NIAAA Director's Report
on Institute Activities to the 163rd Meeting of the National Advisory Council on Alcohol Abuse and Alcoholism

May 9, 2023
Hybrid Meeting

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Director
National Institute on Alcohol Abuse and Alcoholism
National Institutes of Health

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

In Memoriam: George Fein, PhD

Dr. George Fein was a long-time faculty member in the Department of Psychiatry at the University of California San Francisco and the San Francisco VA Medical Center. Following his career in academic medicine, he founded Neurobehavioral Research, Inc. and served as its President and Chief Executive Officer.

Dr. Fein was renowned as an innovative researcher. He advanced our understanding of the impacts of aging, alcohol and other substance use disorders, and psychiatric disorders on brain structure and function. He made the pivotal finding that treatment for and recovery from alcohol use disorder are associated with compensatory functional network alterations in the brain.

Dr. Fein was an outstanding scientist, esteemed colleague, and generous mentor. He will be sorely missed.

In Memoriam: John Littleton, MD, PhD

Dr. John Littleton received his training in Pharmacology and Medicine at Kings College in England and continued there as a faculty member. He moved to the University of Kentucky where he spent the rest of his career.

His groundbreaking research contributed to our understanding of the development of functional tolerance to alcohol, the role of L-type Ca2+ channels in the physiology of alcohol actions, alcohol-nicotine interactions, and the use of mammalian cell culture models to study alcohol effects. His work with high throughput pharmacological screening in plant cell cultures led to the identification of several lead compounds that demonstrated preclinical efficacy in reducing alcohol's effects on the central nervous system. Dr. Littleton played a key role in exploring the mechanism of action of acamprosate that led to its approval by the FDA as a treatment for alcohol use disorder.

He was a generous mentor for many trainees and junior faculty. He will be missed.

In Memoriam: Enoch Gordis, MD

Dr. Enoch Gordis served as the NIAAA director from 1986 to 2001. Dr. Gordis emphasized science as a way of understanding alcohol use disorder. Trained in internal medicine, he conducted research in the laboratory of Dr. Solomon Berson and Nobel Laureate Dr. Rosalyn Yalow during his residency at Mount Sinai Hospital in New York. Subsequently he worked in Dr. Vincent P. Dole's research laboratory at New York's Rockefeller University, where he began his career in the study of addiction. He later worked with psychiatric researcher Dr. Ruth Fox, who helped introduce disulfiram in the United States as a medication to treat alcohol problems. In 1971, Dr. Gordis founded and directed a new alcohol treatment program at Elmhurst Hospital in Queens, NY. He remained there until his appointment to NIAAA.

At NIAAA, Dr. Gordis is remembered as a visionary leader. During his tenure as director, he oversaw the launch of several innovative research initiatives, including the Collaborative Study on the Genetics of Alcoholism, the National Longitudinal Alcohol Epidemiologic Survey, the Integrative Neuroscience Initiative on Alcoholism, and the Combined Pharmacotherapies and Behavioral Interventions clinical study.

Dr. Gordis' leadership embodied his love of science, his compassion as a clinician, and his demeanor as a gentleman. He inspired many and left a lasting impact on NIAAA, NIH, and the alcohol research field.

