

Mitochondrial and Psychosocial Stress-related Regulation of FGF21 in Humans

Mangesh Kurade

MiSBIE Symposium 2025

What is FGF21?

Fibroblast Growth Factor - 21

A Liver-Derived Metabolic Hormone

Produced mainly by the liver; also expressed in muscle and immune tissues.

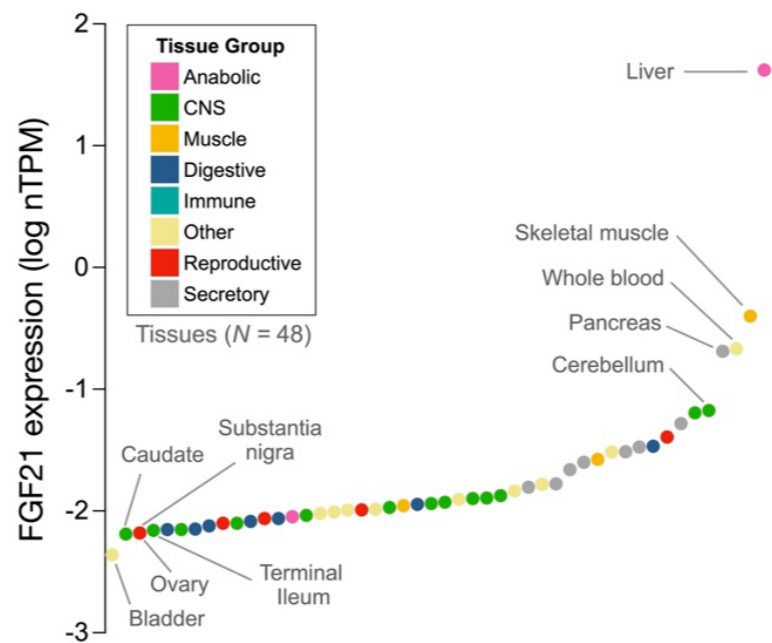
Signals through FGFR1 + β -Klotho, widely expressed in metabolic organs.

Key Physiological Roles

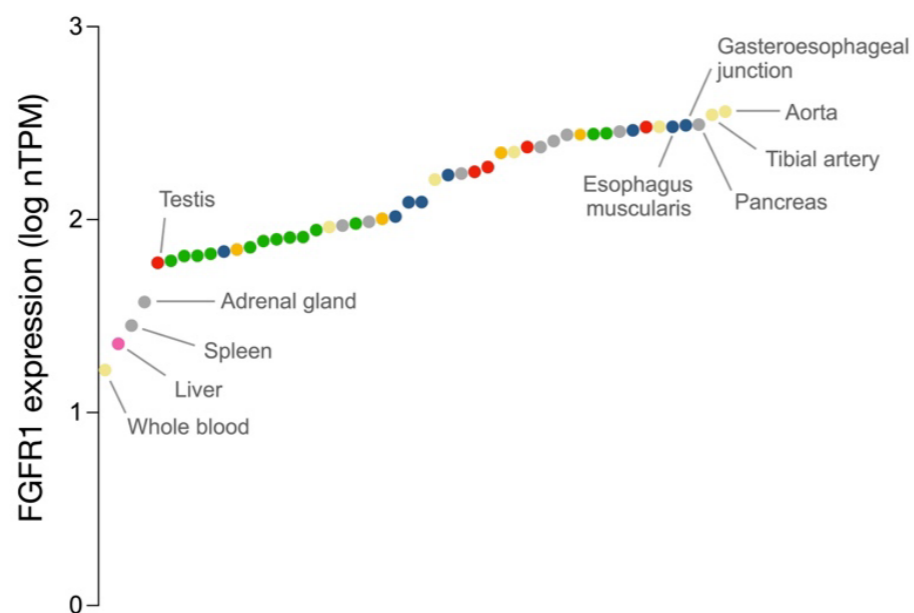
- **Regulates energy balance during metabolic stress.**
- **Increases during fasting, starvation, low glucose, cold exposure, and mitochondrial stress.**
- **Promotes fatty acid oxidation, improves insulin sensitivity,**

FGF21 and receptor complex expression across human tissues using Gtex data set

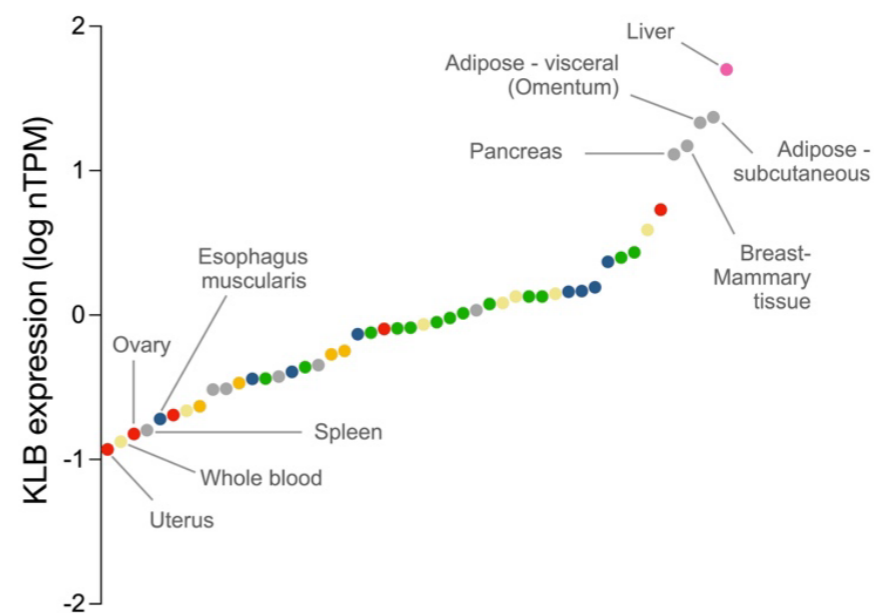
a *FGF21* expression



b *FGFR1* (all isoforms) expression



c β -Klotho (*KLB*) expression



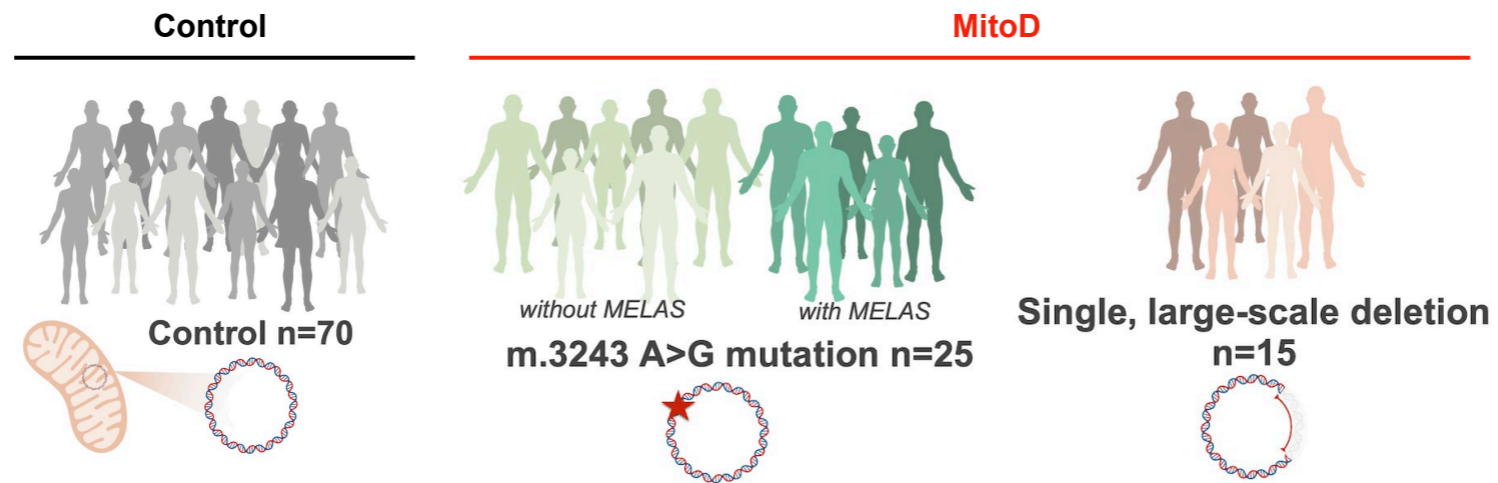
Objectives

FGF21 as a biomarker of Mitochondrial disease

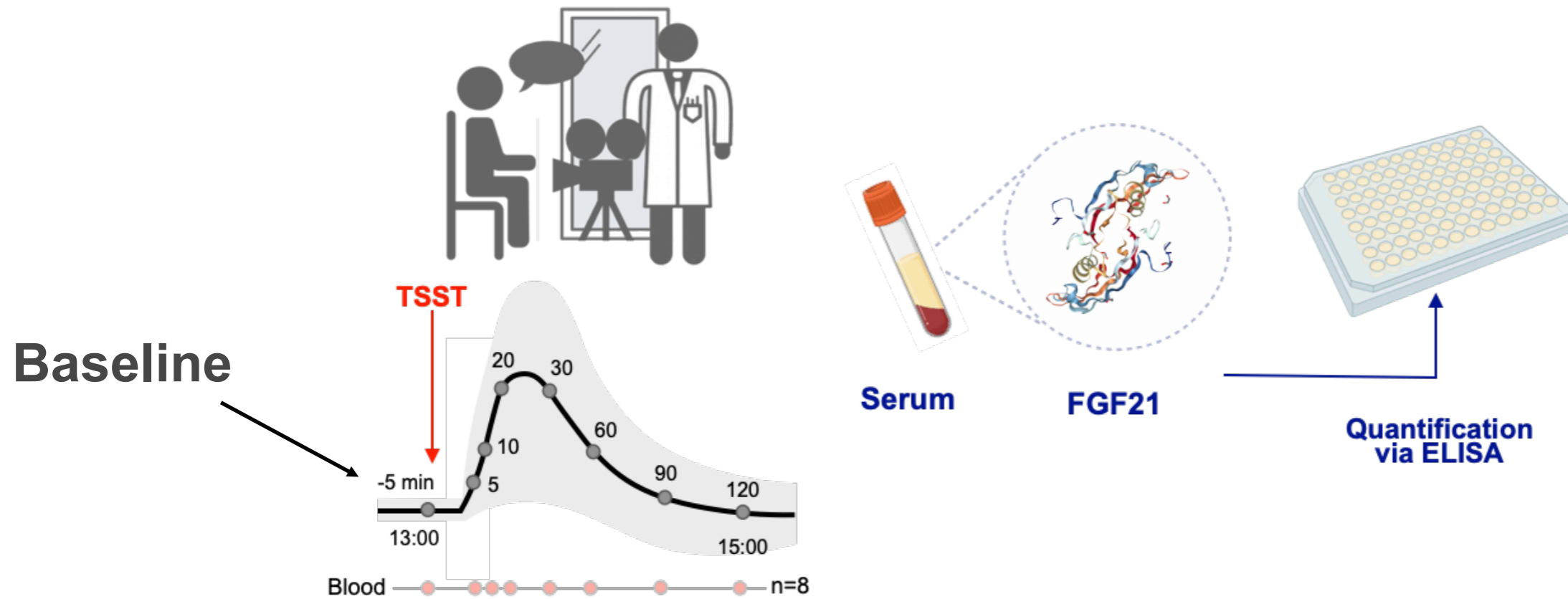
Does acute psychosocial stress affect circulating FGF21?

Do different psychosocial states affect FGF21 expression?

