

Expanding FASD Prevention: Combined Parental Alcohol Use Shapes Offspring Aging and Chronic Disease Risk

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National Institute
on Alcohol Abuse
and Alcoholism

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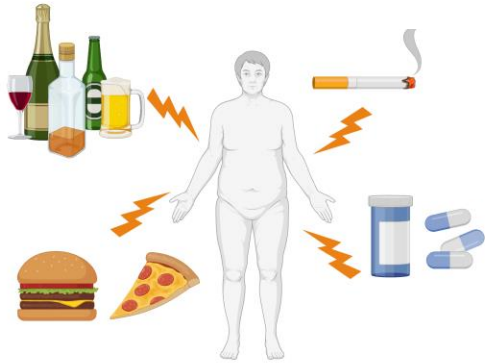
Paternal Contributions to FASDs

Is Dad the missing piece?



What does this mean? Can paternal alcohol use explain the wide variation in FASD severity and prevalence?

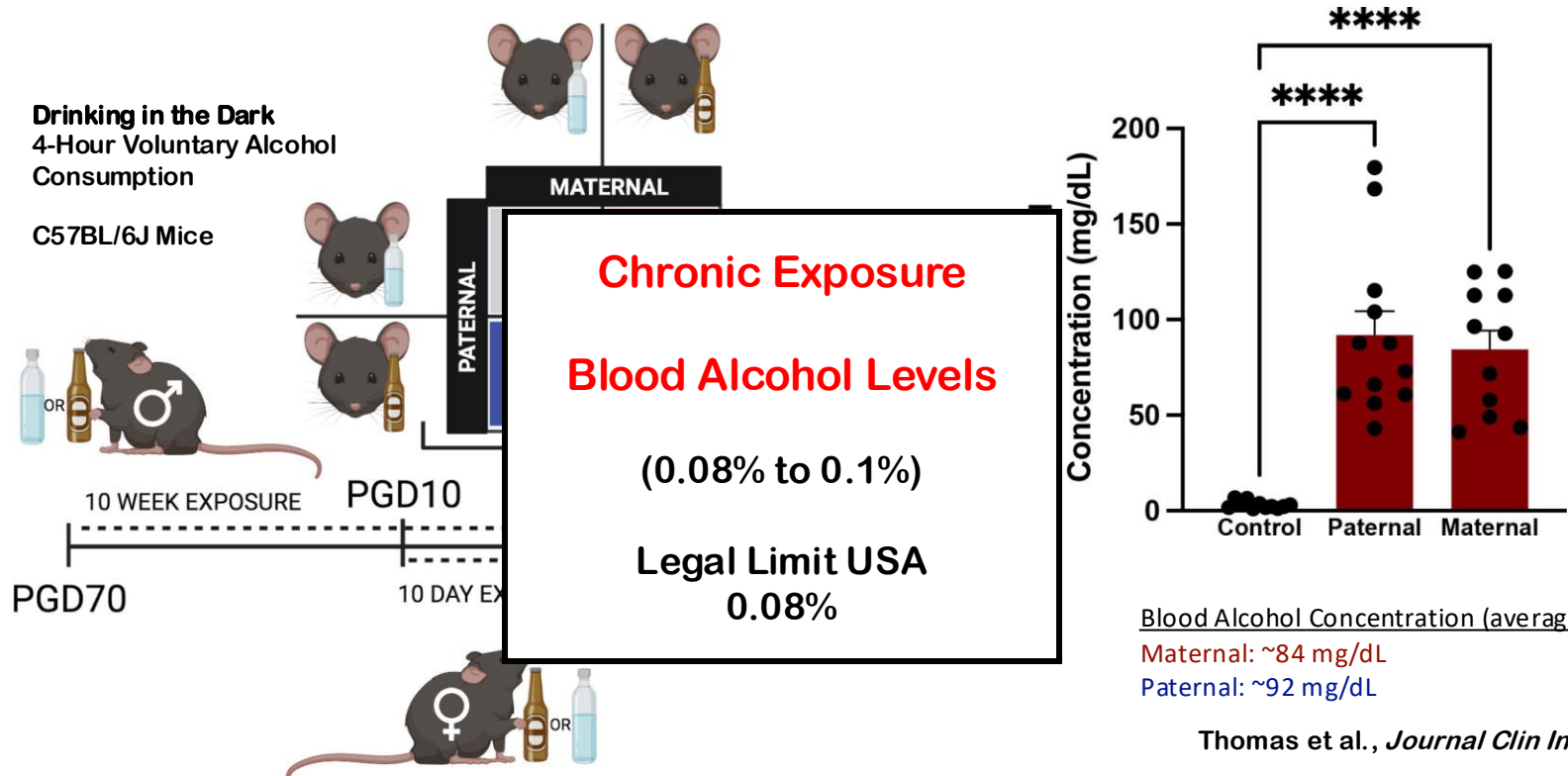
Paternal Contributions to FASDs



Preconception Male Lifestyle & Health

What does this mean? I wanted to know what happens if both Mom and Dad drink; do things get worse?

Dual Parental Model of Alcohol Exposure



What does this mean? We developed a mouse model to examine what happens when both Mom and Dad drink.

Paternal Contribution to Fetal Alcohol Syndrome?

Time for a stiff drink

Average number of drinks per capita consumed in the past week, by decile, among adults aged 18 and over.

The top 10% of American adults – 24 million of them, consume an average of 74 drinks per week or more than 10 drinks per day.



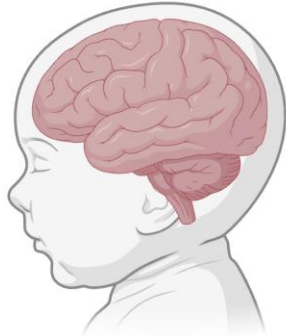
Number of drinks per week

Philip J. Cook, Paying the Tab: The Costs and Benefits of Alcohol Control (Figure). Bose et al., 2017 National survey on drug use and health

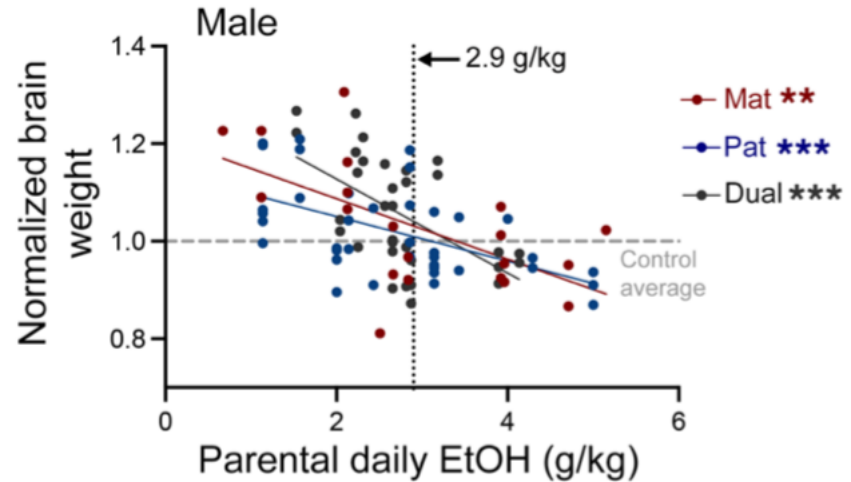
What does this mean? In the US, 8.3% of all adults of reproductive age consume 2 to 10 drinks per day. Our model approximates this population.