Remembering Enoch Gordis, MD
Staff Reflections

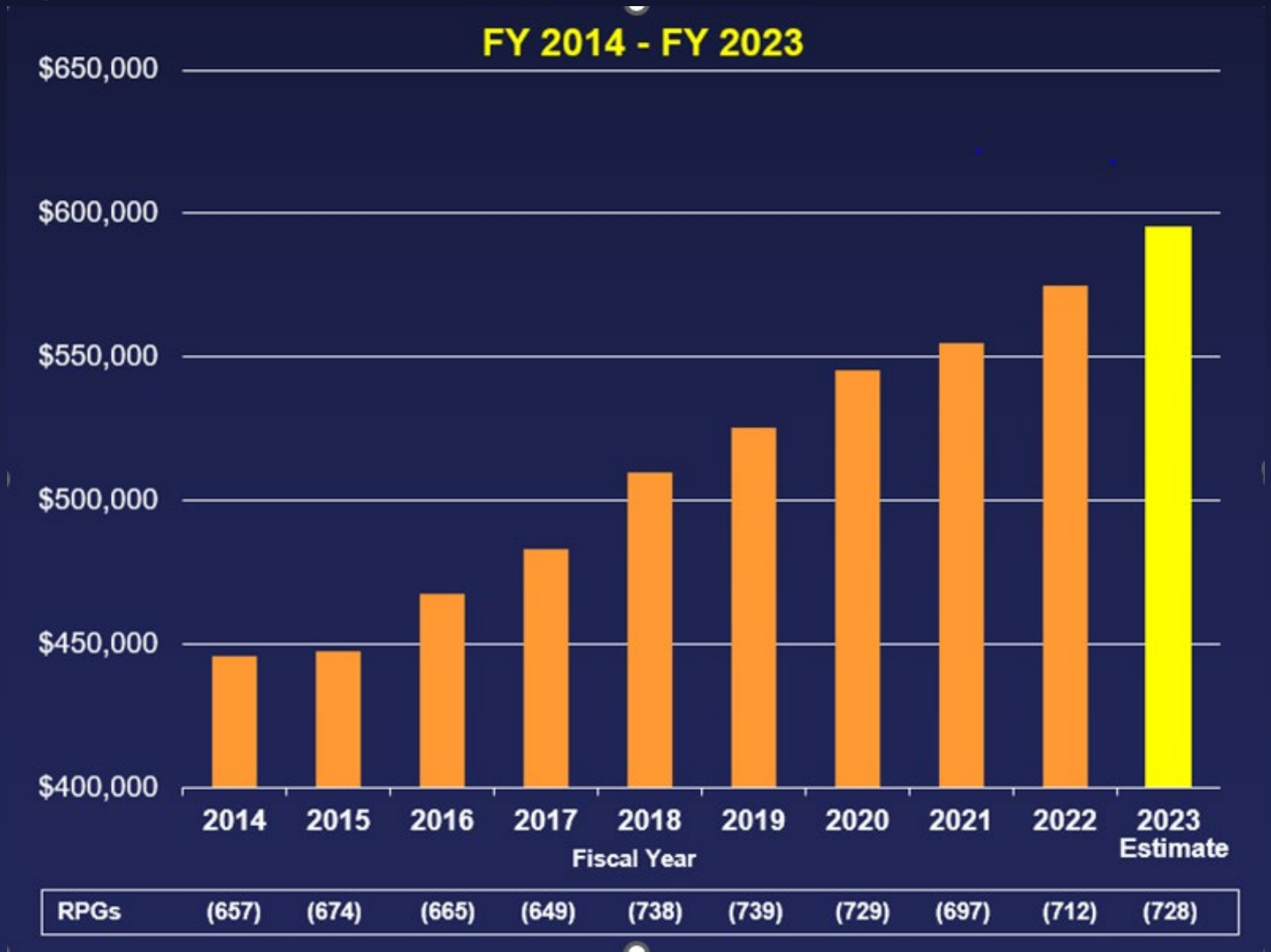
- "He set a tone of collegiality and shared purpose that made NIAAA a place where people felt respected and valued as individuals, beyond their roles in the workplace."
- "Not only was Dr. Gordis a leader in the field, he was instrumental in creating the 'family' atmosphere at NIAAA. His passing is a great loss to humankind."
- "He was a Great Soul, indeed! Someone who always made you feel like you were the most important person in the world."
- "I'll never forget the kindness Dr. Gordis offered in 2001 when my husband was battling an aggressive cancer. Whenever he came to my office with a quick business question, Dr. Gordis always asked first about how my family and I were doing and offered words of sympathy and consolation. That meant the world to me."
- "His ragged sweater and his goofy erupting laugh which, on a good day, we could hear throughout the suite at Willco! He was a great guy."
- "His genuine interest in a wide range of scientific issues and determination to advance understanding of how to reduce the burden of alcohol problems laid the foundation for much of the research that continues now. The considerable success of NIAAA and the broader alcohol research enterprise will always owe a debt to Dr. Gordis."

