



**MEDICINE**  
TEXAS A&M HEALTH SCIENCE CENTER

# Half the Equation: Why Fathers Matter in FASD Risk

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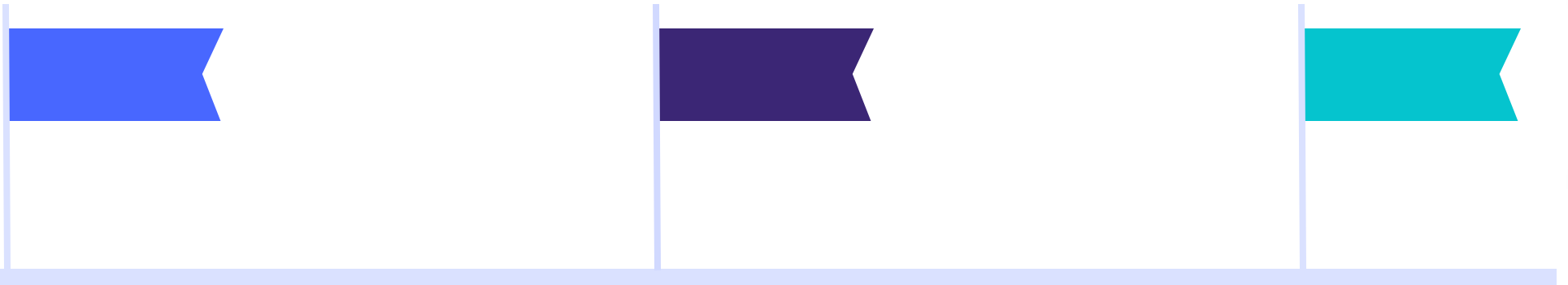
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# Historical Neglect of Paternal Contributions to FASD



1918

Stockard & Papanicolaou, 1<sup>st</sup>  
Experimental Report (guinea pigs)

20th Century

Maternal-only focus following  
1973 clinical description of FASD

Early 2000s

Paternal interest grows



## Early Paternal Alcohol Findings

- 1 Birth Metrics
- 2 Organ Development
- 3 Neurological and Hormonal Changes
- 4 Behavioral Phenotypes
- 5 FASD-Like Outcomes

# Evidence from Other Paternal Exposures



## Chronic Stress

Stress → offspring stress reactivity



## Diet

Poor diet → metabolism & weight problems



## Pollutants

Pesticides & air pollution → altered brain development.



## Substance Use

Drugs (e.g., cocaine, nicotine) → behavior & reward pathways



The image features a white background with decorative geometric shapes in the corners. The top-left corner has a light blue circle with a yellow 'd' shape inside. The top-right corner has a yellow semi-circle, a blue semi-circle, a red semi-circle, and a grey circle. The bottom-left corner has a teal semi-circle, a purple circle, a grey circle, a red semi-circle, a blue semi-circle, and a yellow semi-circle. The bottom-right corner has a light blue circle, a purple arc, and a red arc.

*“It’s the DNA, right?”*

# The 'Missing Heritability' Problem

## Heritability Estimate for AUD

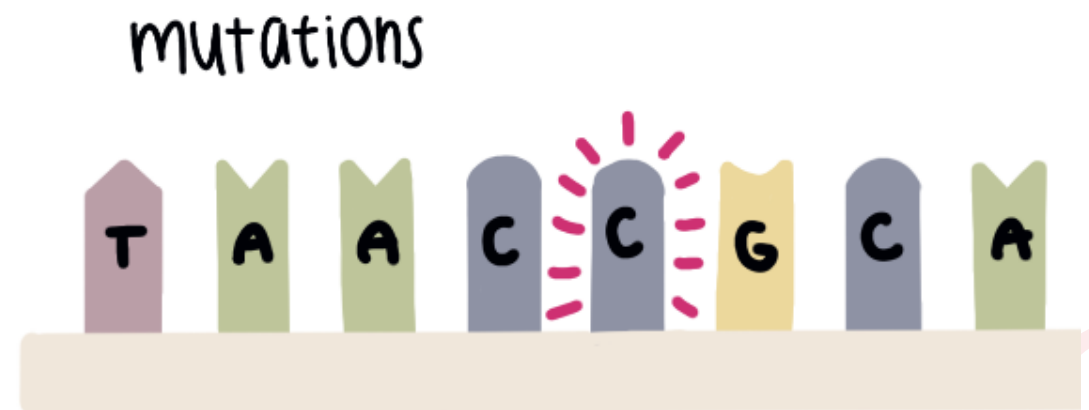
- Twin and adoption studies estimate alcohol use disorder (AUD) heritability at ~50%.

## GWAS Findings on AUD

- Genome-wide association studies (GWAS) account for < 1% of this heritability.

## The Concept of Missing Heritability

- There must be other mechanisms beyond DNA sequence variation that contribute to familial AUD risk.





## Sperm Carry More than DNA



### **Chemical “tags” on genes**

DNA methylation determines when and where genes are turned “on” or “off”.



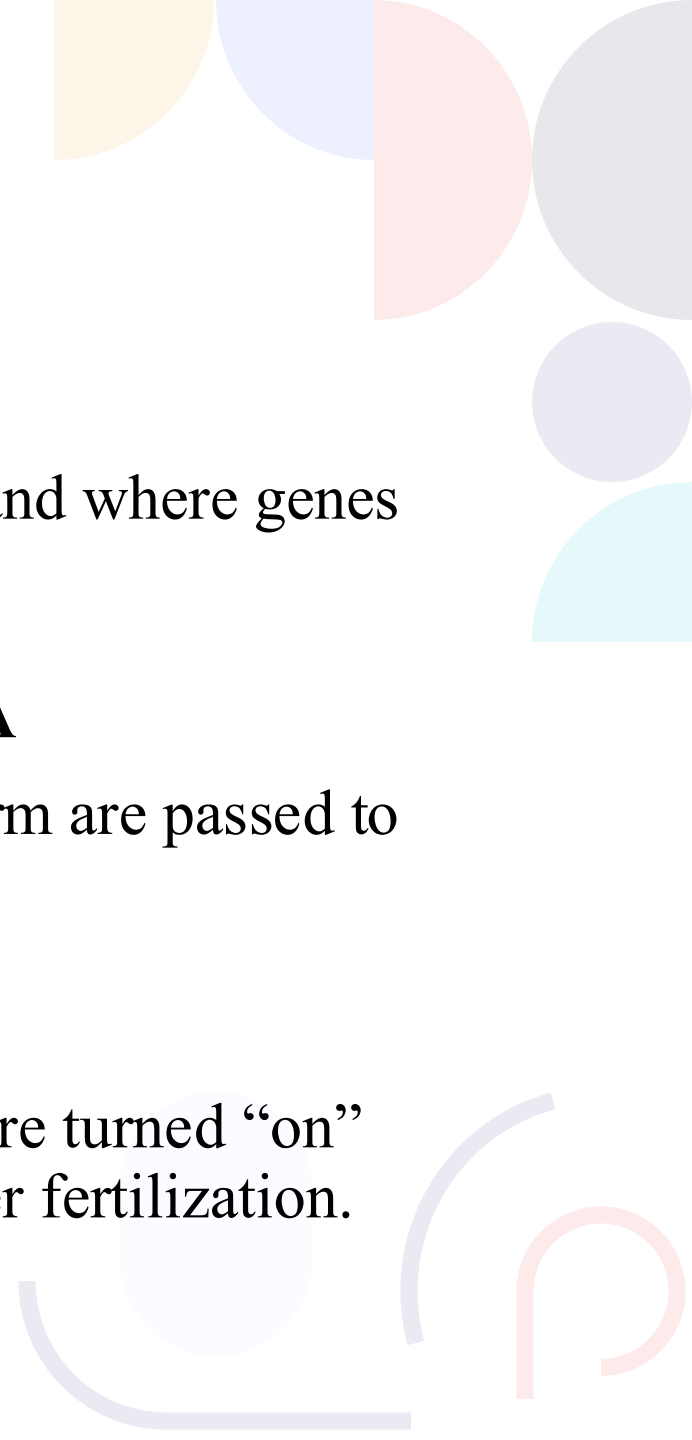
### **Proteins that “hang out” with DNA**