Dose-Dependent Changes in Placental & Craniofacial Growth

Microcephaly



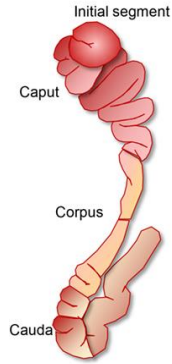
Brain Weight
Body Weight



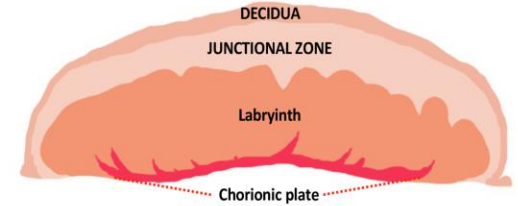
Thomas et al., *Journal Clin Invest.* 2023

What does this mean? We see dose-dependent impacts from maternal, paternal, and Dual-Parental alcohol exposures.

Maternal & Paternal Alcohol Exposure & Mitochondrial Stress



Morula		
DEGs	Top 5 Canonical Pathways	p-value (E ^Λ)
1,263 ↓ 417, 619 ↑	Mitochondrial Dysfunction	-7
	Oxidative Phosphorylation	-7
	Granzyme A Signaling	-6
	Sirtuin Signaling Pathway	-4
	Inhibition of Angiogenesis	-3



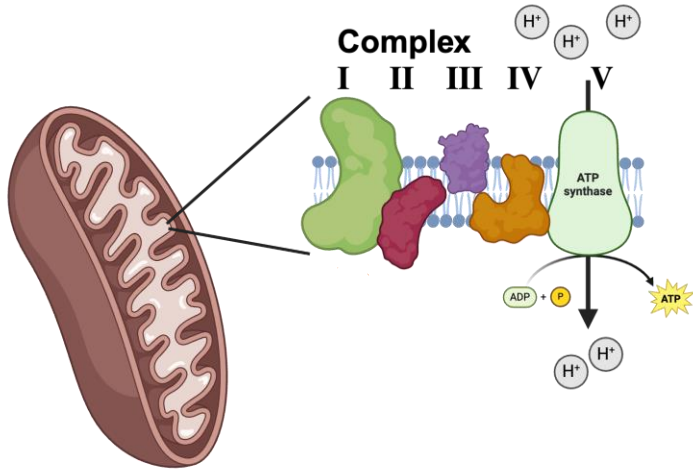
Epididymis		
DEGs	Top 5 Canonical Pathways	p-value (E ^Λ)
1,423 ↓ 940, 483 ↑	Oxidative Phosphorylation	-7
	Mitochondrial Dysfunction	-6
	Protein Ubiquination Pathway	-6
	EIF2 Signaling	-5
	eIF4 and p70S6K Signaling	-5

Number of DEGs	Top 5 Canonical Pathways	p-value (E ^Λ)
431 ↓ 175, 256 ↑	Oxidative Phosphorylation	-12
	Mitochondrial Dysfunction	-10
	EIF2 Signaling	-7
	Sirtuin Signaling Pathway	-6
	Estrogen Receptor Signaling	-4

Roach et al., *Andrology*, 2023; Roach et al., *Mol Hum Repro* 2023

What does this mean? Our analysis suggests that maternal and paternal alcohol exposures alter offspring mitochondrial health.

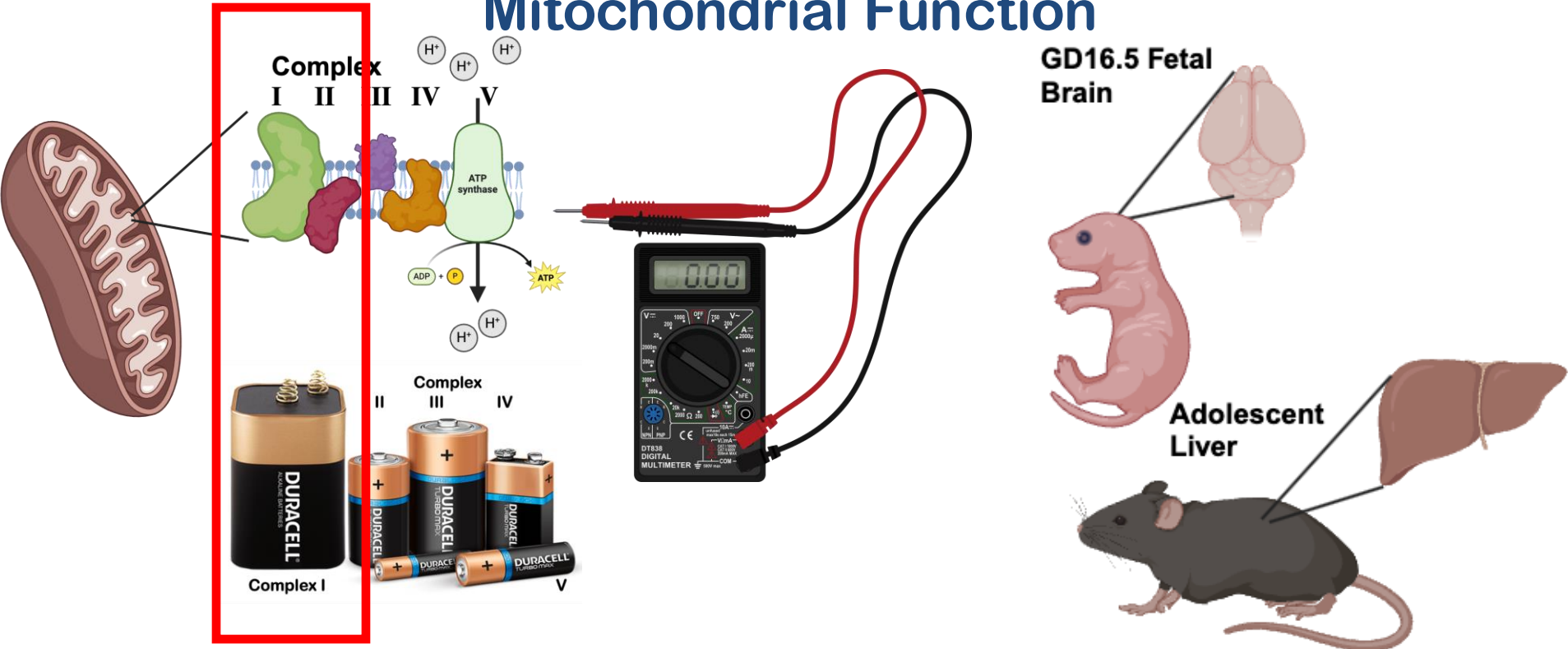
Paternal Alcohol Use Causes Heritable Mitochondrial Stress



Hypothesis: The mitochondrial stress caused by chronic alcohol exposure causes an adverse form of mitochondrial adaptation in offspring.

