Insulin, Glucose, and the Brain: What does this mean for persons with Schizophrenia

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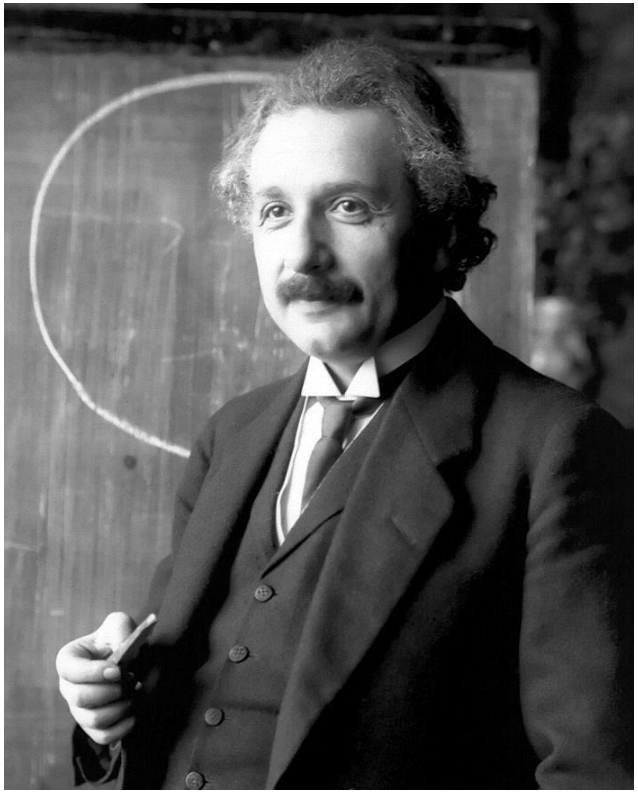
Objectives

1. Review and recognize the historical overlap between metabolic health and schizophrenia pathophysiology

2. Review bidirectional relationships between insulin action in the brain and schizophrenia pathophysiology

3. Recognize how addressing this overlap can lead to better treatment outcomes

The Why

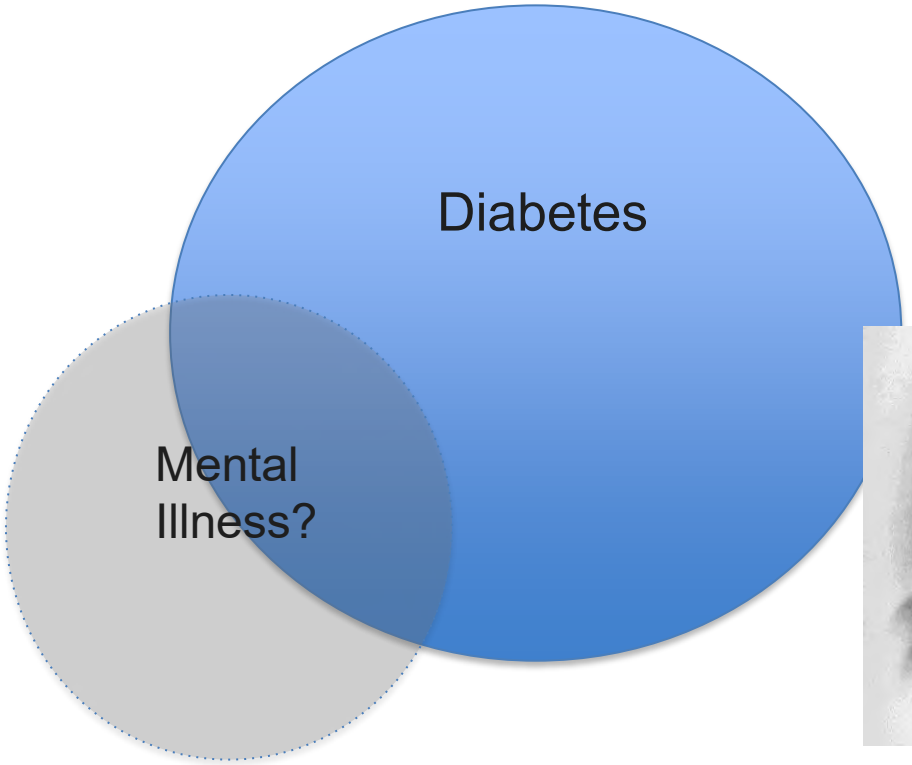


The two decades of life lost

- Patients with Severe Mental Illness have a 20% reduced life-expectancy and a 2x of standardized mortality ratio from CV disease (Hennekens C 2005)

- >50% are obese, ~25% are overweight (Correll 2010)

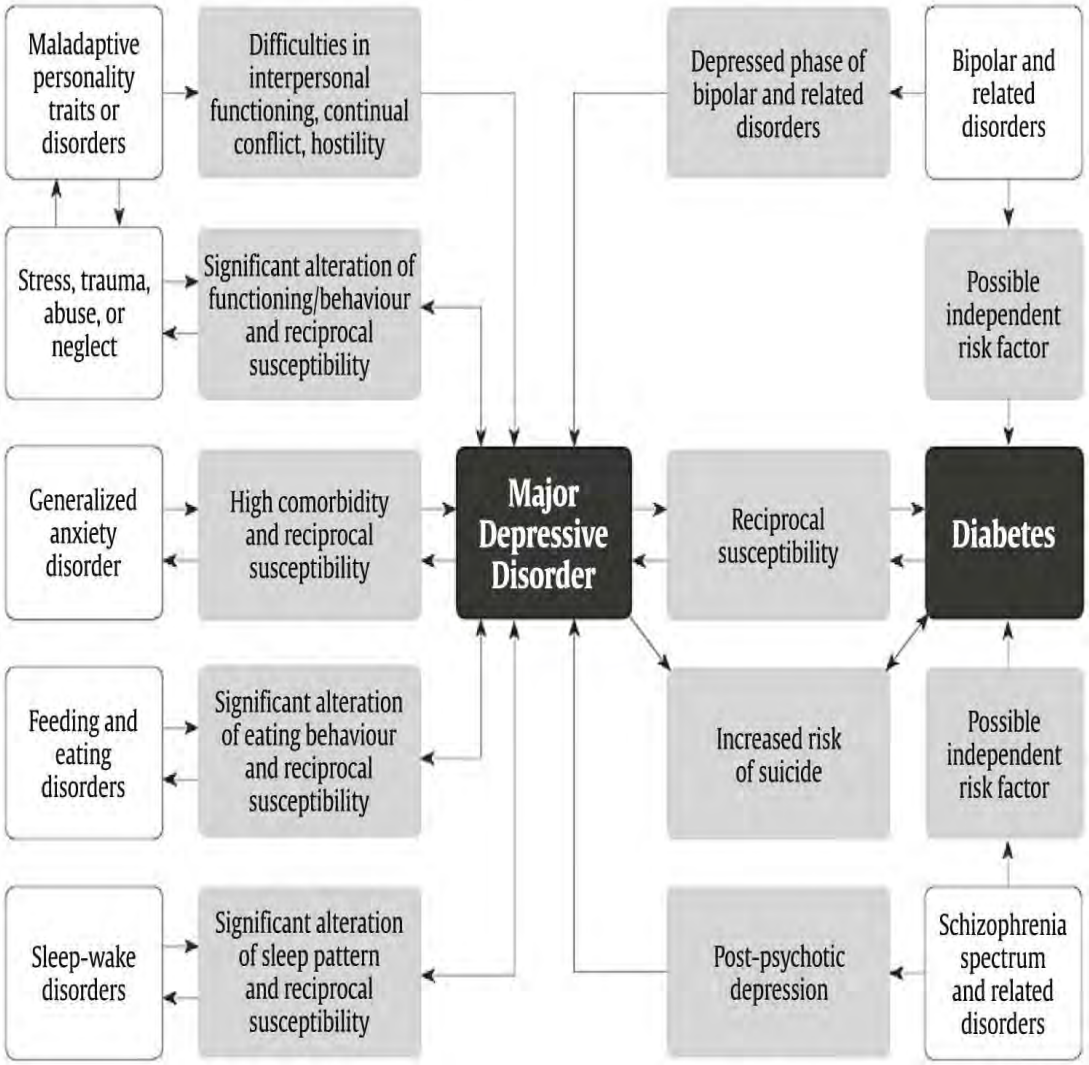
Diabetes and Mental Illness



"diabetes is a consequence of prolonged sorrow"
Thomas Willis, 17th century

"*diabetes is a disease which shows itself in families in which insanity prevails"*
Sir Henry Maudsley, 18th century

Interplay between diabetes and mental illnesses



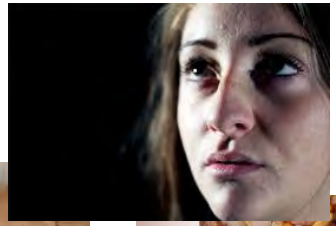
Robinson et al., 2018

Factors associating mental illness with obesity/diabetes

Mental Illness → Diabetes, Obesity, MetS

Illness biology

Genetic links between SCZ and metabolic dysfunction



Life style factors:

Poor self care
High smoking rates
Inactivity
Poor dietary habits

Treatments:

