NIAAA Director's Report
on Institute Activities to the 161st Meeting of the National Advisory Council on Alcohol Abuse and Alcoholism

September 8, 2022
Hybrid Meeting

George F. Koob, Ph.D.
Director
National Institute on Alcohol Abuse and Alcoholism
National Institutes of Health

https://www.niaaa.nih.gov/about-niaaa/advisory-council

In Memoriam – Logan E. Johnson

Logan Johnson, an NIAAA post-baccalaureate Intramural Research Training Award (IRTA) fellow, passed away on June 11, 2022. Prior to joining NIAAA, Logan earned a Bachelor of Science in Pharmacology/Toxicology and a second degree in Biology from the University of Toledo. While at NIAAA, Logan quickly made his mark in the Intramural Section on Medicinal Chemistry — making friends easily, collaborating with many, and handling diverse projects professionally. He was exemplary in his work ethic and deeply cared for anyone and everyone around him.

NIAAA Budget

- NIAAA is closing out FY 2022. NIAAA received a total of $554.9 million for FY 2022.
- The budget for FY 2023 has not been finalized.

NIAAA Funding Opportunities

(See Director's Report for Complete Listing)

Funding Opportunity Announcement (FOA) Issued by NIAAA

Early Liver Transplantation Cohort Study for Alcohol-Associated Liver Diseases (R01, RFA-AA-22-003). To support collaborative research projects conducted by multidisciplinary teams on early liver transplantation (ELT) for patients with alcohol-associated liver disease (ALD). The FOA encourages observational clinical studies to examine factors that influence the criteria for patient selection for ELT and that influence post-ELT outcomes. *Contact: Dr. Zhigang (Peter) Gao*

Notice of Special Interest (NOSI) Issued by NIAAA

Notice of Change to NOT-AA-20-018, "Notice of Special Interest: Secondary Analyses of Existing Alcohol Research Data." To encourage the utilization of data from the NIH-sponsored *All of Us* initiatives to conduct secondary analyses as specified in the previous notice. It also updates the previous notice with an additional research objective to examine differences in alcohol consumption alone or in combination with other substance use, risk and protective factors, and comorbid psychiatric and/or chronic physical conditions in people who consume alcohol. These factors may contribute to poor health outcomes in certain NIH-designated U.S. health disparity populations (NOT AA 22 014). *Contact: Dr. Wenxing Zha, Dr. Abbas Parsian and Dr. Laura Kwako.*

Advancing Diversity, Equity, and Inclusion in the Alcohol Field

- Current NIAAA-supported funding opportunities and efforts to expand health disparities research:
  - Alcohol Health Services Research (PAR-22-156/157/158/159), encourages research on reducing health disparities as one way to address the treatment gap)
  - Administrative Supplements to Support "All of US" and Health Disparities-Related Pilot Research Projects at NIMHD-Funded Research Centers in Minority Institutions (RCMI) NOT-MD-22-015
  - HEAL Initiative: Availability of Administrative Supplements to Support Strategies to Increase Participant Diversity, Inclusion and Engagement in Clinical Studies NOT-NS-22-066

- Examples of NIAAA-supported funding opportunities and efforts to enhance diversity in the alcohol research enterprise and beyond:
  - New PEDP requirement now included in Requests for Applications for Specialized Alcohol Research Centers (P50) and Comprehensive Alcohol Research Centers (P60) (RFA-AA-22-001/002)
  - Diversity supplements

NIH Loan Repayment Program (LRP)

The NIH LRP was established by Congress to recruit and retain highly qualified health professionals into biomedical or biobehavioral research careers by repaying up to $50,000 annually of a researcher's qualified educational debt (plus fees and taxes) in return for a commitment to engage in NIH mission-relevant research.