Up to 10% of histones in human sperm are passed to offspring.



### **Small (but mighty!) RNAs**

Tiny RNA can control which genes are turned “on” or “off” during the first few days after fertilization.



RESEARCH ARTICLE · [Volume 67, Issue 1, P105-113, July 2024](#) · [Open Access](#)

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# Paternal Preconceptional Alcohol Use Disorder With the Offspring's Mortality Risk

[Priscilla MY Lee, PhD](#) <sup>1</sup>  · [Xin Xu, MD](#)<sup>2</sup> · [Jiang B Du, PhD](#)<sup>3,4</sup> · [Jiong Li, PhD](#)<sup>1,3,4</sup>

[Affiliations & Notes](#)  [Article Info](#) 

- **Nationwide Danish study**
- **2 million births (1980-2012)**
- **Father with AUD *before* conception**

**Increased Odds of  
Stillbirth**

**23%**

**Higher Infant  
Mortality Risk**

**23%**

**Elevated Mortality  
After First Year**

**28%**

# Impact of Timing on Offspring Mortality



- **Timing of AUD diagnosis *does* matter**
- **AUD <1 year before conception → greatest risk**
- **85–111% higher mortality ages 15–40**
- **↑ deaths from infections & circulatory disease**

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## RESEARCH ARTICLE



# Does paternal alcohol consumption affect the severity of traits of fetal alcohol spectrum disorders?

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J. Phillip Gossage<sup>2</sup> | Wendy O. Kalberg<sup>2</sup> | Marlene De Vries<sup>3</sup> | Luther K. Robinson<sup>4</sup> |  
David Buckley<sup>2</sup> | Melanie Manning<sup>5,6</sup> | Charles D. H. Parry<sup>2,7</sup>  | H. Eugene Hoyme<sup>8</sup> |  
Barbara Tabachnick<sup>9</sup> | Soraya Seedat<sup>3</sup>

## Links to Child Outcomes

### **Physical Impacts on Children**

Children of fathers who engaged in binge drinking (5+ drinks per occasion) tend to be shorter in stature and have smaller head circumferences.

### **Cognitive Impacts on Children**

These children score lower on verbal intelligence assessments.

### **Independent Influence of Paternal Drinking**

The harmful effects persist even after accounting for maternal alcohol use and tobacco exposure.