Antipsychotics **
Antidepressants
Mood stabilizers

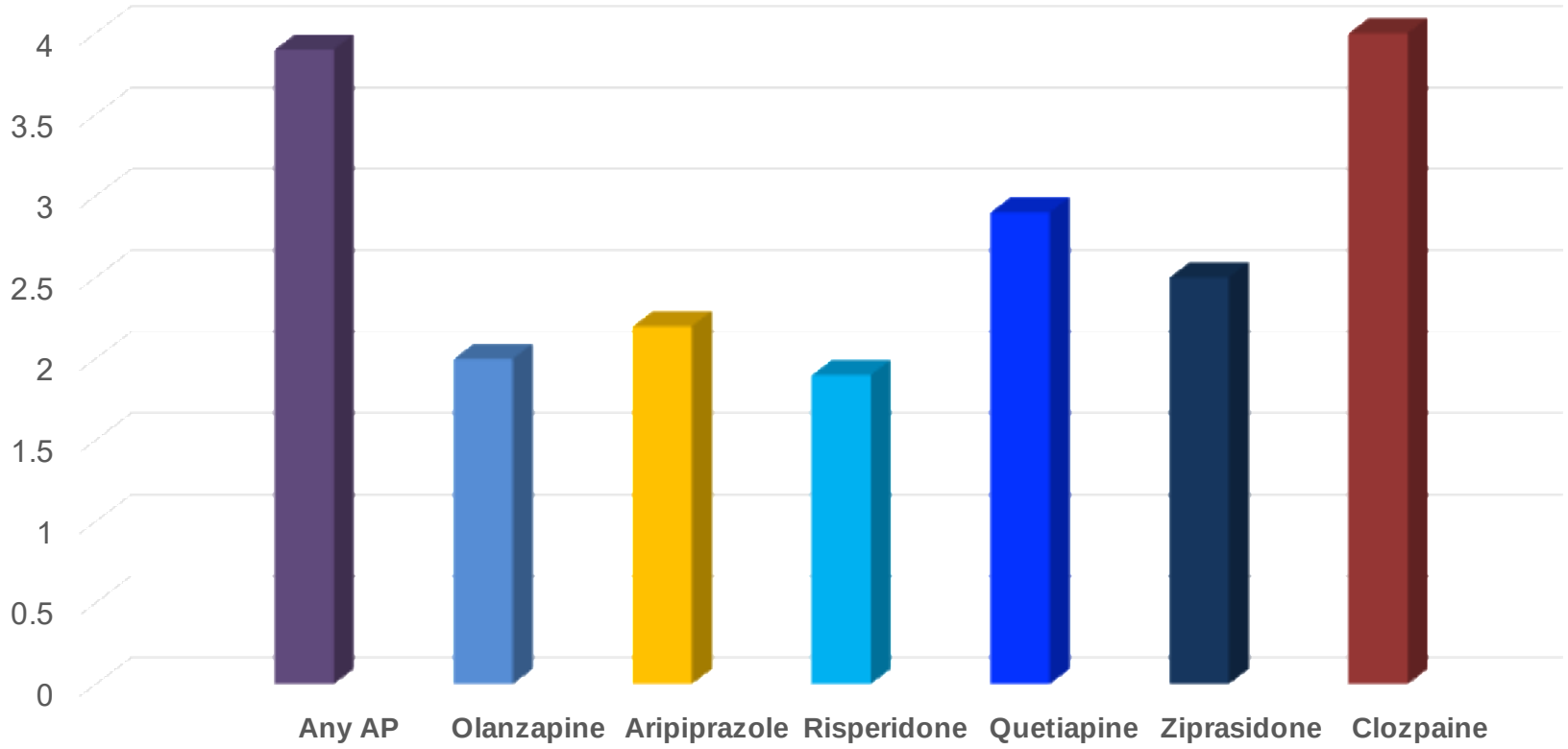
Systems factors

Reduced access to physical care
"Silo working": Poor co-ordination between health providers
Policy ambiguities

Treatment advances in schizophrenia

- "Second generation" antipsychotics (AP): reduced burden of motor-related side-effects as compared to "first generation antipsychotics"
- Significant metabolic side-effects:
  - Weight gain
  - Insulin resistance
  - Atherogenic lipid profile

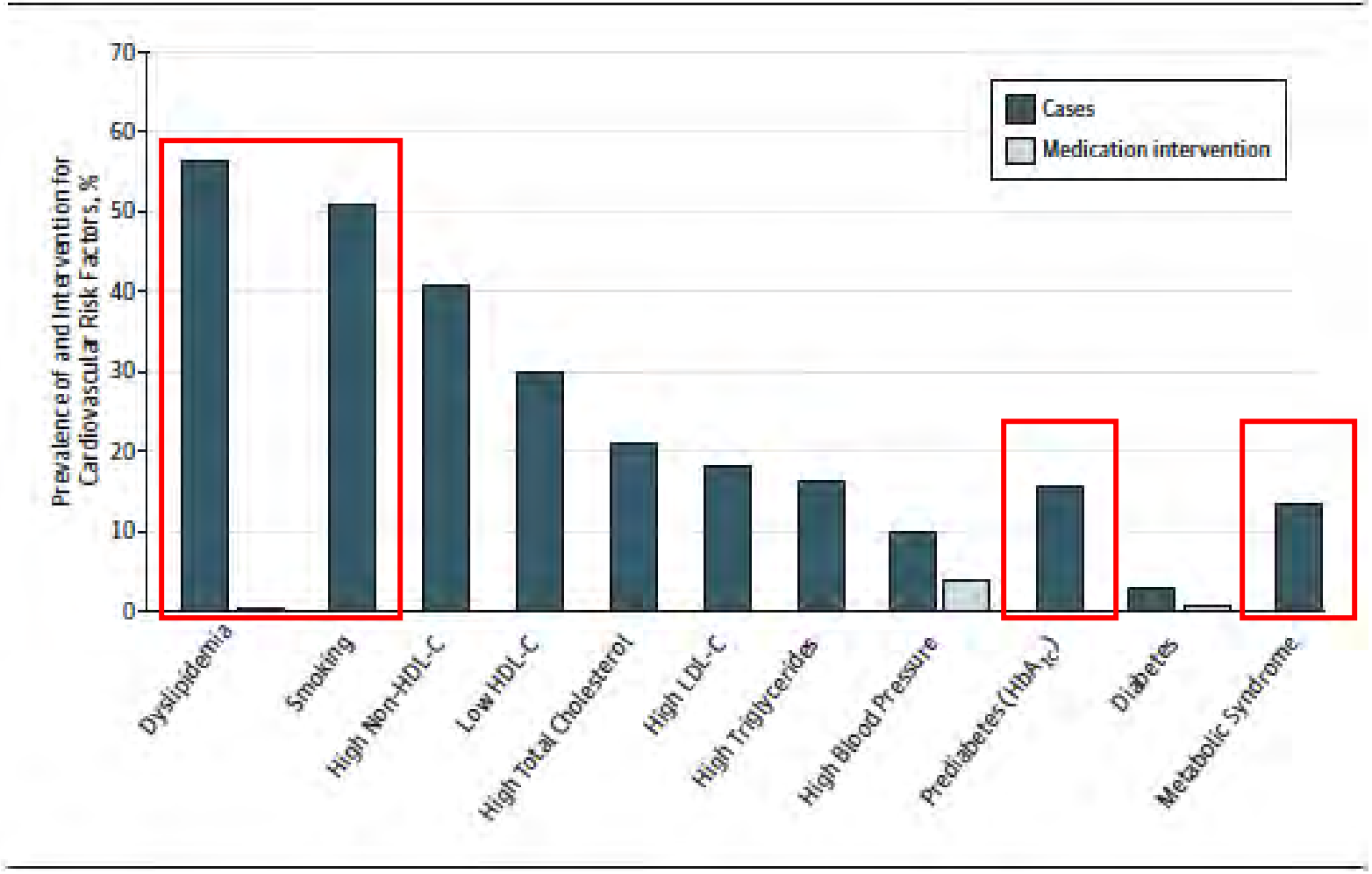
AP-Related Risk of Diabetes in Schizophrenia



Danish population based cohort study (all persons born 1977-2013; n= 2.7 million, 49,582,279 person years); Hazard risk Diabetes after AP vs risk in AP-naïve SCZ

Rajkumar et al, 2017

How well are we dealing with it?



Correll et al, 2014

Implications beyond cardiovascular morbidity & mortality

- Medication compliance
- Self-esteem
- Hospitalization rates
- Quality of life
- Social retreat
- Social care costs

De Hert et al, 2006, 2007; Lyketsos et al, 2002; McCrone et al, 2008

Summary: objective 1

- Cornerstone of our management strategies cause metabolic problems
- Metabolic problems add to the burden of illness
- Newer targets/strategies sorely needed

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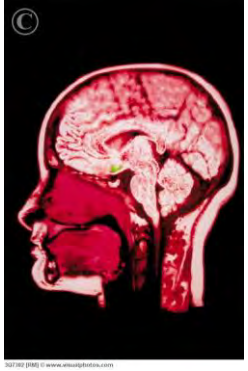
Metabolic abnormalities and the brain



- Smaller hippocampal and cortical volume seen with insulin resistance
- Intranasal insulin does not seem to work in schizophrenia patients
- CNS insulin resistance in schizophrenia
- Do metabolic aberrations (chronic) block improvement?

