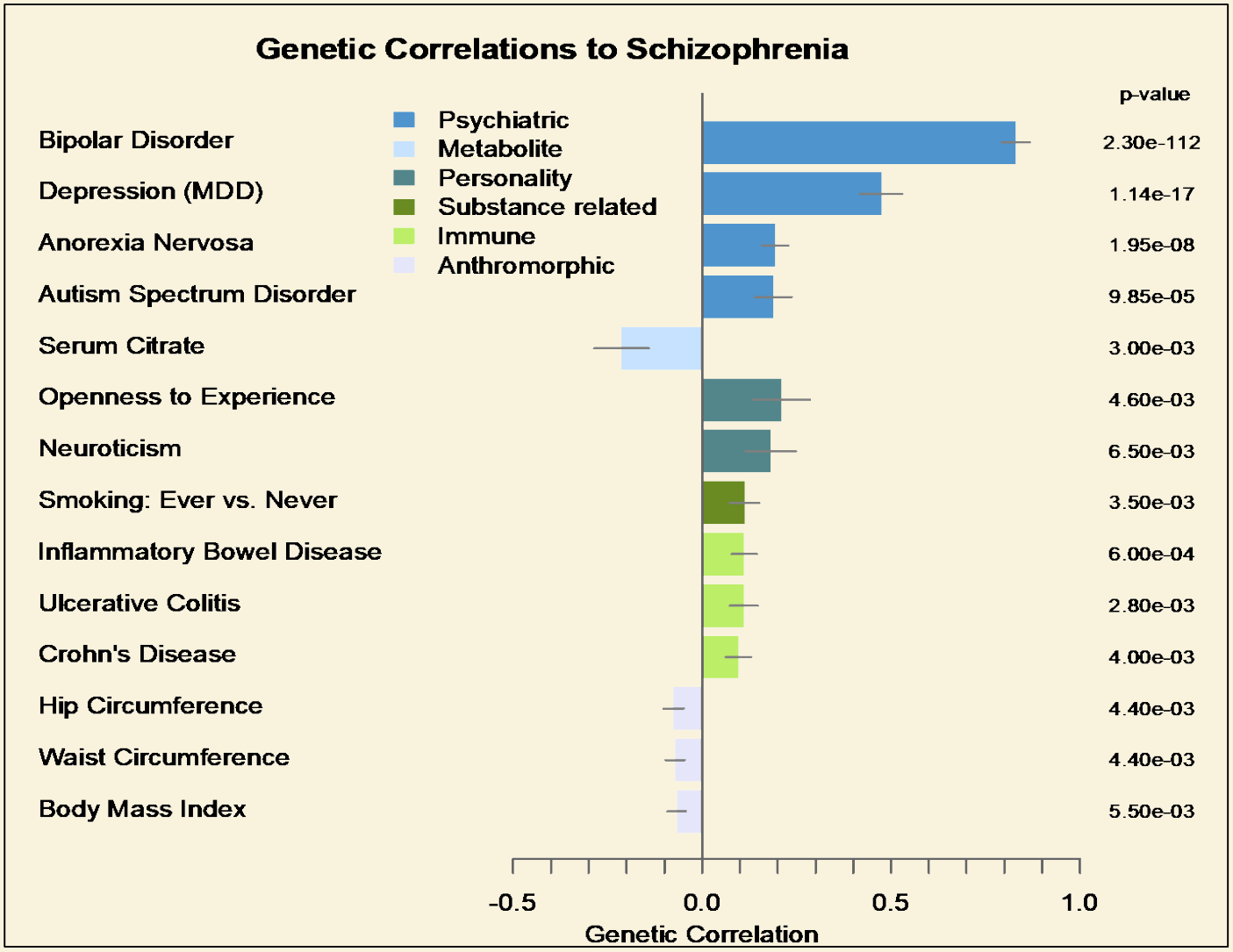
- Blockade of D2R and D3R by APDs blocks DA's inhibition of insulin secretion (increases insulin).

People in Early Psychosis

People in Early Psychosis at Highest Risk for Metabolic Side Effects of Antipsychotics

- Often underweight at baseline
- First exposure to antipsychotic medications
- Age/stage of life
  - May still be growing

Genetic Correlations to Schizophrenia



Duncan et al, Genetic correlation analysis reveals transdiagnostic...Schiz Bull, in press

Guidelines for Monitoring

- Lab Testing
  - Baseline
  - 3 months after initiation
  - Annual

(American Diabetes Association, 2004)

Guidelines for Monitoring (cont.)

- Tests:
  - Lipids
    - Triglycerides
  - Hemoglobin A1c
  - Fasting Glucose

(American Diabetes Association, 2004)

Guidelines for Monitoring (cont.)