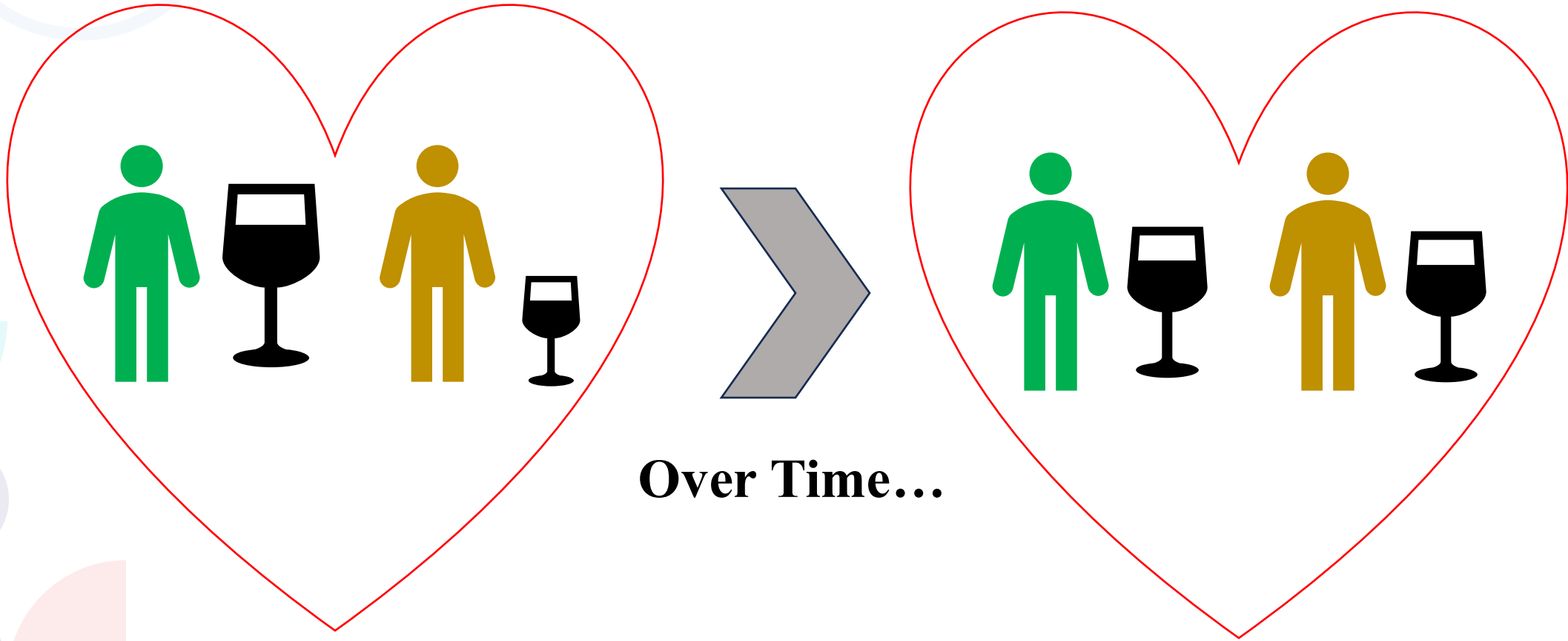


## The Risk Is Highest When Both Parents Drink

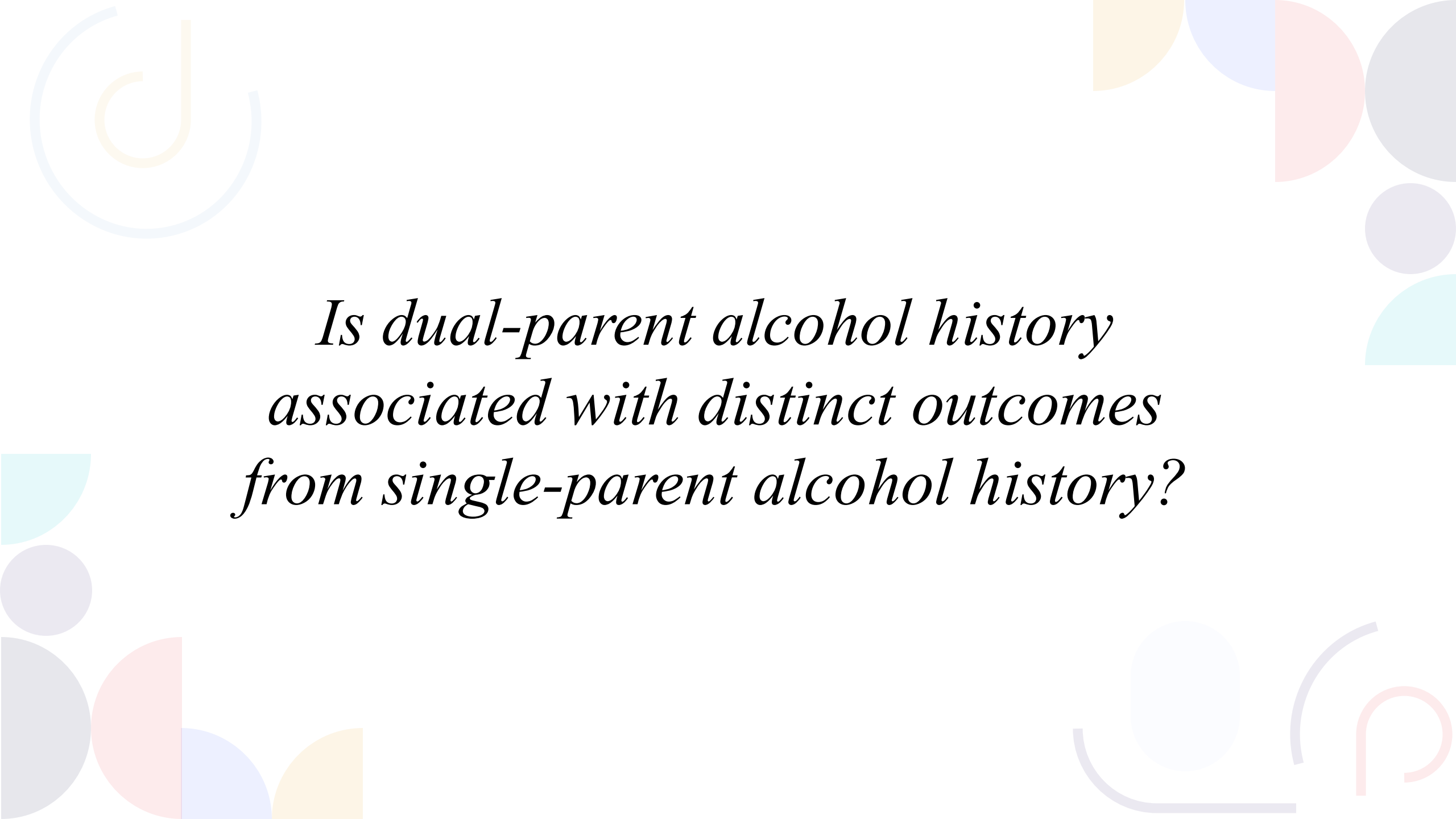


The most prominent effects were seen when alcohol exposure occurred through *both parents*.

# The Partner Influence Hypothesis



*FASD Research does not consistently assess/report paternal alcohol exposure.*



*Is dual-parent alcohol history  
associated with distinct outcomes  
from single-parent alcohol history?*

# Data Source: All of Us Research Program

- National, diverse database of research participants (U.S.)  
<https://www.researchallofus.org/>
- Integrates:
  - Survey data
  - Electronic Health Records (EHR)
  - Physical measurements
  - Genomics

- Includes: Family history of AUD

**Family history question: *Including yourself, who in your family has had an alcohol use disorder?***

NIH National Institutes of Health

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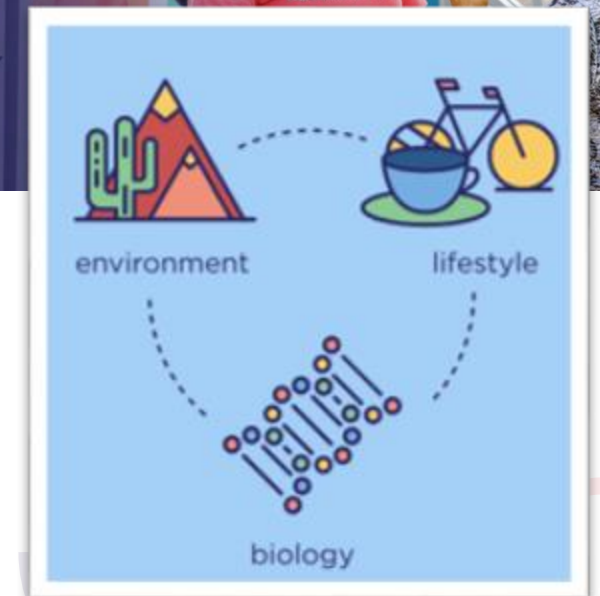
**From promise to progress.  
The future of health  
research is now.**

The *All of Us* Research Program is accelerating research advances and precision medicine.

Our nationwide community of participants and researchers is partnering together to ensure that everyone is included in research. The information our participants generously share is fueling thousands of studies to better understand health and disease and enable more tailored and equitable approaches to care.