To view eligibility criteria and to learn more, visit https://www.lrp.nih.gov/

- Current LRP notices:
  - Clinical Researchers (LRP-CR): NOT-OD-22-140
  - Pediatric Research (LRP-PR): NOT-OD-22-149
  - Health Disparities Research (LRP-HDR): NOT-OD-22-150
  - Research in Emerging Areas Critical to Human Health (LRP-REACH): NOT-OD-22-153
    - NIAAA Priority Areas:
      - Basic science in metabolism, health effects, and neuroscience
      - Preclinical studies for the development of medications
      - Projects using computational and data science approaches

FY22 Deadline is November 17, 2022 – Note only one application cycle per year

Closing the Treatment Gap: Recovery

- September is National Recovery Month, which increases awareness and understanding of alcohol and substance use disorders
- Most people who need treatment receive no treatment of any kind, and little is known about what sustains longer-term recovery
- NIAAA has defined recovery from Alcohol Use Disorder (AUD) based on qualitative feedback from key recovery stakeholders (Hagman et al 2022)
  - Recovery is viewed as both a process of behavioral change and an outcome that incorporates time periods for two key components:
    - Remission from DSM-5 AUD
    - Cessation from heavy drinking (a non-abstinent recovery outcome)
  - The NIAAA definition also emphasizes the importance of biopsychosocial functioning and quality of life in enhancing recovery outcomes
- NIAAA recently released a funding opportunity announcement (PAR-22-158/159) that included a focus on research to learn more about the risk and resiliency factors related to recovery and relapse, including the factors that allow some people to recover without receiving formal treatment

Closing the Treatment Gap: Integrating Treatment of Alcohol Use Disorder and Alcohol-Associated Liver Disease

- **Deaths from ALD increased by 22% between 2019 and 2020** (White et al, 2022)
- **ALD has become the leading indication for liver transplantation in the US** (Sedki et al, 2022)
- **Treating AUD with medications reduces the chances of ALD and the progression of existing ALD** (Vannier et al., 2022)

- **On July 12-13, NIAAA hosted a workshop, Clinical Trial Design for Integrated Care for Patients with Alcohol Use Disorder and Alcohol-associated Liver Disease, to:**
  - **Review the status of the integrated care models for patients with ALD in clinical settings.**
  - **Achieve common understanding of how to address the coexistence of ALD and AUD in clinical research.**
  - **Identify approaches for treating alcohol use in patients with liver disease.**

Closing the Treatment Gap: Healthcare Professionals Core Resource on Alcohol (HPCR)

- The HPCR consists of 14 interconnected articles covering the basics of what every healthcare professional needs to know about alcohol.
- It was developed by NIAAA with guidance from practicing physicians and clinical psychologists with busy clinicians in mind.
- NIAAA is promoting the Core Resource through the following activities:
  - Outreach to academic institutions, professional organizations, health plans, websites and apps for healthcare professionals, and other federal agencies
  - Social media posts and ads
  - Webinar planned for November

Closing the Treatment Gap: Women's Health

- Studies suggest that women are more likely than men to experience a variety of alcohol-related harms at comparable doses
- Women are less likely than men to receive AUD treatment (Gilbert et al., 2019)
- Only 26% of 230 structural neuroimaging studies on substance use over 23 years evaluated sex differences (Lind et al., 2017)
- More research is needed to better understand sex differences in alcohol use and consequence

- The NIAAA-sponsored 2022 National Conference on Alcohol and Opioid Use in Women and Girls will take place October 20-21. The purpose of the meeting is to identify directions for future research on harmful alcohol and opioid use in this population. It will also highlight strategies that are already working to address these problems with the goal of replicating and bringing effective interventions to population scale.

What's Ahead?