- At each visit
  - Vital signs
    - BP
    - Weight
      - Review weight trends with patient
- Initiate and maintain relationship with PCP

(American Diabetes Association, 2004)

Treatment Options

- Lifestyle/Behavioral Management
- Diet
  - microbiome
- Physical Exercise
- Medication
  - Metformin or other metabolic medications
- Integrated healthcare

Substance Abuse and Mental Health Services Administration
SAMHSA

Diet

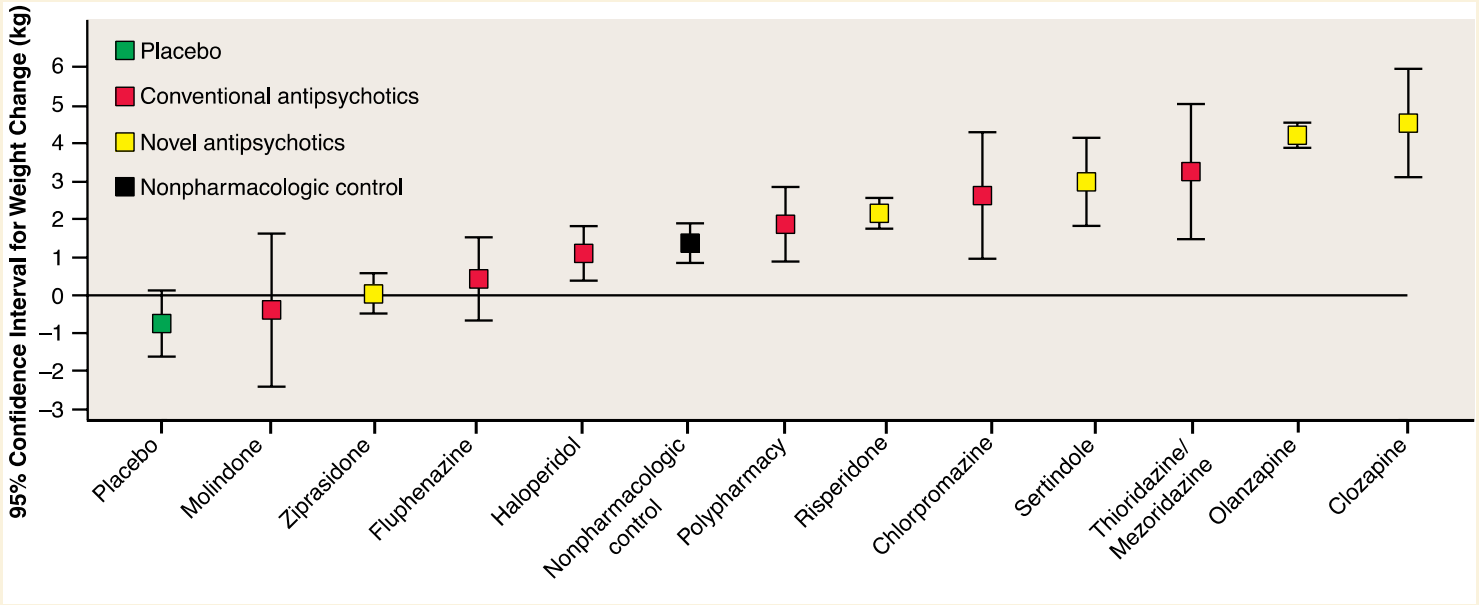
- Modified Mediterranean diet
- Fish & nut oils
- Leafy greens
- Citrus
- Microbiota Accessible Carbos

Medication Options

- Antipsychotic medications
  - Relative risks for weight gain, insulin resistance
- Metabolic medications
  - Appetite suppression
  - Glucose regulation
  - Lipid regulation

Relative Risks for APD on weight

FIGURE 1. 95% Confidence Intervals for Weight Change After 10 Weeks on Standard Drug Doses, Estimated From a Random Effects Model