MiSBIE Cohort Overview



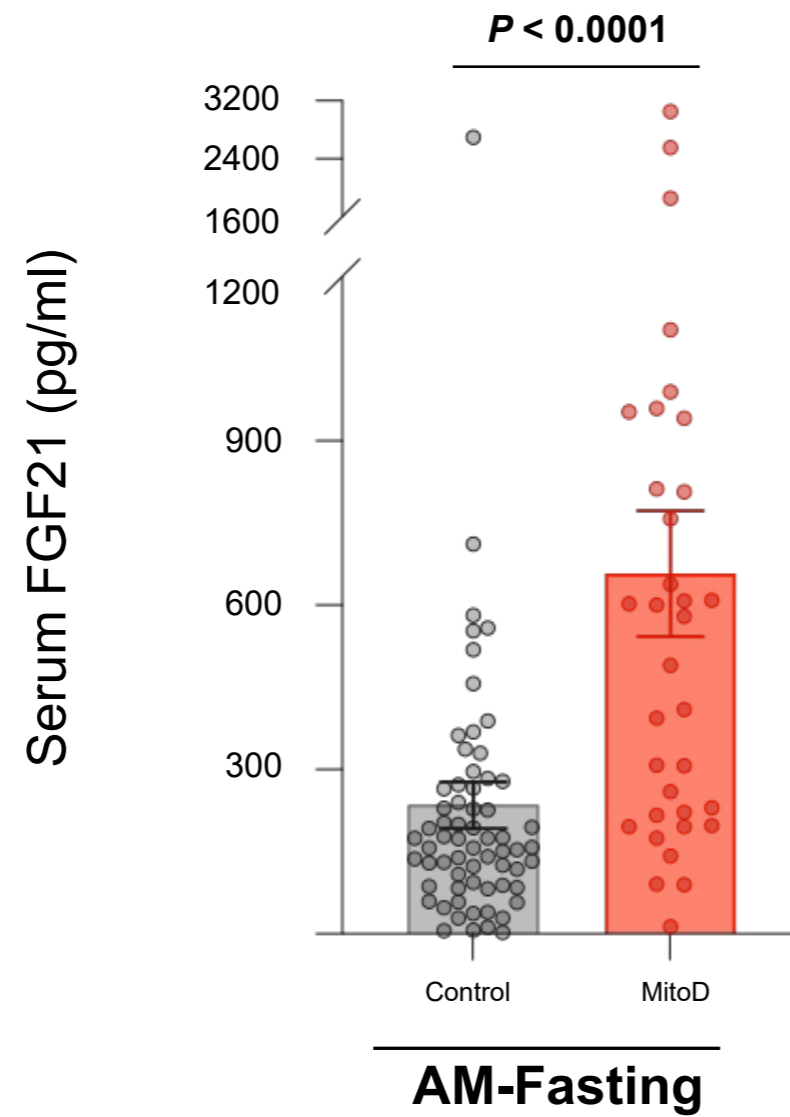
Sample collection and Processing



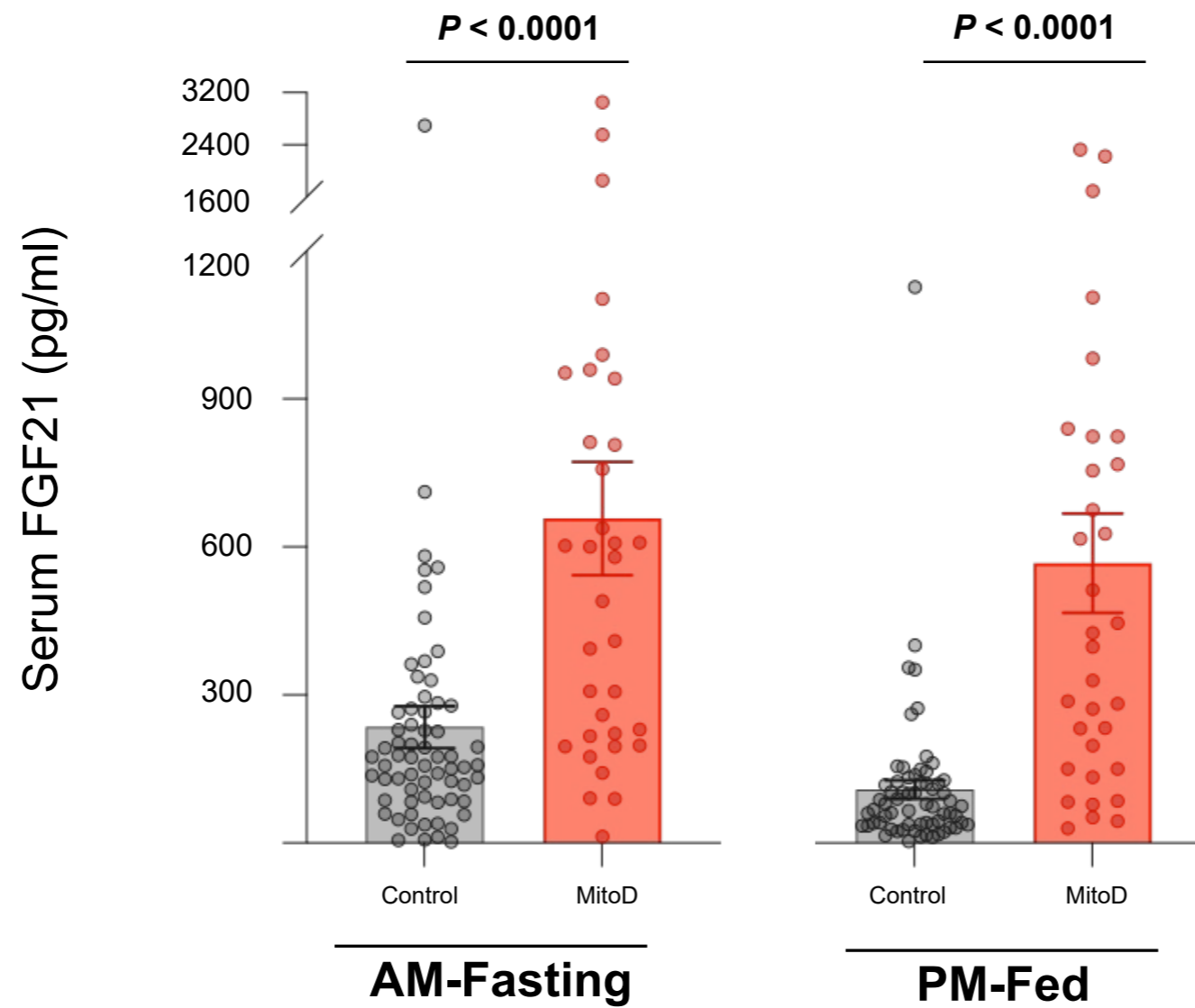
Fasting + 8 stress time points

**Do FGF21 levels differ between
Controls and MitoD ??**

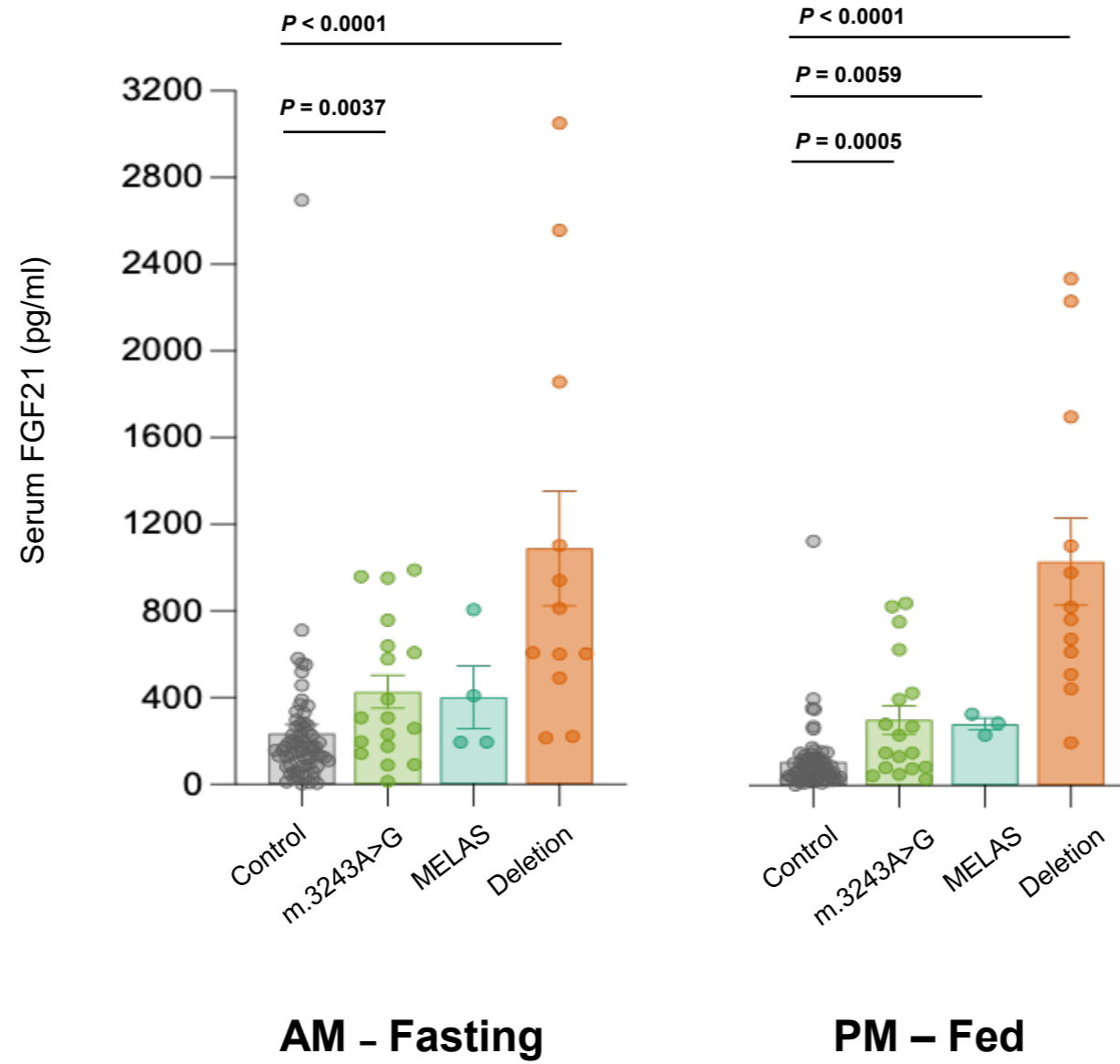
Serum FGF21 is elevated in mitochondrial disease



Serum FGF21 is elevated in mitochondrial disease

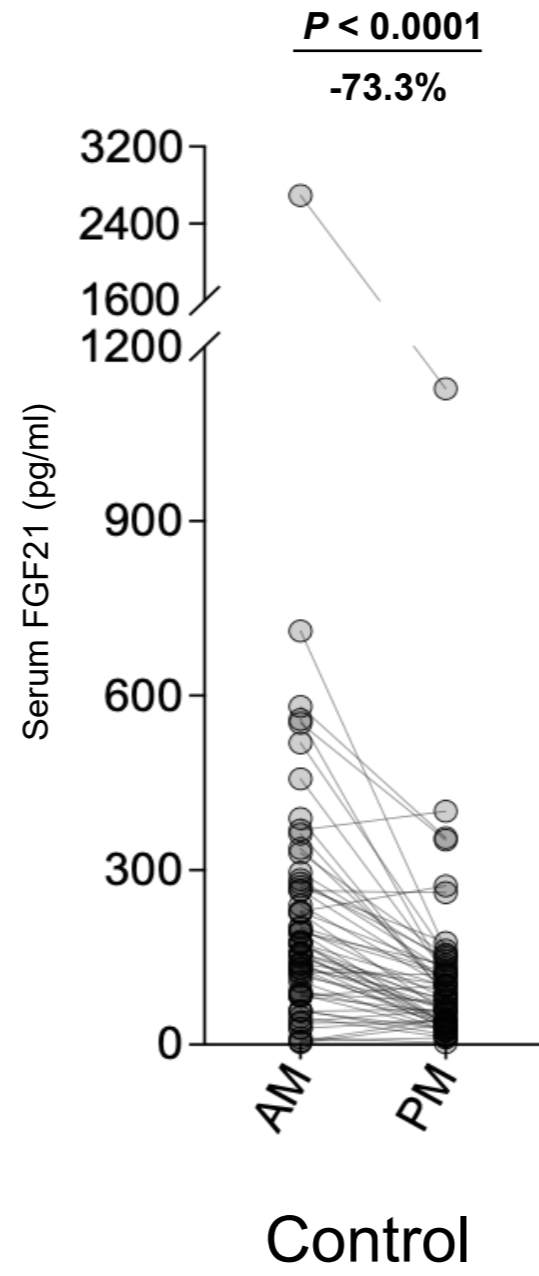


Serum FGF21 is elevated in mitochondrial disease

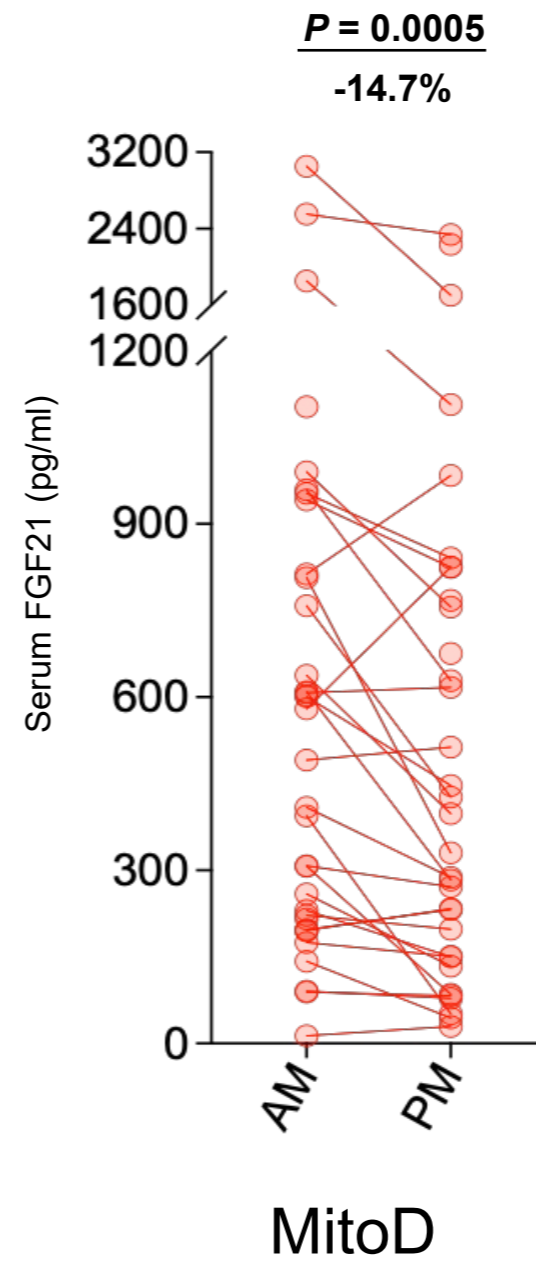
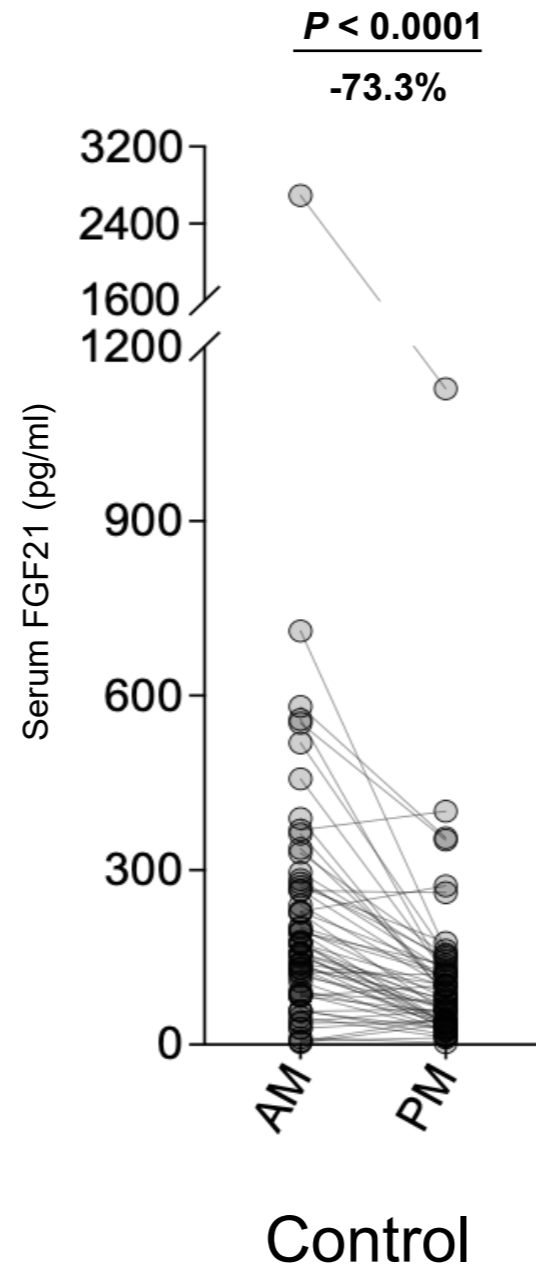


Fasting vs Fed States and FGF21

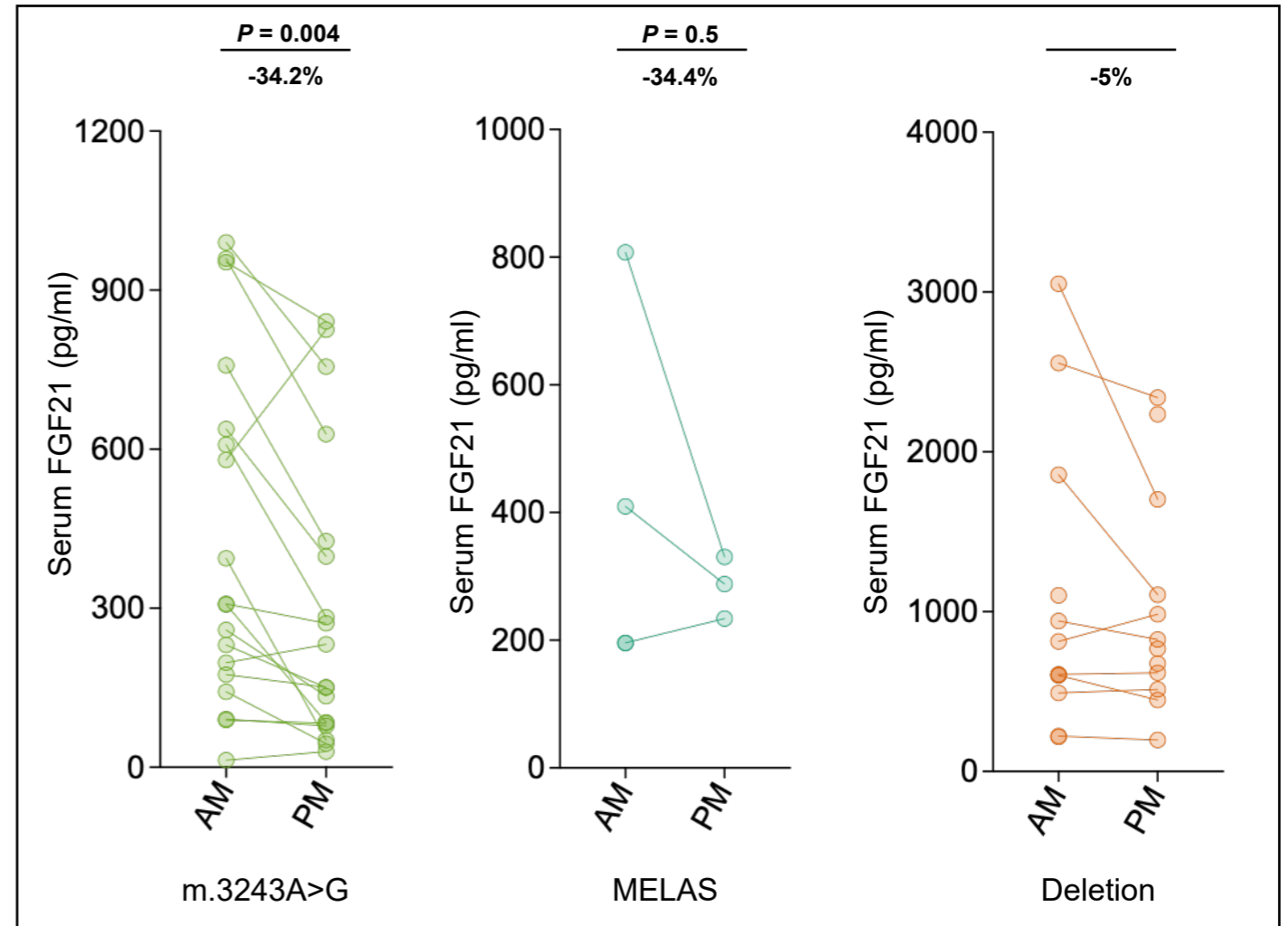
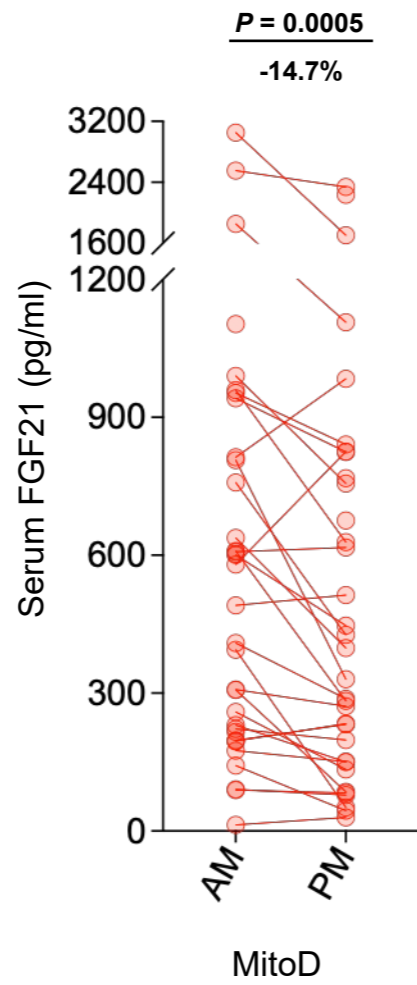
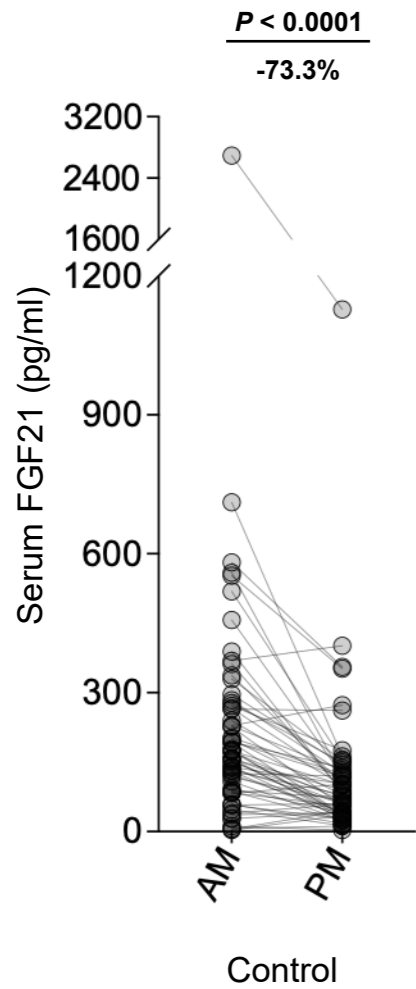
FGF21 decreases from AM to PM