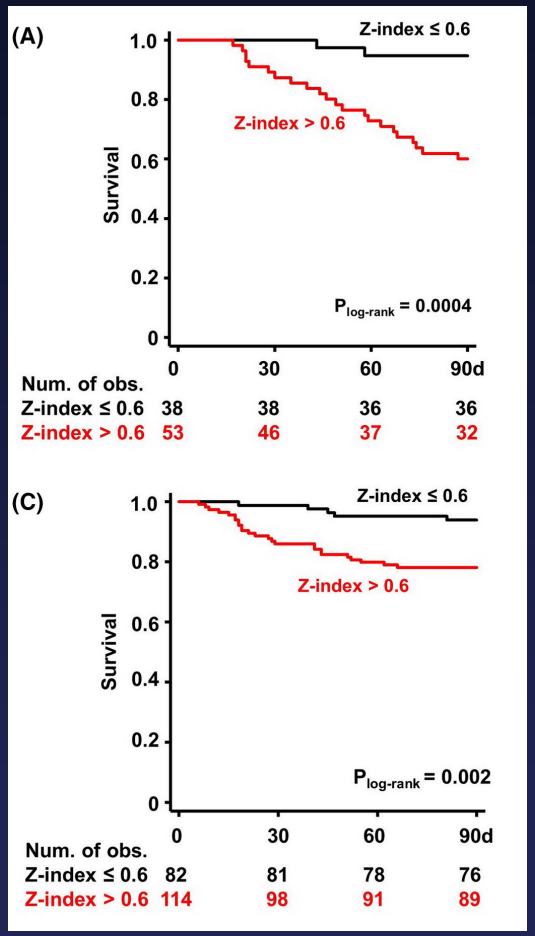
Scientific Sessions

1. Defining mechanisms that link sleep with Substance and Alcohol Use Disorders
2. Reprogramming Glia for Brain Recovery: A Potential Future SUD Therapy
3. Understanding human neurodevelopment amid a broader social context

More information: https://apps1.seiservices.com/nida-niaaa/frontiers/

Research Highlights

Lipoprotein Z, a Hepatotoxic Lipoprotein, Predicts Outcomes in Alcohol-associated Hepatitis



Z index predicts 90-day survival in AH: Kaplan-Meier curves of 90-day survival in two different AH patient cohorts categorized by baseline Z-index cutoff at 0.6.

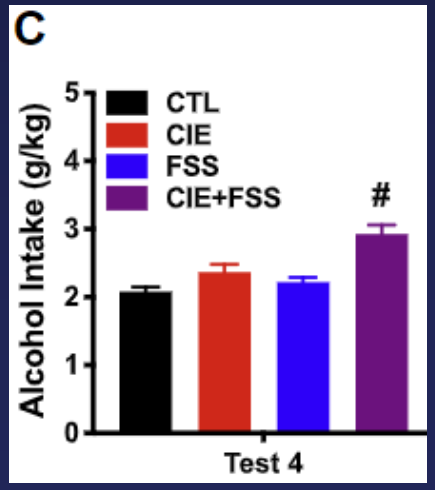
Lipoprotein Z (LP-Z) is an LDL-like particle found with a high frequency in patients with alcohol-associated liver disease. Impaired lipoprotein metabolism in AH leads to the accumulation of LP-Z in the circulation, which is hepatotoxic. The investigators found that the ratio in the serum of LP-Z / total LDL, named the Z-index, could predict 90-day survival independent from the most used prognostic scoring system (MELD) for disease prognosis, thus providing a new risk-stratification tool. They also found that LP-Z, at serum concentration in AH, causes direct cytotoxicity in human hepatocytes *in vitro*.

(**Hu K et al. Hepatology. 2022 Apr;75(4):968-982. doi: 10.1002/hep.32203. Epub 2021 Dec 7. PMID: 34662439**)

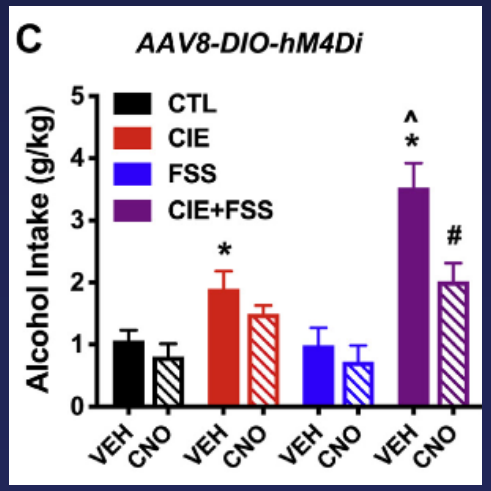
Dynorphin/Kappa Activity Within the Extended Amygdala Contributes to Stress-Enhanced Alcohol Drinking in Mice