Remembering Enoch Gordis, MD

March 2014
Mark Keller Honorary Lecture
NIH Clinical Center Auditorium

NIAAA Budget

For fiscal year 2023, NIAAA received $596.6 million, including a $1.3 million AIDS transfer. This represents a $21.7 million (or 3.8%) increase over fiscal year 2022.



NIAAA Funding Opportunities

(See Director's Report for Complete Listing)

- **Advancing mHealth Interventions for Understanding and Preventing Alcohol-Related Domestic Violence:** This Notice seeks to advance the development, testing, and implementation of scalable, low resource, and remotely delivered interventions via mobile devices (mHealth) that rely on communication technologies for reducing and preventing alcohol consumption and domestic violence. NOT-AA-23-003 (Contact: Dr. Robert Freeman)

- **HIV Prevention and Alcohol:** NIAAA intends to publish a new Notice of Funding Opportunity (NOFO) to solicit applications to expand the HIV/AIDS prevention toolkit among alcohol impacted populations with a range of patterns of episodic and long-term use and associated behavioral and biological risks for HIV acquisition. The NOFO is expected to be published in Spring 2023. NOT-AA-23-005 (R01 Clinical Trials Optional), NOT-AA-23-006 (R34 Clinical Trials Optional) (Contact: Dr. Kendall Bryant)

NIH Science and Technology Research Infrastructure for Discovery, Experimentation, and Sustainability (STRIDES) Initiative

- **Goal: Reduce economic and process barriers to using cloud services**
- STRIDES provides:
  - Discounts and favorable pricing on computing, storage and related services from Amazon Web Services, Google Cloud Platform, and Microsoft Azure
  - Consultation and technical support
  - Training and certification
- This opportunity is open to NIH funded researchers: grants, cooperative agreements, intramural program, and contracts.
  - Enroll at **cloud.nih.gov**
- The NIAAA Data Archive is supported by the STRIDES Initiative
- Future STRIDES Initiative activities will promote data access across NIH and NIH-funded institutions
- NIAAA representatives: Dr. Dan Falk and Dr. Elizabeth Powell

Request for Information on "Preaddiction"

- NIDA and NIAAA issued a Request for Information (RFI) inviting input on the use of a term like "preaddiction" for identifying and intervening in substance misuse and mild/early-stage substance use disorder within healthcare settings.
- The term "preaddiction" has been proposed as a way to: raise public awareness about potentially harmful patterns of substance use, spur greater utilization of screening and brief intervention, prevent overdose, and promote the development of new interventions.
  (McLellan AT, Koob GF, Volkow ND. Preaddiction-A Missing Concept for Treating Substance Use Disorders. JAMA Psychiatry. 2022 Aug 1;79(8):749-751. PMID: 35793096)
- Input was sought both on the terminology to describe this concept and the concept itself, including potential benefits and drawbacks of adopting such a term.
- The RFI was open March 13-April 27. Feedback will be analyzed and inform discussions about the concept of preaddiction.