Hajek 2014; Fan 2011, 2013; Mackenzie et al 2018; Agarwal 2020a, 2020b

Metabolic abnormalities and cognition

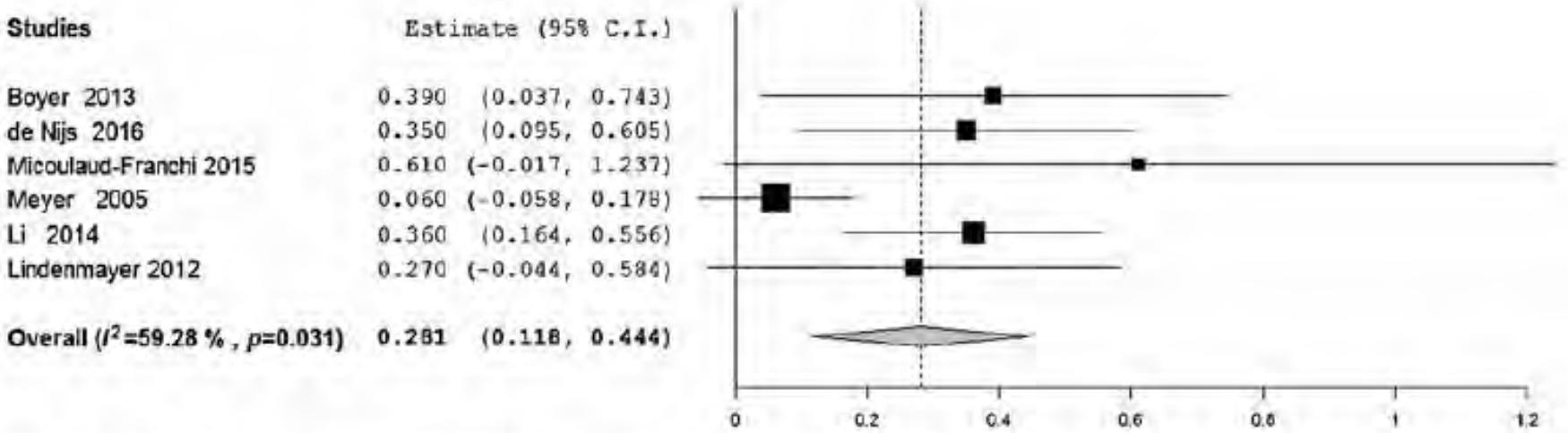


Fig. 2. Forest plot of cognitive differences between schizophrenia patients with and without metabolic syndrome.

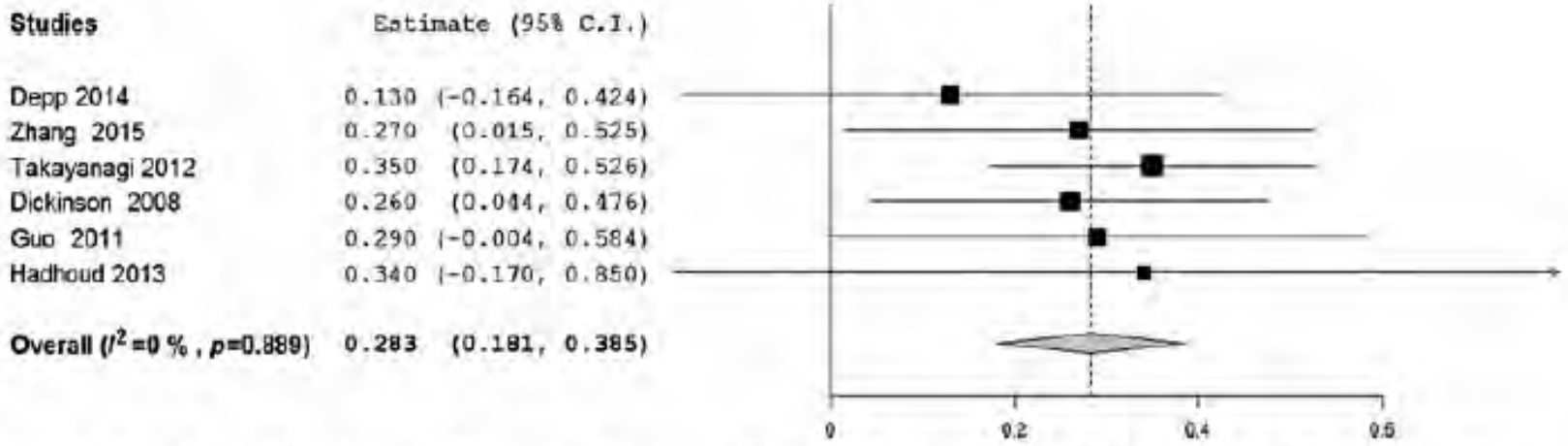


Fig. 3. Forest plot of cognitive differences between schizophrenia patients with and without diabetes mellitus.

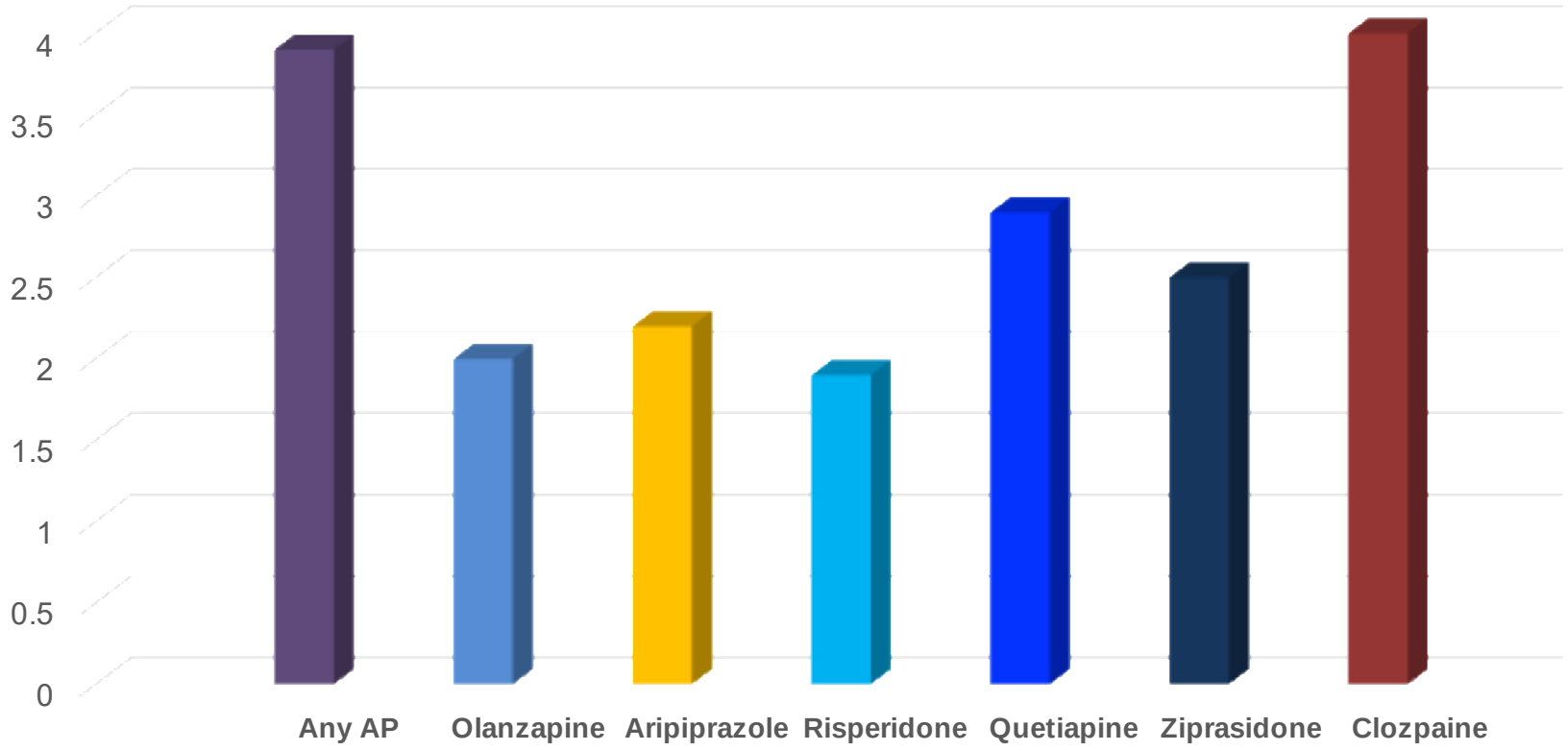
Bora et al, 2017

Poor metabolic health predicts mental illness

- Avon Longitudinal Study of Parents and Children
- 10,463 individuals
- Elevated insulin levels (a marker of insulin resistance) during puberty predict development of psychosis in early adulthood
- Elevated BMI predict development of mood disorders

Perry et al., JAMA Psychiatry 2021

Antipsychotic(AP)-Related Risk of Diabetes in Schizophrenia



- Danish population based cohort study (all persons born 1977-2013; n= 2.7 million, 49 582279 person years); Hazard risk Diabetes after AP vs risk in AP-naïve SCZ

Rajkumar A, *et al.* Am J Psychiatry 2017

Metabolic abnormalities and cognition

CATIE: small effect on cognition of doubtful clinical relevance

Do metabolic aberrations block improvement?