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- |   |   |
|---|---|
| <input checked="" type="checkbox"/> Self    | <input checked="" type="checkbox"/> Daughter    |
| <input checked="" type="checkbox"/> Mother  | <input checked="" type="checkbox"/> Son         |
| <input checked="" type="checkbox"/> Father  | <input checked="" type="checkbox"/> Grandparent |
| <input checked="" type="checkbox"/> Sibling |   |



# Sample Selection & Variables of Interest

- My research question: Does parental history of AUD increase risk for offspring consuming more alcohol or receiving their own AUD diagnosis?
- Sample Selection: Adults (18+) who completed alcohol use survey answers *and* provided family history of AUD data
- AUD Diagnosis in Participants:
  - Derived from EHR diagnosis codes
  - Binary outcomes: Yes/No
- Drinking Frequency & Quantity were derived from self-reported survey measures

# Sample Selection & Variables of Interest

- Drinking Frequency – How *often* individuals drink
  - Question: “How often do you drink alcohol?”
- Drinking Quantity – How *many* drinks in a session
  - Question: “How many drinks do you typically consume when drinking?”
- Behavioral Interpretation

## Response Options:

*Never*

*Monthly or less*

*2-4 times/month*

*2-3 times/week*

*≥4 times/week*

## Response Options:

*1-2 drinks*

*3-4 drinks*

*5-6 drinks*

*7-9 drinks*

*≥10 drinks*

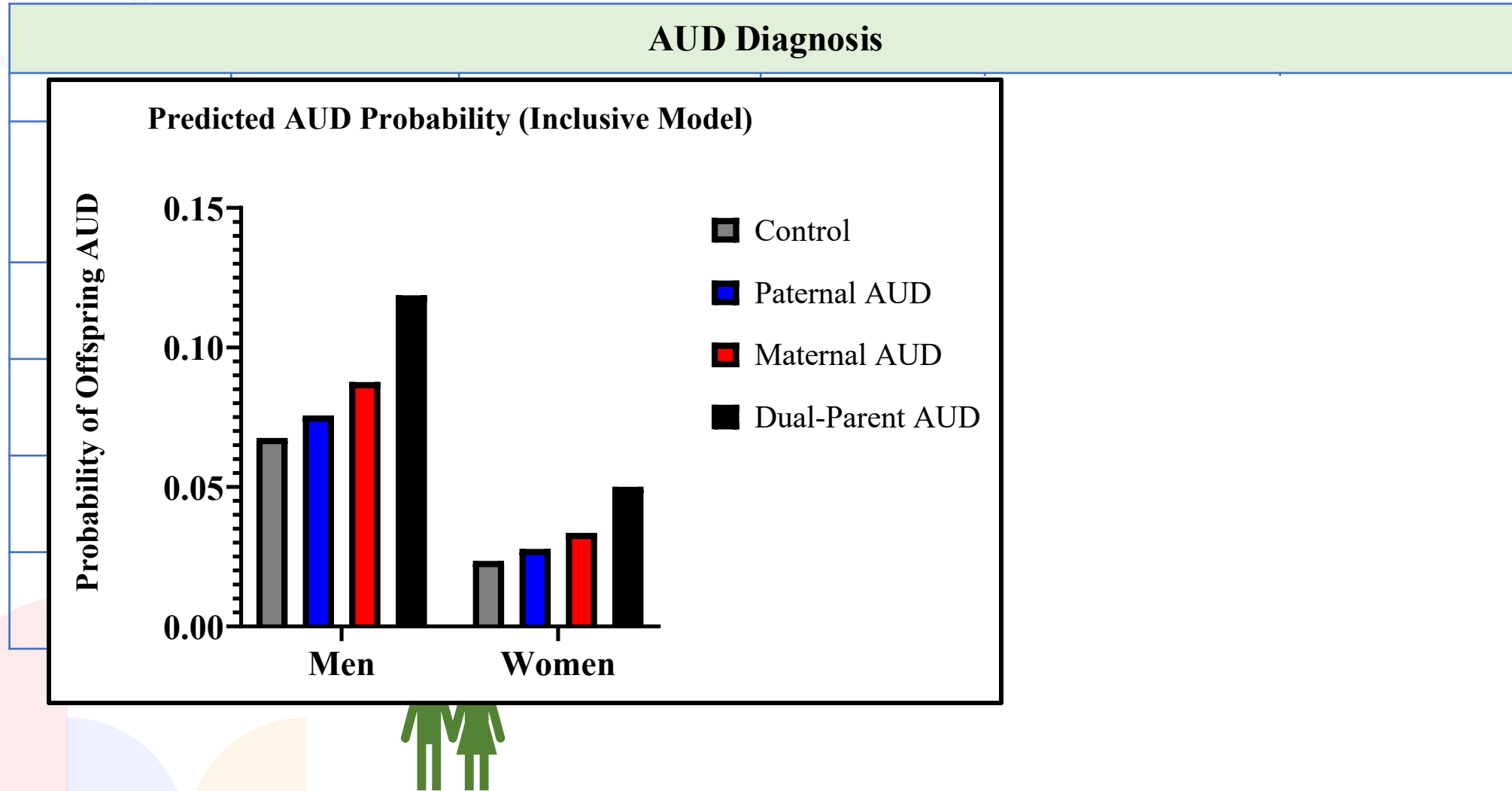
# Statistical Analyses - A Tale of Two Models

- AUD Diagnosis: Logistic regression
- Self-Reported Frequency & Quantity: Linear regression
- Control Group: Family history of AUD, *but not in parents*
- Parallel models
- Model S (Strict):
  - Includes Parent AUD **only**
  - Excludes: any additional family AUD
- Model I (Inclusive):
  - Includes Parent AUD regardless of other family AUD