In an animal model of combined stress and alcohol dependence in male mice, researchers tested the hypothesis of a role of the dynorphin/kappa opioid receptor (DYN/KOR) system in stress-enhanced alcohol consumption. Forced swim stress combined with chronic intermittent ethanol exposure led to a robust and reproducible increase in alcohol consumption that was mediated by DYN/KOR activity in the extended amygdala. Forced swim stress increased prodynorphin levels in the CeA and chemogenetic silencing of dynorphin expressing CeA neurons or micro-injection of a kappa antagonist into the CeA blocked the increased alcohol consumption produced by the forced swim stress and CIE. Additional research is needed to determine whether similar effects are observed in female mice.

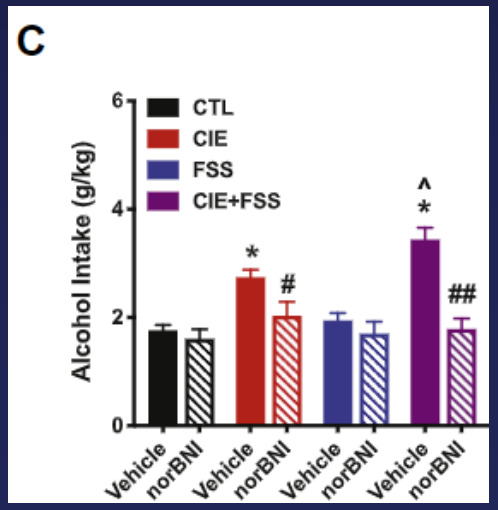
Increased alcohol intake in stress-exposed animals



Inhibition of central amygdala neurons attenuates stress-enhanced alcohol consumption



KOR antagonism attenuates stress-enhanced alcohol consumption

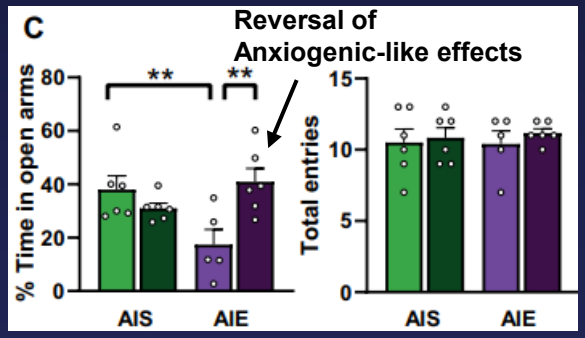


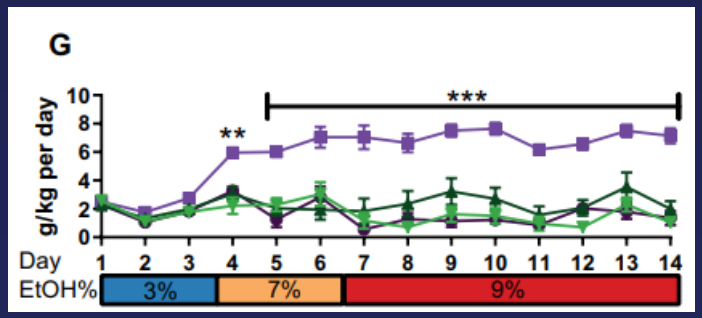
(Haun HL, Lebonville CL, Solomon MG, Griffin WC, Lopez MF, Becker HC. Biol Psychiatry. 2022 Jun 15;91(12):1019-1028. doi: 10.1016/j.biopsych.2022.01.002. Epub 2022 Jan 10. PMID: 35190188)

Targeted Epigenomic Editing Ameliorates Adult Anxiety and Excessive Drinking After Adolescent Alcohol Exposure

Adolescent alcohol exposure in rat models produces epigenetic modifications in synaptic activity response element (SARE) that decreases cytoskeleton associated protein (Arc) the central amygdala (CeA). Decreased Arc, in turn, is associated with increased adult anxiety and alcohol consumption. Researchers used CRISPR/dCas9 gene editing to show that increasing histone acetylation at the Arc SARE led to reduced adult anxiety and alcohol consumption in adolescent alcohol exposed rats while increasing histone methylation led to increased anxiety and alcohol consumption in control rats. These findings show a key molecular causal mechanism mediating the epigenetic interaction linking adolescent alcohol exposure to AUD and comorbid anxiety.

