Insulin Resistance and Major Depression: Pathways to Precision Medicine

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August 20th, 2022

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# Major Depressive Disorder: Challenges of Effective Treatment

- 20.6% of US adults experience a depressive disorder in their lifetime (Hasin)

- 50 - 60% of people with major depressive disorder do not respond adequately to antidepressant medication (Rush).

- Major Depressive Disorder (MDD) is complex in its biology, its genetics is challenging to define, and its symptoms vary by person. There may be depression subtypes.

- One subtype of depression might be the insulin-resistant subtype.

Share of the population with depression, 2016
Prevalence of depressive disorders in a given population. This is measured as the age-standardized prevalence, which assumes a constant age structure to compare between countries and through time. Figures attempt to provide a true estimate (going beyond reported diagnosis) of depression prevalence based on medical, epidemiological data, surveys and meta-regression modelling.

Our World in Data

No data 2%   2.5%   3%   3.5%   4%   4.5%   5%   5.5%   6%   >6.5%
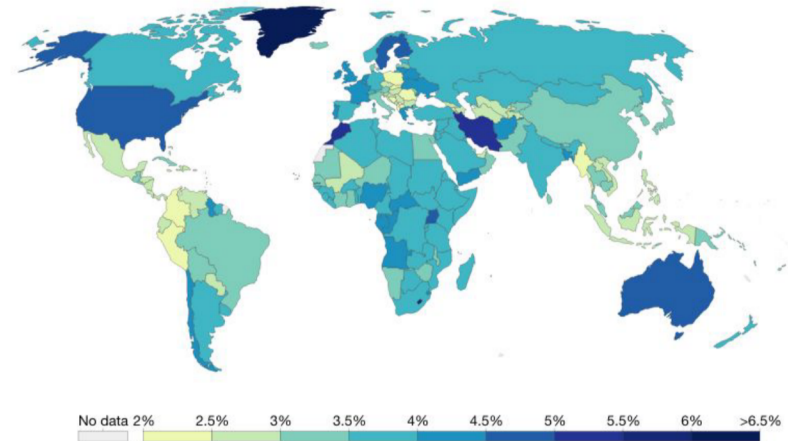
2016 Map of Depression Prevalence

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Insulin Resistance

- Insulin resistance is a physiological state where insulin receptors have a diminished response to the presence of insulin. It can lead to type 2 diabetes.

- Insulin resistance can lead to the inability to utilize glucose in muscle, adipose, and several other tissues.

- Insulin resistance has been associated with several somatic disorders, including cardiovascular disease, chronic kidney disease, Alzheimer's disease, and major depressive disorder.

Insulin Protein

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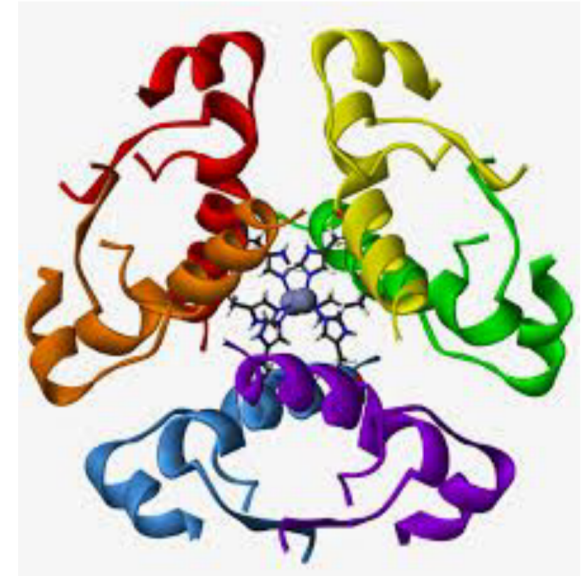
# Is There an Insulin Resistant Subtype of Depression?

"His insulin just kicked in!"

© 2008 Diabetes Health

Study 1: Insulin Resistance and Depression Characteristics

- The Netherlands Study of Depression and Anxiety (NESDA) describes the course and consequences of depressive disorders among adults 18 - 65.

- We measured insulin resistance in 1,269 adults with current depression, remitted depression, and non-depressed controls in the Netherlands Study of Depression and Anxiety.

- We measured insulin resistance using three metrics: 1) triglyceride high-density lipoprotein (HDL) ratio; 2) fasting plasma glucose (FPG) (mmol/L), and waist circumference (cm).