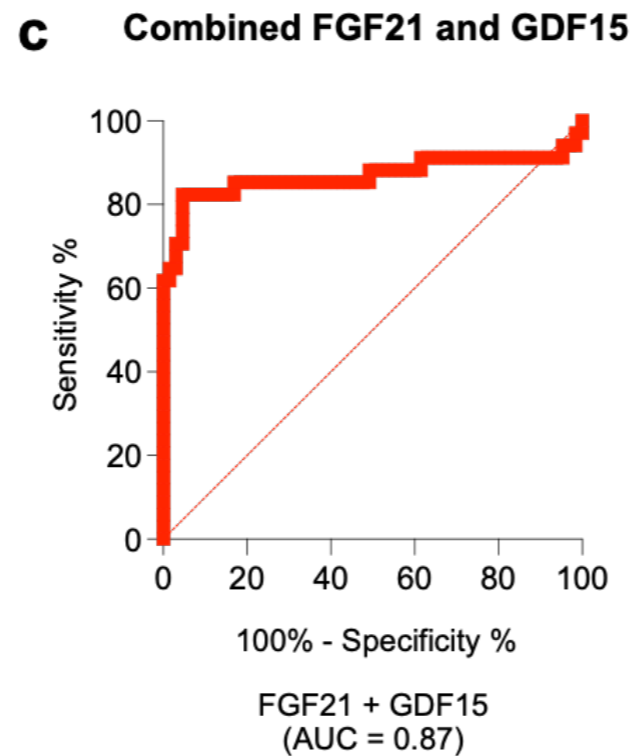
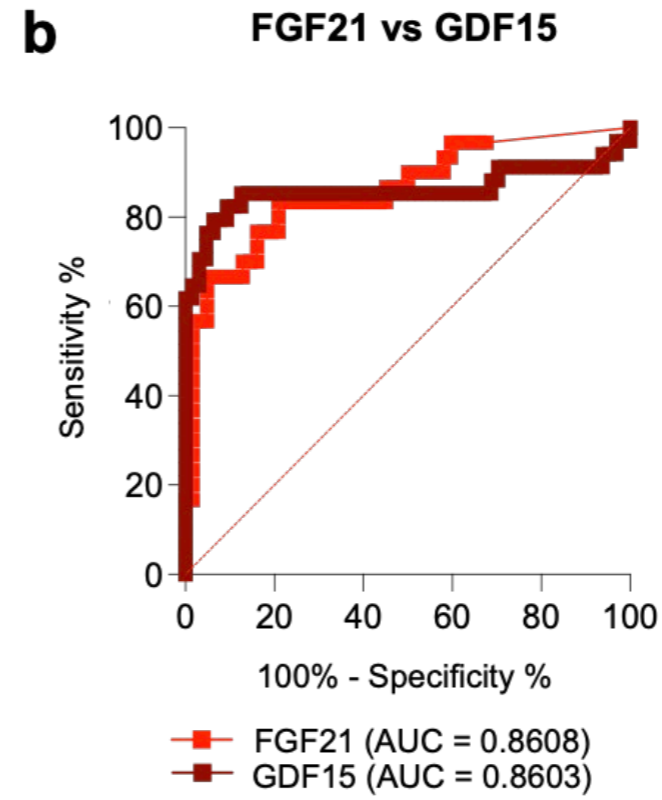
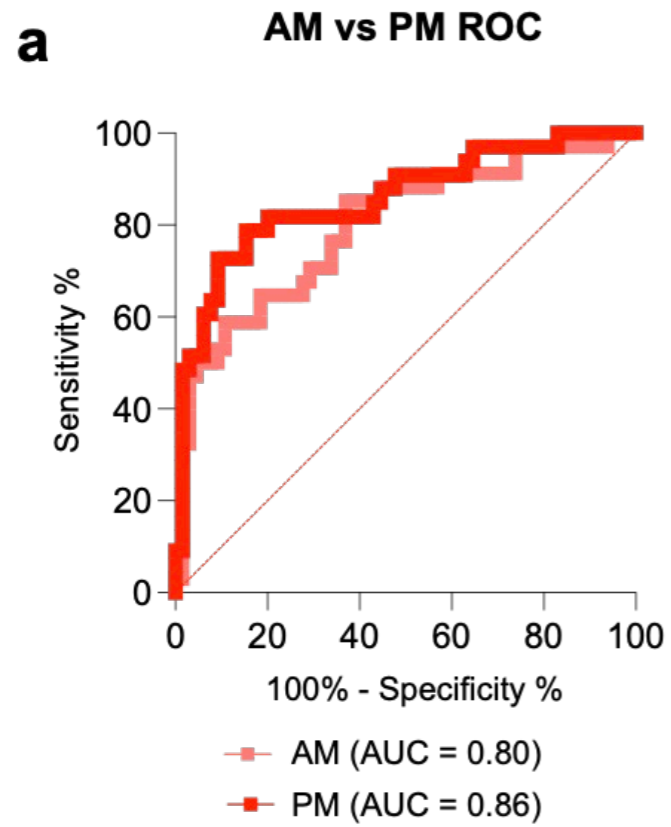
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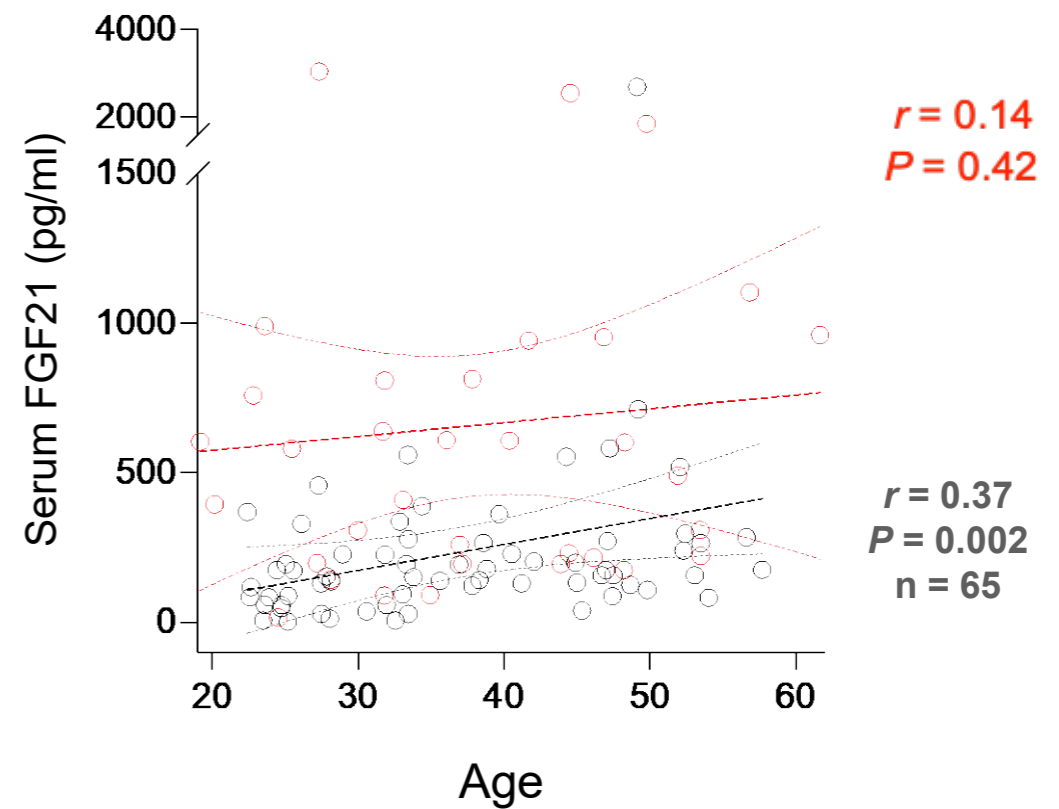
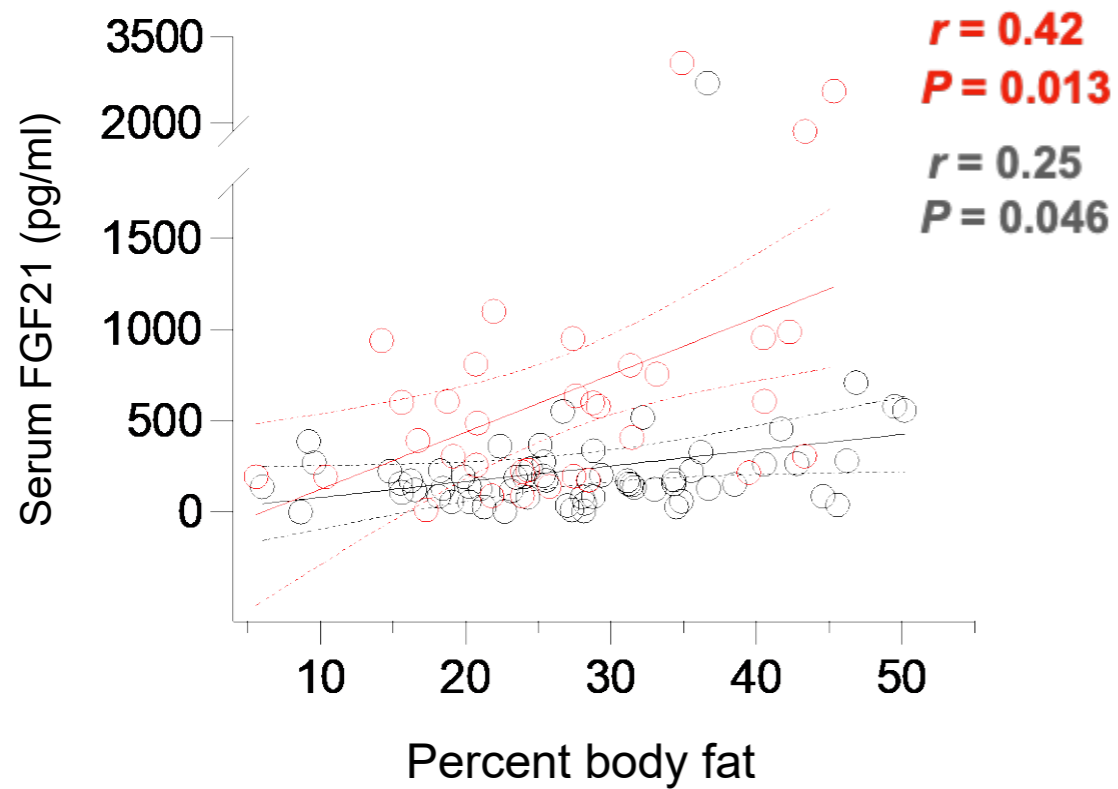


Receiver Operating Characteristic

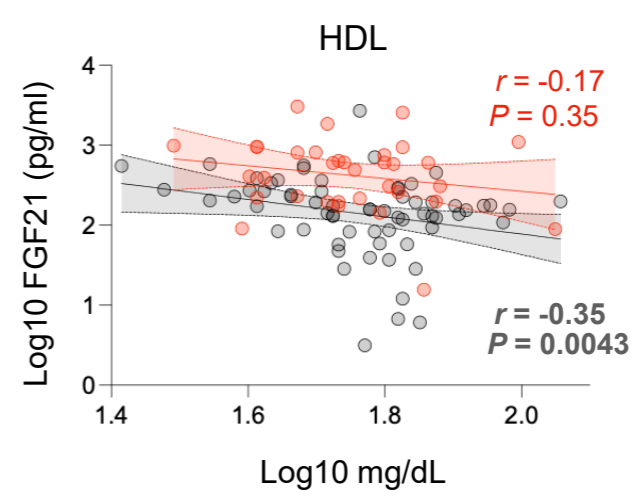
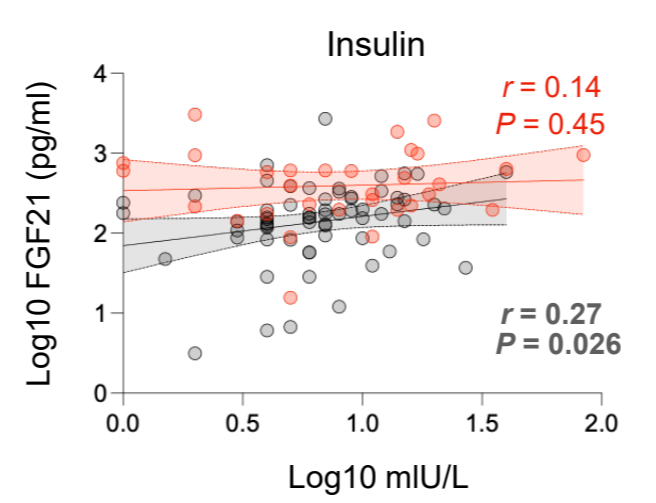
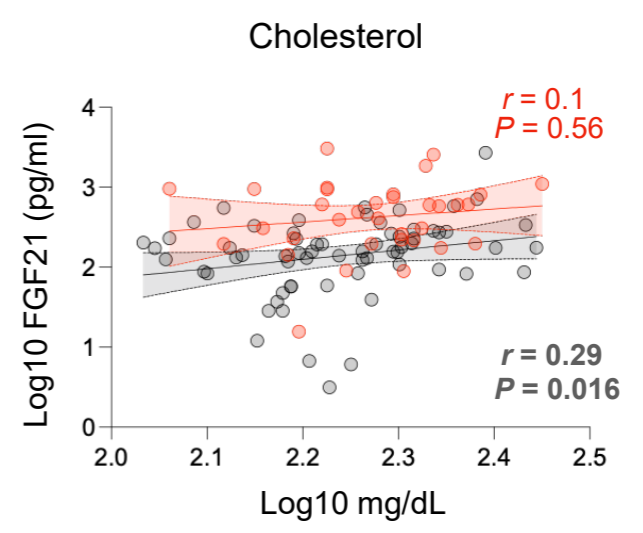
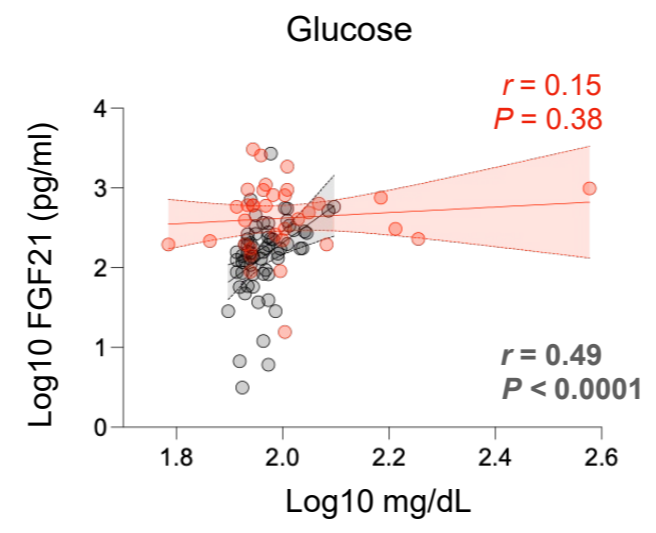
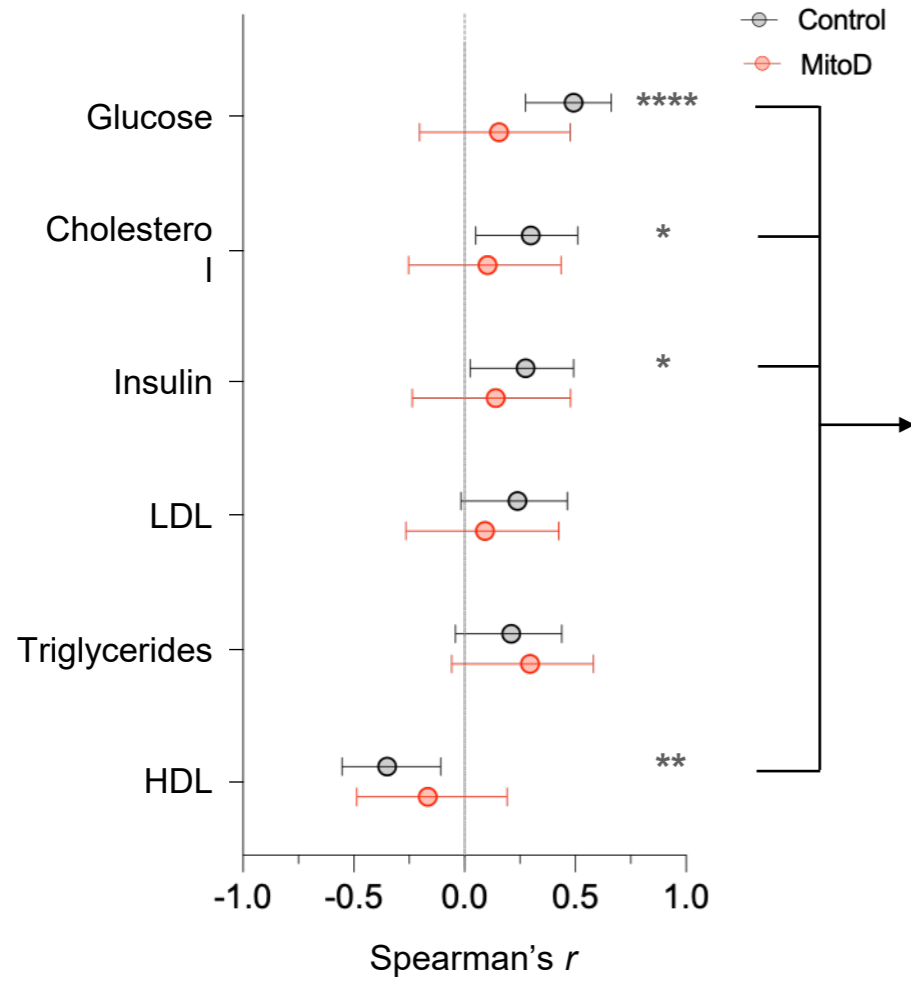