Mackenzie, Kowalchuk, Agarwal et al 2018

Antipsychotic medications & diabetes

Antipsychotics

Weight gain

Direct effects on pathways of glucose metabolism

Type 2 Diabetes

Kowalchuk et al 2018

Effects of antipsychotics on glucose metabolism

RODENT MODEL

Single peripheral doses

- Olanzapine*^
- Clozapine*^
- Risperidone*
- Iloperidone*

Healthy, normal weight rats

Impaired insulin sensitivity* and/or secretion ^

Chintoh et al. 2008; 2009
Hahn et al. 2014
Houseknecht et al. 2008
Martins et al. 2010
Albaugh et al. 2010
Wu C et al. 2014

HUMAN MODEL

Sub-chronic to acute oral dose olanzapine (1 study aripiprazole):

Teff K et al. 2013
Vidarsdottir et al. 2010
Sacher et al. 2008;
Hahn et al. 2014

Early disturbances in parameters of glucose and lipid metabolism

Insulin, the brain, and metabolism

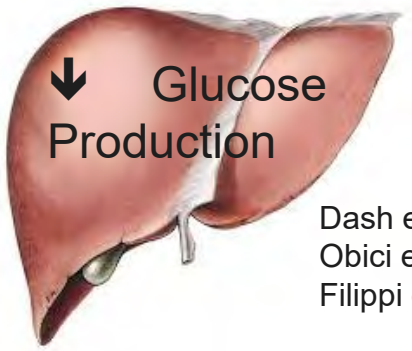
Appetite

Schilling et al, 2014
Hallschmid et al, 2012

Novak et al, 2014
Kullmann et al, 2016

Cognition

Insulin



Dash et al, 2015
Obici et al, 2002
Filippi et al, 2012

Psychopathology and motivation

Venkatasubramanian et al, 2007
Zhang et al, 2015
Caravaggio et al, 2015

Summary: objective 2

- Two-way relationship between metabolic and psychiatric disorders
- Use metabolic liability as an investigative opportunity: a testable hypothesis
- Discover newer targets
- Focus on both central and peripheral players

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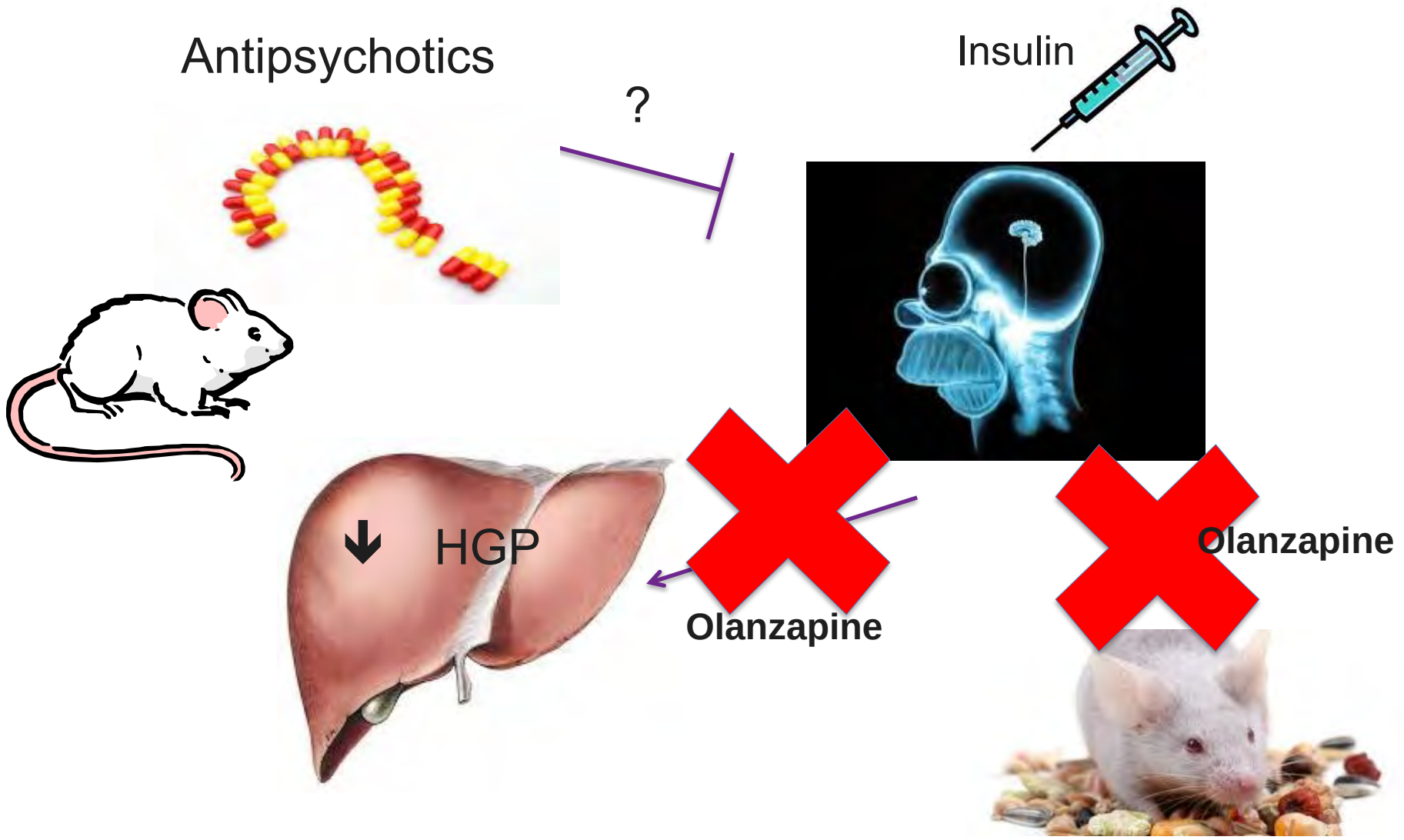
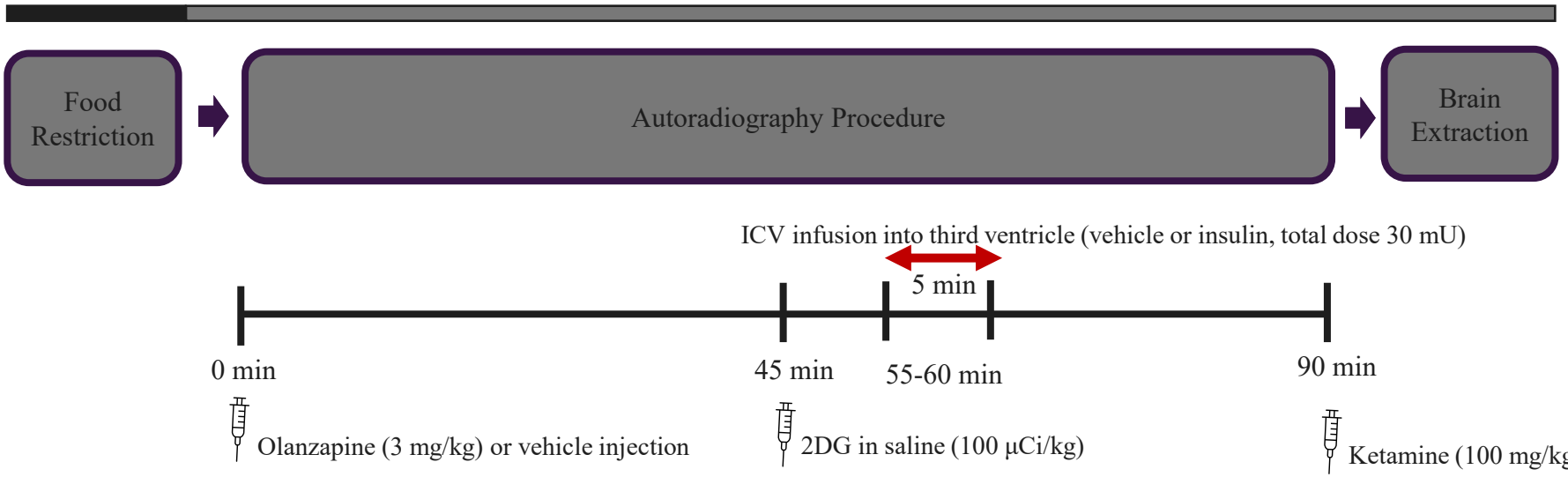
Antipsychotics and brain insulin resistance?