- We measured depression symptoms using the Inventory of Depression Symptomatology. Scores range from 0 to 87, with a higher score indicating greater depression severity.

NESDA
Netherlands Study of Depression and Anxiety

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Insulin Resistance was Positively Associated with Current Major Depressive Episode and Severity of Depression Symptoms
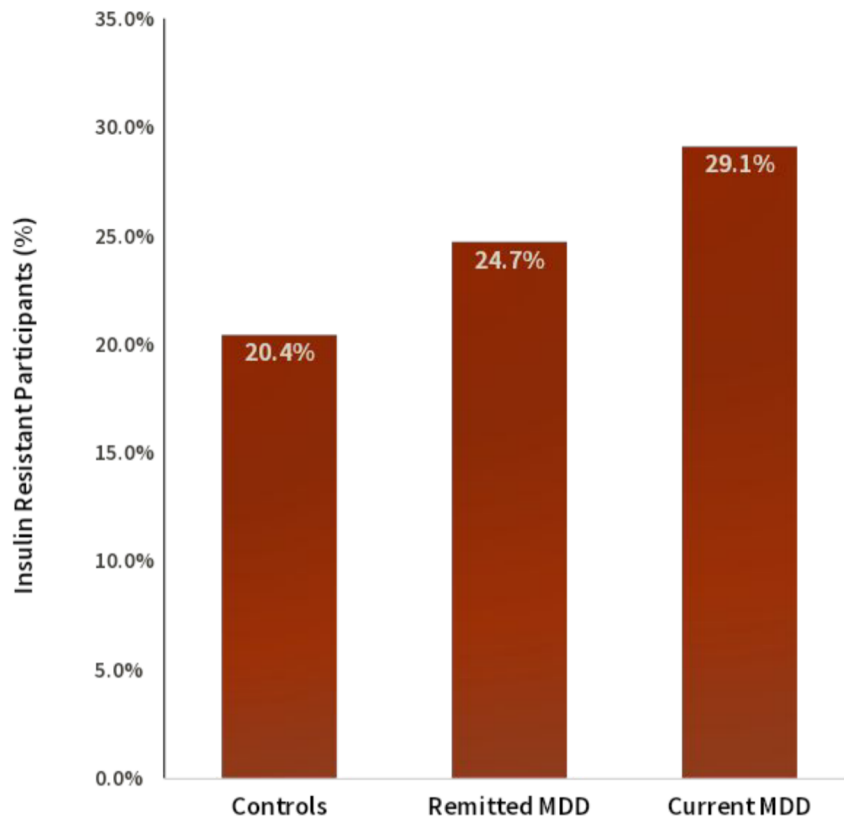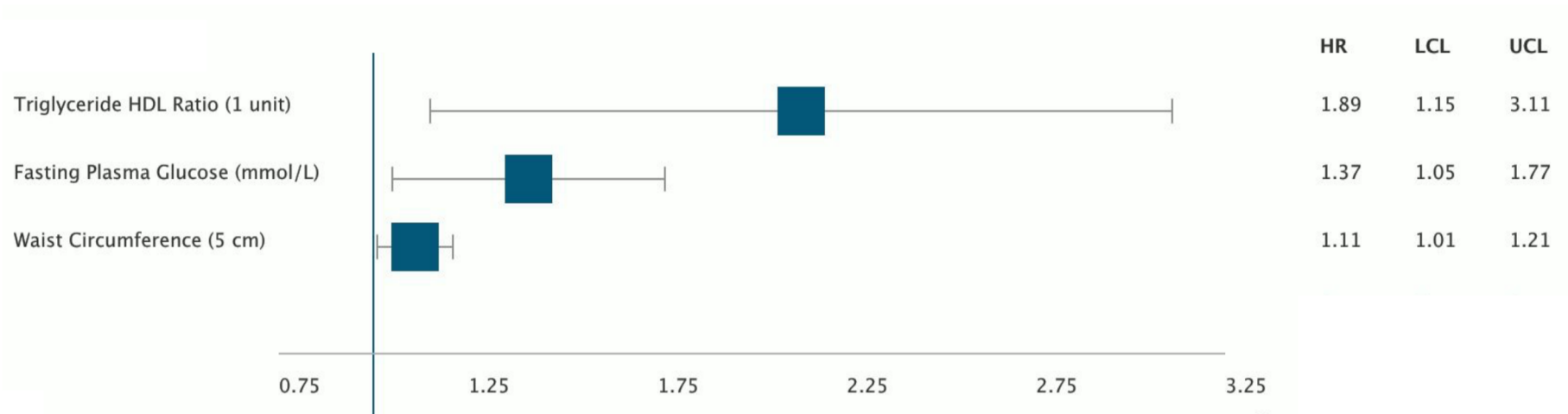