FGF21 is correlated with percent body fat and age

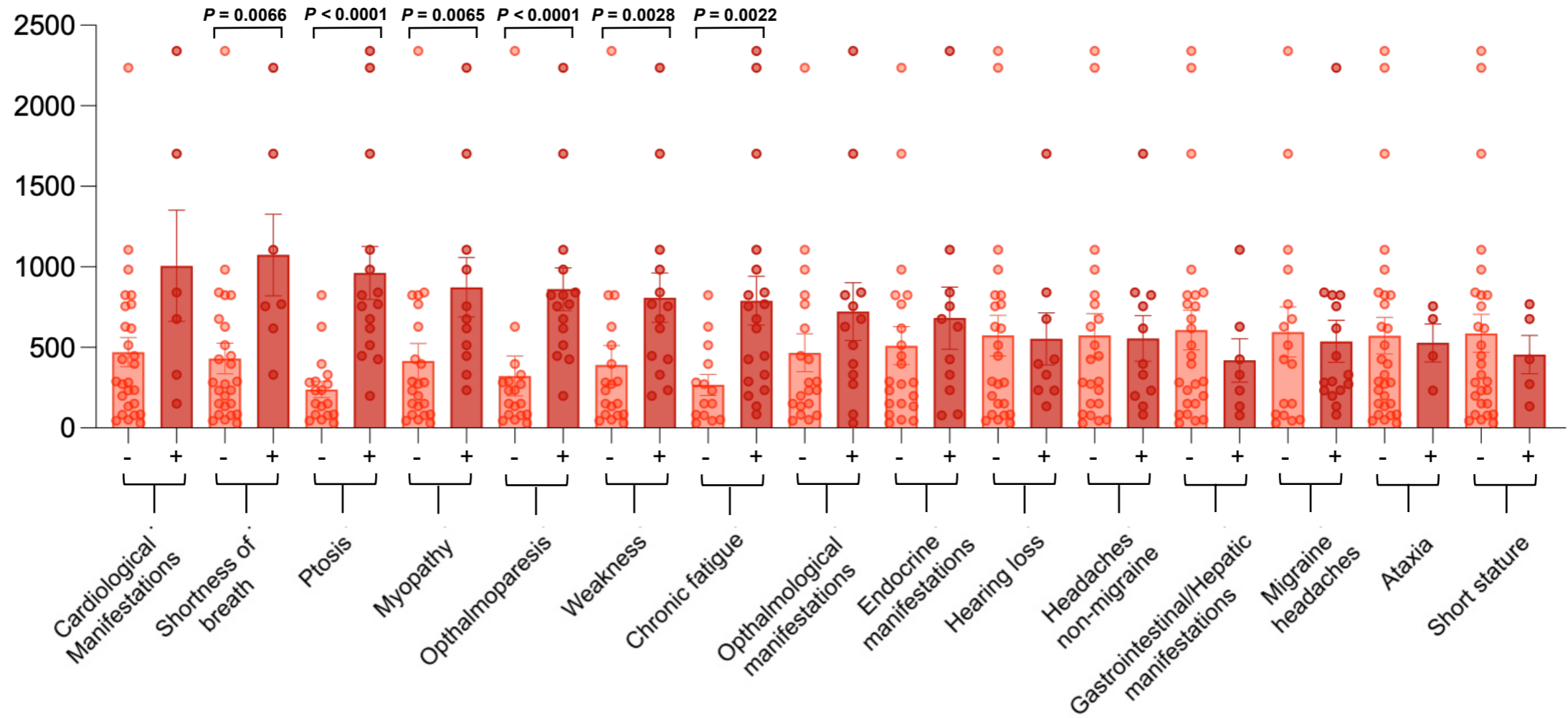
- Control
- MitoD



Metabolic biomarkers are correlated with FGF21 in controls

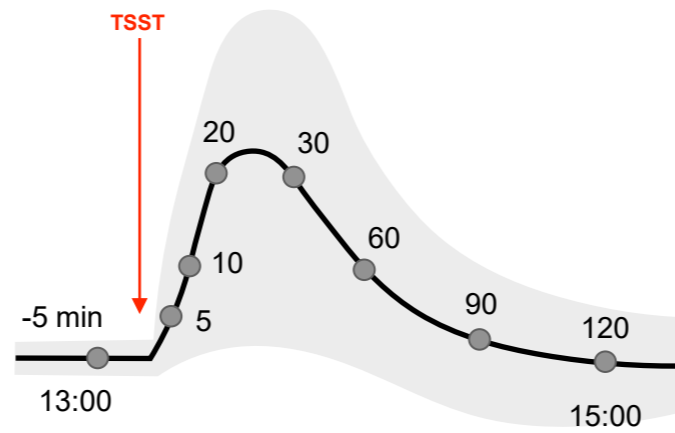
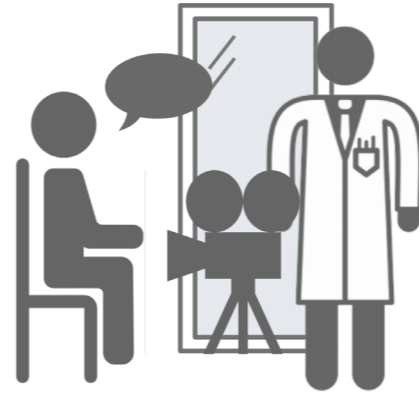


FGF21 is higher in MitoD patients who experience energy intensive disease symptoms



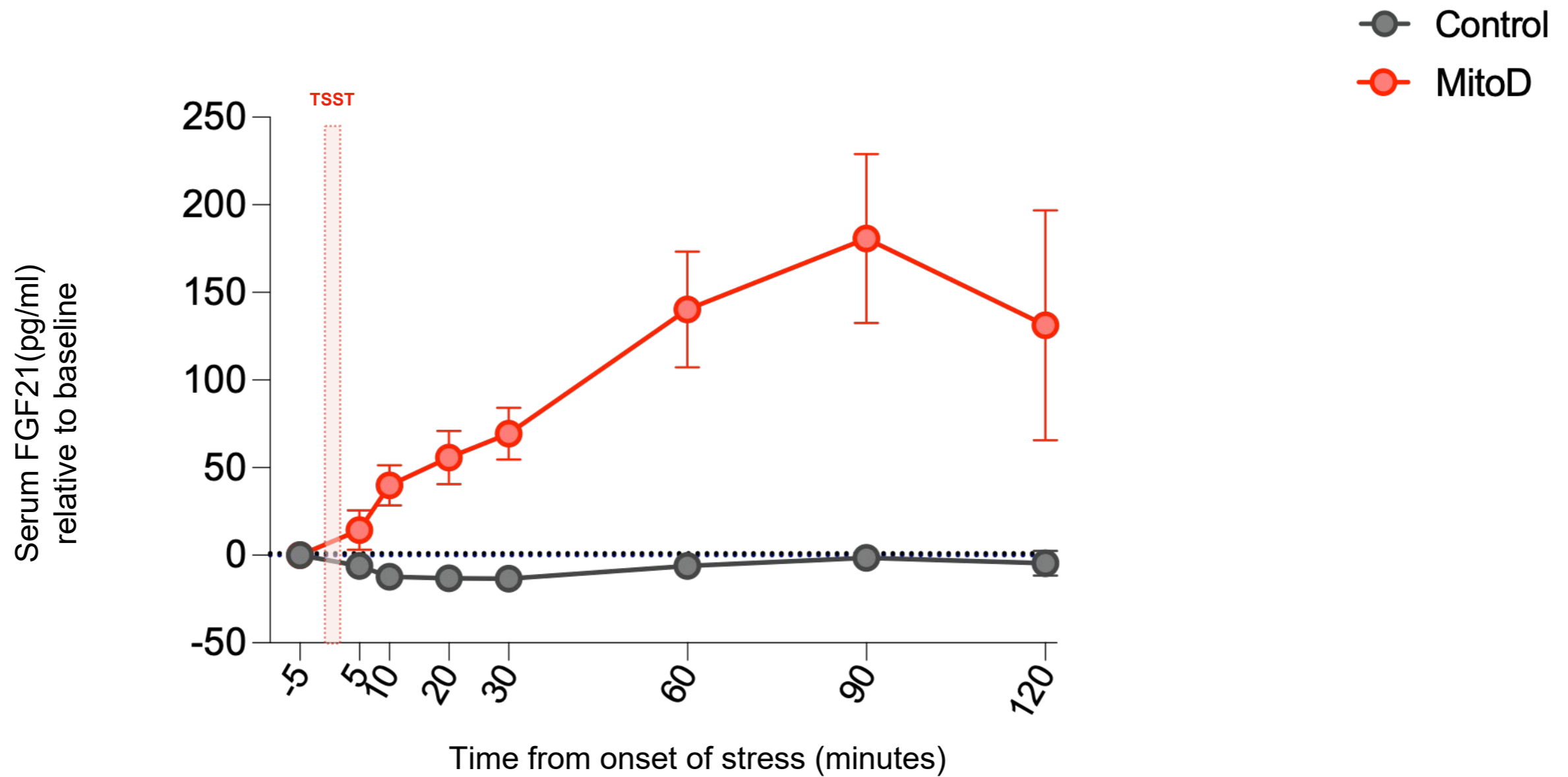
Is circulating FGF21 responsive to acute psychosocial stress?

TSST paradigm

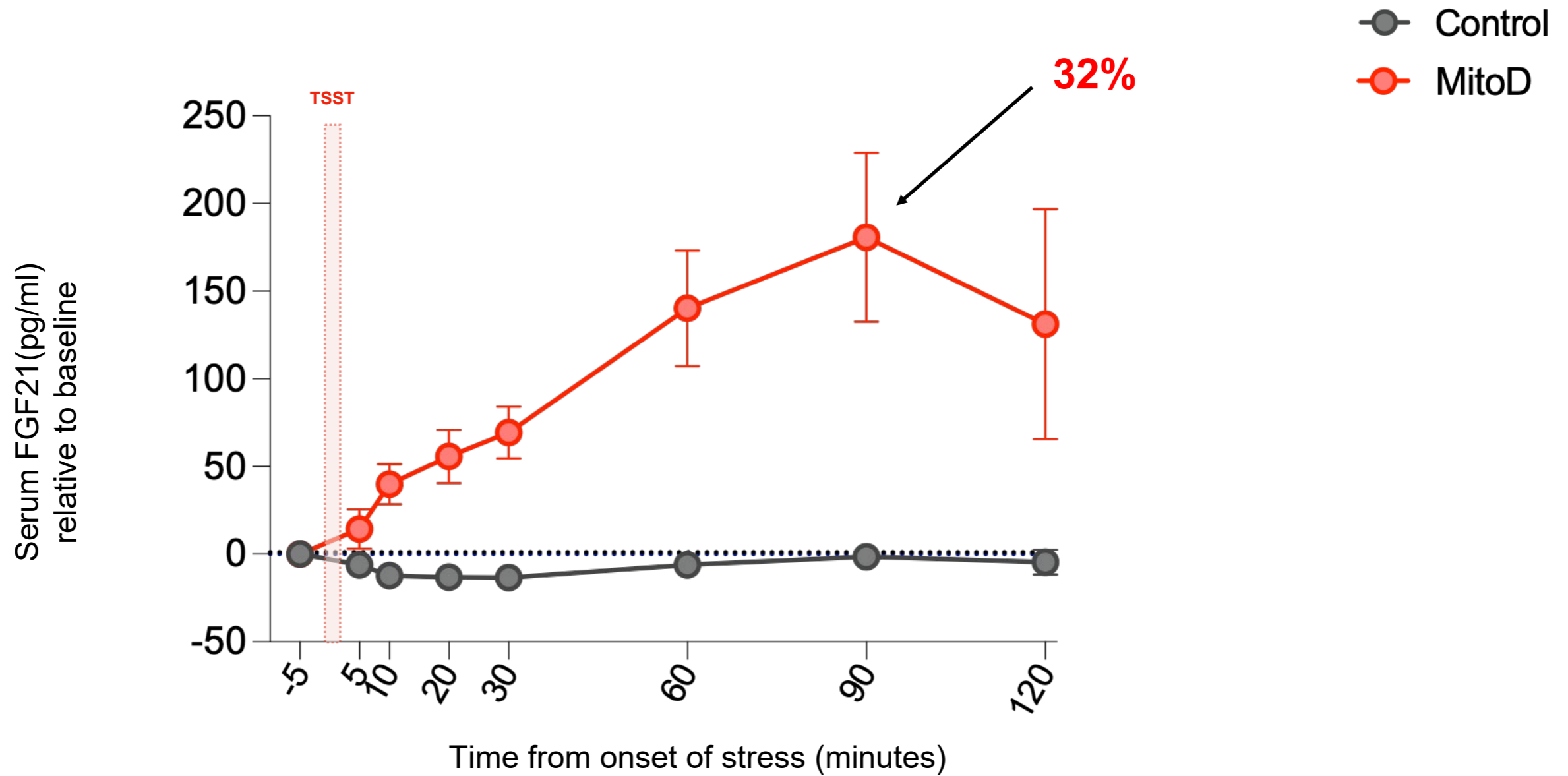


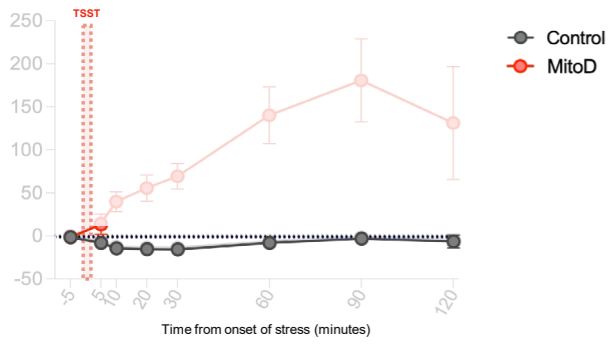
Blood —●—●—●—●—●—●—●—●— n=8

Serum FGF21 is reactive to acute psychosocial stress and shows contrasting response in MitoD

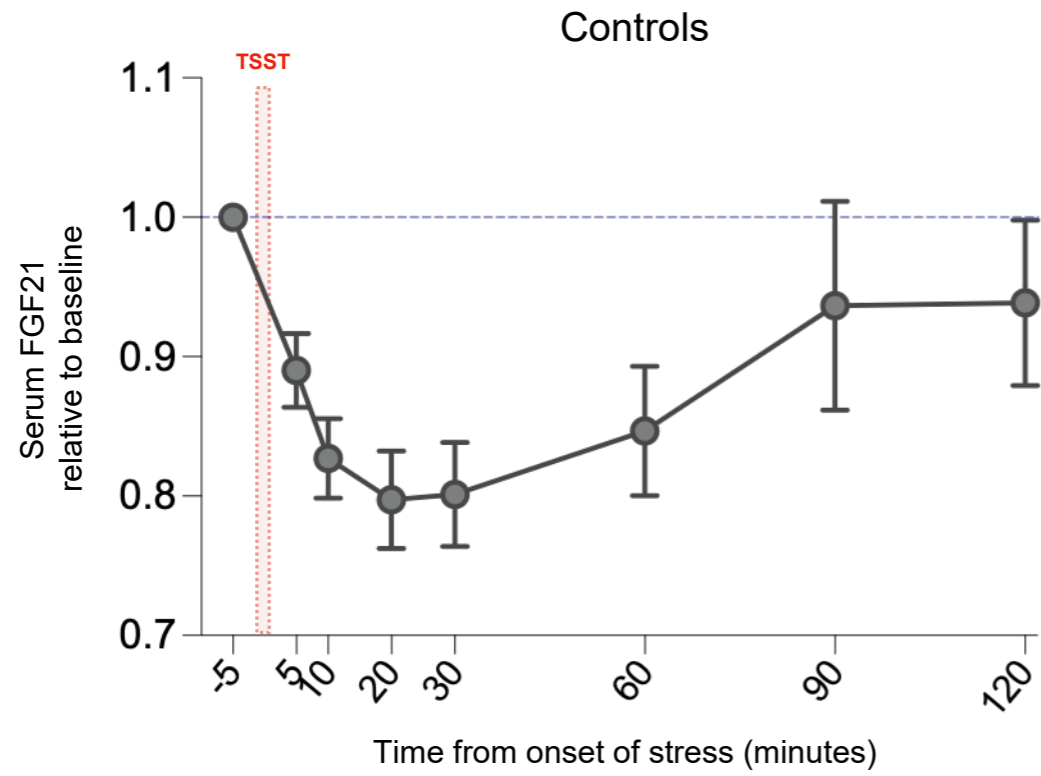


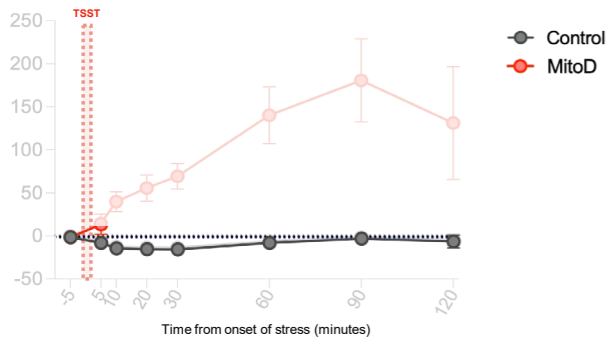
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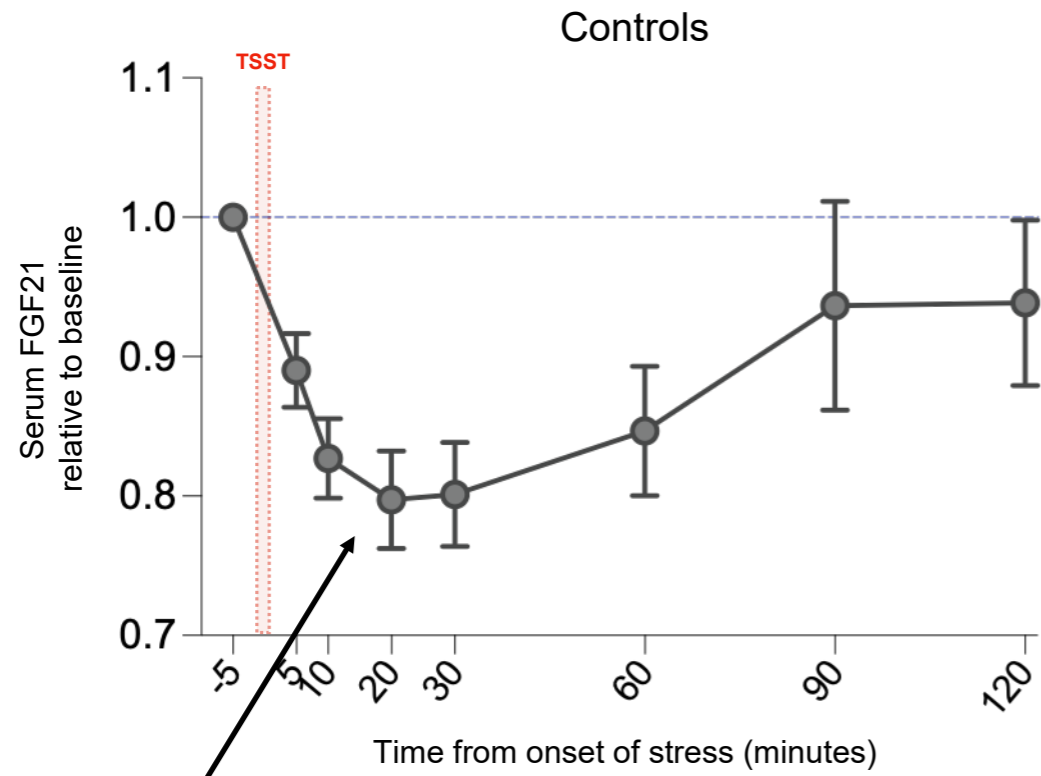