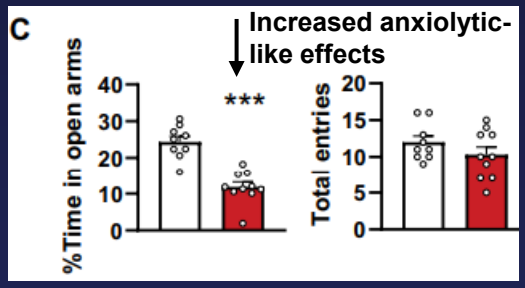
dCas9-P300 reverses epigenetic and behavioral consequences in adolescent alcohol exposed rats

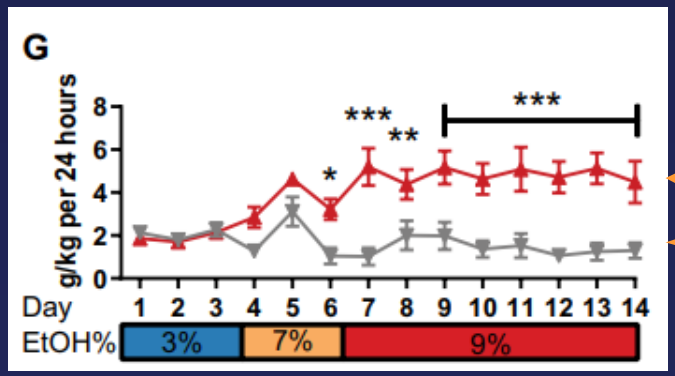




Reversal of Increased alcohol consumption

dCas9-KRAB induces epigenetic and behavioral consequences in control rats





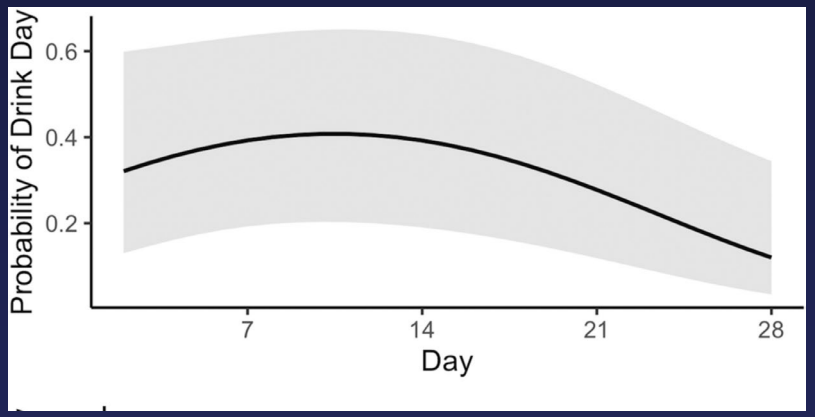
Increased alcohol consumption

(Bohnsack JP, Zhang H, Wandling GM, He D, Kyzar EJ, Lasek AW, Pandey SC. Sci Adv. 2022 May 6;8(18):eabn2748.)

Development and Preliminary Effectiveness of a Smartphone-based, Just-in-Time Adaptive Intervention for Adults with Alcohol Misuse Who Are Experiencing Homelessness

Adults experiencing homelessness have 8X higher rates of alcohol use disorder. This study investigated the development and preliminary effectiveness of a smartphone-based, just-in-time adaptive intervention to reduce alcohol use among this population using brief ecological momentary assessment. Over a 4-week period, individuals showed a decrease in alcohol use and high levels of satisfaction with the intervention.