- Insulin resistance was positively associated with having current major depressive disorder compared to being a control participant: Odds Ratio = 1.5; 95% Confidence Interval = 1.1 to 2.1

- Insulin resistance was **not** associated with remitted major depressive disorder: Odds Ratio = 1.1; 95% Confidence Interval = 0.8 to 1.6

- Insulin resistance was positively associated with depression severity: For every unit increase in insulin resistance, depression severity score was 2.4 points higher; 95% Confidence Interval: 1.1 to 3.8.

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Is There an Insulin Resistant Subtype of Depression?

Study 2: Insulin Resistance as Risk Factor for New Cases of Depression

- We measured insulin resistance in 601 adults without a lifetime history of depression in The Netherlands Study of Depression and Anxiety.
- Participants were given a psychiatric interview at each study visit: 0, 2, 4, 6, and 9 years after enrollment.
- Insulin resistance was measured using fasting blood glucose, waist circumference, and triglyceride-HDL ratio.

	HR	LCL	UCL
Triglyceride HDL Ratio (1 unit)	1.89	1.15	3.11
Fasting Plasma Glucose (mmol/L)	1.37	1.05	1.77
Waist Circumference (5 cm)	1.11	1.01	1.21

# Summary: What We Know So Far

Depression Status

- Insulin resistance was associated with an episode of major depressive disorder status.

Depression Characteristics

- Insulin Resistance was positively associated with depression severity and chronicity among participants in an episode of major depressive disorder.

Risk for Developing Depression

- Triglyceride-HDL, waist circumference, and fasting plasma glucose each ratio positively predicted new cases of depression in a 9-year follow-up period among disorder-free individuals.
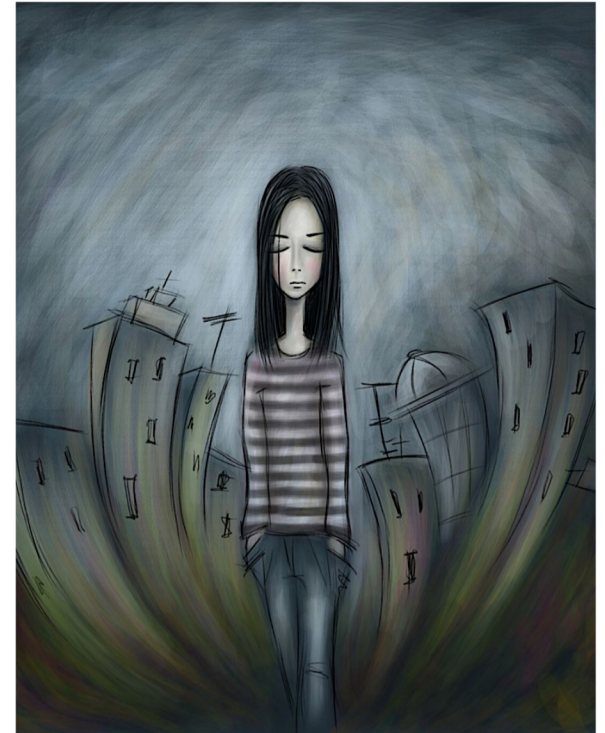
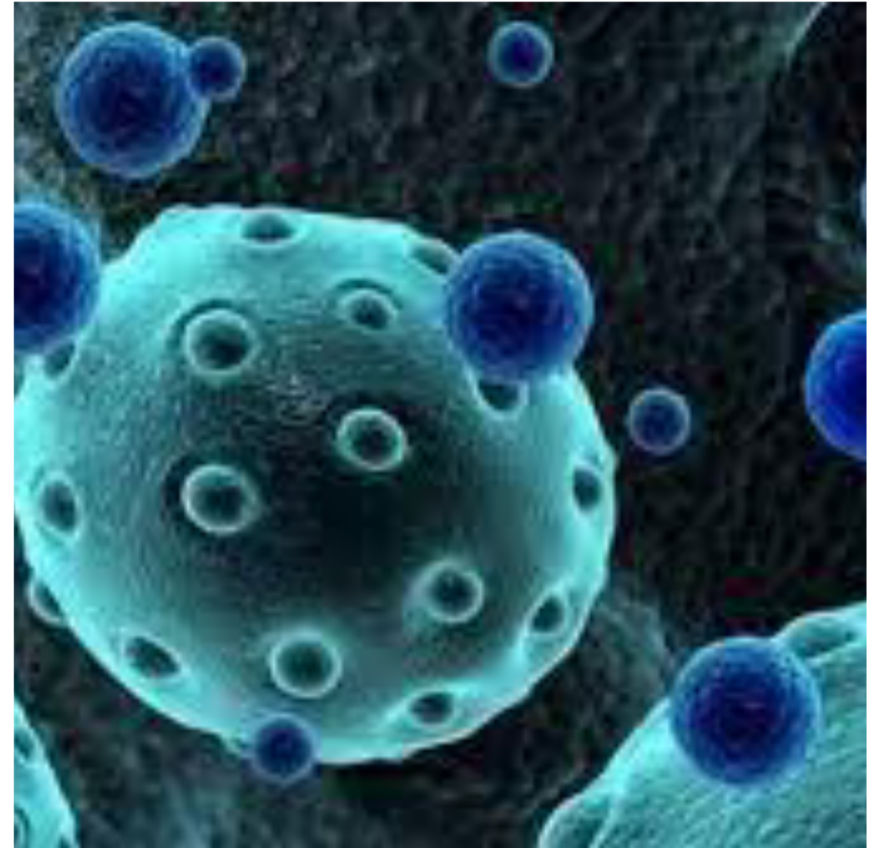# Next Steps in Precision Medicine for Depression: Measuring Insulin Resistance in the Brain