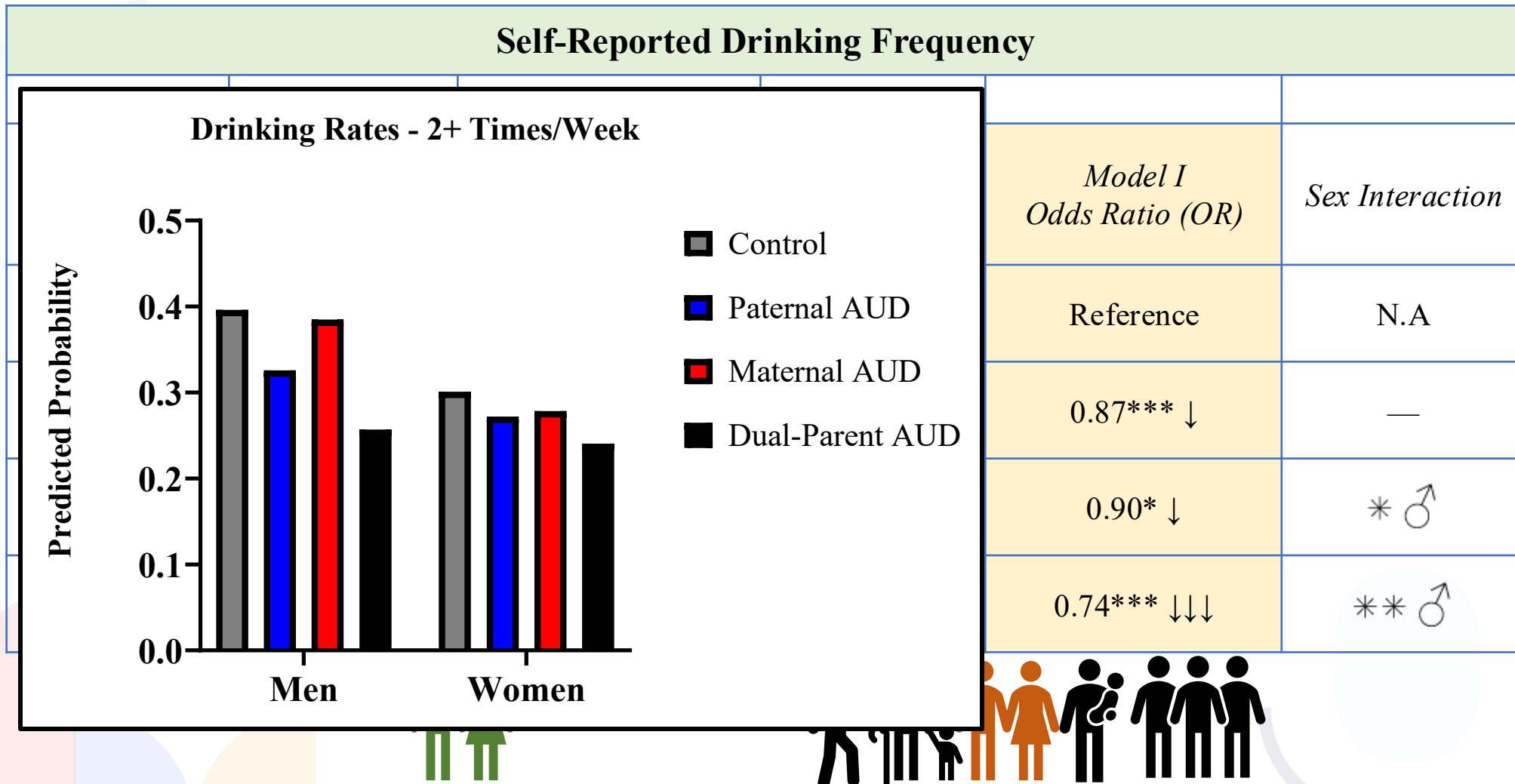


Feature	Model S
ex <input checked="" type="checkbox"/> Self	<input checked="" type="checkbox"/> Daughter
<input checked="" type="checkbox"/> Mother	<input checked="" type="checkbox"/> Son
I <input checked="" type="checkbox"/> Father	<input checked="" type="checkbox"/> Grandparent
<input checked="" type="checkbox"/> Sibling	
Validity strength	Internal

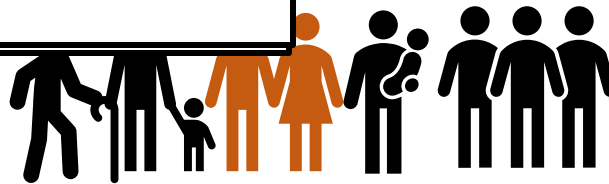
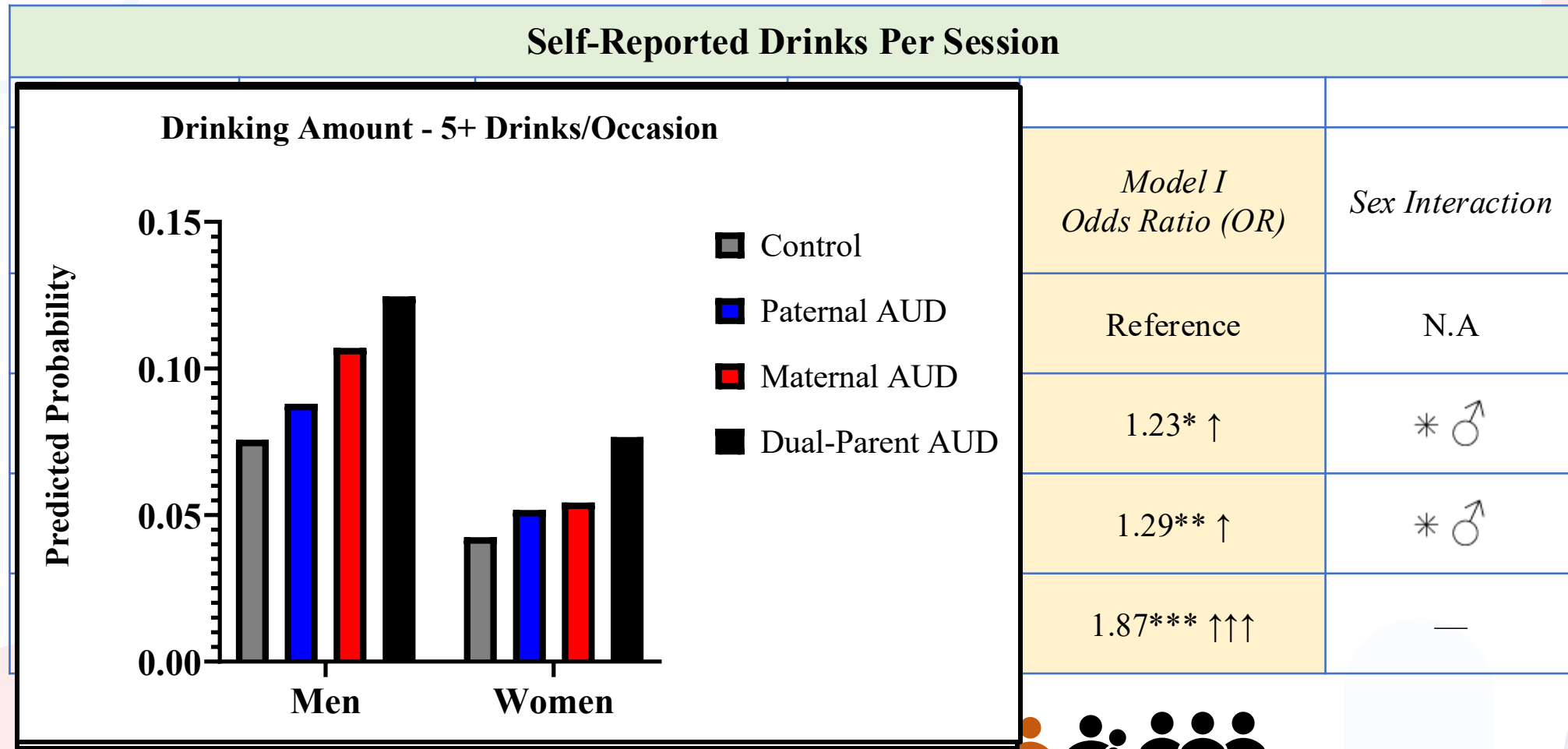
# Results – Parental AUD & Risk of Offspring AUD



# Results – Parental AUD & Offspring Drinking Frequency



# Results – Parental AUD & Offspring Drinking Quantity



# Limitations & Future Directions

**Conclusions:** Dual-parental AUD increases risk of offspring AUD & instances of episodic, moderate-to-heavy drinking, compared to single-parent AUD and non-parent family history of AUD.