FGF21 Stress reactivity in controls

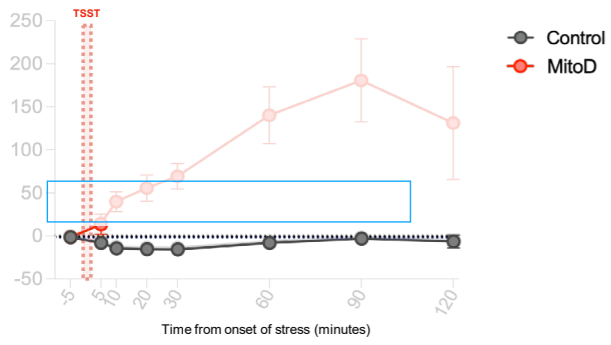




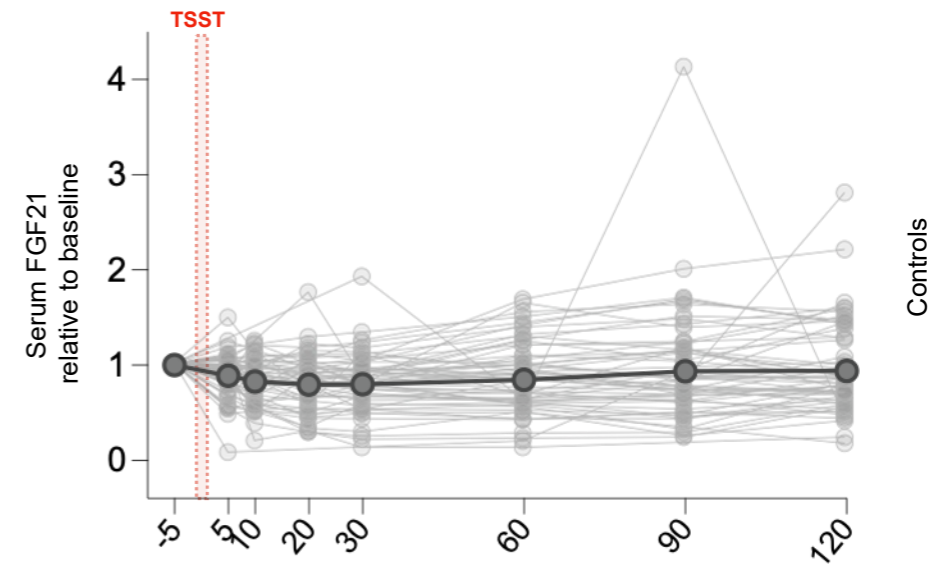
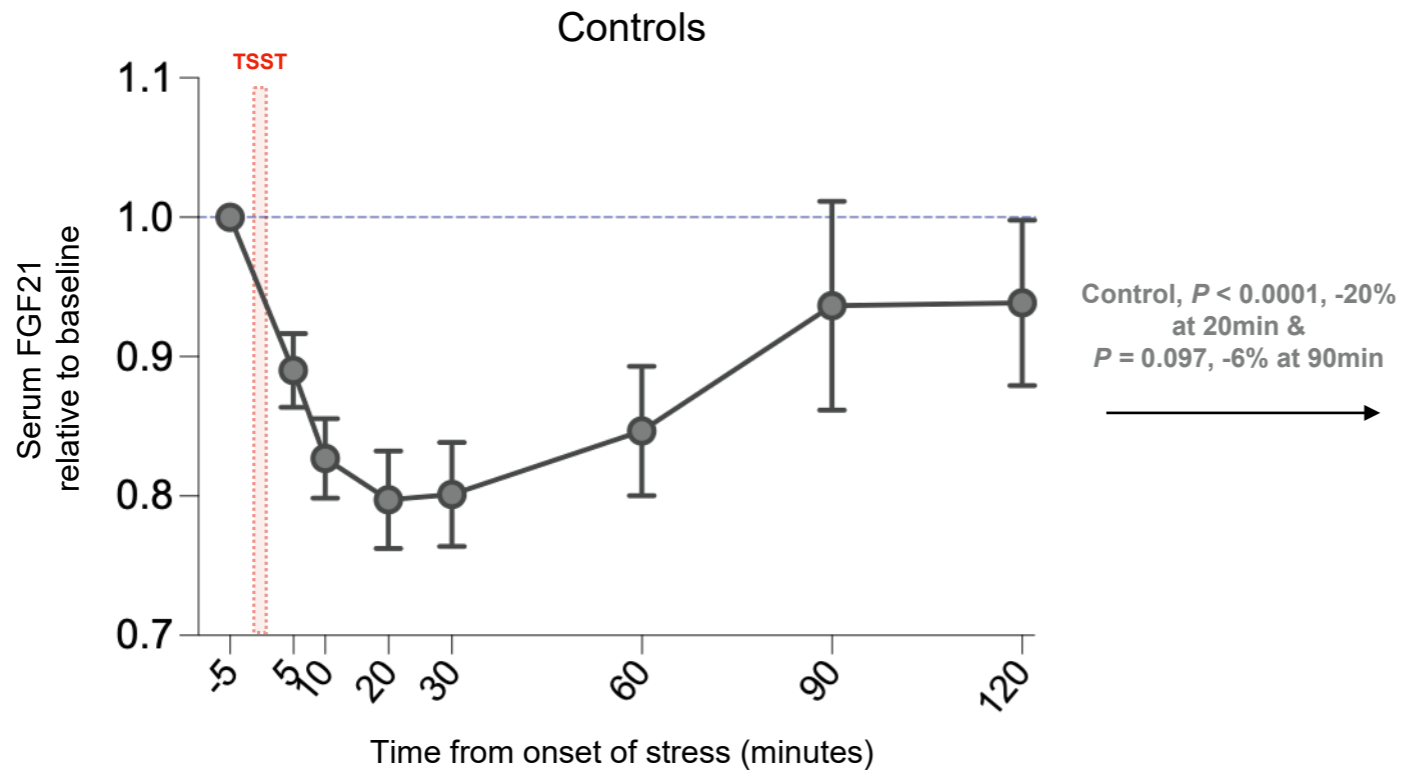
FGF21 Stress reactivity in controls



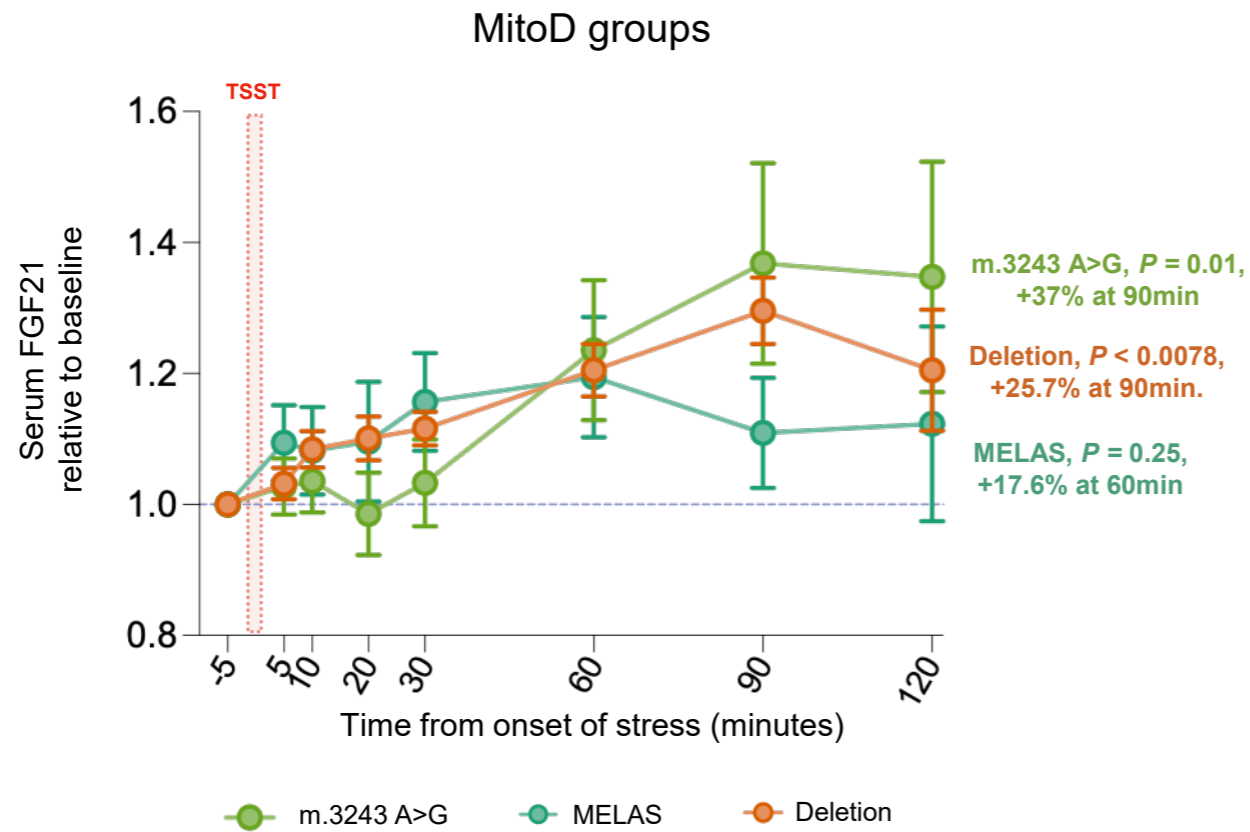
-20%



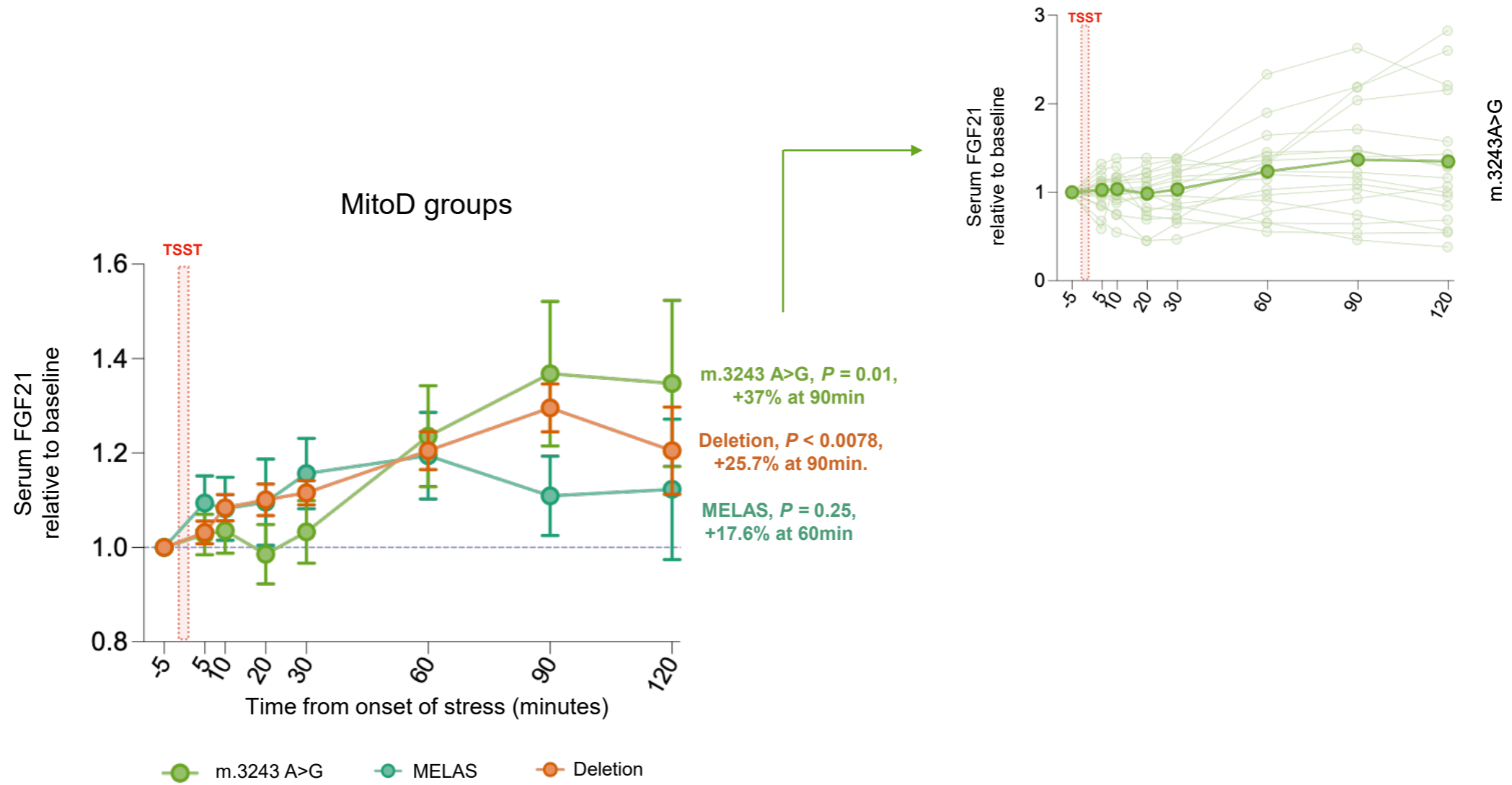
FGF21 Stress reactivity in controls



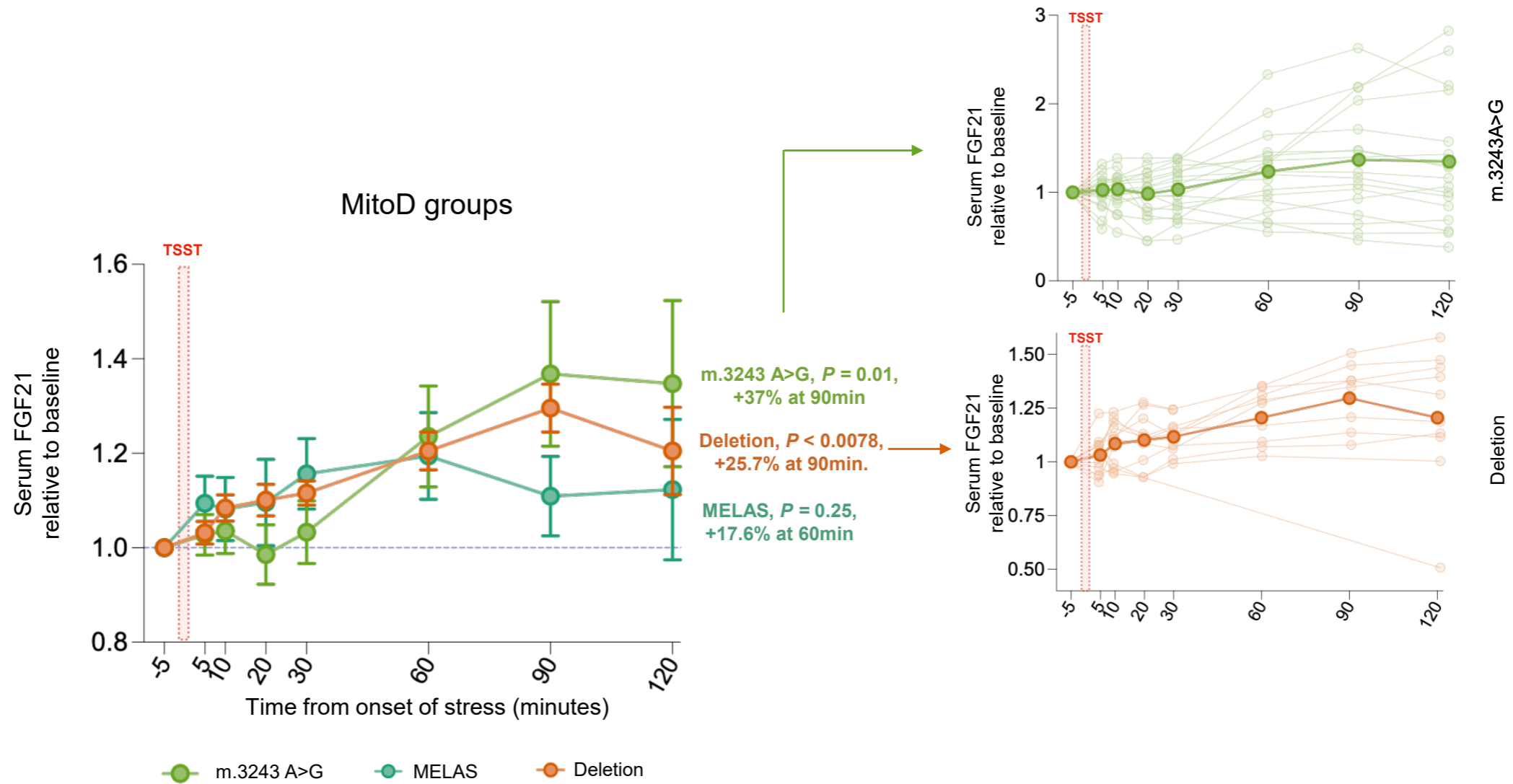
FGF21 Stress reactivity in MitoD subgroups