Recent NIAAA Scientific Meetings

- **The Annual Public Meeting of the Interagency Coordinating Committee on Fetal Alcohol Spectrum Disorders (ICCFASD)** was held virtually on April 17. Participating federal agencies provided updates on their activities related to FASD. A special panel included information on "Community-Engaged Research: What Works from Lived Experience Perspectives" as well as the FASD Family Navigator Program.

  https://www.niaaa.nih.gov/news-events/meetings-events-exhibits/public-meeting-interagency-coordinating-committee-fetal-alcohol-spectrum-disorders-iccfasd-april

- **The Interagency Work Group on Drinking and Drug Use in Women and Girls** held a webinar on March 10 focused on research findings from epidemiological and neuroscience research, including developments in behavioral treatments and pharmacotherapies for women who drink at harmful levels. The webinar also highlighted ongoing collaborative activities to improve access to high quality, gender-relevant mental health and addiction treatment services among women and girls.

  https://www.niaaa.nih.gov/major-initiatives/interagency-work-group-drinking-and-drug-use-women-and-girls

Diversity, Equity, Inclusion, and Accessibility Efforts

- **Scientific Diversity Officer:** A vacancy announcement was posted last month, and we are in the early stages of the selection process. We anticipate completing the process in the next few weeks.
- **Funding Opportunity Announcement: Research Opportunities for New and "At-Risk" Investigators to Promote Workforce Diversity:** To support R01 grant applications from New Investigators and At-Risk Investigators from diverse backgrounds, including those from groups underrepresented in the health-related sciences (PAR-22-181)
- **Workforce Diversity:** To increase diversity in the alcohol research field, NIAAA's participates in the "Maximizing Opportunities for Scientific and Academic Independent Careers" (MOSAIC) Program. We announced three new NIAAA-supported MOSAIC scholars in 2022.

What's Ahead?

- The **Alcoholism and Stress: A Framework for Future Treatment Strategies** meeting will be held May 16 - 19, 2023 in Volterra, Italy.

- **National Institute on Aging-NIAAA joint workshop on the impact of alcohol misuse on the onset and progression of Alzheimer's disease and its related dementias** will be held as a hybrid meeting on July 26 - 27, 2023, at the Natcher Conference Center on the main NIH campus. The workshop aims to identify research gaps and challenges to advance our understanding of the relationship between alcohol misuse and dementias. More information is forthcoming.

Communications Update

- In recognition of **Alcohol Awareness Month** in April, NIAAA shared social media messages and engaged in a Twitter chat with the American Society of Addiction Medicine about alcohol myths and treatment.

- NIAAA launched a major update to **Alcohol Facts and Statistics**, a popular online resource which consistently ranks among the most viewed NIAAA webpages. It has been updated with recent alcohol statistics, expanded with demographic information, and reorganized for improved readability and navigability. The link is available on the NIAAA homepage and in the ***Alcohol's Effects on Health*** section of our website.

https://www.niaaa.nih.gov/alcohols-effects-health/alcohol-topics/alcohol-facts-and-statistics

RESEARCH HIGHLIGHTS

Earlier Initiation of and Escalation to High-Intensity Drinking in Young Adults Predicts Future Alcohol Misuse

High-intensity drinking (HID), defined as consuming 10 or more drinks in a row, is a particularly concerning drinking behavior. This study used a sample of 451 young adults who reported past 30–day drinking while in 12th grade and initiated HID by age 20. Initiating HID by grade 11 (vs later) was associated with higher average weekly alcohol consumption, HID frequency, and AUDIT score at age 20 years. Delaying HID initiation may reduce the likelihood of acute and long-term negative alcohol use.