What is the difference between central and peripheral insulin resistance?

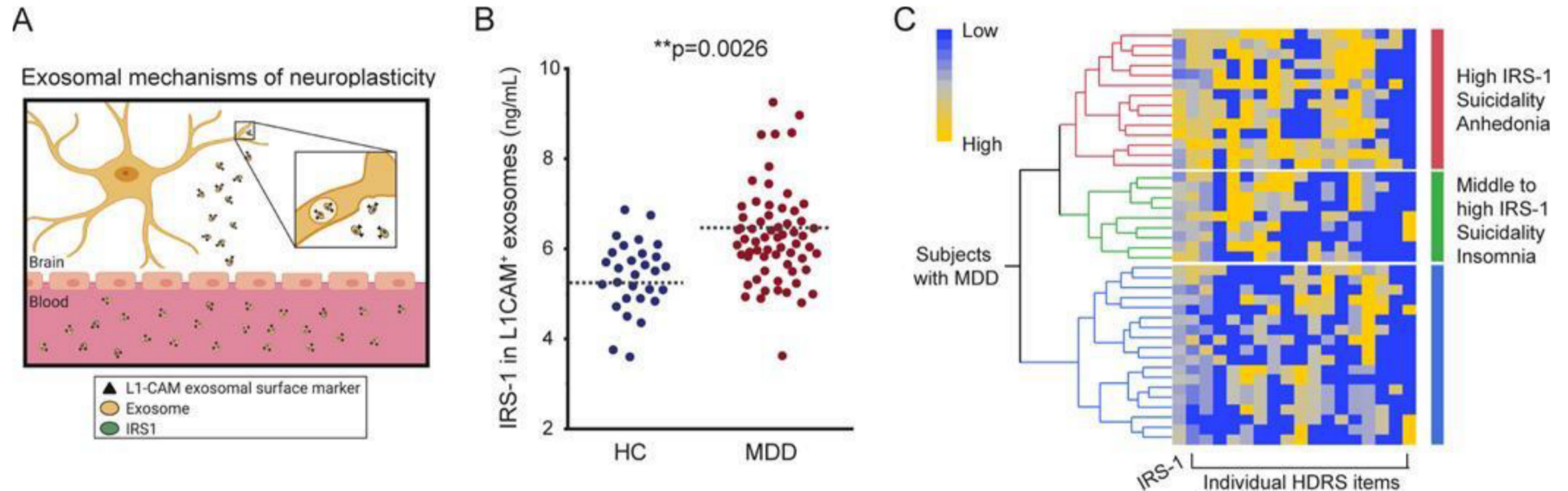Recent developments in exosome research allow us to estimate insulin resistance in the central nervous system.