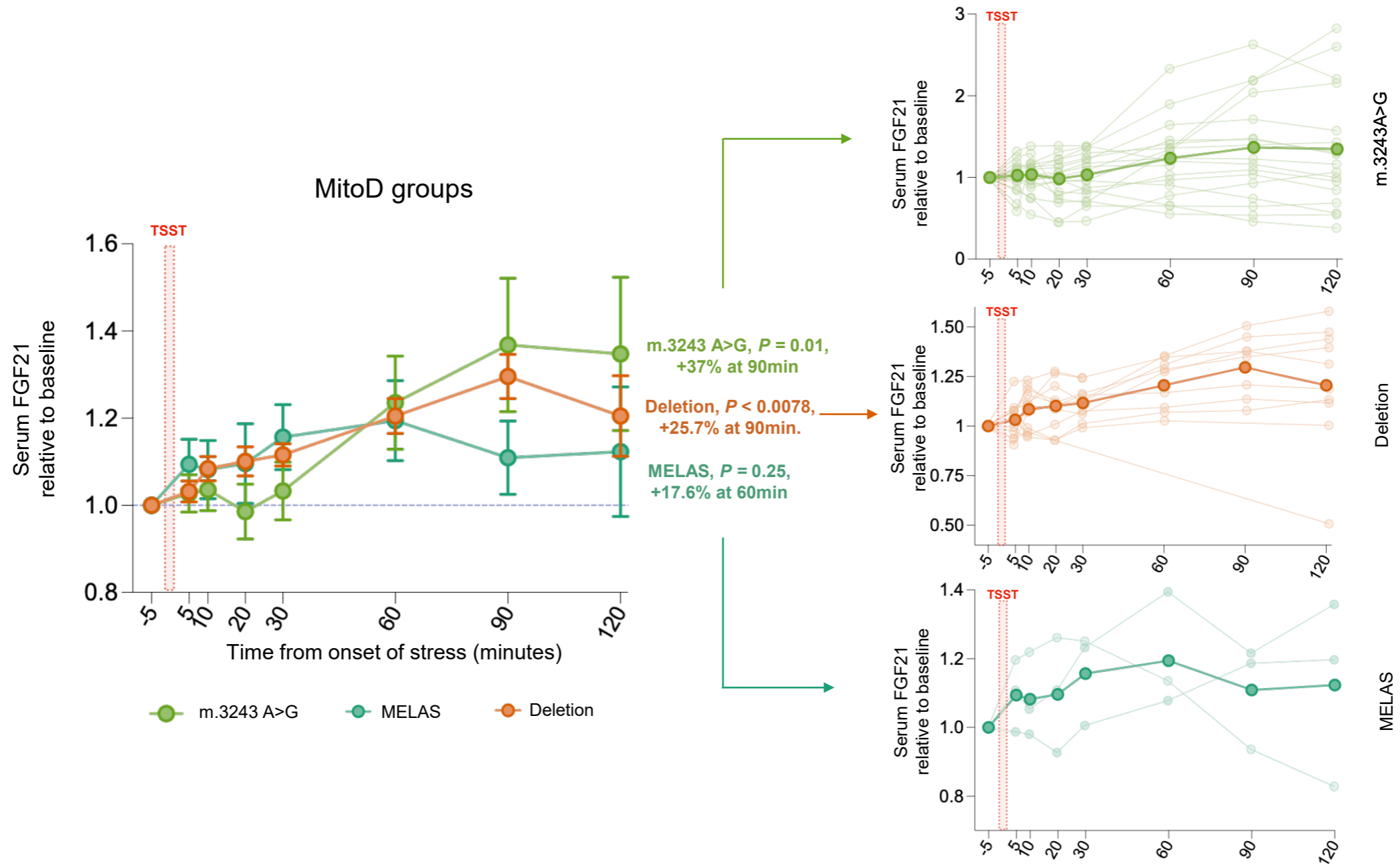
FGF21 Stress reactivity in MitoD subgroups



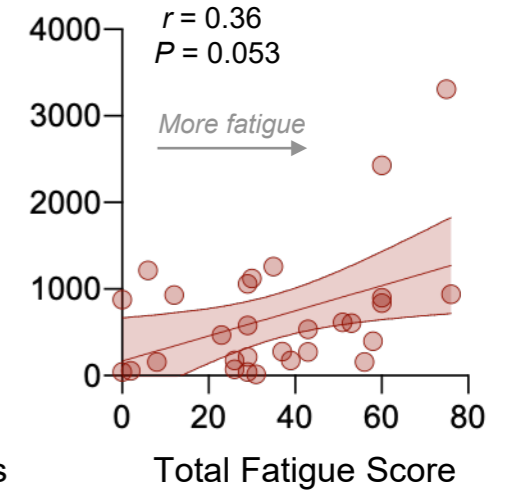
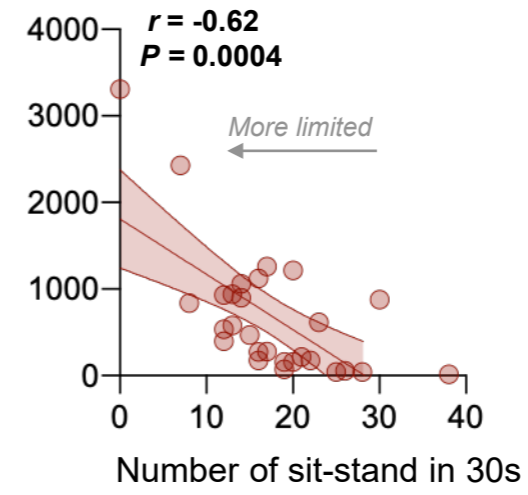
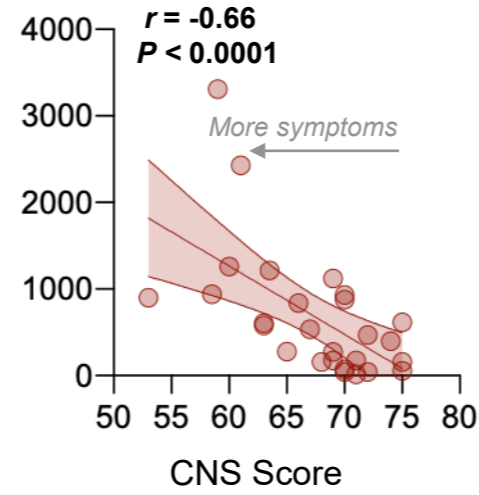
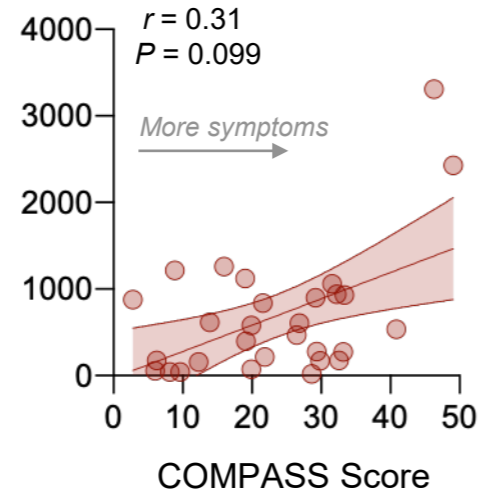
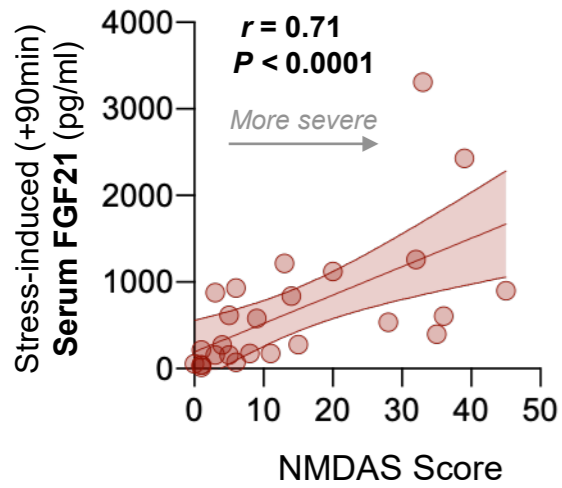
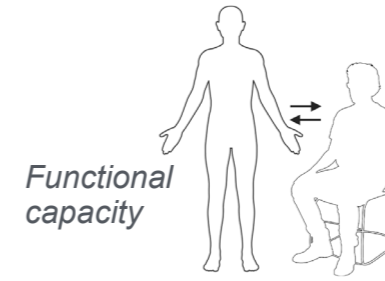
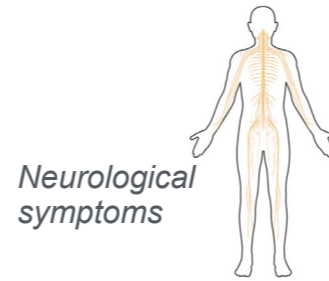
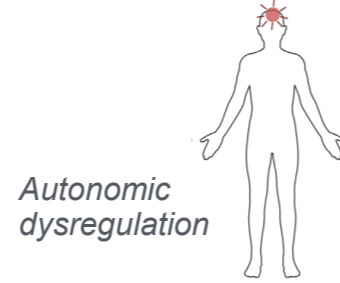
FGF21 Stress reactivity in MitoD subgroups



FGF21 Stress reactivity in MitoD subgroups



FGF21 correlates with disease burden

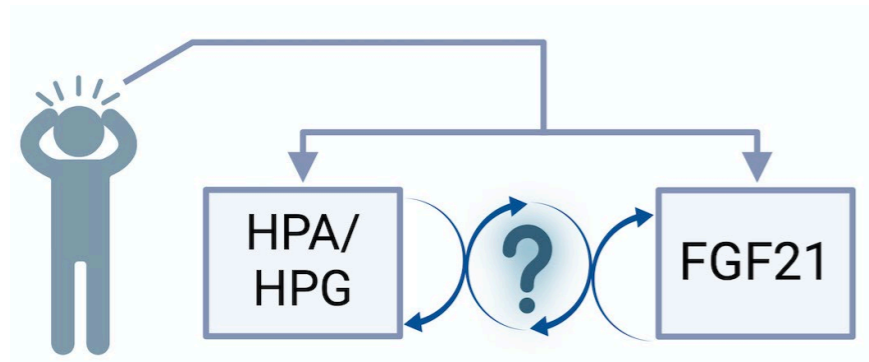


How does FGF21 interact with stress hormones?

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Steroids/hormones of

Hypothalamic-Pituitary-Adrenal and Hypothalamic-Pituitary-Gonadal Axes

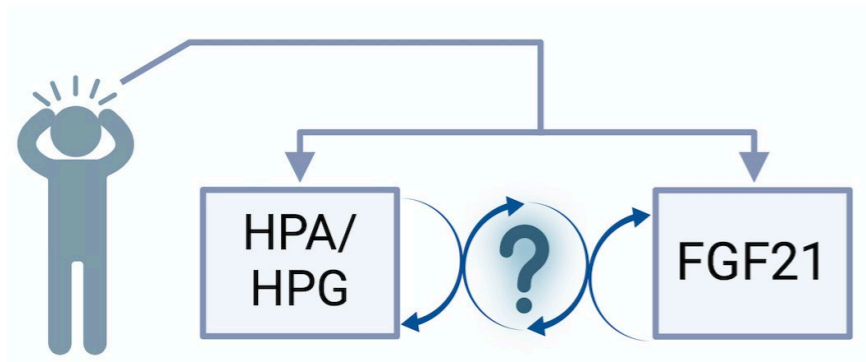


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Steroids/hormones of

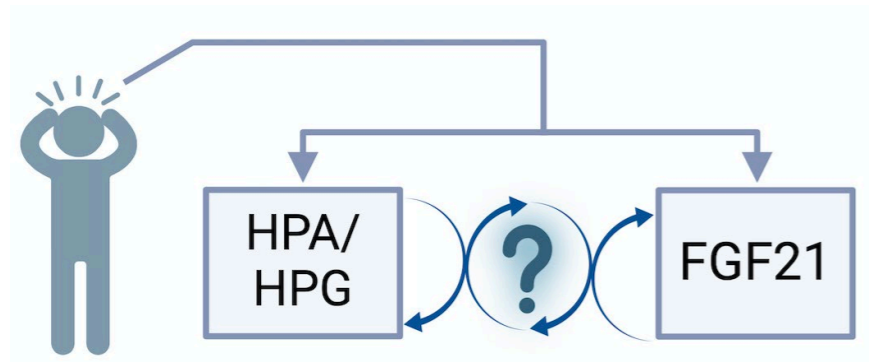
**Hypothalamic-Pituitary-Adrenal
and
Hypothalamic-Pituitary-Gonadal
Axes**

+

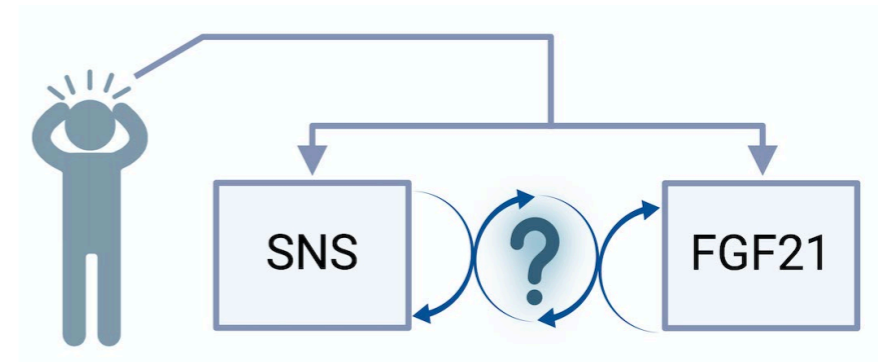


How does FGF21 interact with stress hormones?

Steroids/hormones of
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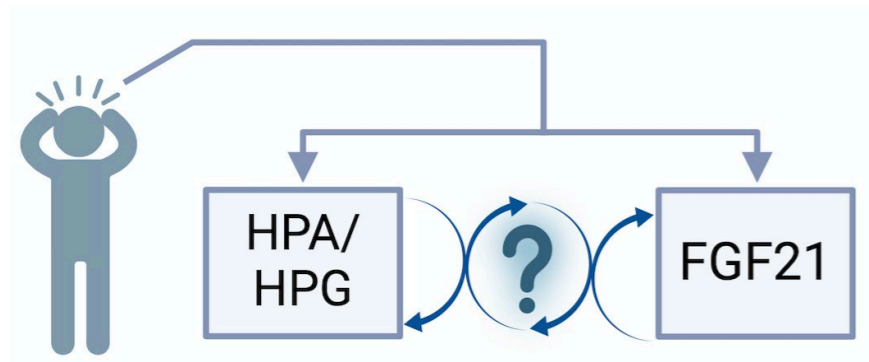
Hormones of
**Sympathetic-Nervous-System
Axis**



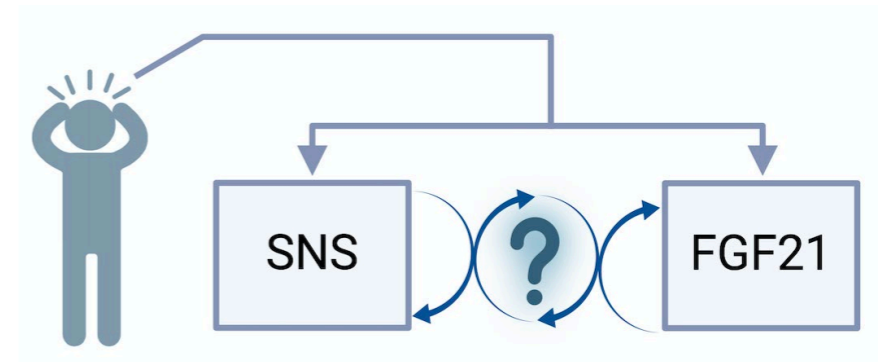
+

How does FGF21 interact with stress hormones?

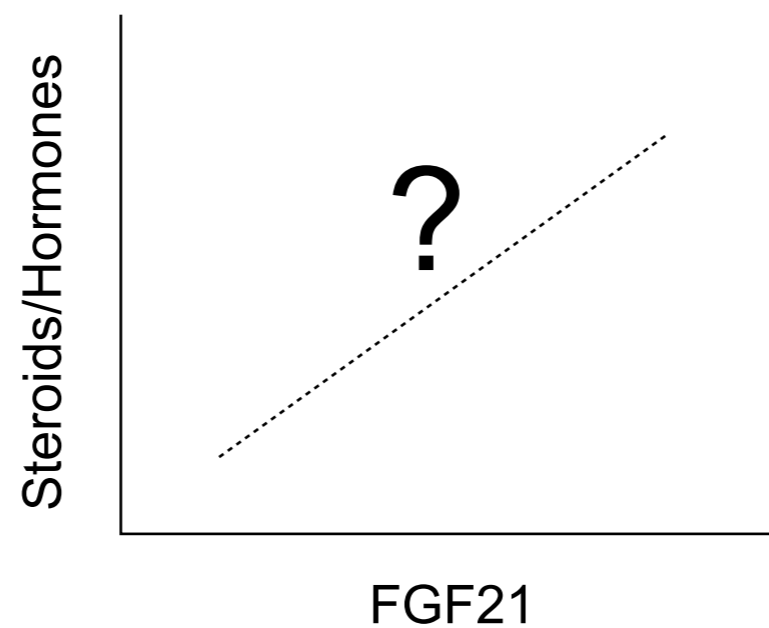
Steroids/hormones of
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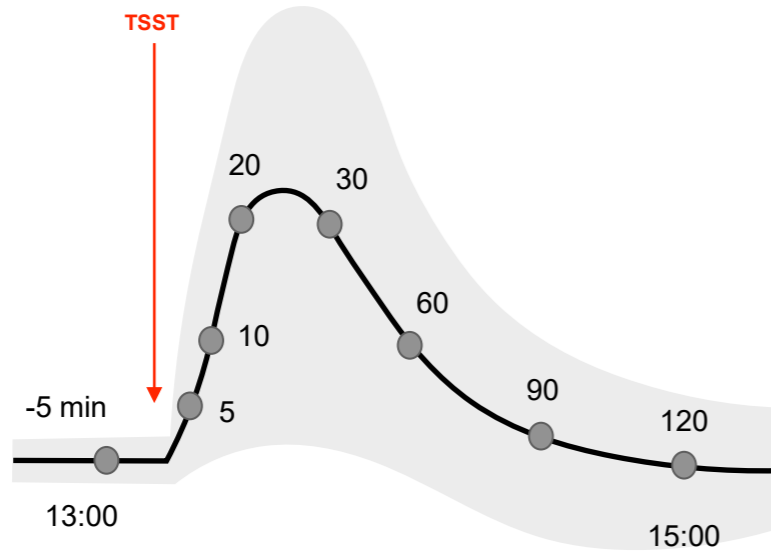
Hormones of
**Sympathetic-Nervous-System
Axis**



Correlation



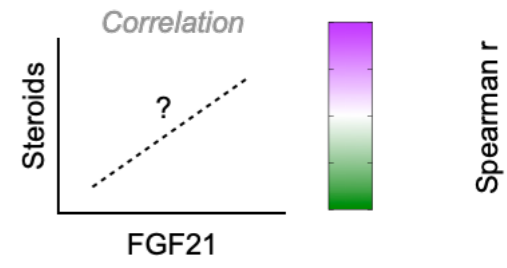
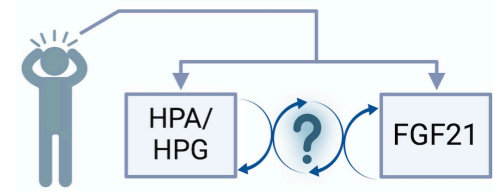
How does FGF21 interact with stress hormones?