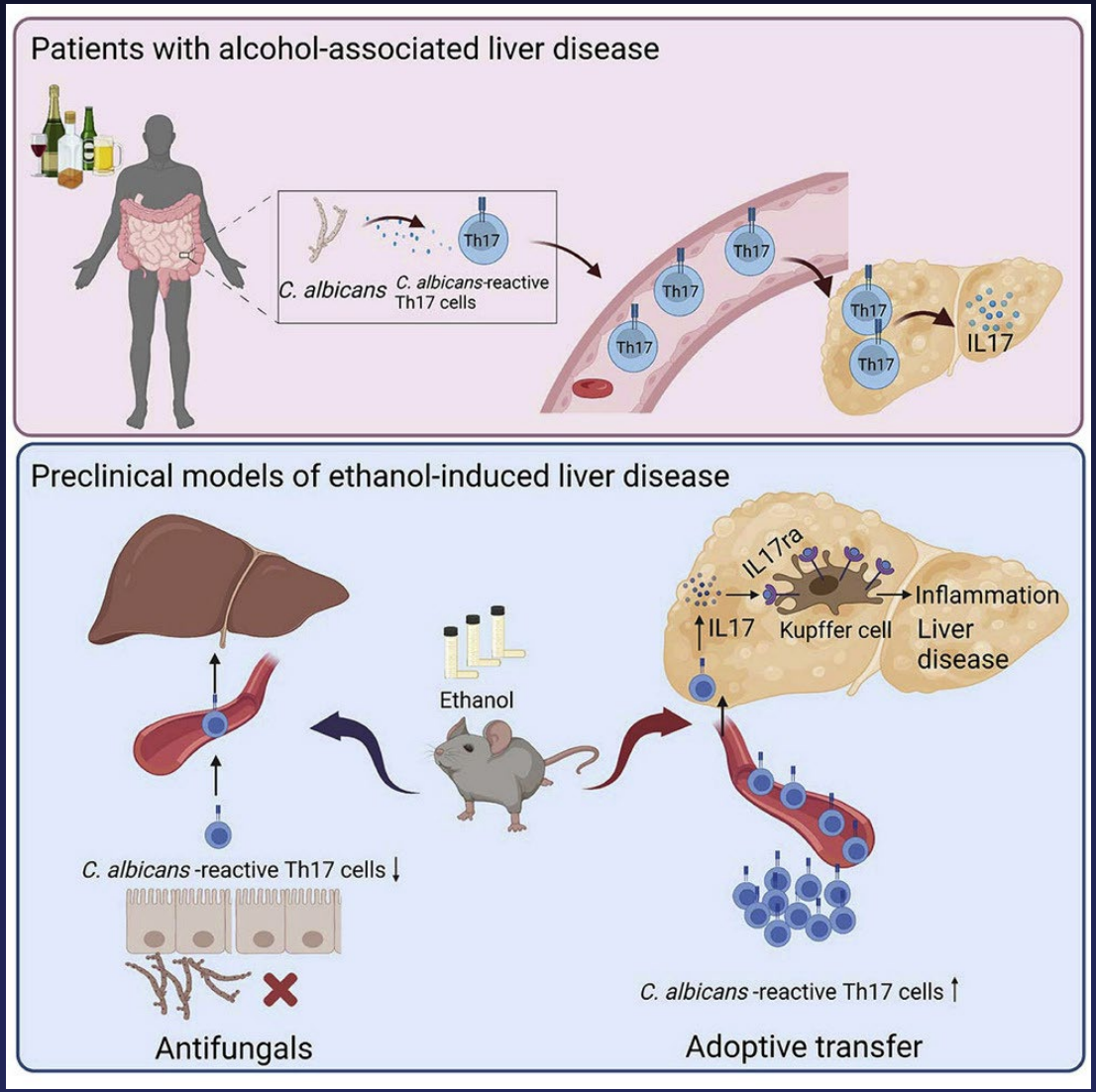
Table 3. Negative Binomial Regression Associations Between High-Intensity Drinking (HID) Initiation and Escalation and Average Weekly Consumption and HID Frequency at Age 20 Years[a]

	Average weekly consumption		HID frequency	
	Bivariate, IRR (95% CI)	Multivariable, aIRR (95% CI)	Bivariate, IRR (95% CI)	Multivariable, aIRR (95% CI)
HID initiation (vs grade 12 or later)				
By grade 11	1.28 (1.01-1.61)	1.40 (1.10-1.79)	1.83 (1.13-2.97)	2.01 (1.25-3.22)
Escalation from first drink to HID (vs ≥1 y)				
Same year	0.85 (0.58-1.25)	0.87 (0.62-1.23)	1.27 (0.61-2.64)	1.29 (0.70-2.38)
Escalation from first binge to HID (vs ≥1 y)				
Same year	1.03 (0.81-1.32)	1.12 (0.87-1.44)	1.49 (0.92-2.41)	1.66 (1.06-2.61)