Allison, 1999

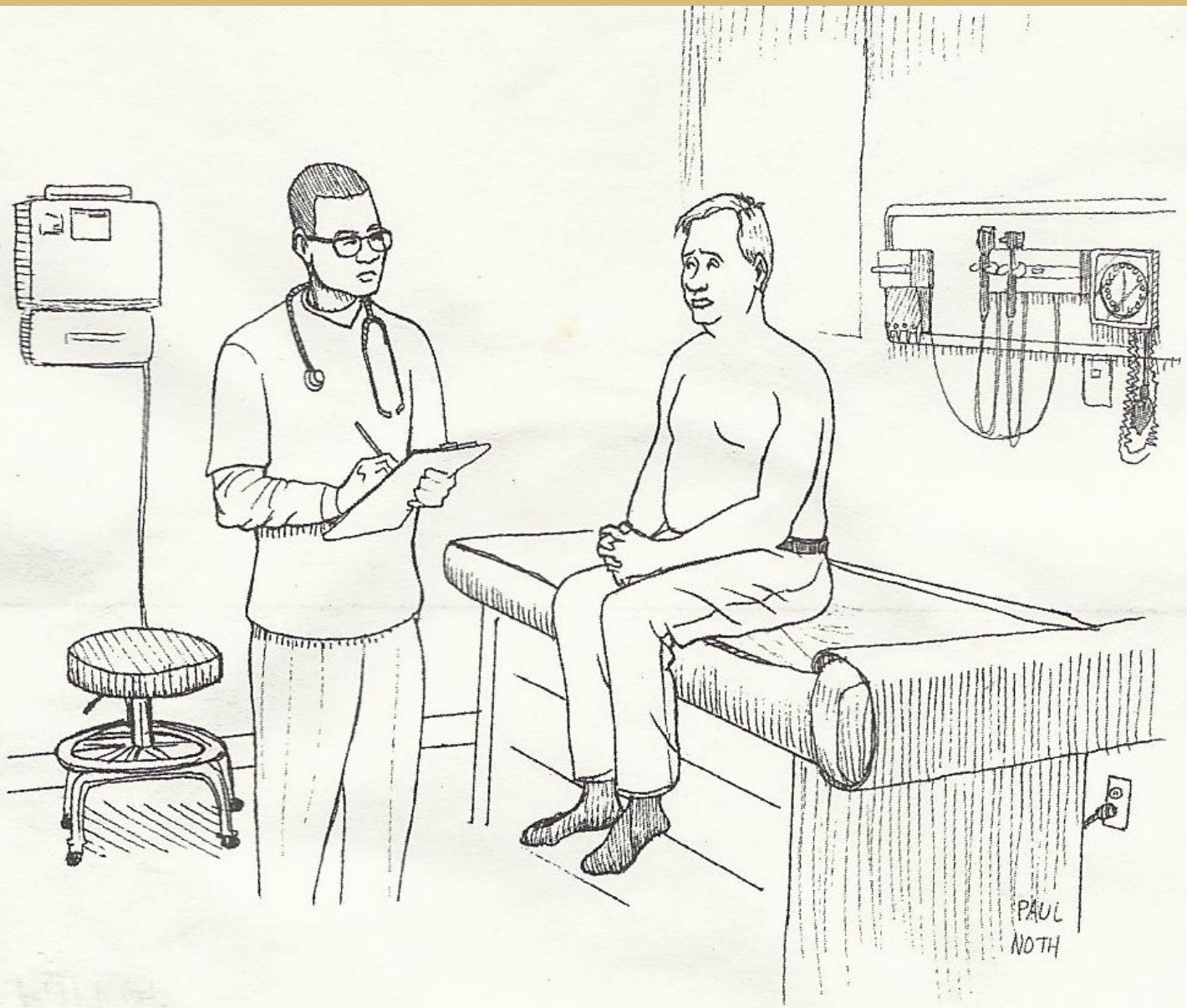
Substance Abuse and Mental Health Services Administration
SAMHSA

Antipsychotic Side Effects

	CPZ	HAL	CLZ	RSP/ PPD	OLZ	QTP	ZPS
↑QTc	++	+	+	+	+	+	+++
Sedation	++++	+	++++	+	+++	+++	+
TD	+++	++++	0	+	+	+	+
Wt gain	++	+	+++	++	+++	++	+/-
Glucose	+++	+	+++	+	+++	++	0

Antipsychotic Side Effects (cont.)

	EPS	PRO	QTc	Sedation	TD	Wt gain	Glu
ARI	+	-	+	+/-	?/++	+	0
ANP	+	0	+	+++	?	+	+
ILO	0	++	++	++	?	++	+
LUR	+	+	0	+/-	+	0	0