What does this mean? I suspect that Mom and Dad's alcohol use transmits a memory to the offspring that compromises long-term mitochondrial function.

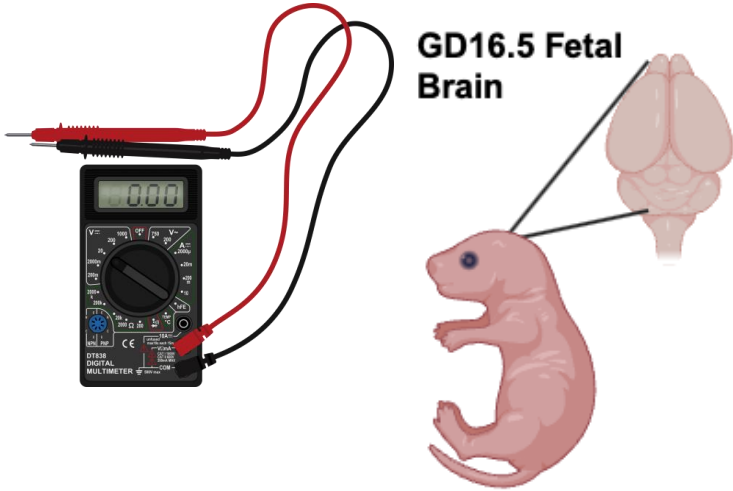
Paternal Alcohol Use Alters Offspring Mitochondrial Function



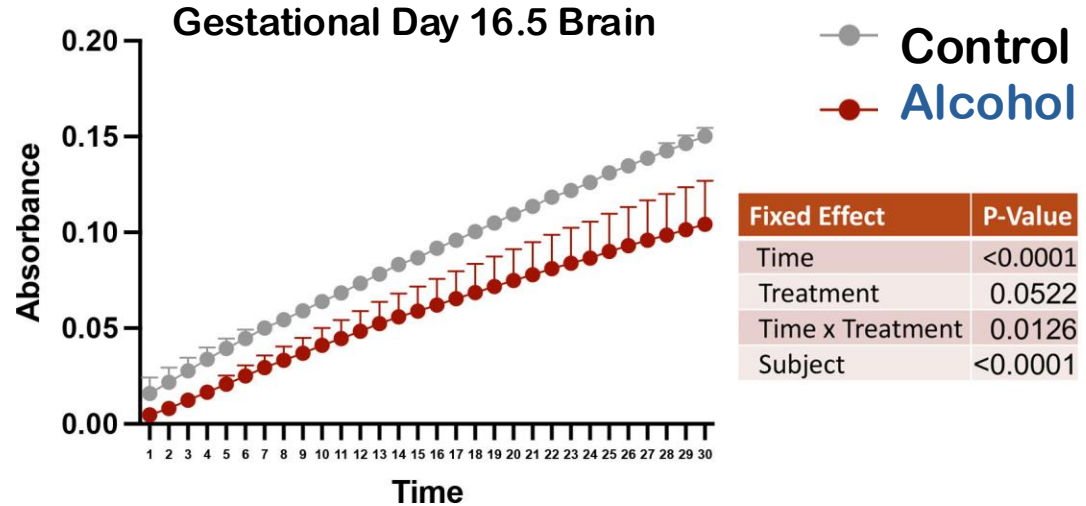
What does this mean? I wanted to know if dad's drinking impacts his children's mitochondria .

Paternal Alcohol Use Alters Offspring Mitochondrial Function

Paternal Exposure Only



Fetal Development

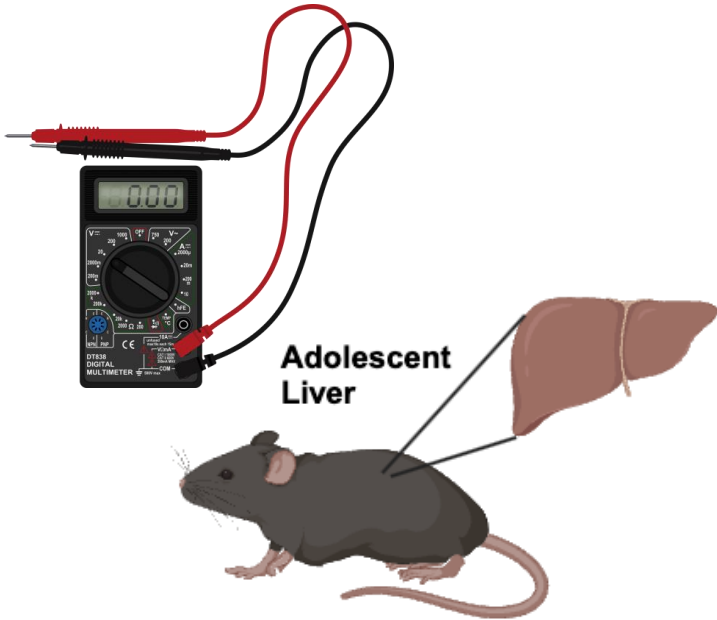


Bhadsavle *unpublished*

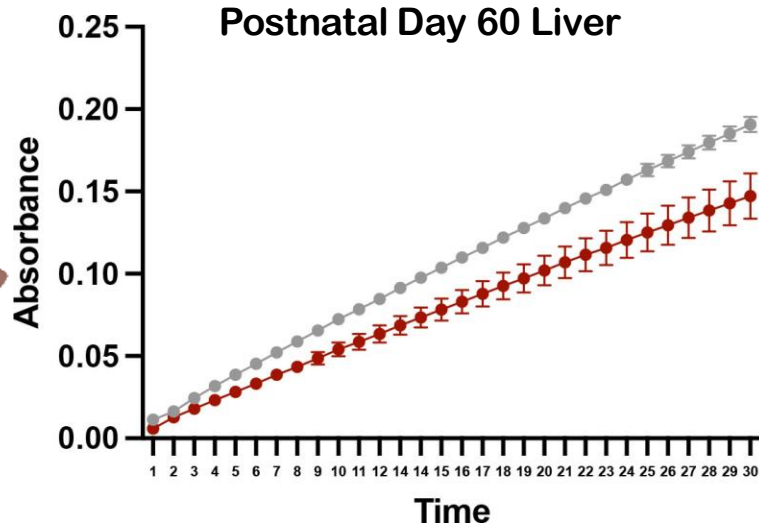
What does this mean? Paternal alcohol use changes mitochondrial function in the developing brain.