All 8 timepoints measured in parallel across the stress time course

Blood ———●●●●●●●●————— n=8

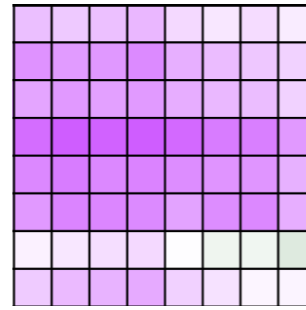
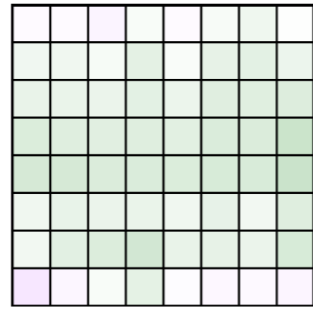
How does FGF21 interact with stress hormones?



Cortisol

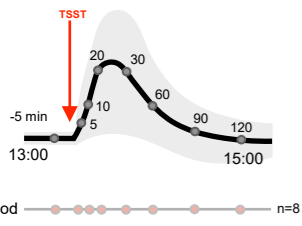
Control

MitoD

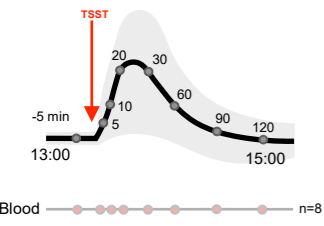
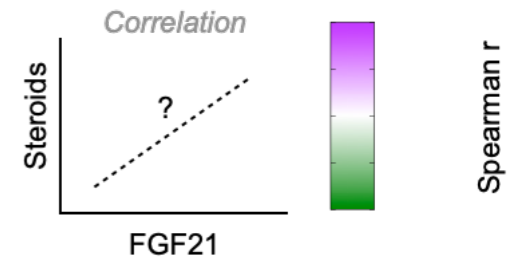
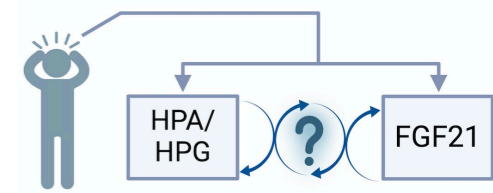


$n = 57-63$

$n = 25-32$



How does FGF21 interact with stress hormones?

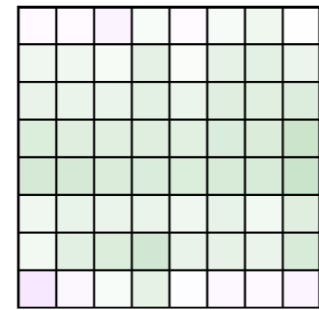


Cortisol

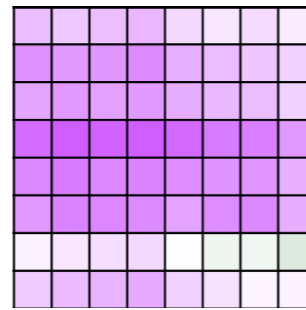
Control

MitoD

Stress timepoints 1-8
for **FGF21**

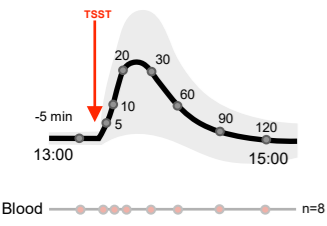
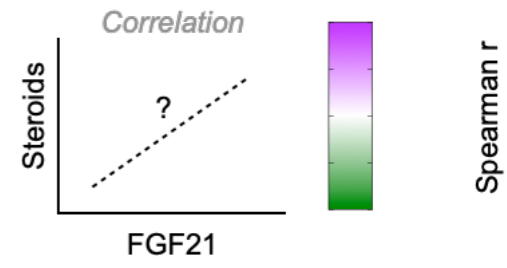
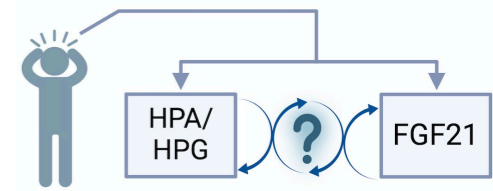


n = 57-63

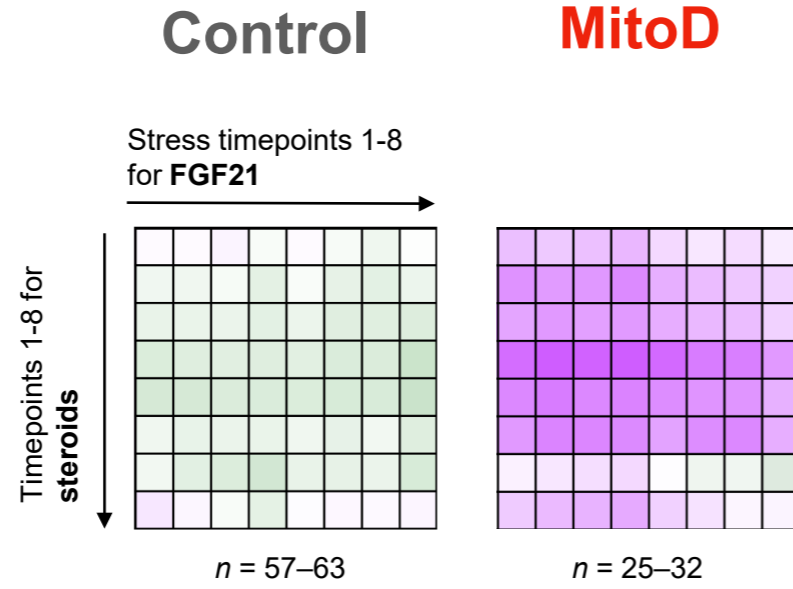


n = 25-32

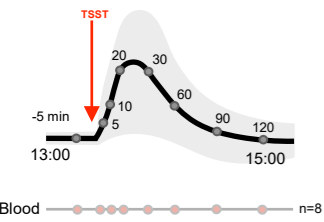
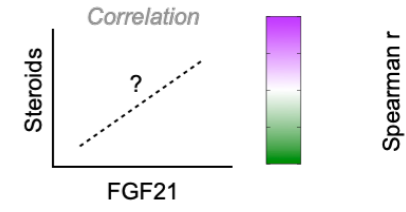
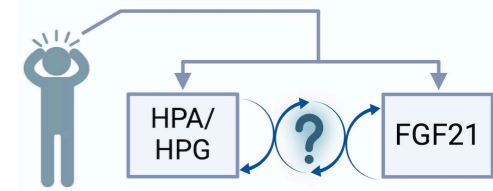
How does FGF21 interact with stress hormones?



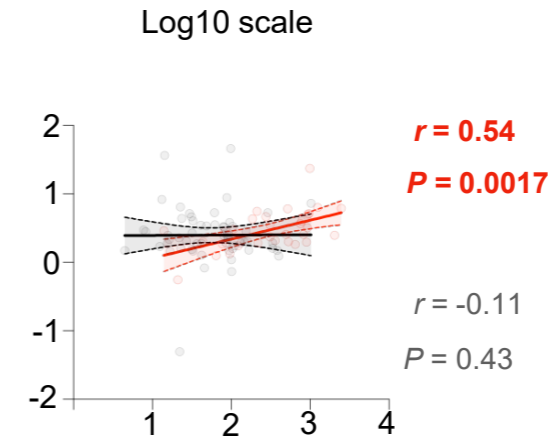
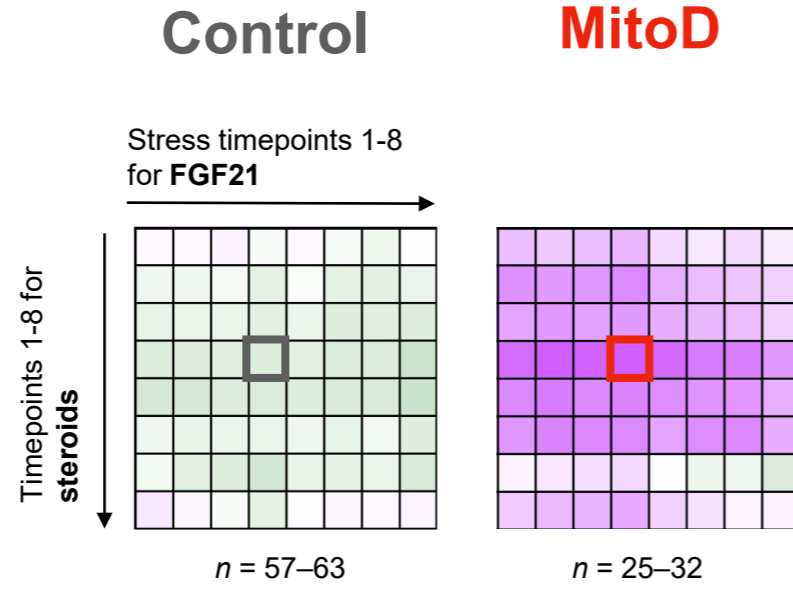
Cortisol



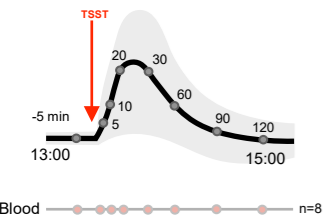
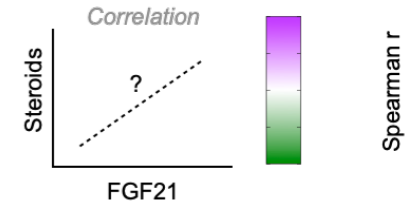
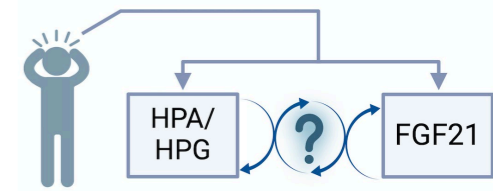
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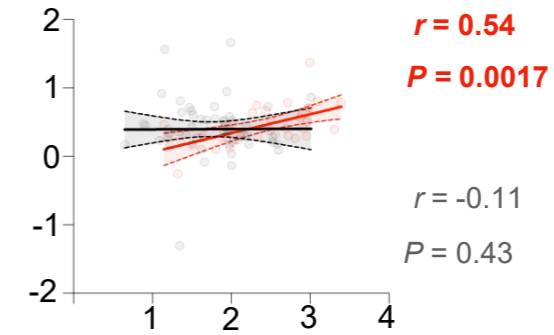
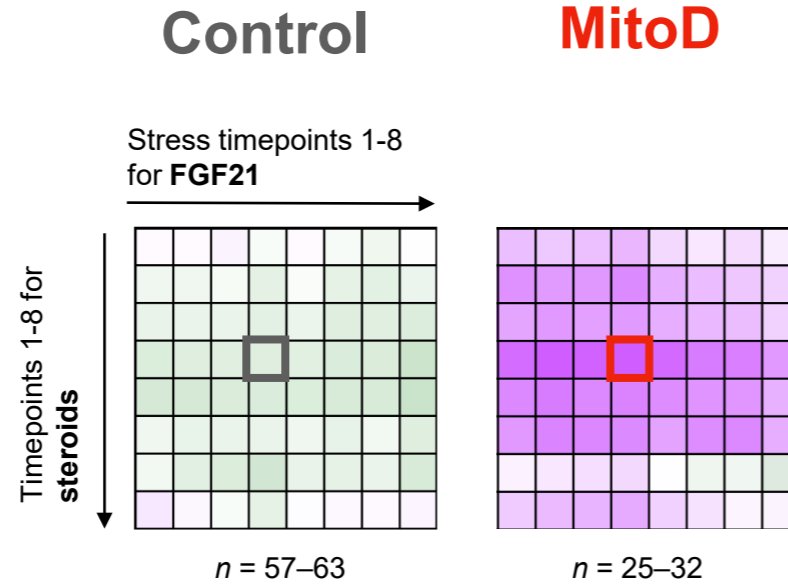
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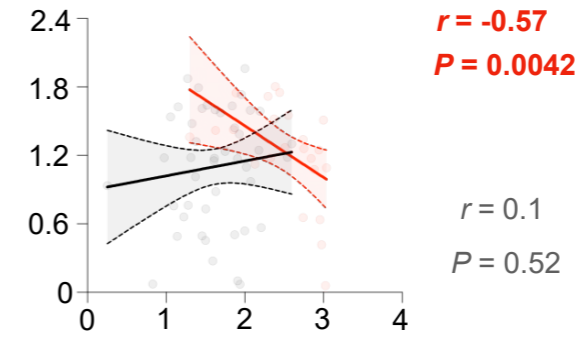
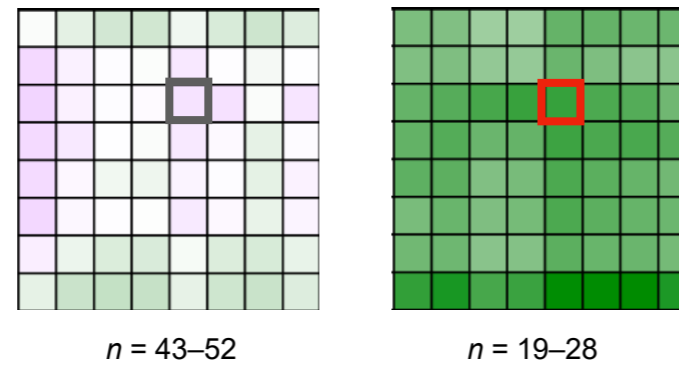
How does FGF21 interact with stress hormones?



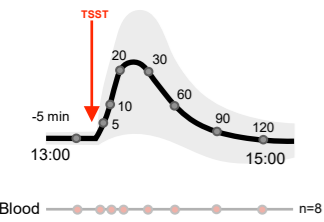
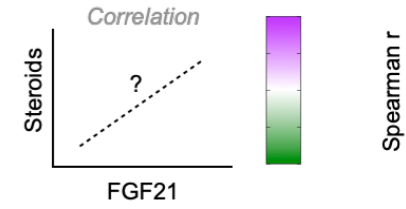
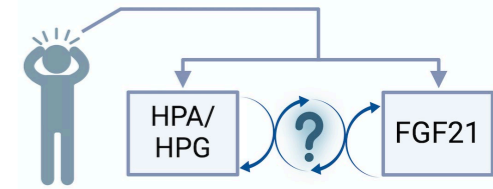
Cortisol



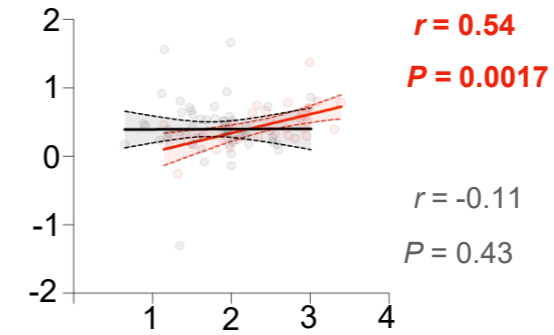
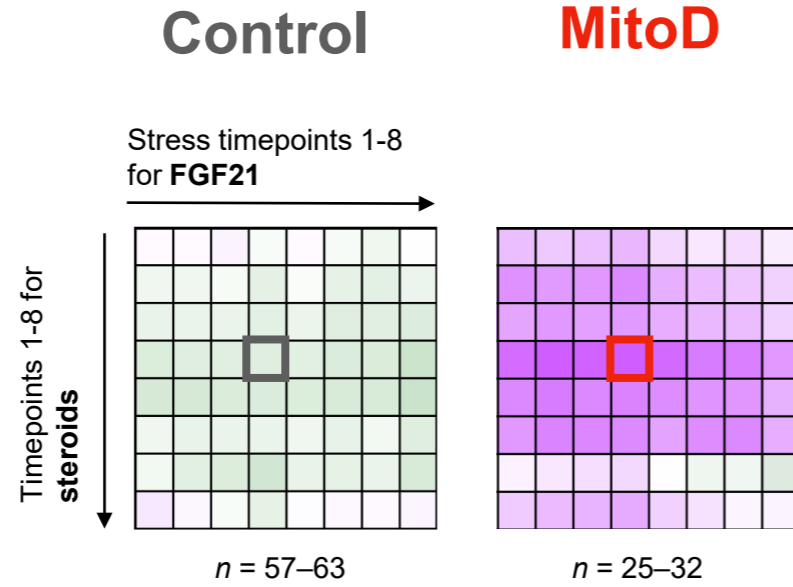
Testosterone



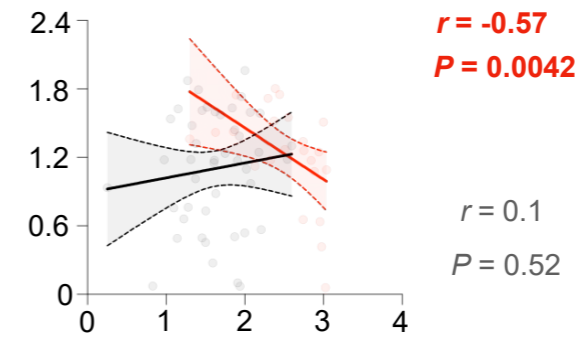
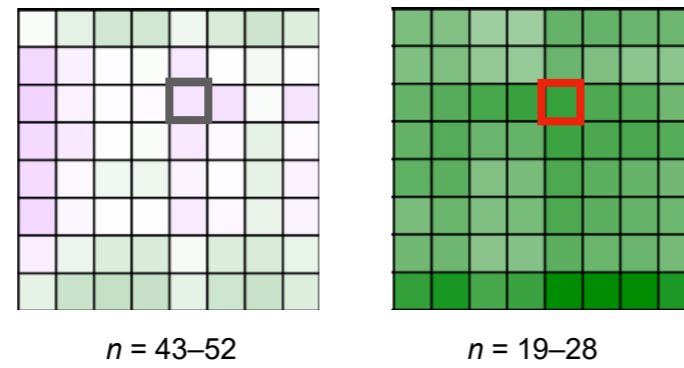
How does FGF21 interact with stress hormones?



