Title Slide

I am a PhD candidate in the Epigenetics of Severe Mental Disorders Group with Stéphanie. Thank you for selecting my proposal for this meeting. I will share my vision for moving research forward by incorporating the ketogenic diet as an intervention in the treatment of severe mental disorders. I´ll approach this through the lens of epigenetics and mitochondrial function.

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 – and some of them in our group. One interesting question to consider is whether metabolic signals are the mechanism by which the environment interacts with our genome.

Slide 2: Mitochondrial epigenetics

Epigenetic nuclear mechanisms have evolved to couple gene expression to the metabolic state of the cell. Metabolic intermediates that are substrates or co-factors for epigenetic modifications are all derived from metabolic pathways within mitochondria. This figure has been greatly simplified just to highlight that mitochondria generate SAM which is the universal methyl donor for both nuclear and mitochondrial methylation. The mitochondria generate most co-substrates required for histone modifications.

Slide 3: Mitochondrial dysfunction

The accumulation of environmental insults leads to mitochondrial damage. Shrinkage of the inner membrane is seen where ATP is produced, so the mitochondria produce less ATP, have increased Reactive Oxygen Species production leading to inflammation, as well as altered gene expression and impaired signaling to nuclear DNA.

Slide 4: What is the classic ketogenic diet and how can it help?

The recommended diet is very low in carbohydrates which shifts metabolism from burning glucose to burning fat. This process produces Ketone bodies believed to be a more efficient fuel source for the mitochondria – as well as modulating signaling pathways.

Slide 5: Reported therapeutic effects

The diet has beneficial, stabilizing effects on metabolic and mental health.

-It has been used as an evidence-based treatment for intractable epilepsy for 100 years.

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

-For individuals whose symptoms were poorly controlled with medication, significant improvements were reported using the Hamilton Depression Rating Scale, the Montgomery-Åsberg Depression Rating Scale, and PANSS. Subjects with BPD report a stabilizing, antidepressant effect, while subjects with SCZ report a reduction of auditory hallucinations, and delusions.

Slide 6: Astrocytes also generate ketones

Which is great due to local proximity to neurons, but in a heavily fatty diet, ketone bodies are produced in excess, especially in astrocytes in the hypothalamus. Chronic over production of ketones in the hypothalamus desensitizes neurons to metabolic hormones such as insulin, leptin, and ghrelin. Antipsychotics are known to alter these hormones and are associated with metabolic disturbances. So, the influence of ketone bodies on metabolism in psychiatry warrants more research.

Slide 7: Project title – Mental Health is Metabolic Health

Research aims – To identify:

Epigenetic/gene expression changes associated with the KD

Mechanisms associated with symptom reduction/positive outcomes

Slide 8: Project title – 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

Interactions between DNAm and mitochondria:

1. nDNAm: nuclear DNAm impact on mitochondrial metabolism
2. nDNA expression: influence of nuclear gene expression on enzymes which may cause mtDNA methylation
3. Metabolites: effect of mitochondrial metabolites on nDNAm
4. mtDNA SMPs: burden of mtDNA mutations and haplogroups on nDNA methylation.