Paternal Alcohol Use Alters Offspring Mitochondrial Function

Paternal Exposure Only



Adolescence / Early Adult



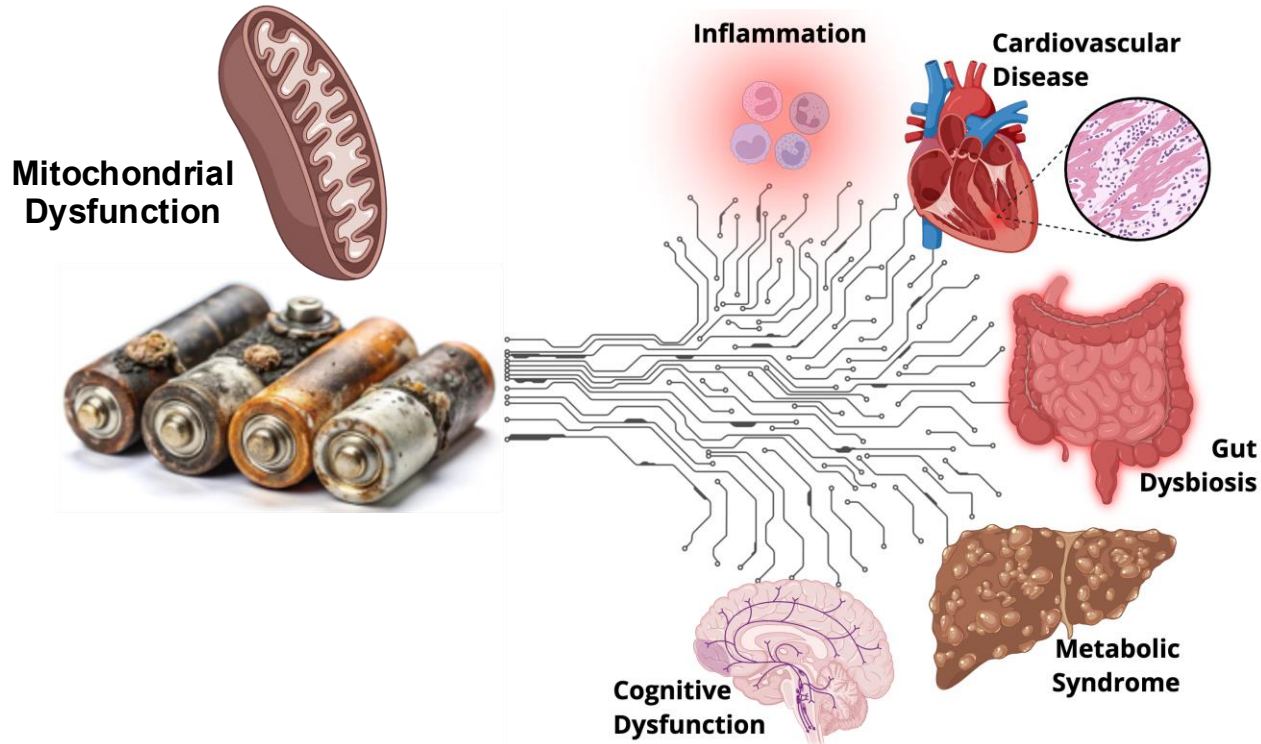
Control
Alcohol

Fixed Effect	P-Value
Time	<0.0001
Treatment	0.0068
Time x Treatment	<0.0001
Subject	<0.0001

Bhadsavle *unpublished*

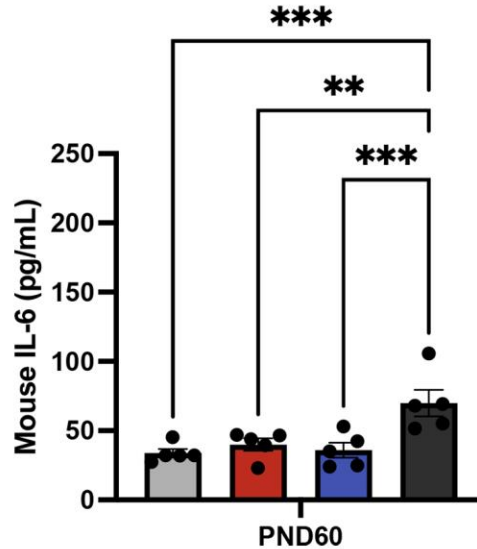
What does this mean? Chronic paternal alcohol use has long-term effects on his children's mitochondrial function – even into late adolescence / early adulthood.

Paternal Alcohol Use Alters Offspring Mitochondrial Function

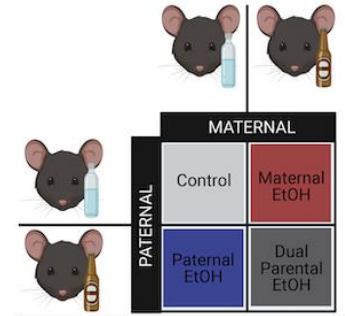


What does this mean? Altered mitochondrial function and downstream inflammation drive chronic disease.

Paternal Alcohol Use Alters Offspring Mitochondrial Function



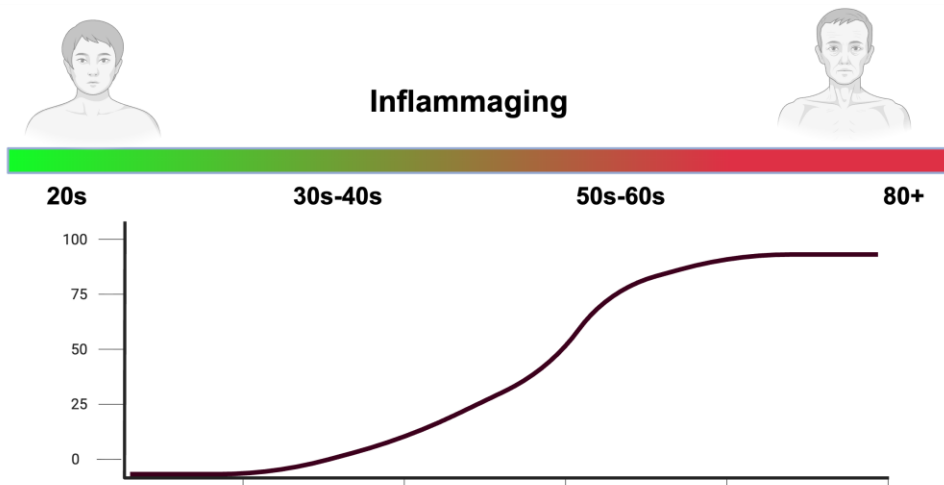
Time $p < 0.0001$
Alcohol $p < 0.0001$
Interaction $p < 0.0001$