## Limitations

- Controls have a family history of AUD
  - National Health Interview Survey (1988): **43% of U.S. adults (about 76 million people)** have been exposed to alcoholism in their family.
- Parental AUD does not confirm that preconception/prenatal exposure occurred.
  - ~40% of individuals with AUD report initiating alcohol use (**first full drink**) **before age 15**, another ~40% between 15–17, and ~20% initiate at age 18 or later. (Grant & Dawson, 1997)
  - 2/3s of individuals with AUD are **diagnosed by age 25**. (Hingson et al., 2006)
  - Mean age of first child in the U.S: Mothers: **27** (Brown, Hamilton, Kissin, & Martin, 2025), Fathers: **25.5** (CDC National Survey of Family Growth)

# Limitations & Future Directions

**Conclusions:** Dual-parental AUD increases risk of offspring AUD & instances of episodic, moderate-to-heavy drinking, compared to single-parent AUD.

## Limitations

- Have not investigated contributing factors (SES, polysubstance use, age)... *YET* 😊

## Future Directions

- Investigate co-occurring diagnoses common in individuals with FASD
- Incorporate genetic data provided by same participants into analyses
- Ask questions such as, “Does dual-parent AUD history interact with offspring variation in BDNF to predict episodic drinking?”

# Modeling Dual-Parent Exposures in Mice

In humans, factors that contribute to FASD symptoms include:

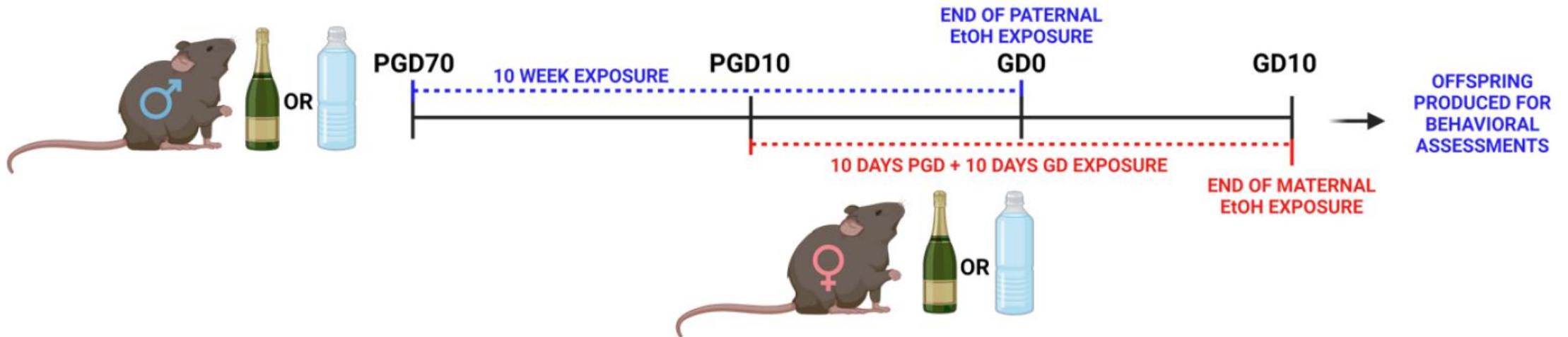
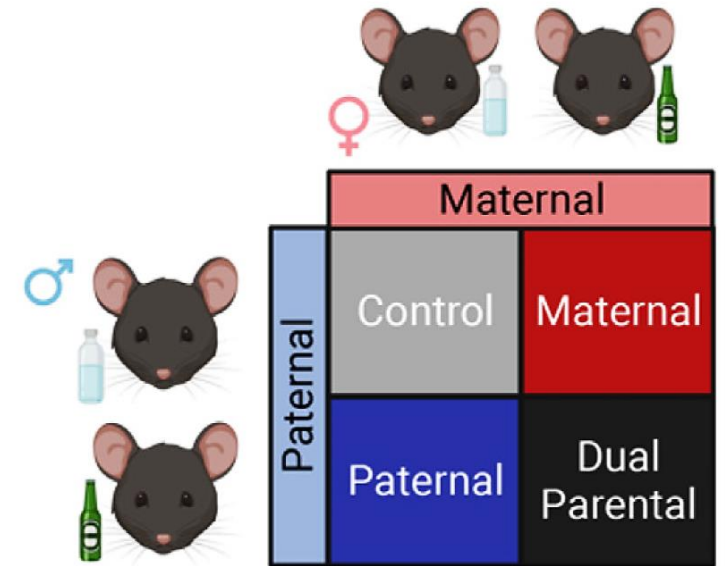
1. The amount/timing of alcohol exposure during pregnancy
2. Offspring sex and gender
3. Offspring age at assessment
4. Maternal health/diet
5. Maternal age
6. Maternal/prenatal stress
7. Maternal polysubstance use
8. Paternal substance use
9. Offspring early-life stress
10. Housing conditions (preclinical models)
11. Genetics

# Modeling Dual-Parent Exposures in Mice

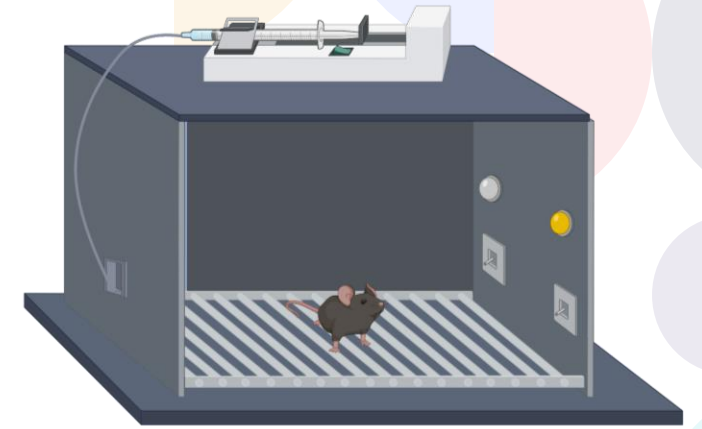
Collaborator: Dr. Michael Golding & Dr. Destani Derrico

Alcohol Exposure: Voluntary Drinking

Goal: Test single vs dual-parent exposure effects on offspring alcohol-seeking behaviors



# Operant Self-Administration of Ethanol in Middle-aged Offspring (*Ongoing investigation*)



## *Which Group Drinks the Most?*

	Easy Access Drinking (1 lever press)	Difficult Access Drinking (incremental lever presses)	Extinction (Forced Abstinence)	Reinstatement (Easy Access Drinking after abstinence)
Males	Dual-Parent	Dual-Parent	Dual-Parent	Dual-Parent
Females	Dual-Parent	Paternal-Only & Dual-Parent	-	Paternal-Only & Dual-Parent

## Where Research Should Go Next



Study how alcohol alters sperm epigenetics and RNA content



Longitudinally follow children born to fathers with alcohol exposure



Integrate paternal alcohol use screening into FASD risk assessments

*We need more models that incorporate both parents.*



*Investing in families starts  
with investing in parents.*

# Acknowledgements

**PI: Dr. Rajesh Miranda**

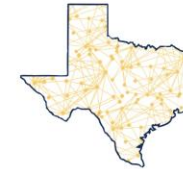
- Dr. Deepa Upreti
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- Rosaline Kumar
- Nadia Samiya
- Shamika Bhikule