Kowalchuk et al, 2017; Castellani et al, 2018

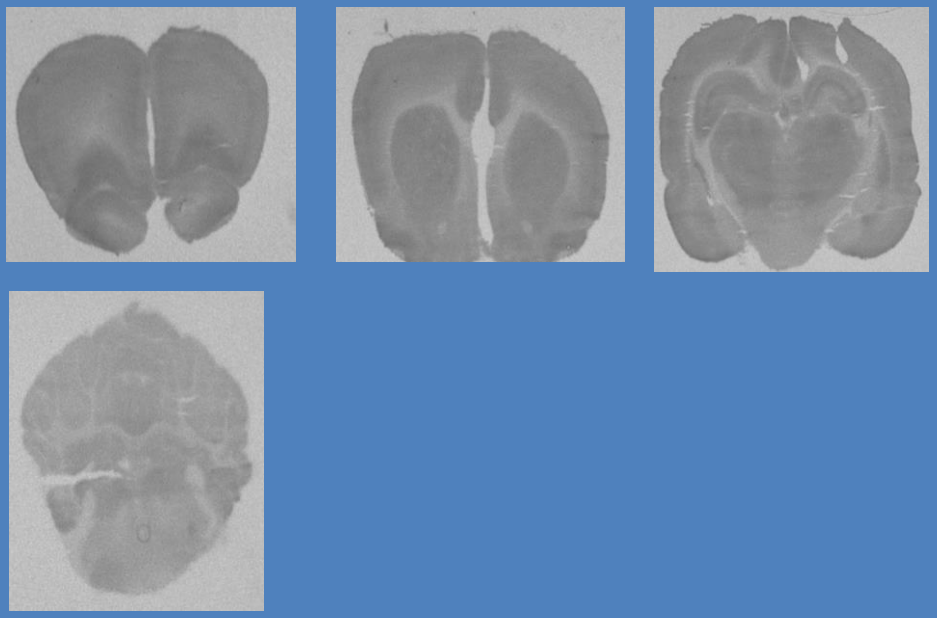
Rodent 2DG Protocol



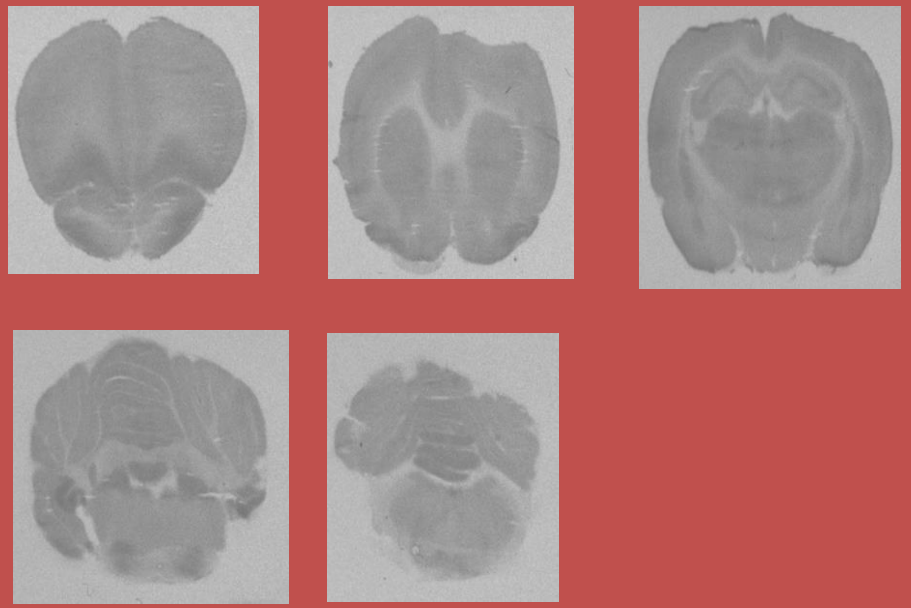
Experimental Groups (ICV-Peripheral)

VEH-VEH	VEH-OLA
INS-VEH	INS-OLA

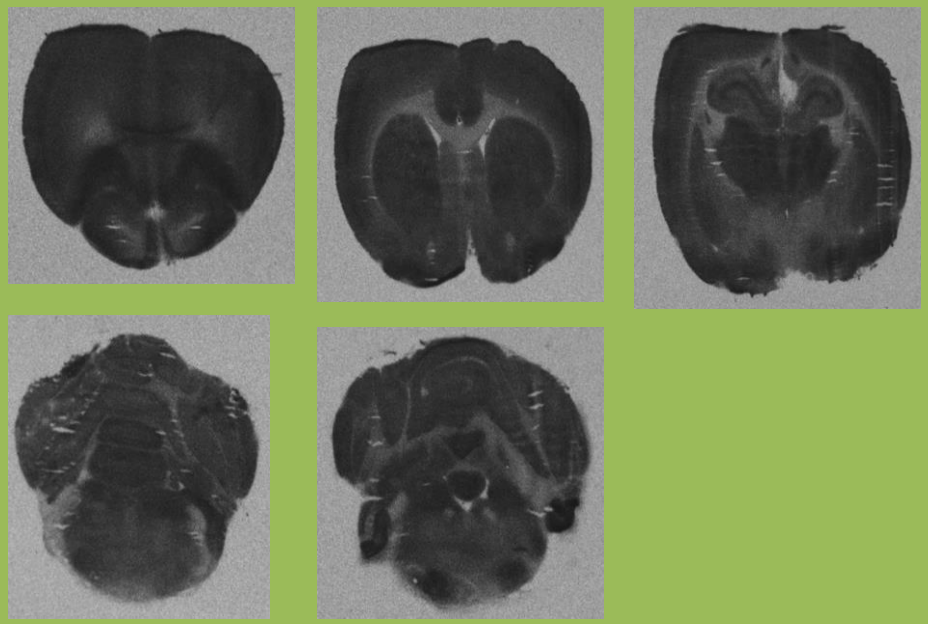
VEH-VEH



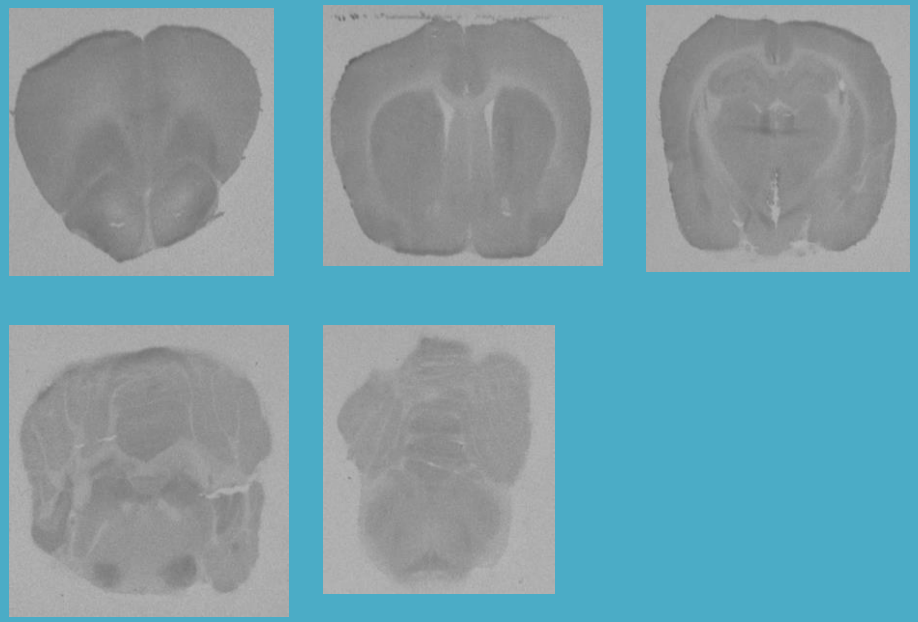
VEH-OLA



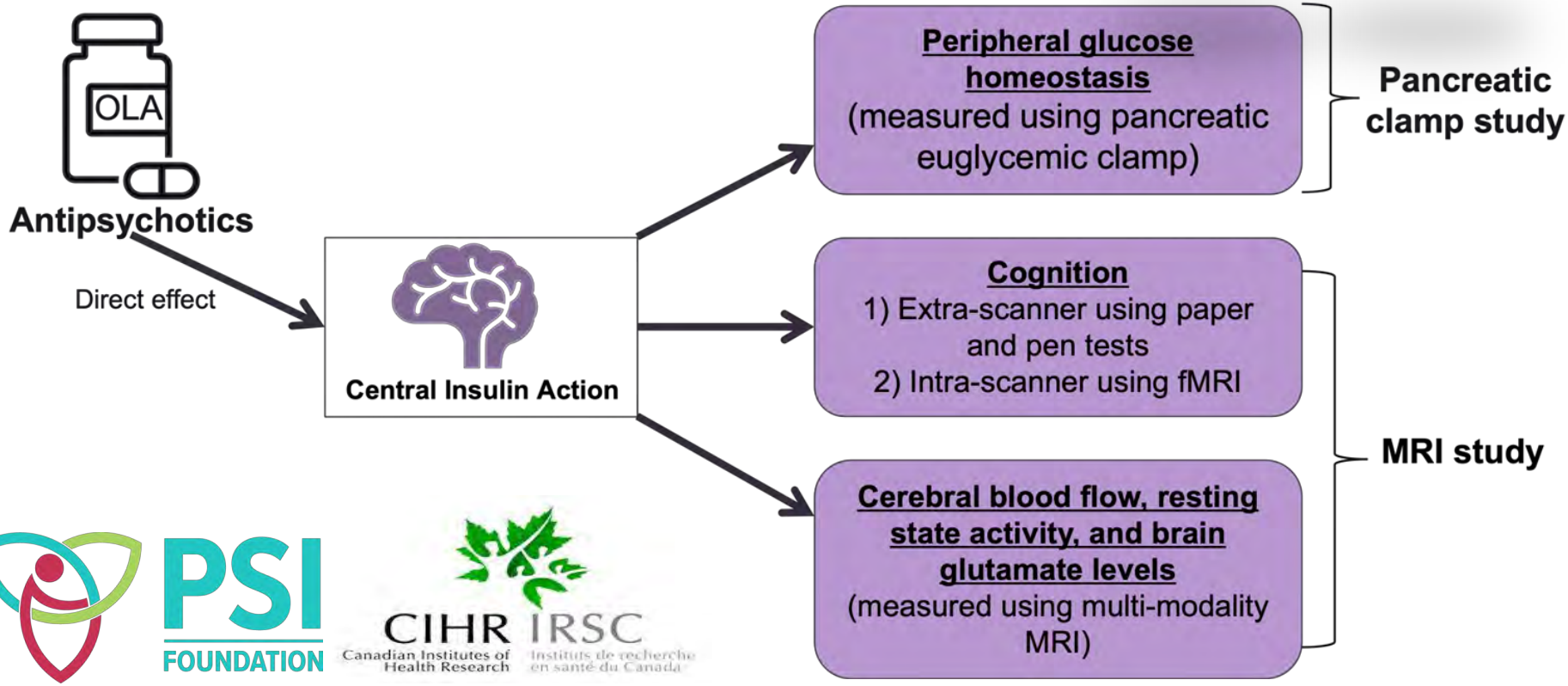
INS-VEH



INS-OLA



Do antipsychotics block brain insulin action in humans?