Patrick ME, Evans-Polce RJ, Arterberry BJ, Terry-McElrath Y. Initiation of and Escalation to High-Intensity Drinking in Young Adults. JAMA Pediatr. 2023 Mar 1;177(3):286-293. PMID: 36716022

A Fungal *Candida albicans*-Specific Th17 Cell-Mediated Response Contributes to Alcohol-Associated Liver Disease

Alcohol-associated liver disease (ALD) is accompanied by an imbalance of the intestinal fungal microbiome (mycobiome dysbiosis). Proinflammatory cytokines, such as IL-17, produced mainly by T helper 17 (Th17) lymphocytes, is a contributing factor of autoimmune and inflammatory conditions. This report found that T-helper 17 cells reactive to the yeast *Candida albicans* increase in the blood and liver of patients with ALD. In a mouse model, data show that molecular activation of T-cells reactive to *Candida* developed more severe ethanol-induced liver disease and an antifungal agent decreased ethanol-induced liver disease. Results suggests that *Candida albicans*-reactive T helper 17 cells migrate from the intestine to the liver, where they contribute to the development of ALD.

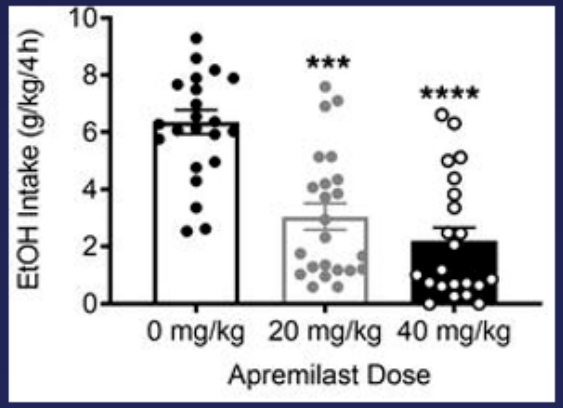


Zeng S, Rosati E, Saggau C, Messner B, Chu H, Duan Y, Hartmann P, Wang Y, Ma S, Huang WJM, Lee J, Lee SM, Carvalho-Gontijo R, Zhang V, Hoffmann JP, Kolls JK, Raz E, Brenner DA, Kisseleva T, LeibundGut-Landmann S, Bacher P, Stärkel P, Schnabl B. Candida albicans-specific Th17 cell-mediated response contributes to alcohol-associated liver disease. Cell Host Microbe. 2023 Mar 8;31(3):389-404. PMID: 36893735

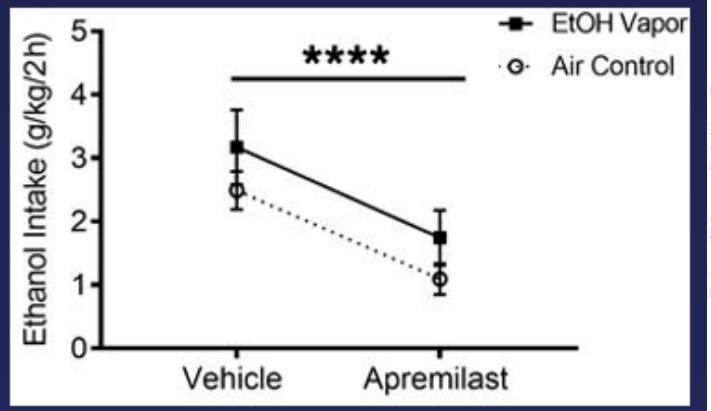
Preclinical and Clinical Evidence for Suppression of Alcohol Intake by Apremilast

Phosphodiesterases are a superfamily of enzymes that hydrolyze the cyclic nucleotides cAMP and cGMP. Apremilast is a phosphodiesterase type 4 (PDE4) inhibitor and currently FDA-approved for the treatment of psoriasis. Via PDE 4 inhibition, apremilast elevates intracellular cAMP levels, which is thought to decrease levels of some pro-inflammatory mediators and increase the production of certain anti-inflammatory mediators. Apremilast reduced excessive alcohol intake in preclinical animal models and in non-treatment-seeking humans with AUD in a double-blind, placebo-controlled Phase 2a study.