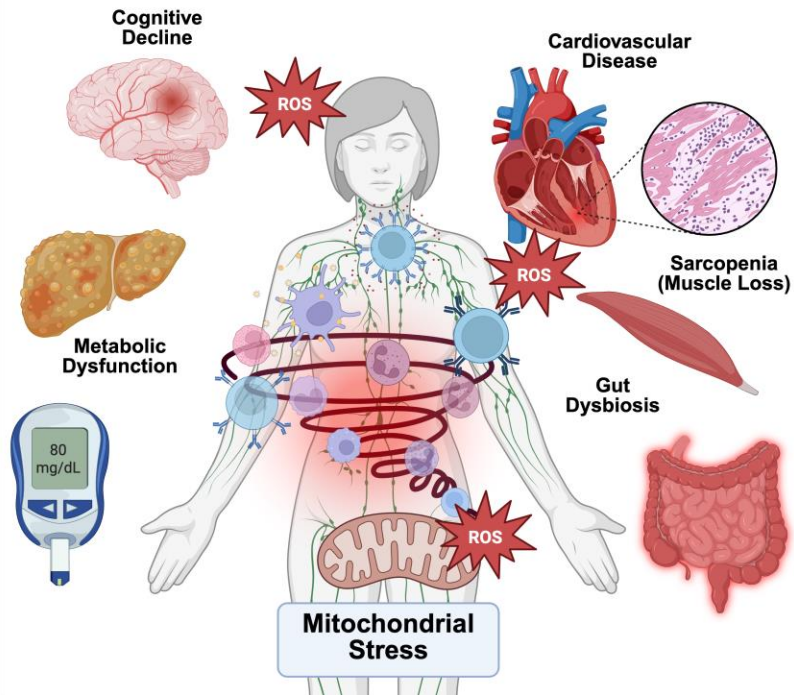
Inflammatory IL-6 Expression Across Life – Basel et al., 2025

What does this mean? We see evidence that parental alcohol use causes increased chronic inflammation that persists across the life course.

Heritable Mitochondrial Stress and Inflammaging

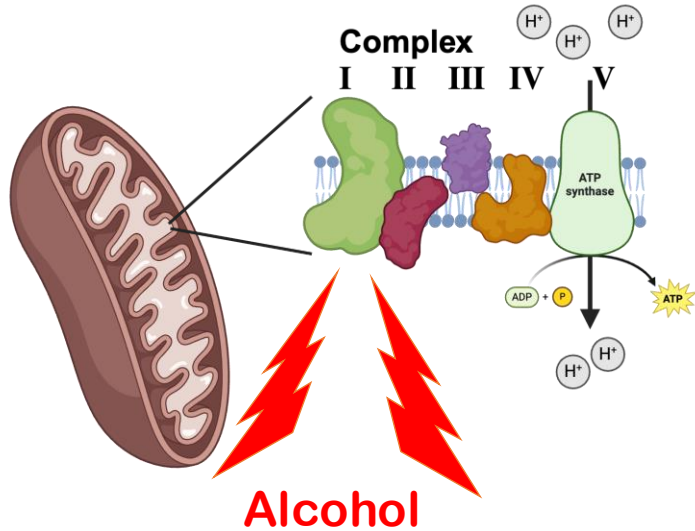


Inflammaging is chronic, low-grade, sterile inflammation that accelerates aging and drives age-related diseases.



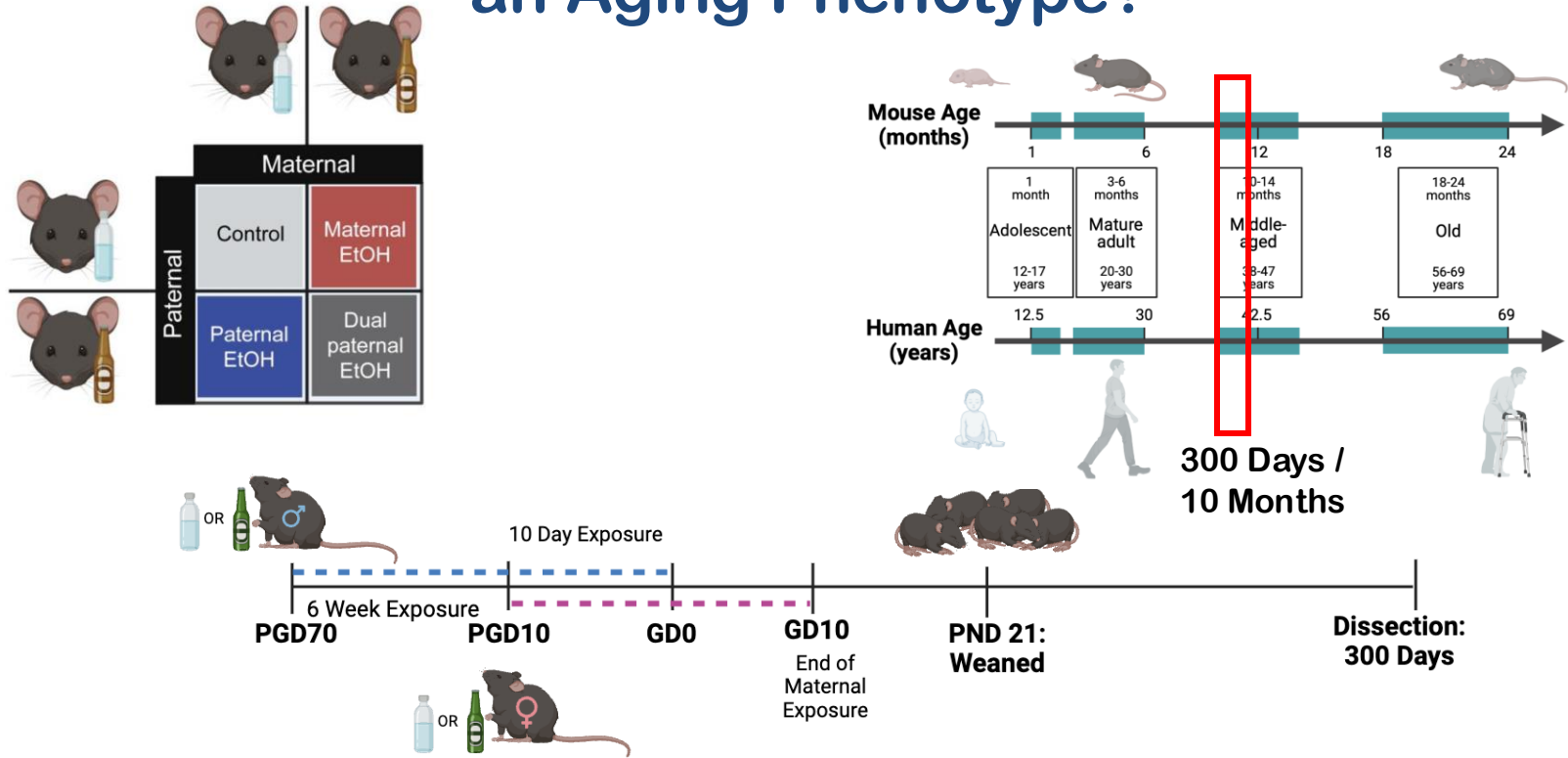
What does this mean? Increased inflammation accelerates the onset of age-related disease and frailty.

Heritable Mitochondrial Stress and Inflammaging



Hypothesis: The mitochondrial stress caused by chronic parental alcohol exposure causes an adverse form of mitochondrial adaptation that predisposes offspring to accelerated aging and chronic disease.