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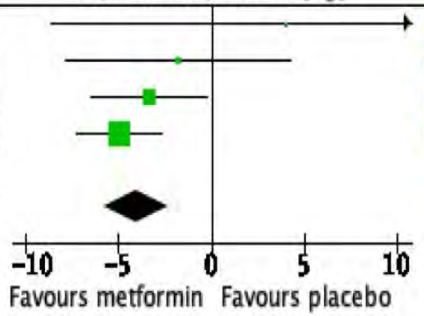
CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

Prevention of weight gain in SMI

Study or Subgroup	Metformin Mean [kg]	Metformin SD [kg]	Metformin Total	Placebo Mean [kg]	Placebo SD [kg]	Placebo Total	Weight	Mean Difference IV, Random, 95% CI [kg]
Arman 2008a	36.03	12.81	16	32.03	22.45	16	1.9%	4.00 [-8.67, 16.67]
Baptista 2006	63.8	10.2	19	65.6	8.5	18	8.4%	-1.80 [-7.84, 4.24]
Rado 2016a	2.54	2.35	12	5.88	5.23	13	31.0%	-3.34 [-6.46, -0.20]
Wu 2008a	1.9	2.72	18	6.87	4.23	19	58.7%	-4.97 [-7.25, -2.69]
Total (95% CI)			65			66	100.0%	-4.03 [-5.78, -2.28]

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.91$, df = 3 ($P = 0.41$); $I^2 = 0\%$

Test for overall effect: $Z = 4.52$ ($P < 0.00001$)

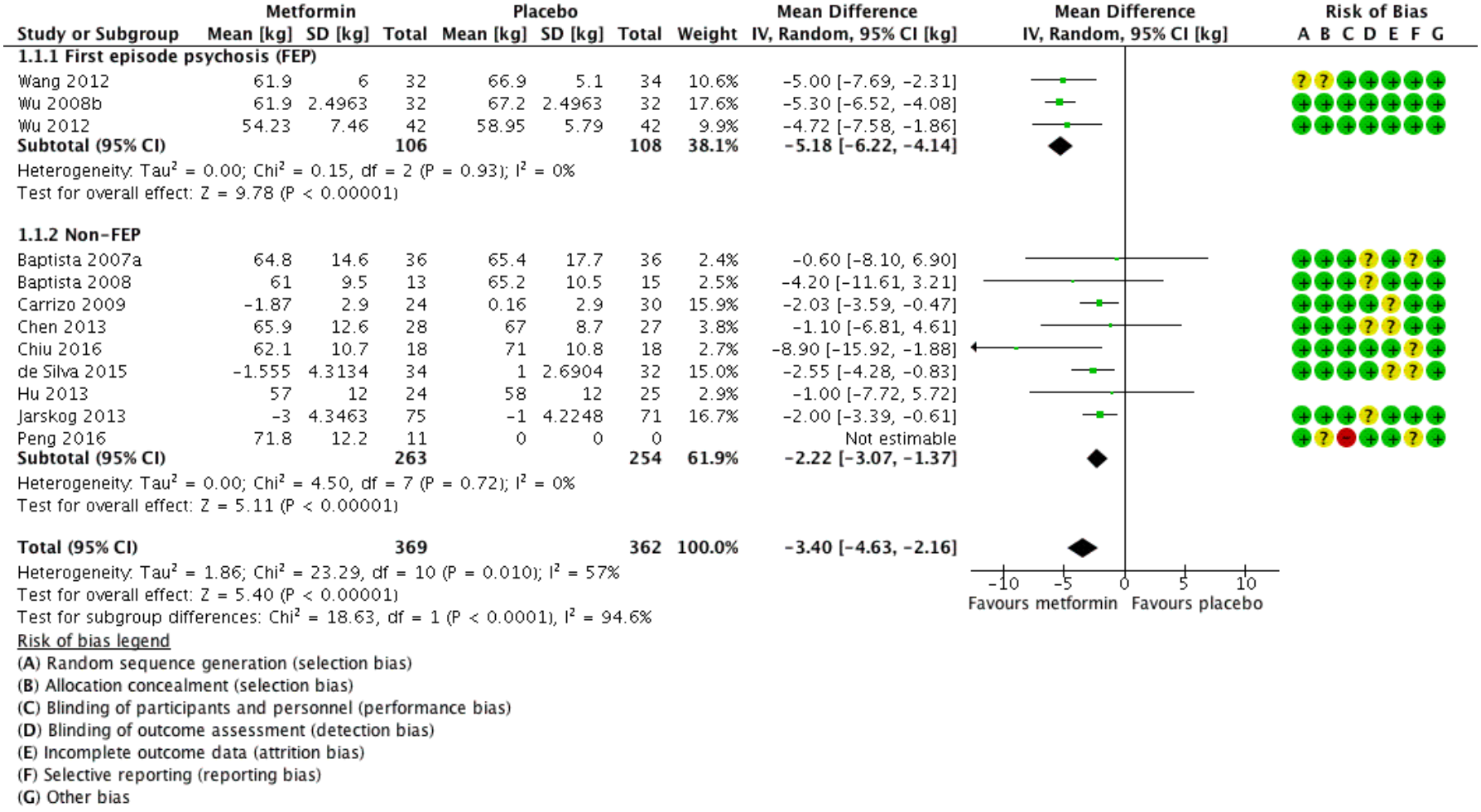


Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Agarwal et al, 2022

Metformin for treatment of weight gain



Study or Subgroup	Metformin Mean [kg]	Metformin SD [kg]	Metformin Total	Placebo Mean [kg]	Placebo SD [kg]	Placebo Total	Weight	Mean Difference IV, Random, 95% CI [kg]	Risk of Bias A B C D E F G
1.1.1 First episode psychosis (FEP)									
Wang 2012	61.9	6	32	66.9	5.1	34	10.6%	-5.00 [-7.69, -2.31]	? ? + + + + +
Wu 2008b	61.9	2.4963	32	67.2	2.4963	32	17.6%	-5.30 [-6.52, -4.08]	+ + + + + + +
Wu 2012	54.23	7.46	42	58.95	5.79	42	9.9%	-4.72 [-7.58, -1.86]	+ + + + + + +
Subtotal (95% CI)			**106**			**108**	**38.1%**	**-5.18 [-6.22, -4.14]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 2 (P = 0.93); I² = 0%									
Test for overall effect: Z = 9.78 (P < 0.00001)									
1.1.2 Non-FEP									
Baptista 2007a	64.8	14.6	36	65.4	17.7	36	2.4%	-0.60 [-8.10, 6.90]	+ + + ? + ? +
Baptista 2008	61	9.5	13	65.2	10.5	15	2.5%	-4.20 [-11.61, 3.21]	+ + + ? + + +
Carrizo 2009	-1.87	2.9	24	0.16	2.9	30	15.9%	-2.03 [-3.59, -0.47]	+ + + + ? + +
Chen 2013	65.9	12.6	28	67	8.7	27	3.8%	-1.10 [-6.81, 4.61]	+ + + ? ? + +
Chiu 2016	62.1	10.7	18	71	10.8	18	2.7%	-8.90 [-15.92, -1.88]	+ + + + + ? +
de Silva 2015	-1.555	4.3134	34	1	2.6904	32	15.0%	-2.55 [-4.28, -0.83]	+ + + + ? ? +
Hu 2013	57	12	24	58	12	25	2.9%	-1.00 [-7.72, 5.72]	
Jarskog 2013	-3	4.3463	75	-1	4.2248	71	16.7%	-2.00 [-3.39, -0.61]	+ + + ? + + +
Peng 2016	71.8	12.2	11	0	0	0		Not estimable	+ ? - + + ? +
Subtotal (95% CI)			**263**			**254**	**61.9%**	**-2.22 [-3.07, -1.37]**	
Heterogeneity: Tau² = 0.00; Chi² = 4.50, df = 7 (P = 0.72); I² = 0%									
Test for overall effect: Z = 5.11 (P < 0.00001)									
Total (95% CI)			**369**			**362**	**100.0%**	**-3.40 [-4.63, -2.16]**	
Heterogeneity: Tau² = 1.86; Chi² = 23.29, df = 10 (P = 0.010); I² = 57%									
Test for overall effect: Z = 5.40 (P < 0.00001)									
Test for subgroup differences: Chi² = 18.63, df = 1 (P < 0.0001), I² = 94.6%									

Mean Difference IV, Random, 95% CI [kg]