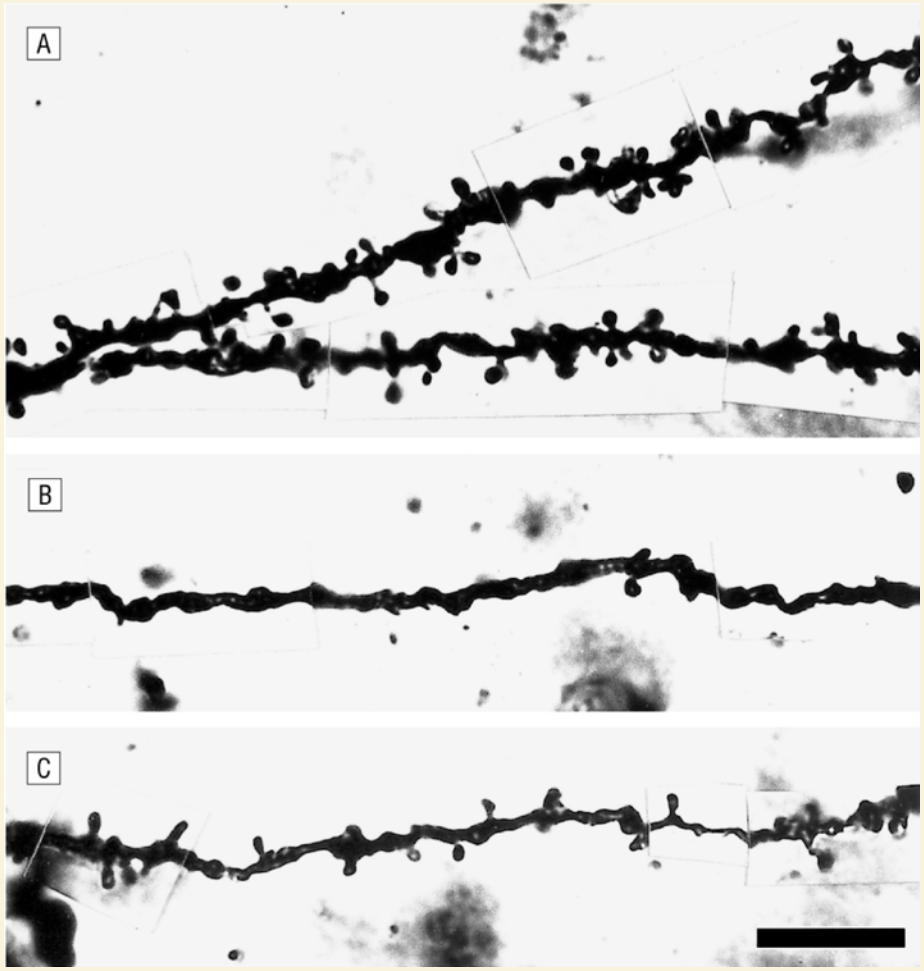
"Will I still be able to not exercise?"

Dendritic Spine Reduction in Schizophrenia

- Dendritic spines: area 46[a]
- Non-schizophrenic individual

- Schizophrenic individual #1

- Schizophrenic individual #2



(Glantz, 2000)

Aerobic Exercise Improves Cognitive Functioning in People with Schizophrenia

- Cognitive deficits pervasive, treatment options limited
- 10 controlled trials, 385 patients
- 20-60” 2-4x/week, 4-24 weeks aerobic or mixed
- Exercise significantly improved global cognition
- Effect size = 0.43
- Greater exercise → greater cognitive gain
- Exercise trainer → greater efficacy
- Working memory: g = 0.39
- Social cognition: g = 0.71
- Attention/vigilance: g = 0.66
- Processing speed, verbal memory, visual memory, problem solving = NS

(Firth et al, 2016)

How Does Exercise Exert Beneficial Effects?

- Neurotransmitter effects
  - Endorphins, endocannabinoids (AEA)[1]
  - Norepinephrine, serotonin, dopamine[2]
- Neurotrophic effects
  - *Brain Derived Neurotrophic Factor* (BDNF)[1]
- Glycogen storage in astrocytes
  - Frontal cortex + hippocampus[3]
- Tighter glucose regulation[4]

(Meeusen, 1995)
(Matsui, 2012)
Jensen, 2011)

Exercise Recommendations for Managing Psychiatric Disorders

- Consider current capacity
- 30 to 60 min, 3 to 7 days/week
- More is better, to a point (3 hours/week)
- Mix aerobic + strength training (150 + 2)
- Intensity: 60% to 85% HRmax (220 - age)
- Have client choose activity
  - Access, cost, familiarity, enjoyment
  - Variation vs. repetition

HRmax, maximum heart rate

Substance Abuse and Mental Health Services Administration SAMHSA

Assessing Response to Exercise

- Adherence to plan
- Changes in core symptoms
- Changes in sleep, appetite, energy, well-being
- Refinement of plan
- Triggers to lapse
- Goals

Take Home - Exercise

- Metabolic risks are greatest at onset of treatment
- Exercise is a potent and important treatment for mind and body
- Discuss diet and exercise at every visit

Take Home

- Links between psychosis and metabolic disease
- Consider metabolic risks of antipsychotic medication choice
  - Shared Decision Making
- Monitor metabolic outcomes closely
- Intervene early and often

Resources

- PEPPNET: https://med.stanford.edu/peppnet.html
- Psychosis Summit: http://www.psychosissummit.com
- On Track NY Medical Manual: http://www.ontrackny.org/portals/1/Files/Resources/MedicalManual_2015.01.21.pdf

Substance Abuse and Mental Health Services Administration SAMHSA

QUESTIONS?