Do Parental Alcohol Exposures Program an Aging Phenotype?



What does this mean? We developed a mouse model to examine parental alcohol and the impacts on aging.

Parental Alcohol Exposures And Aging

Cage E

Igloo
Tunnel
Abund
Gum
Manza

Cait et al. *BMC Biology* (2022) 20:15
<https://doi.org/10.1186/s12915-021-01184-0>

BMC Biology

RESEARCH ARTICLE Open Access

Conventional laboratory housing increases morbidity and mortality in research rodents: results of a meta-analysis

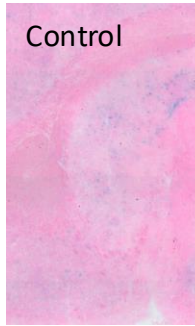
Jessica Cait¹, Alissa Cait², R. Wilder Scott³, Charlotte B. Winder⁴ and Georgia J. Mason^{1*}



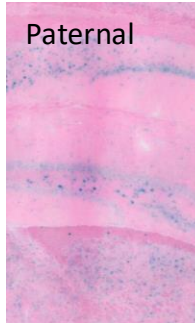
What does this mean? Cage enrichment is necessary to overcome the stress of alcohol withdrawal and prevent BOTH pregnancy loss and pup loss.

Parental Alcohol Exposures And Aging

Brain (Hip



Control



Paternal

nature
protocols

PROTOCOL

<https://doi.org/10.1038/s41596-021-00505-5>



Algorithmic assessment of cellular senescence in experimental and clinical specimens

J. Kohli^{1,7}, B. Wang^{1,7}, S. M. Brandenburg¹, N. Basisty², K. Evangelou³, M. Varela-Eirin¹, J. Campisi², B. Schilling², V. Gorgoulis^{3,4,5,6} and M. Demaria¹

Phase I
Senescence
validation

- SA-β-Gal or lipofuscin plus proliferation markers
- p16, p21, lamin B1 and core senescence transcripts
- Core SASP secreted proteins

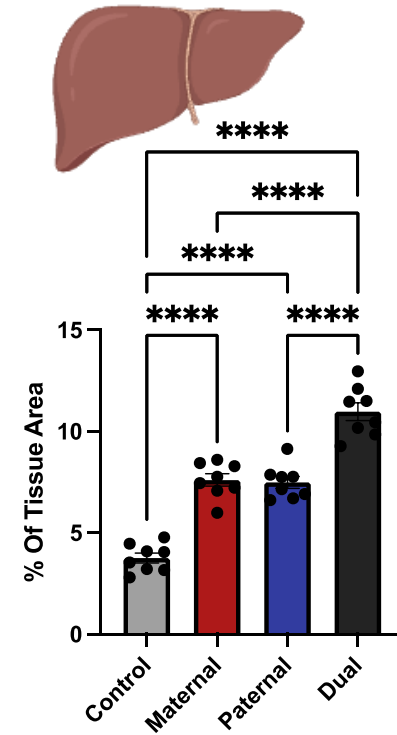
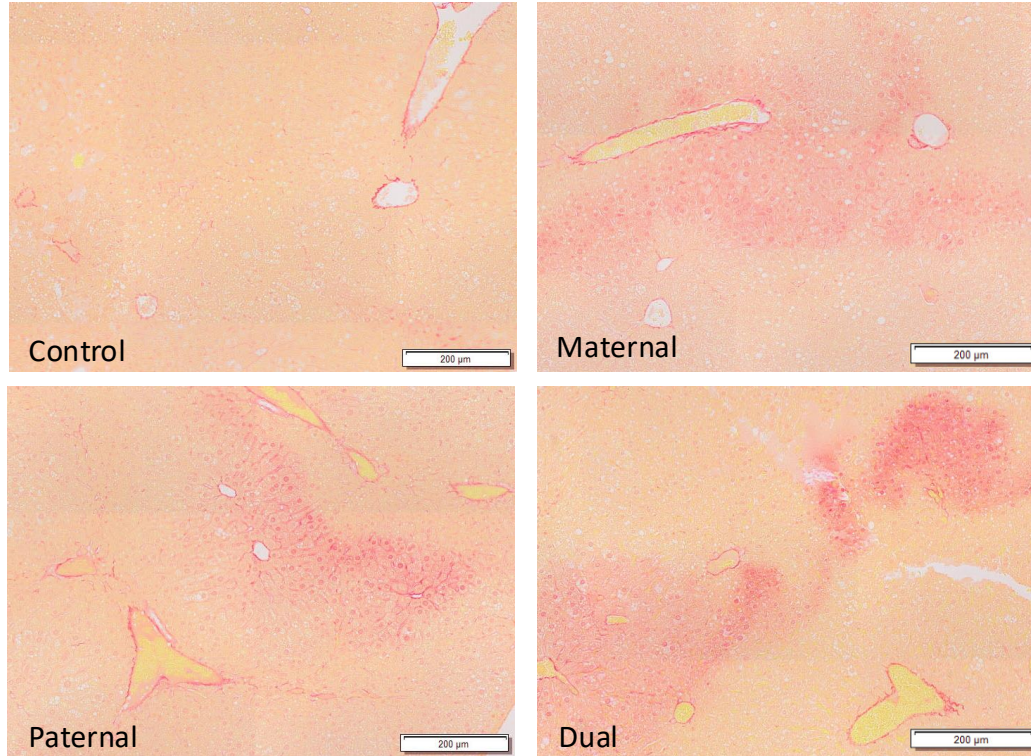


Aging & Disease 2025

What does this mean? We observed evidence that parental alcohol use drives increased senescence and inflammation in the middle-aged brain.