Probability of Drink day



Participants showed:
- **decrease in probability of any drinking**
- **decrease in heavy episodic drinking**
- **decrease in drinks per day**

Model-implied trajectory of probability of drinking on a given day during the study period

(Walters ST, Mun EY, Tan Z, Luningham JM, Hébert ET, Oliver JA, Businelle MS. Alcohol Clin Exp Res. 2022 Jul 23. doi: 10.1111/acer.14908. Epub ahead of print. PMID: 35869820.)

Constructs Derived From the Addiction Cycle Predict Alcohol Use Disorder Treatment Outcomes and Recovery

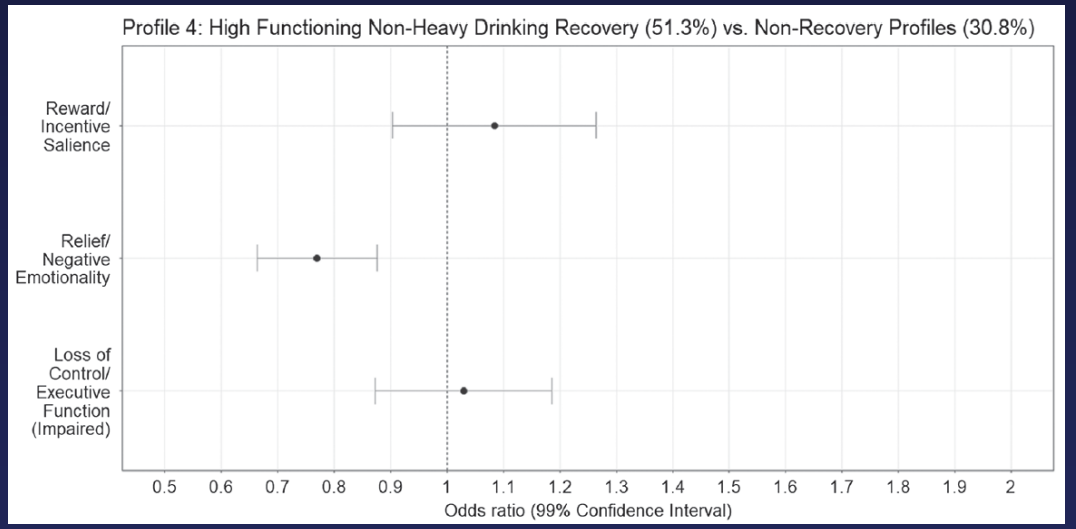
A 3 stage addiction cycle comprising 3 domains of dysfunction has been proposed as a heuristic framework for understanding AUD. This study validated the domains of the addiction cycle (incentive salience, negative emotional states, and executive function) using measures from Project MATCH and COMBINE, two of the largest multisite alcohol clinical trials ever conducted. The results support the utility of domains in predicting AUD treatment outcomes and recovery. The authors noted that the addiction cycle domains were more strongly associated with outcomes than AUD symptoms.

Four latent recovery profiles reflecting differing levels of drinking and functioning were derived based on indicators of alcohol use

Alcohol Consumption Outcomes at 1 Year Following Treatment

Predictor	Percent heavy drinking days (PHDD)	
	β	*B* (*SE*), *p* value
Reward/incentive salience	.01	0.35 (.87), $p = .690$
Relief/negative emotionality	**.09**	**2.69 (.53), $p < .001$**
Loss of control/executive functioning	.001	0.02 (1.17), $p = .988$
Study, MATCH = 1	**−.13**	**−8.61 (2.19), $p < .001$**
Sex, male = 1	.05	3.17 (1.48), $p = .032$
Age	−.01	−0.04 (.06), $p = .478$
Racial and ethnic identity, non-Hispanic white = 1	.03	2.19 (1.67), $p = .190$
Marital status, married = 1	−.02	−1.20 (1.26), $p = .341$
Years of education	−.03	−0.43 (.29), $p = .139$
Family history of AUD	.01	0.34 (1.41), $p = .812$
AUD symptom count	.04	0.86 (.54), $p = .111$
Model R^2		0.03
R^2 with only ANA domains		0.02