National Institute  
on Alcohol Abuse  
and Alcoholism

**K99 AA032336 (SKR)**  
**K12 GM154716 (SKR)**  
**F32 AA029866 (SKR)**  
**L40 AA030427 (SKR)**  
**R01 AA028406 (RCM)**

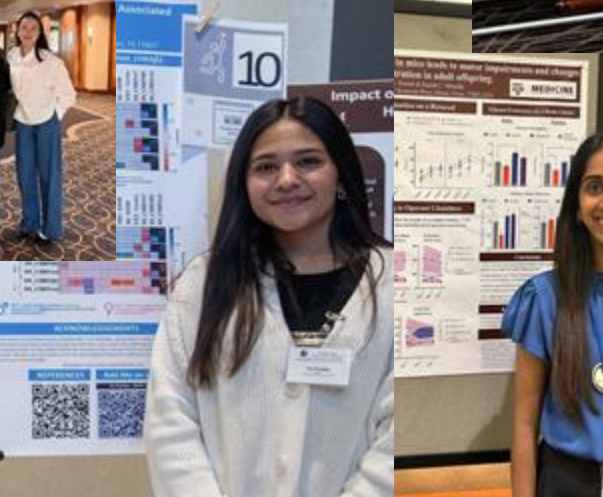
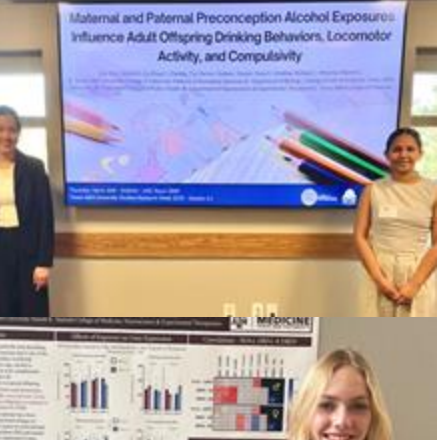
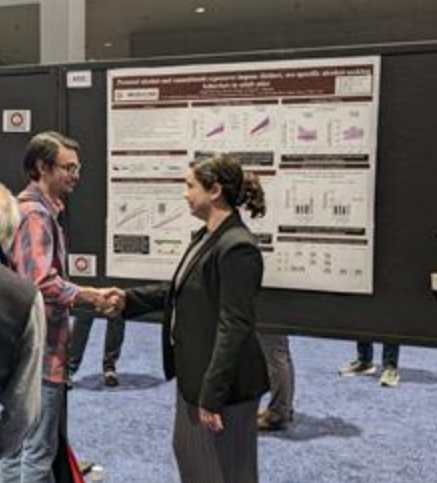
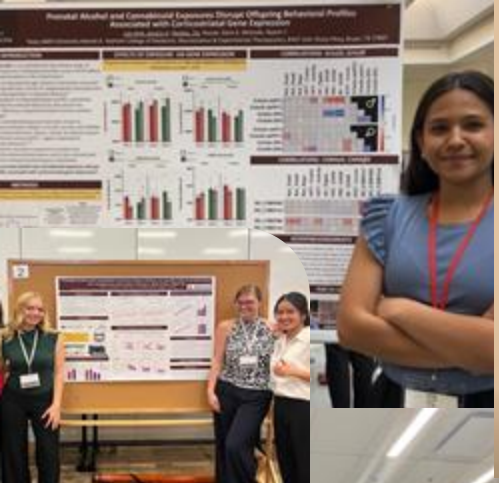
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RESEARCH FOUNDATION  
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I gratefully acknowledge *All of Us* participants for their contributions, without whom this research would not have been possible. I also thank the National Institutes of Health's *All of Us Research Program* for making available the participant data examined in this study.







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# Paternal Drinking Patterns

## Fathers of Children with FASD

- Drank alcohol during pregnancy: **73%**
- Average 12oz drinks per session: **11.5**
- A higher prevalence of reported past and current drinking problems.

## Fathers of Unexposed Controls

- Drank alcohol during pregnancy: **48%**
- Average 12oz drinks per session: **8**
- Fewer reported past and current drinking problems.

## All of Us – Distribution of Ages

<b>Age Group</b>	<b>N</b>	<b>% of All of Us sample</b>
18–24	4,224	<b>4.21%</b>
25–34	14,239	<b>14.18%</b>
35–44	13,968	<b>13.91%</b>
45–54	14,964	<b>14.91%</b>
55–64	21,097	<b>21.01%</b>
65+	31,899	<b>31.77%</b>

<b>Parental AUD Group</b>	<b>Female (Mean ± SD)</b>	<b>Male (Mean ± SD)</b>
Control	57.32 (16.48)	61.97 (16.49)
Paternal	55.59 (16.05)	61.40 (16.29)
Maternal	54.96 (16.08)	60.05 (16.19)
Dual	53.56 (15.87)	59.69 (16.31)



ELSEVIER

Contents lists available at [ScienceDirect](#)

# Alcohol

journal homepage: <http://www.alcoholjournal.org/>



## Maternal, paternal, and dual-parental alcohol exposures result in both overlapping and distinct impacts on behavior in adolescent offspring

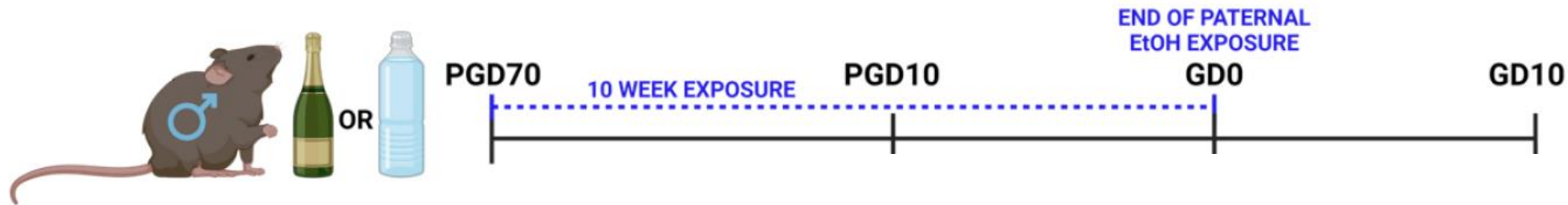
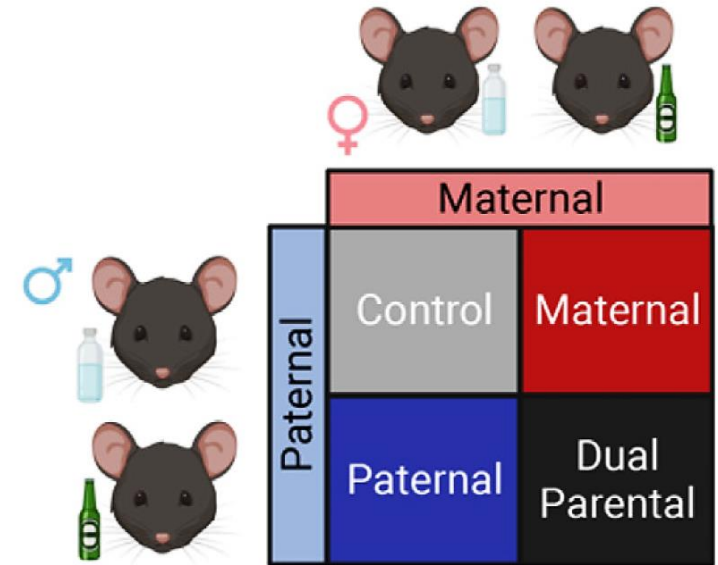