Parental Alcohol Exposures And Aging

Sirius red - Fibrosis Male Offspring

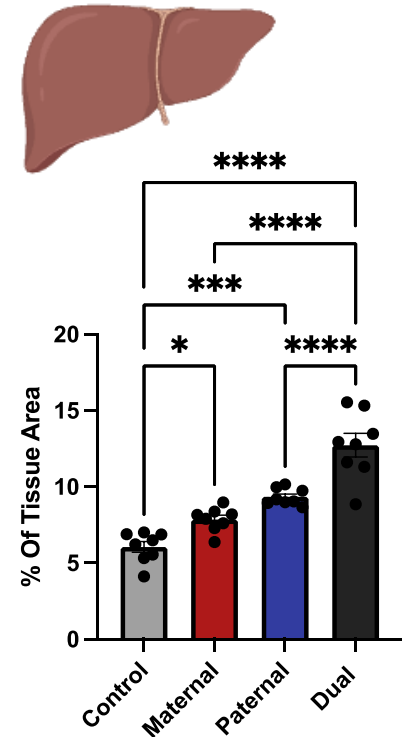
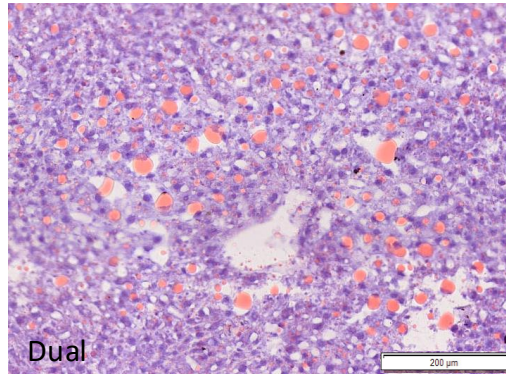
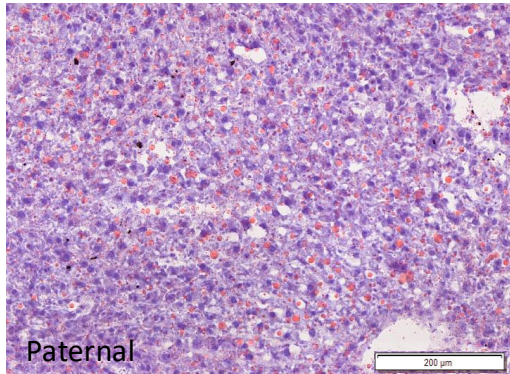
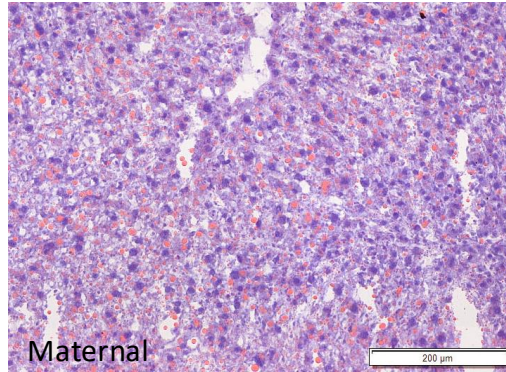
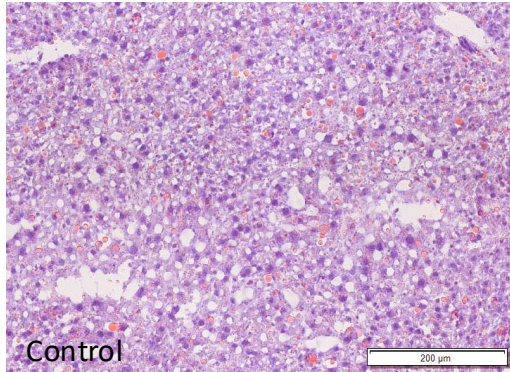


Basel et al., *Aging & Disease* 2025

What does this mean? We observed evidence that parental alcohol use causes increased liver fibrosis in middle-aged males.

Parental Alcohol Exposures And Aging

Oil Red O - Fatty Liver

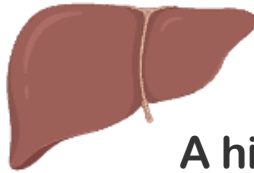
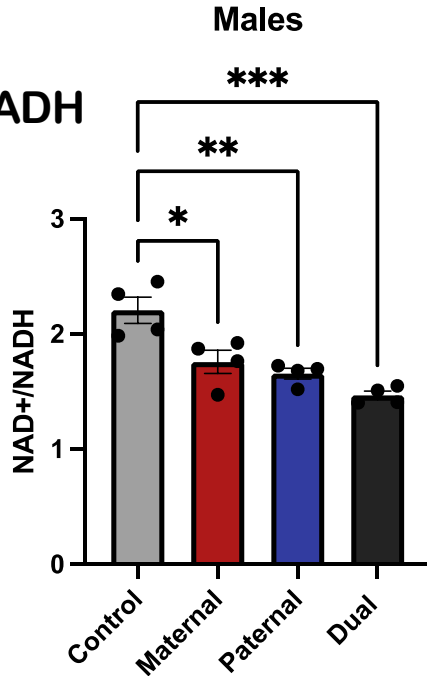


Basel et al., *Aging & Disease* 2025

What does this mean? We observed evidence that parental alcohol use drives fatty liver disease in middle-aged males.

Parental Alcohol Exposures Alter Mitochondrial Function In Middle Age

Ratio of
NAD⁺ to NADH



A high NAD⁺/NADH ratio is primarily maintained by **Complex I activity**.

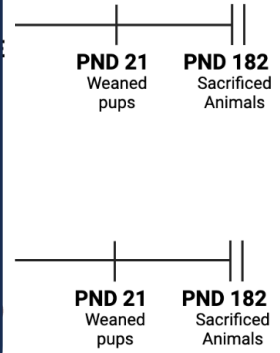
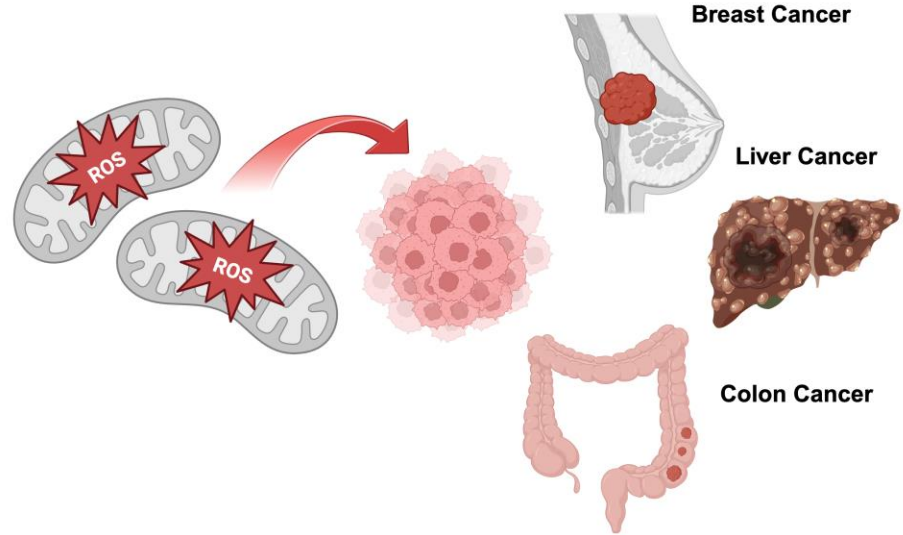
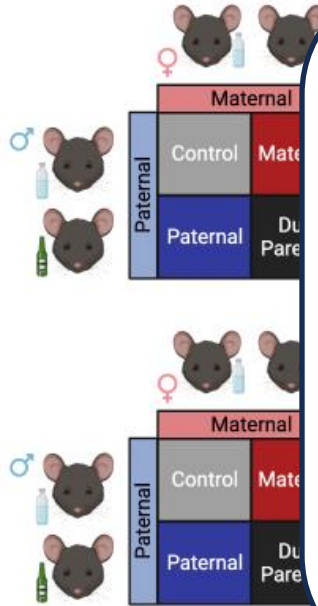


Basel et al., *Aging & Disease* 2025

What does this mean? We found strong evidence that maternal and paternal alcohol use continues to impact mitochondrial health in middle age.

