Title Slide

My name is Jonelle and I am a PhD candidate in the Epigenetics of Severe Mental Disorders Group with Stéphanie in Bergen. Thank you for selecting my proposal for this meeting. I will share my vision for moving research forward by incorporating the ketogenic diet in the treatment of severe mental disorders. This vision incorporates the role of epigenetics and mitochondrial function in psychiatric disorders.

Slide 1: The Environment

Environmental factors that influence the epigenome also influence mitochondrial function. Many of these factors have already been studied in psychiatric disorders.

Slide 2: Mitochondrial epigenetics (maybe remove the points and just talk)

There are many signaling interactions between the nuclear and mitochondrial genomes including metabolites from xxx and non-coding RNAs. The mitochondria also regulate the production of S-adenosyl methionine (SAM) which is the universal methyl donor for both nuclear and mitochondrial methylation. (through synthesis of ATP and folate). Most co-substrates required for histone modifications are generated through mitochondria. (41-32) phosphorylation, acetylation and deacetylation

Slide 3: Mitochondrial dysfunction

. Dysfunction in the mitochondria can contribute to a range of health issues, including neurological disorders, metabolic disorders, and aging.

Slide 4: What is the classic ketogenic diet?

This project looks at using diet as an intervention.

A ketogenic diet is a very low-carbohydrate diet which helps to keep blood glucose levels low. The body looks for another source of energy and will burn fat instead which produces ketones. These ketones are believed to be a more efficient fuel source for the mitochondria than glucose.

The goal is for the brain to burn ketones instead of glucose and thereby give the

KD shown to have beneficial effects on metabolic health, ie improving blood glucose, body weight, insulin resistance, triglycerides, and cholesterol. This may counteract the effects of metabolic abnormalitites seen with psychotropic medication use. AD and mood stabilizing effects in BP (murphy et al., 2004)

Dietary Fats are digested to FA which are metabolized by the liver through Beta oxidation and transformed into ketone bodies.(Schonfeld and Woutczak, 2016) FA and ketone bodies are then transported across the BBB where they can be used as an energy source.

The generation of ketone bodies provides astrocytes and neurons with a more efficient energy sources than glucose (Zhane et al, 2013)

Slide 5: Reported therapeutic effects

The diet is an evidence-based treatment for Intractable epilepsy and has been used for 100 years. Anti-seizure medications are used in psychiatry as mood-stabilizers.

Detox for alcohol abuse. A study of alcohol detoxification at the National Institute of Drug Abuse showed that individuals on a KD used fewer benzodiazepines while detoxing and less cerebral inflammation when scanned with MRI.

In a study with subjects whose symptoms were poorly controlled with medication, the KD diet reported significant improvements in the Hamilton Depression Rating Scale, the Montogomery-Åsberg Depression Rating Scale and PANSS for SCZ. In SCZ, subjects first report an antidepressant effect, followed by reduction of auditory hallucinations, and finally delusions.

Slide 6: Astrocytes also generate ketones

In a fasting state, but astrocytes in the Hypothalamus can produce ketone bodies from FA in a high fat diet that is not a KD. Here an excess of ketone bodies is produced that overrides the neuron´s sensitivity to hormones such as leptin, insulin, and ghrelin.

Ketones are signaling molecules. There is evidence to suggest that the ketone bodies improve mitochondrial function and increase the number of mitochondria through mitochondrial biogenesis.

Neural network stabilization

Inflammation reduction

Slide 7: Project title - Mental Health is Metabolic Health

Research aims

-To identify:

- Epigenetic / gene expression changes associated with the KD<br> <br> />

- Mechanisms associated with symptom reduction/positive outcome

Slide 8: Mental Health is Metabolic Health

Clinical aims - To foster and support:

Recovery through a low risk metabolic intervention (KD)

Patient engagement in their own recovery

Slide 9: Acknowledgements

.footnote[A Ketogenic Diet Improve Mitochondrial Biogenesis and Bioenergetics via the PGC1ɑ-SIRT3-UCP2 Axis, Hasan-Olive \_\_\_et al\_\_\_, (2019), Neurochemical Research.]

Simply put, a ketogenic diet typically derives about 70-80% or more of total calories from healthful fats. The remaining 20% of calories are derived from carbohydrates and proteins. Eating like this puts your body in a state of ketosis, where it primarily burns fat for energy.

To get into and stay in ketosis, you must restrict carbs and sugar – less than 50 grams per day. This initiates your body to burn the remaining carbohydrates present, after which it moves on to stored glucose (glycogen), and finally it taps into ketones. Ketones are produced by the liver and readily used by the body *for* potent energy production and critical brain-related functions.

WHAT SYMPTOMS OF METABOLIC DISEASE are shared with SMI (look up Pillinger)

* Weight gain
* Dyslipedemia
* Cardiovascular disease
* Cognitive impairment
* Sleep disturbances
* Loss

Studies – Keto diet

* Epilepsy. Rho PMID: 35361967 (anti-seizure meds)

So the term “diet” is somewhat understated, hopefully you can see now that it is actually a “metabolic intervention.”

* Used to treat intractable epilepsy (in children, with good affect in adolescents and adults), however in the 1930’s anti-seizure medication became available and offered a more practical solution.
* Used to treat diabetes in the 1800’s
* Used to help alcoholics detox – in the lab of Nora Volkow, the director of the National Institute of Drug Addiction, subjects adhering to the ketogenic diet during detox used few benzodiazepines than controls, and their MRI scans showed reduced inflammation.
* Has been used to *alleviate* symptoms of anxiety, depression, BPD and SCZ.

Metabolism - Brain Energy – Mitochondria

Metabolism is much more than burning calories – it affects the structure and function of all cells in the human body. Metabolism is regulated by hormones, neurotransmitters, inflammation and epigenetics. And mitochondria are master regulators of metabolism.

Mitochondrial dysfunction or dysregulation can cause many of the symptoms of mental disorders through 5 distinct mechanisms:

1. Cell activity can be overactive
2. Cell activity can be underactive
3. Some cells can develop abnormally
4. Cells can shrink and die (4 and 5 lead to absent brain functions)
5. Cells can have problems maintaining themselves.

Not all of these mechanisms respond adequately to medication – but protocols that support a healthy metabolism also support healthy mitochondrial function.

One such protocol is the ketogenic diet.

Local source of energy - independent of ketone bodies transported across the BBB.

Metabolic support for neurons (Yi et al., 2011)

Shown to have neuroprotective effects and may help prevent neurodegenerative diseases.