-10 -5 0 5 10

Favours metformin Favours placebo

Risk of bias legend

(A) Random sequence generation (selection bias)
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(E) Incomplete outcome data (attrition bias)
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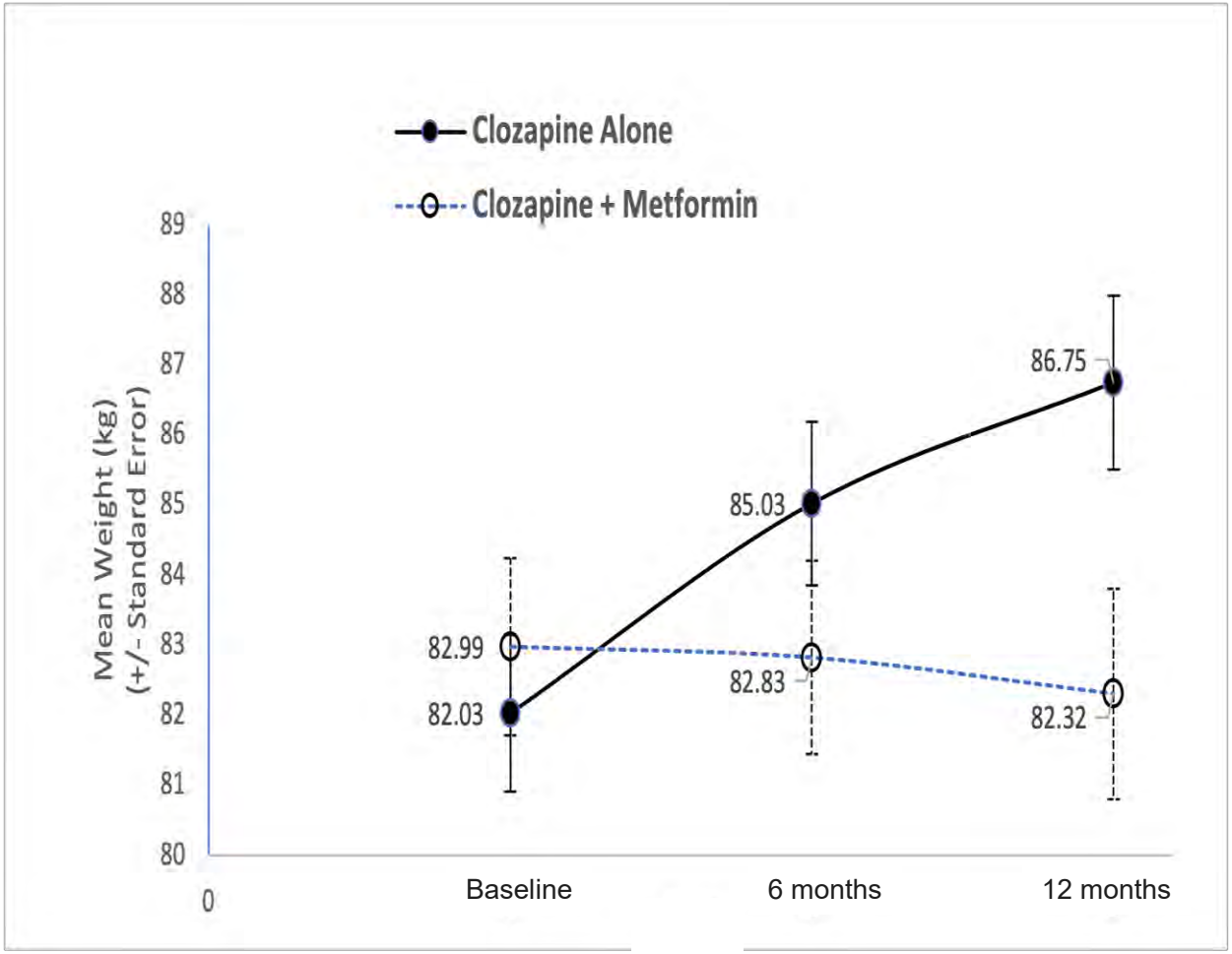
(G) Other bias

Agarwal *et al*. under review

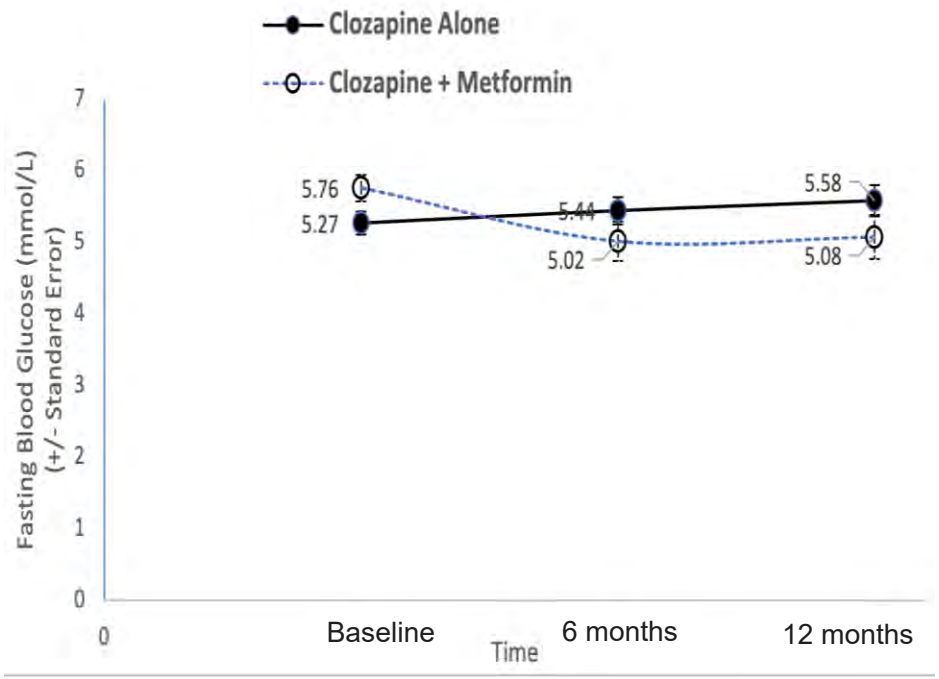
Can metformin prevent clozapine-induced weight gain?



Stogios et al, 2022

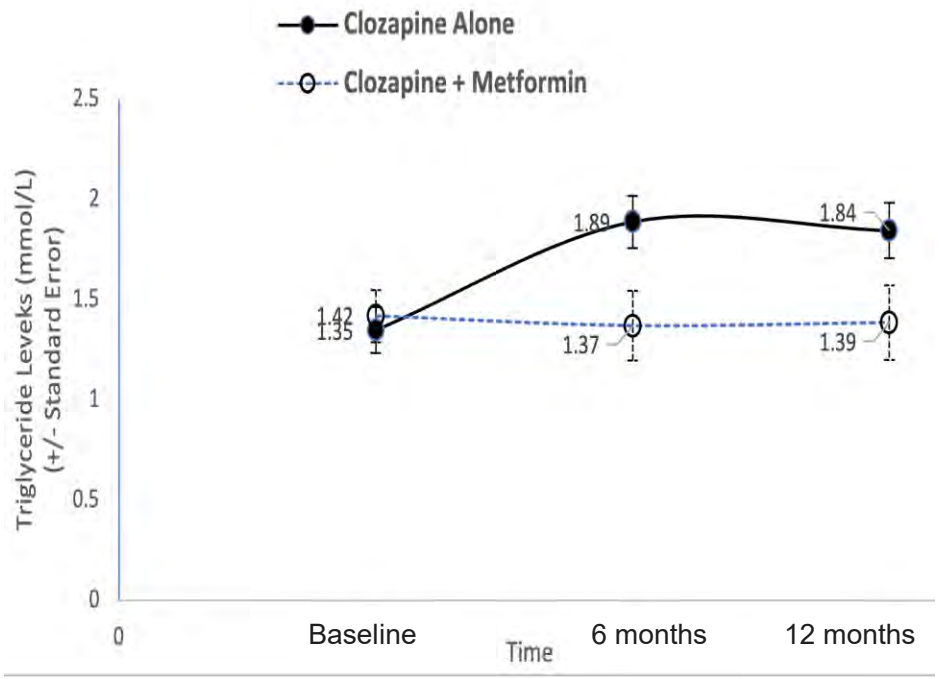
Effect on other metabolic parameters

a) Fasting Blood Glucose (mmol/L)



Controlling for: age, sex, smoking status, baseline glucose

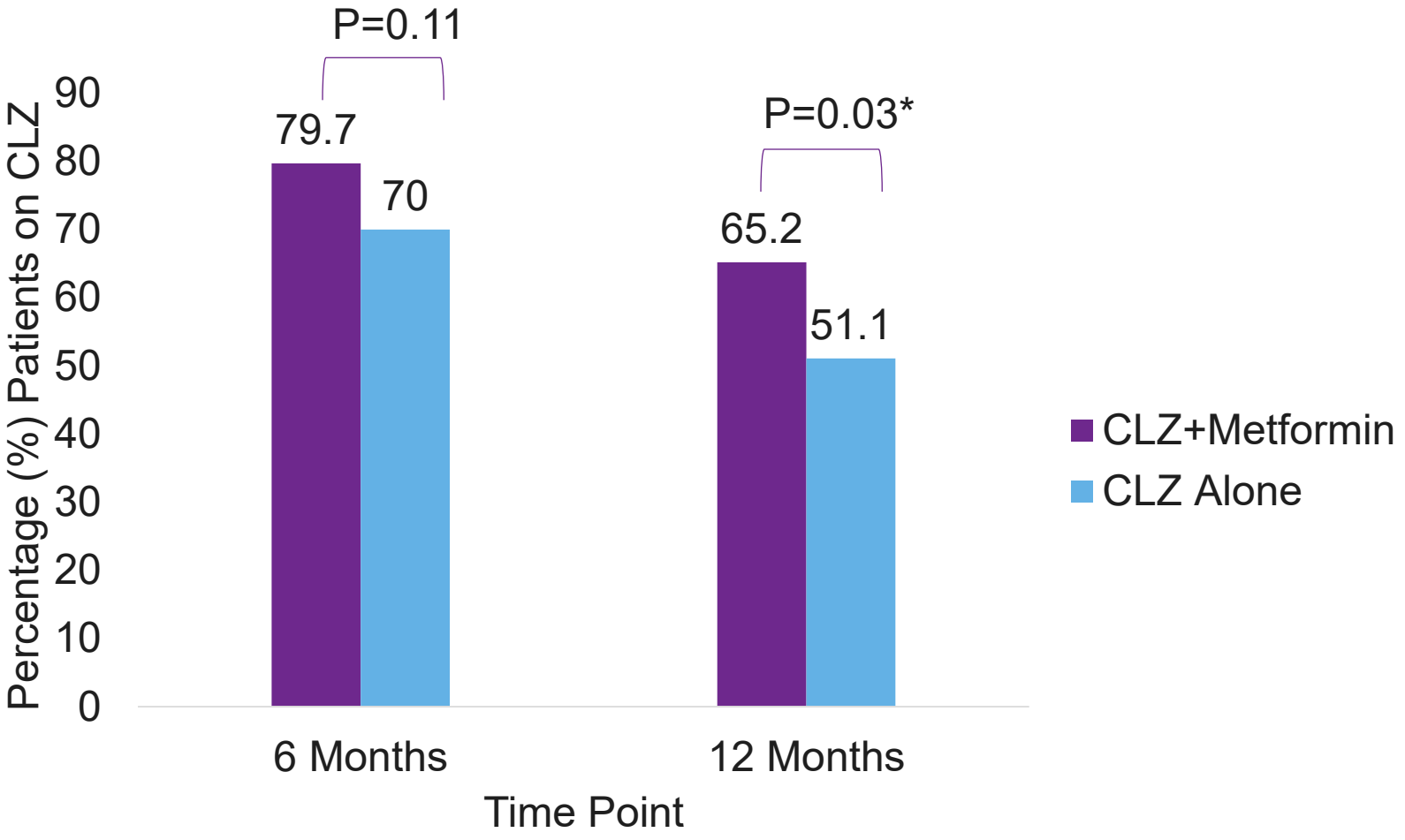
b) Triglycerides (mmol/L)