Parental Alcohol Exposures and Susceptibility to Chronic Disease

Mitochondria & Cancer

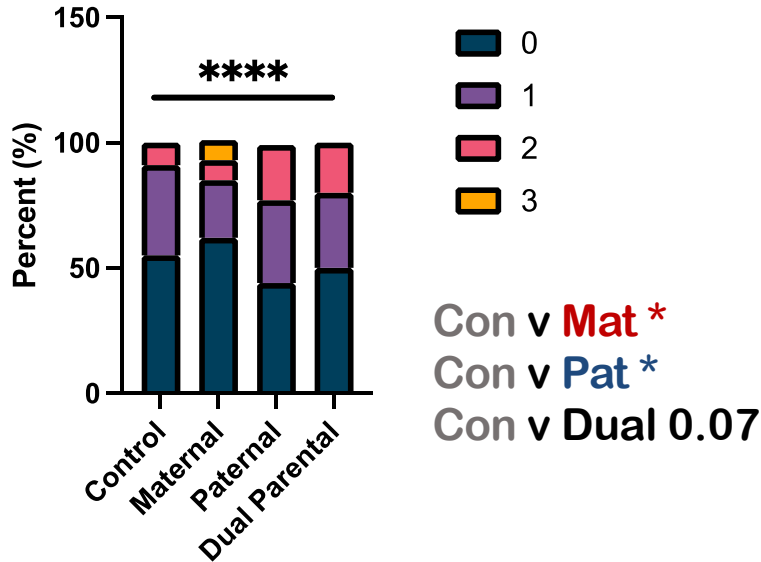


What does this mean? We wanted to know whether increased inflammation increases susceptibility to cancer.

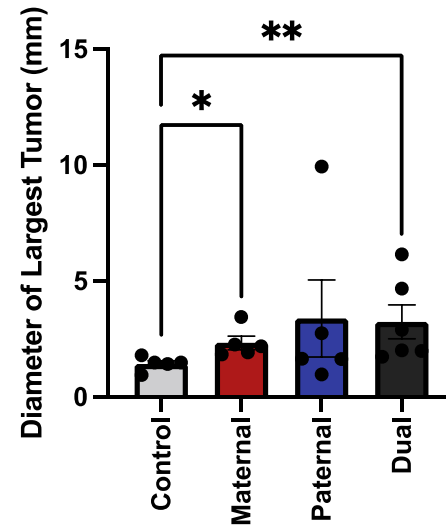
Parental Alcohol Exposures and Offspring Liver Disease

Male offspring Only

Number of Visible Tumors

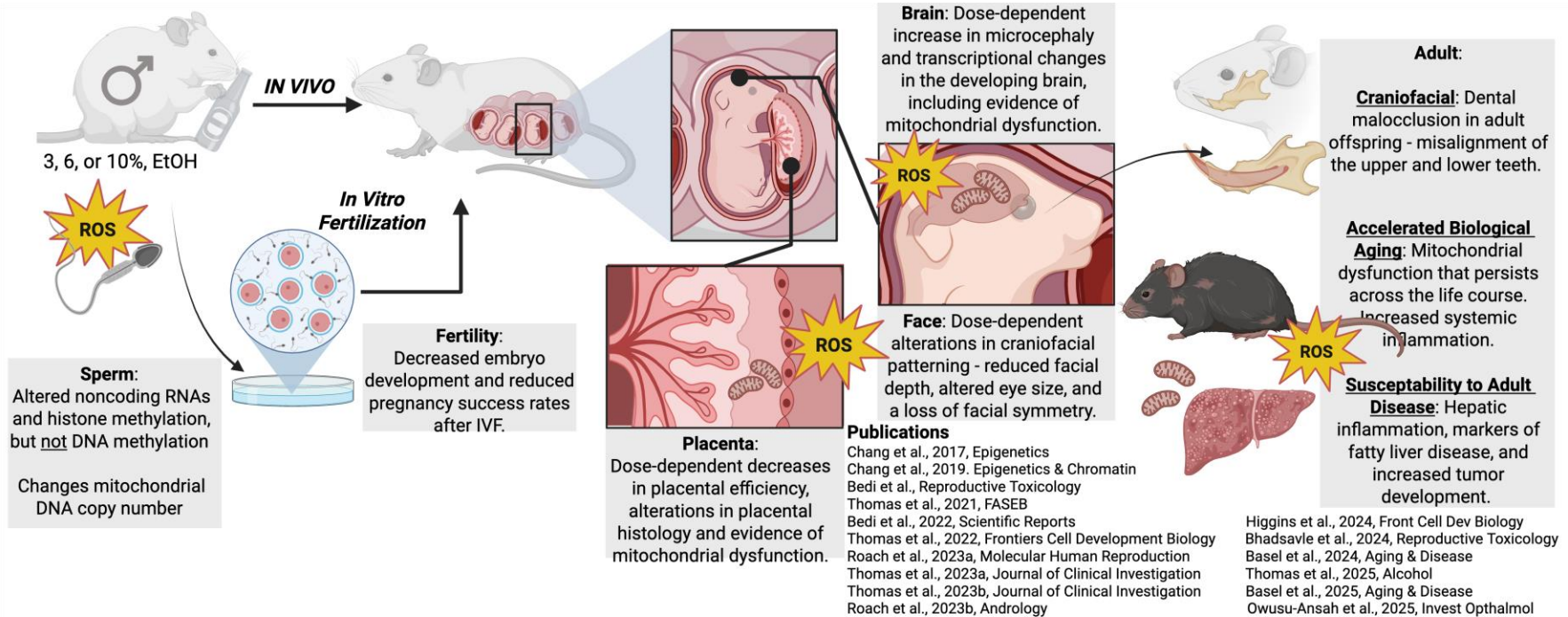


Largest Visible Tumor Diameter DEN Males



What does this mean? We found evidence that chronic parental alcohol use increased the incidence and size of tumors in male offspring.

Summary



Next Steps...

nature aging

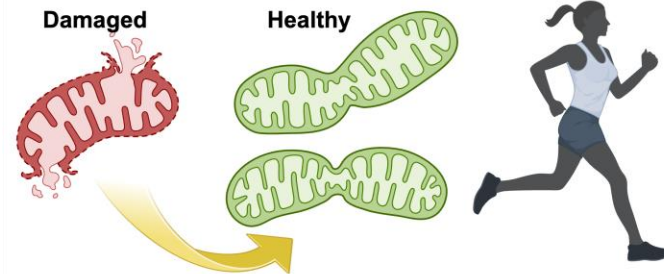


Article

<https://doi.org/10.1038/s43587-025-00996-x>

Effect of the mitophagy inducer urolithin A on age-related immune decline: a randomized, placebo-controlled trial

Mitophagy is a selective process that removes damaged or dysfunctional mitochondria, ensuring mitochondrial quality control.



What does this mean? ~~Or more~~ strategies aimed at improving mitochondrial health may help improve FASD health outcomes.



Samantha Higgins



EMENTS



Supported by C



Nicole Mehta



FOUNDATION
Medical Research Grant
Black Foundation

and Al