What can central insulin resistance tell us about depression and its treatment?

Kapogiannis D, Boxer A, Schwartz JB, et al. Dysfunctionally phosphorylated type 1 insulin receptor substrate in neural-derived blood exosomes of preclinical Alzheimer's disease. *FASEB J*. 2015;29(2):589-596. doi:10.1096/fj.14-262048

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# Central Insulin Resistance Associates with Depression Status and Symptoms

- A sample of 93 participants with major depressive disorder (n = 64) and healthy controls (n = 29) aged 20 – 70 from Stanford University and Mount Sinai School of Medicine.
- Insulin receptor substrate 1 was measured in exosomes to estimate insulin resistance in the nervous system.

Nasca C, Dobbin J, Bigio B, et al. Insulin receptor substrate in brain-enriched exosomes in subjects with major depression: on the path of creation of biosignatures of central insulin resistance. *Mol Psychiatry*. 2021;26(9):5140-5149.

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Preliminary Data from a Long-Term Study of Insulin Resistance and Depression

- Our current research is measuring insulin receptor substrate 1 exosomes in 2000+ adults with and without major depressive disorder and following them for 9 years.

- Preliminary data from this cohort support a positive association between central insulin resistance and depression severity in 60 subjects; 30 with depression and 30 non-depressed controls (p < .01).

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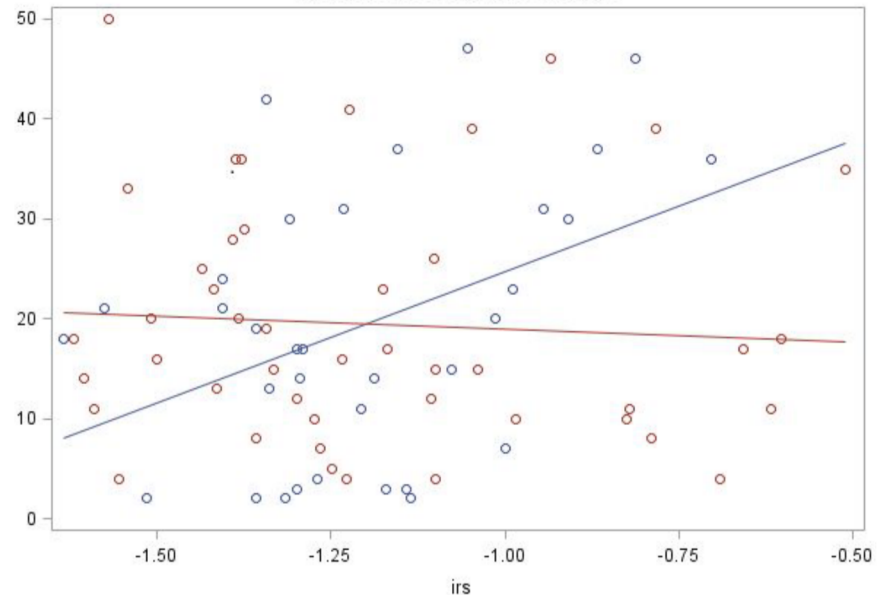
Next Steps and Future Directions

- Examine how central insulin resistance affects depression symptoms and course over many years.

- Compare central insulin resistance and peripheral insulin resistance. Do they have a similar relationship to depression?

- Extend the panel of biomarkers measured in exosomes to assess inflammatory, neurotrophic and other mediators of depression.

- Test depression treatments related to insulin resistance in the future and measure how they change our biology.

https://www.technologynetworks.com/neuroscience/blog/can-precision-psychiatry-give-us-new-ways-to-treat-mental-health-disorders-358877

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Acknowledgments

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The Neurobiology of Insulin Resistance and Major Depressive Disorder

Insulin resistance, an unmasked culprit in depressive disorders: Promises for interventions

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Highlights

- IR is a pathological proinflammatory state underlying neuropsychiatric and somatic diseases.

- IR is part of a cascade of allostatic load, which is mediated in the periphery and CNS.

- PPAR- γ receptors, glutamate, cortisol are among mediators of peripheral and central crosstalk underlying IR.

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