Kara N. Thomas<sup>a</sup>, Alison Basel<sup>a</sup>, Hayden Reitz<sup>a</sup>, Rachel Toler<sup>a</sup>, Kelly R. Thomas<sup>a</sup>,  
Luke J. Dotson<sup>a</sup>, Tyler Brown<sup>a</sup>, Alan Nguyen Pham<sup>a</sup>, Siara K. Rouzer<sup>b</sup>,  
Rajesh C. Miranda<sup>b</sup>, Michael C. Golding<sup>a,\*</sup>

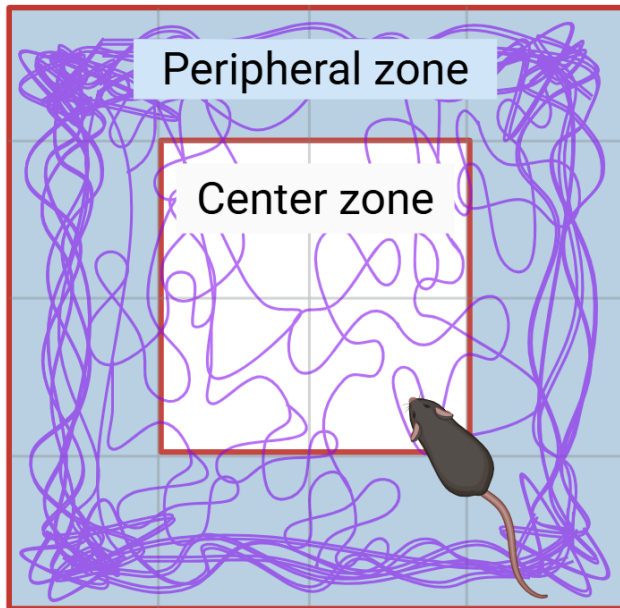
# Modeling Dual-Parent Exposures in Mice

## Alcohol Exposure: Voluntary Drinking

**Goal:** Test single vs **dual** exposure effects on adolescent offspring

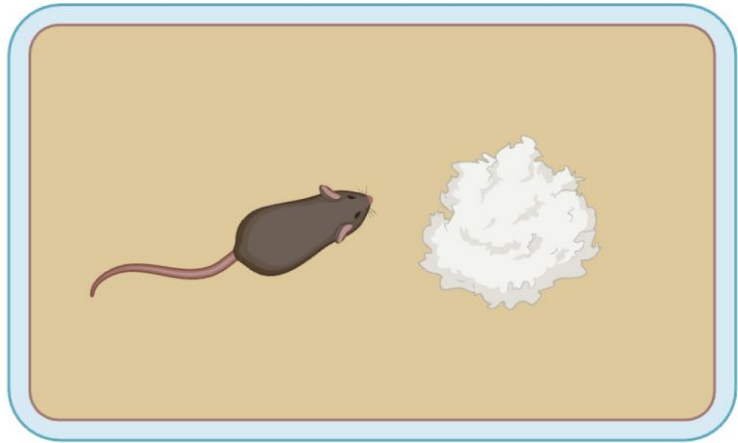


# Anxiety-like Behavior (Open Field Test)



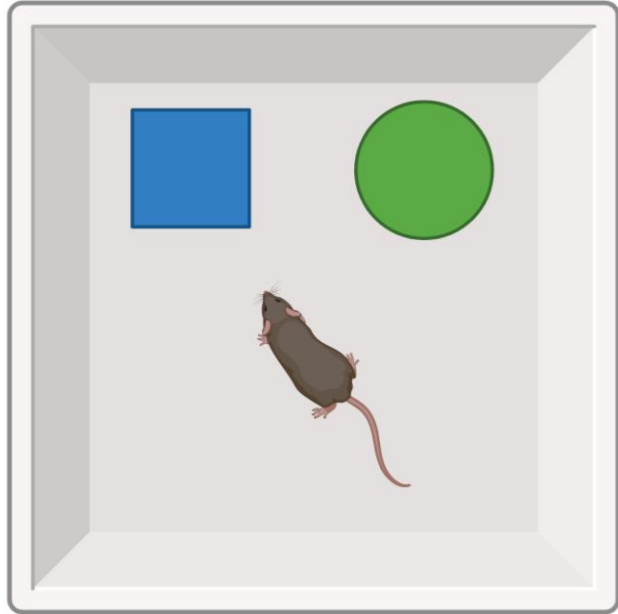
- **Males:** Paternal exposure → less anxious (more center time)
- **Females:** No change
- **Dual Exposure:** No distinct outcomes

## Compulsive-like Behavior (Nestlet Shredding Test)



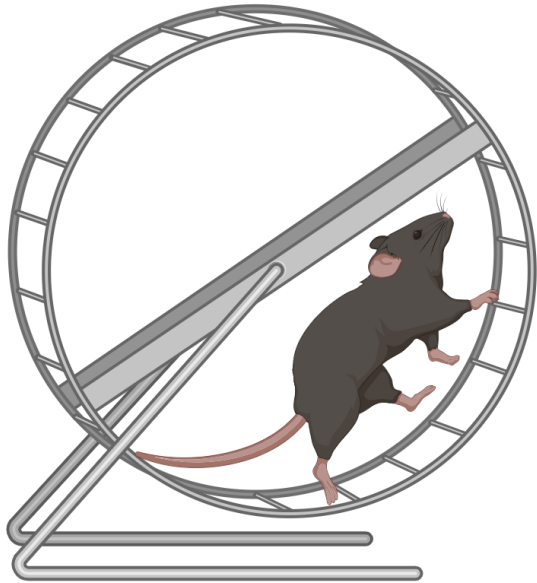
- **Males:** ↑ with Maternal; ↑ with Paternal
- **Females:** ↑ with Paternal
- **Dual Exposure:** No distinct outcomes

## Risk-taking Behavior (Novel Object Preference)



- **Dual Exposure:** Both males and females prefer the novel object - controls preferred the familiar object

# Activity Levels & Circadian Phasing (Running Wheel)



- **16 weeks of voluntary, monitored exercise**
- **Males:** Dual Exposure ↓ running activity, specifically during the nighttime (when mice are most active)
- **Females:** No effect of exposure