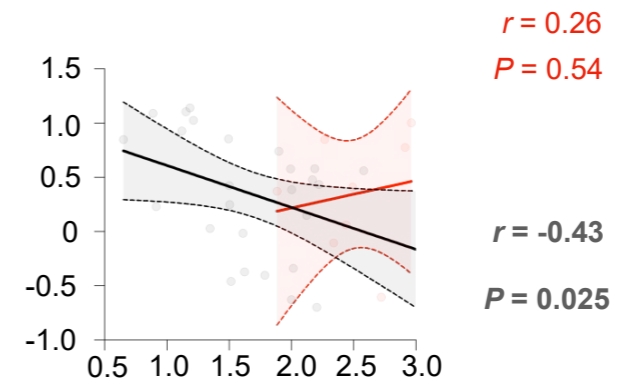
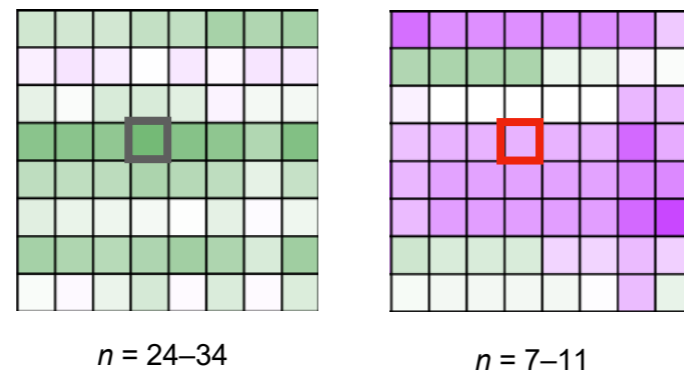
Cortisol



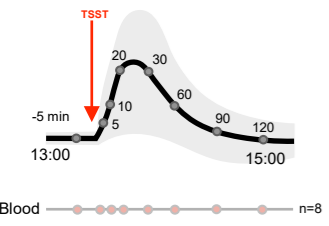
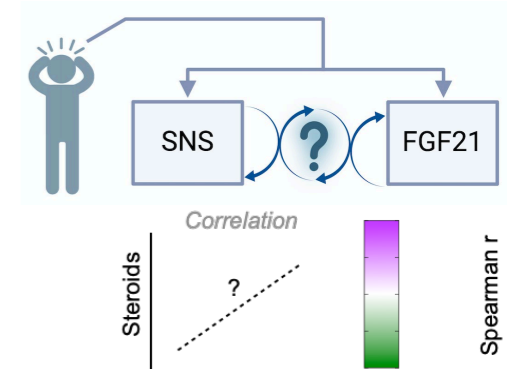
Testosterone



DHEA



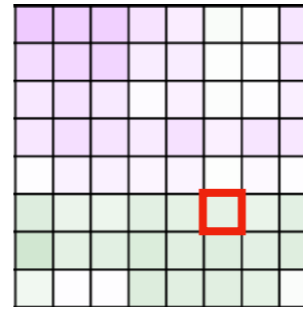
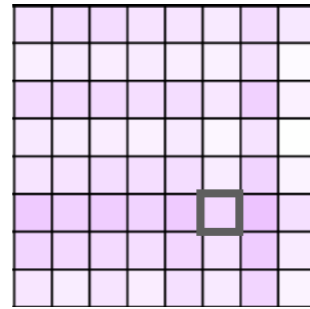
How does FGF21 interact with stress hormones?



Norepinephrine

Control

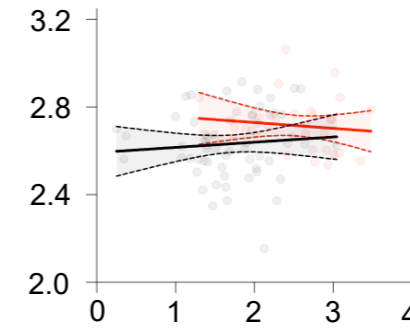
MitoD



n = 58–64

n = 28–35

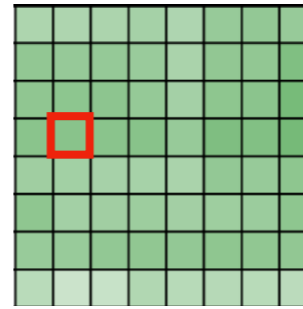
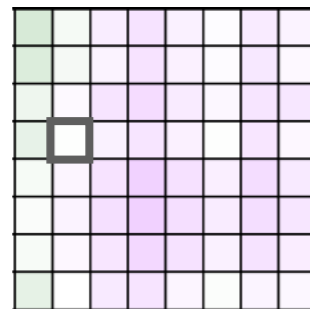
Log10 scale



r = -0.12
P = 0.54

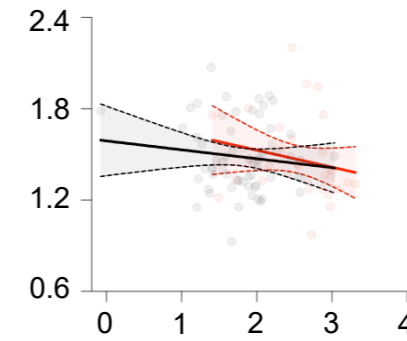
r = 0.14
P = 0.2807

Dopamine



n = 58–64

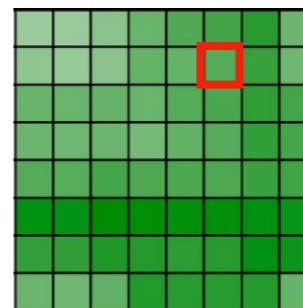
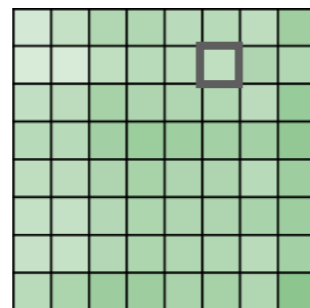
n = 28–35



r = -0.37
P = 0.033

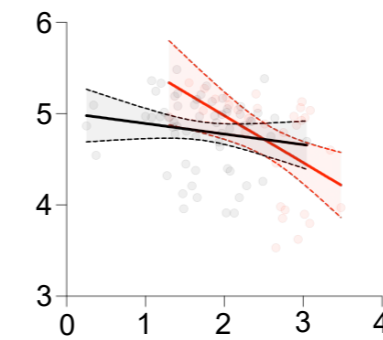
r = -0.006
P = 0.96

Serotonin



n = 58–64

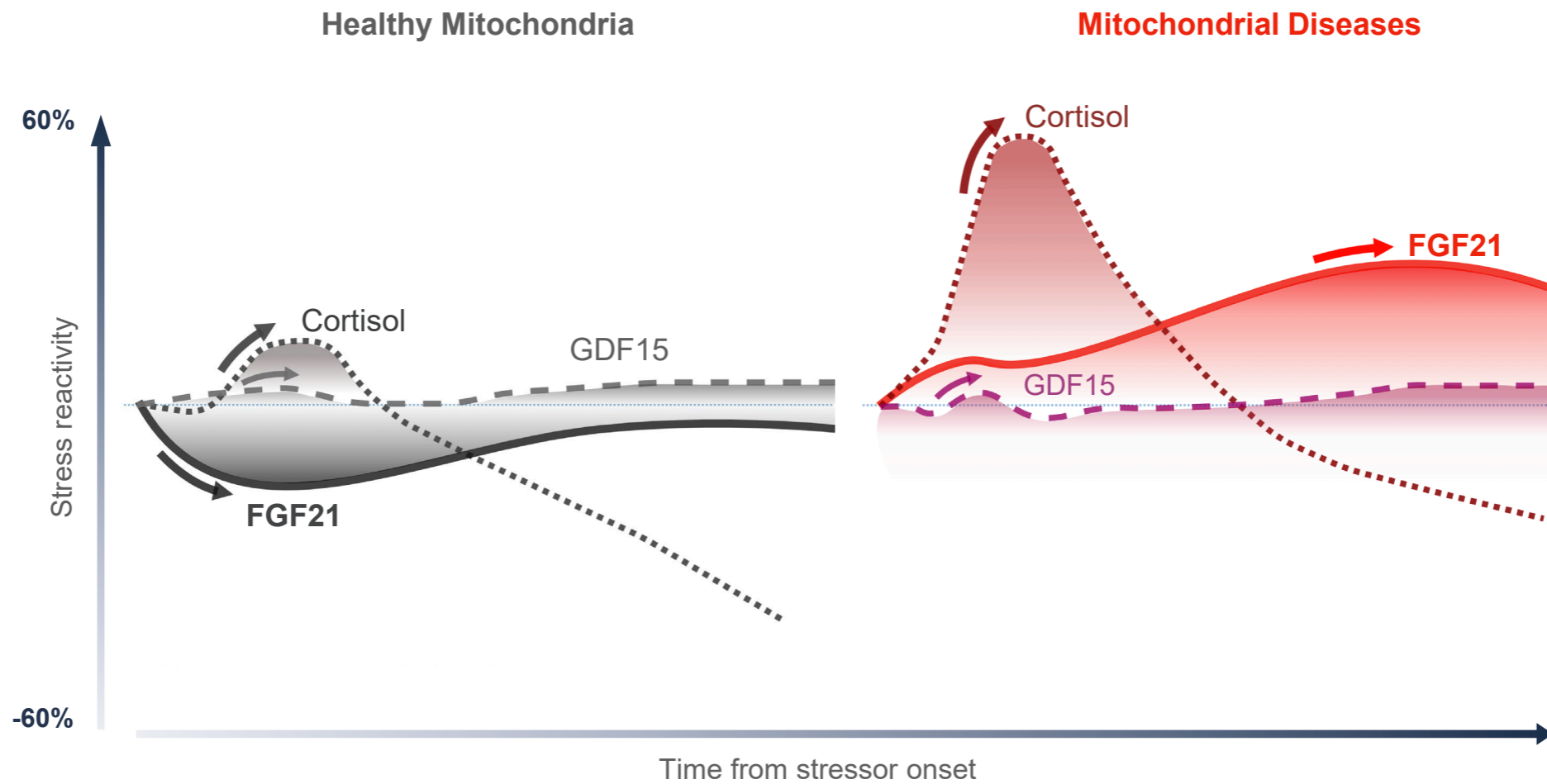
n = 28–35



r = -0.51
P = 0.0035

r = -0.21
P = 0.11

Stress-induced FGF21, GDF15, and Cortisol trajectories in the MiSBIE Study



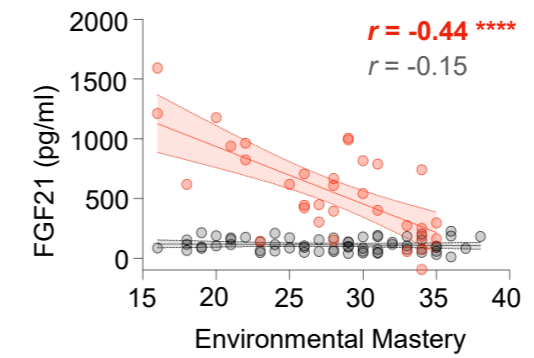
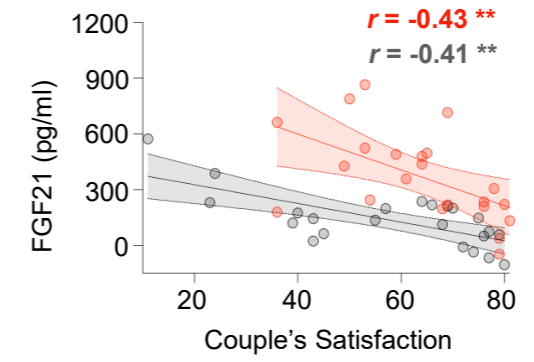
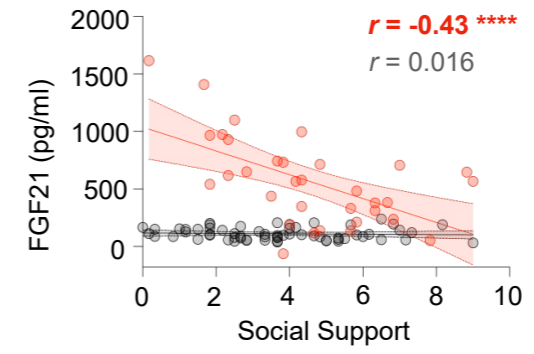
Positive Psychosocial Factors

● Control
● MitoD

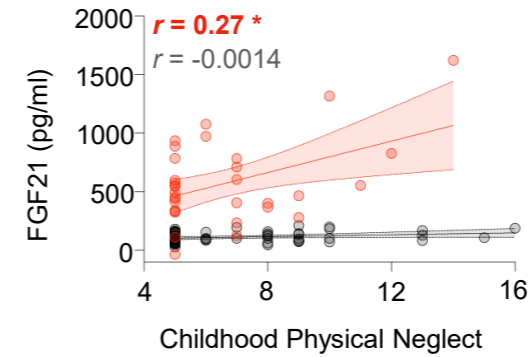
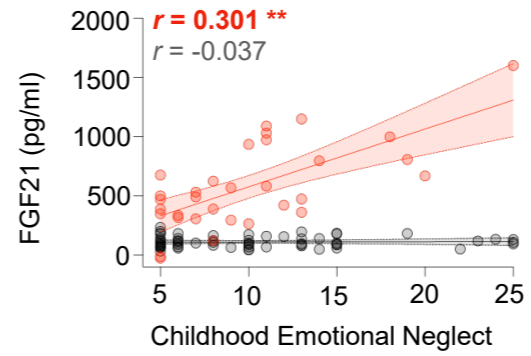
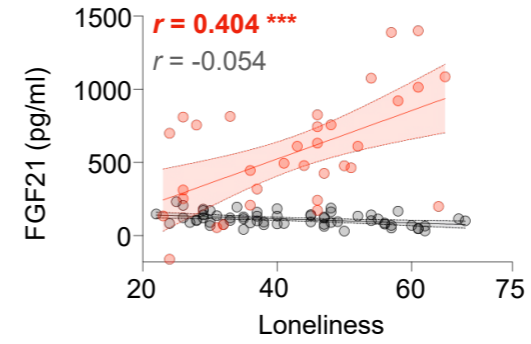
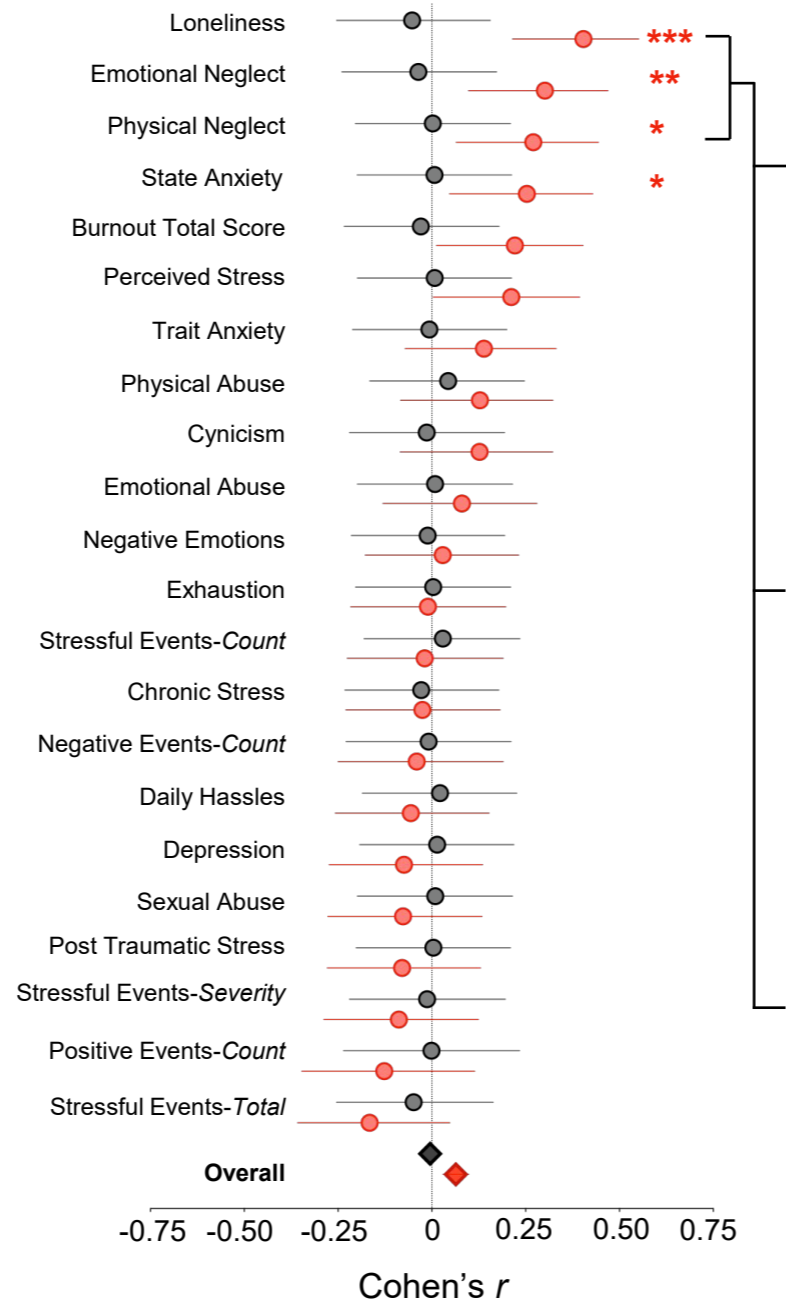


Positive Psychosocial Factors

● Control
● MitoD



Negative Psychosocial Factors



**Validated the associations between FGF21 biology
and psychosocial factors 51,818 UK Biobank participants
of various health statuses**

**Marital separation or divorce and financial difficulties
showed elevated levels of plasma FGF21**

**Engaging in non-exercise-related and non-alcohol-related
leisure and social activities was associated with lower FGF21
levels**

What did we learn?

FGF21 is a robust biomarker of mitochondrial disease, showing markedly elevated baseline levels and strong diagnostic performance

FGF21 is not only a metabolic hormone but also a stress-responsive signal, linking mitochondrial function to psychosocial stress physiology.

FGF21 shows altered coupling with the HPA axis and SNS in MitoD.

FGF21 reactivity reflects clinical disease severity.

Psychosocial environment modulates metabolic stress signaling

What did we learn?

For Mitochondrial disease:

Improves diagnosis of mitochondrial disease, reinforcing FGF21 as a sensitive and informative biomarker

Enables better monitoring of disease severity and progression, using repeated measures rather than single measurements.

For Human health:

Supports integrated care approaches, where managing psychosocial stress may reduce metabolic burden in vulnerable individuals.

Advances personalized medicine, identifying individuals with heightened metabolic sensitivity to stress

Bridges mental and metabolic health, positioning FGF21 as a measurable link between psychosocial stress and physiological energy regulation.



Thank you!
Questions?

BASZUCKI
BRAIN RESEARCH FUND

NIH National Institute
of Mental Health

The Nathaniel
Wharton Fund *nwf*