Controlling for: age, sex, smoking status, baseline triglyceride

Stogios et al, 2022

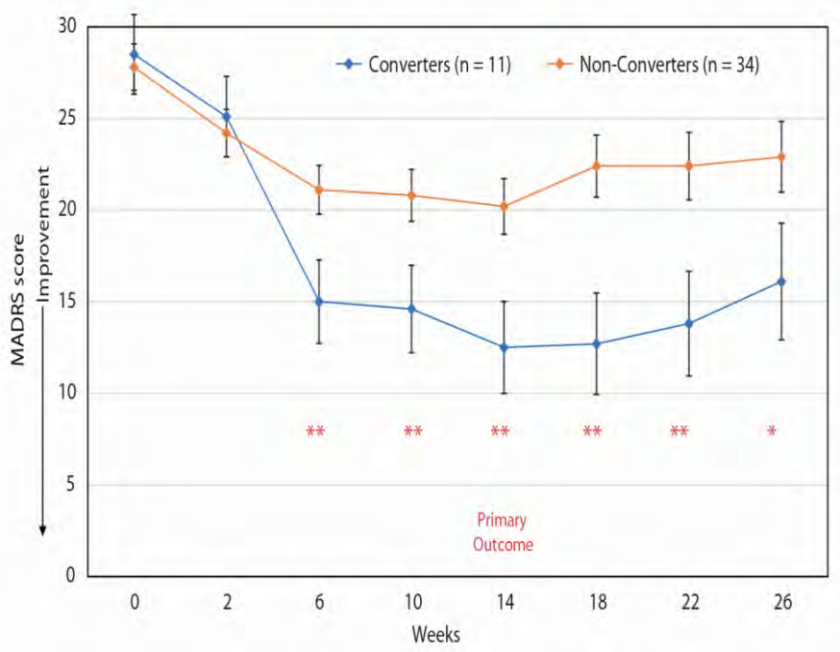
Effect of metformin on clozapine continuation rates

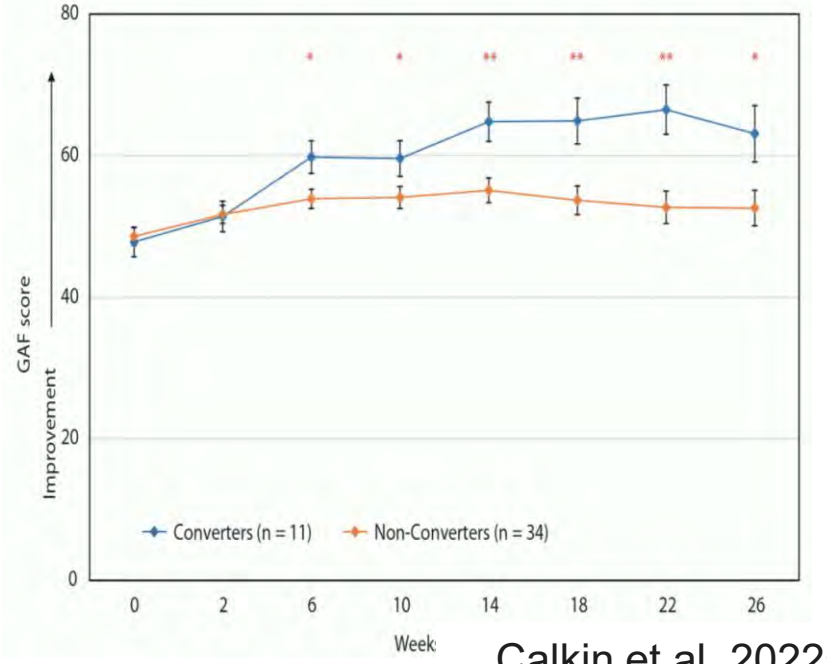


Stogios et al, 2022

Depression-Insulin resistance-Metformin

- 45 insulin resistant (HOMA-IR≥1.8) patients with bipolar depression randomized to metformin (minimum 1500 mg/day) or placebo
- Outcomes of interest: MADRS and GAF
- 10/20 reverted in metformin group; 1/25 reverted in placebo group
- Converters experienced symptom, social, and occupational improvement



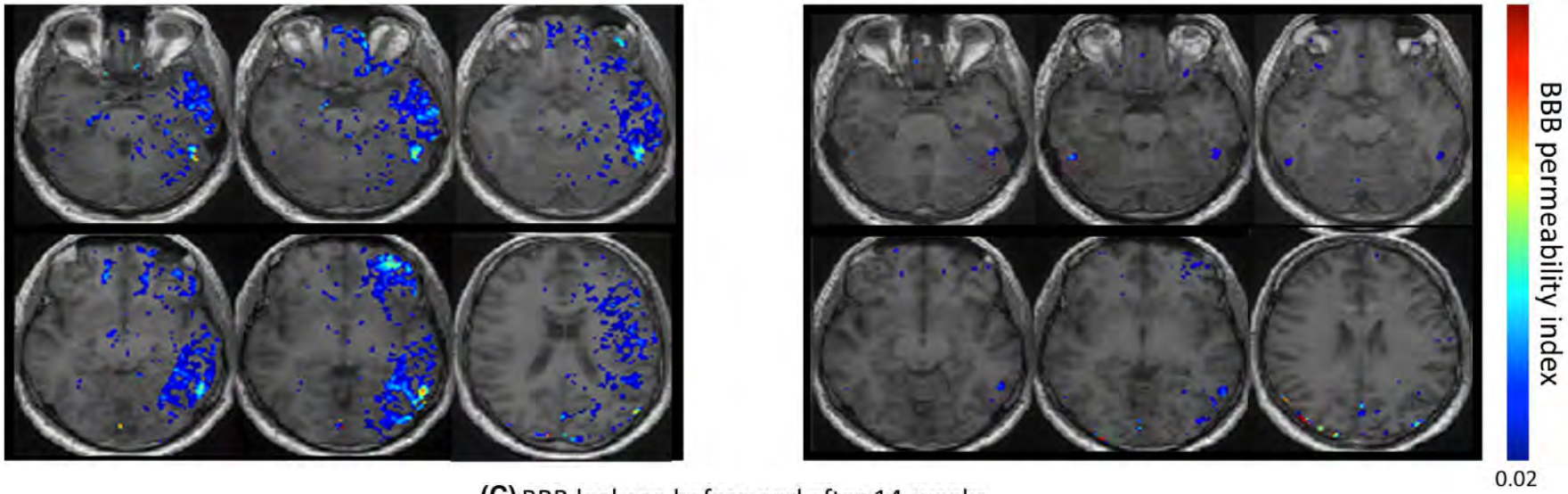


Calkin et al, 2022a

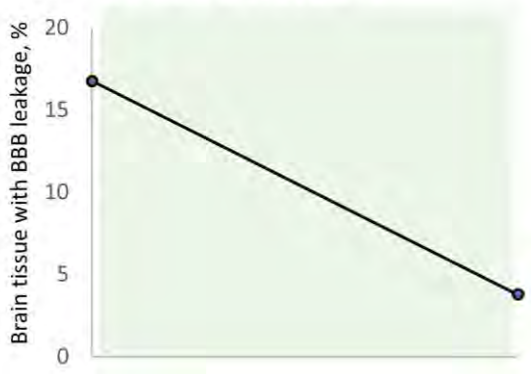
Depression-BBB leakage-metformin

(A) BBB leakage prior to treatment with metformin

(B) BBB repair after 14-weeks treatment with metformin



(C) BBB leakage before and after 14-weeks treatment with metformin



Calkin et al, 2022b

Summary: objective 3

- The brain was long considered an insulin-insensitive organ
- Central regulation of glucose metabolism poorly understood
- Better metabolic health can improve mental health
- Early intervention is likely to be more helpful

Conclusions

High rates of medical co-morbidity, including diabetes, obesity

Low rates of monitoring & treatment

Need to do more

- Early intervention
- New medications/strategies

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Femin Prasad
Emily Smith
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