Addiction Cycle Domains in Predicting Expected Classification in High Functioning Infrequent Drinking vs Non-Recovery Profiles



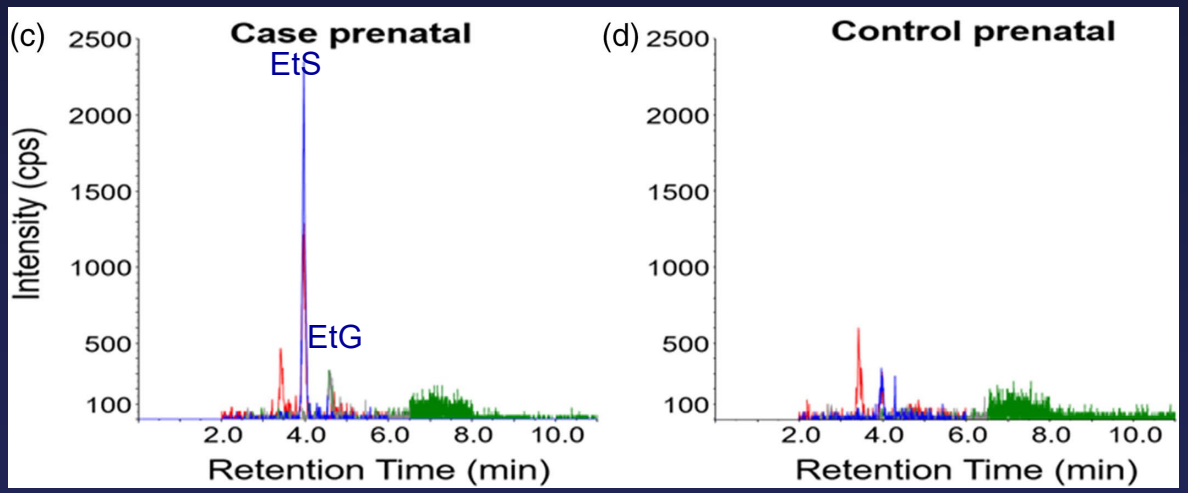
Greater relief/negative emotionality at baseline predicted greater drinking intensity and more frequent heavy drinking.

Only lower relief/negative emotionality predicted membership in the High Functioning Infrequent Drinking Profile (Profile 4) as compared to the nonrecovery profiles.

(Witkiewitz K, Stein ER, Votaw VR, Hallgren KA, Gibson BC, Boness CL, Pearson MR, Maisto SA. Psychol Addict Behav. 2022 Aug 11. doi: 10.1037/adb0000871. Epub ahead of print. PMID: 35951419.)

Prenatal Alcohol Exposure Can Be Determined From Baby Teeth: Proof of Concept

In most of suspected FASD cases, the strength of the diagnosis depends on evidence of prenatal alcohol exposure (PAE), which is often missing. This study developed a technology showing the presence of alcohol biomarkers in naturally shed baby teeth. Further examination of these biomarkers may allow diagnosis of FASD where documentation of prenatal alcohol exposure is otherwise unavailable.



Chromatograms of the direct biomarkers: ethyl glucuronide (EtG), ethyl sulfate (EtS) in tooth powder:

Extract fraction from prenatal dentine collected from case tooth (known PAE),

Extract fraction from prenatal dentine from control tooth.

(Montag AC, Chambers CD, Jones KL, Dassanayake PS, Andra SS, Petrick LM, Arora M, Austin C; Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD). Birth Defects Res. 2022 Aug 15;114(14):797-804. doi: 10.1002/bdr2.2054. Epub 2022 Jun 10. PMID: 35686682)

THANK YOU!

Special thanks to:

Cara Anjos Breeden

Laura Brockway-Lunardi

Kate Masterton

Patricia Powell

Van Van

Aaron White

Bridget Williams-Simmons