Mouse Models

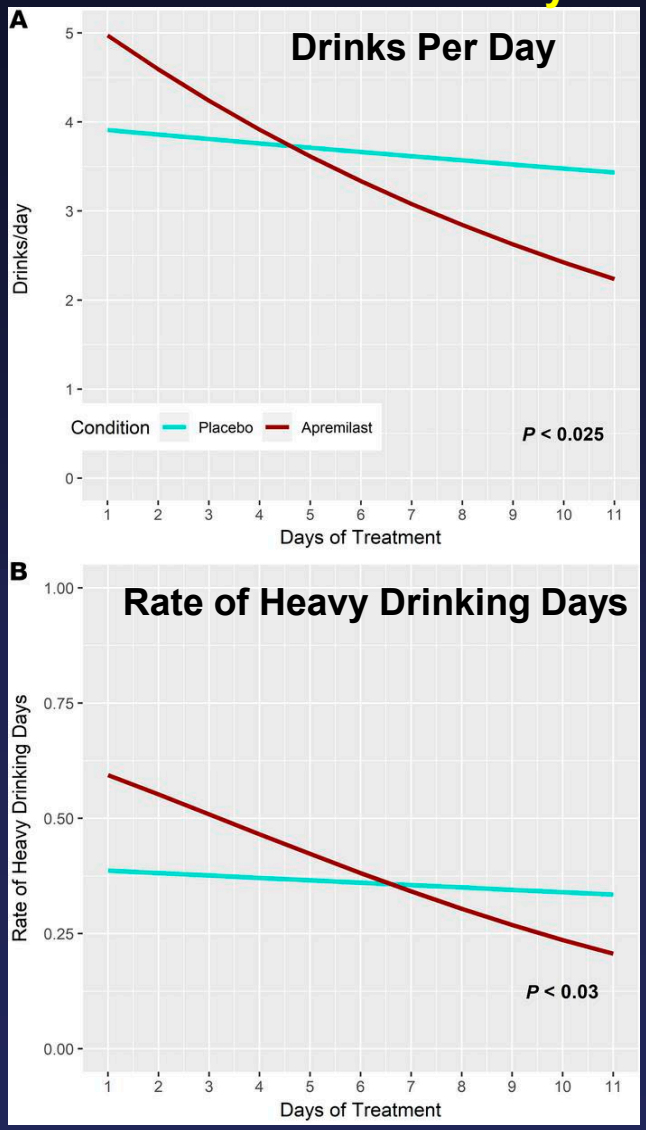


binge-like drinking



alcohol dependence

Human Phase 2a Study

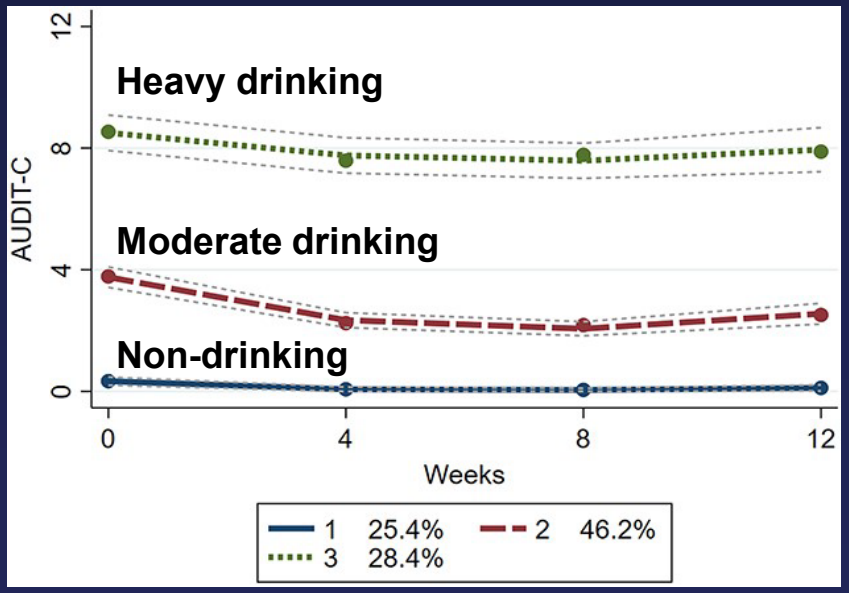


Grigsby KB, Mangieri RA, Roberts AJ, Lopez MF, Firsick EJ, Townsley KG, Beneze A, Bess J, Eisenstein TK, Meissler JJ, Light JM, Miller J, Quello S, Shadan F, Skinner M, Aziz HC, Metten P, Morrisett RA, Crabbe JC, Roberto M, Becker HC, Mason BJ, Ozburn AR. Preclinical and clinical evidence for suppression of alcohol intake by apremilast. J Clin Invest. 2023 Mar 15;133(6):e159103. PMID: 36656645

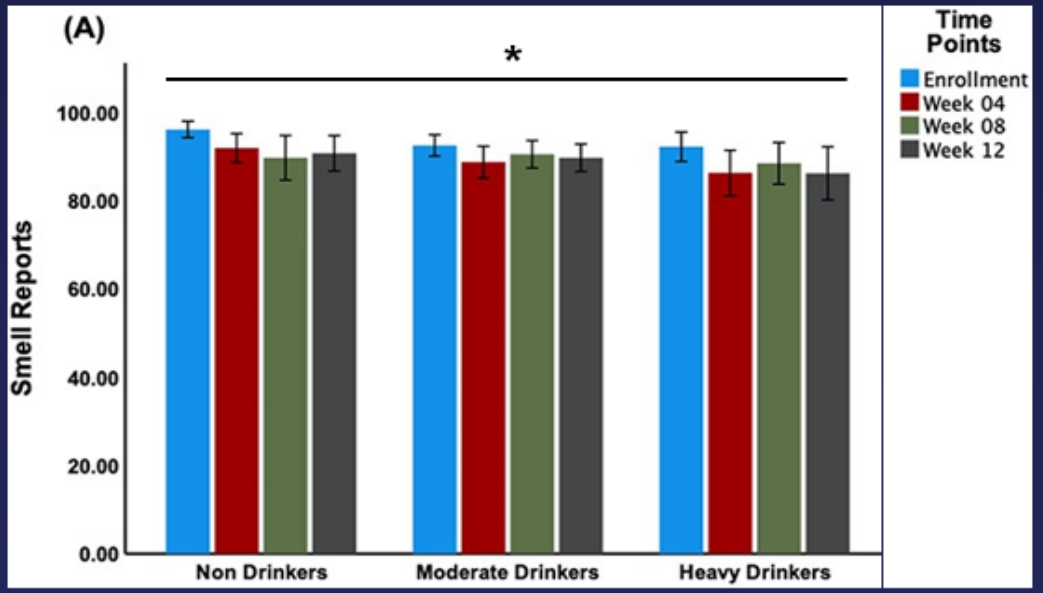
Chemosensory Alterations and Impact on Quality of Life in Persistent Alcohol Drinkers

In this study, researchers observed a significant impairment in smell ability of heavy drinking individuals compared to non-drinking individuals, and the impairment was associated with a deterioration in physical, psychological, social, and environmental quality of life. Early assessment of smell function in individuals with AUD may help predict disease-associated comorbidities, especially in quality of life domains.

Three groups of drinkers based on alcohol consumption at 4 time points



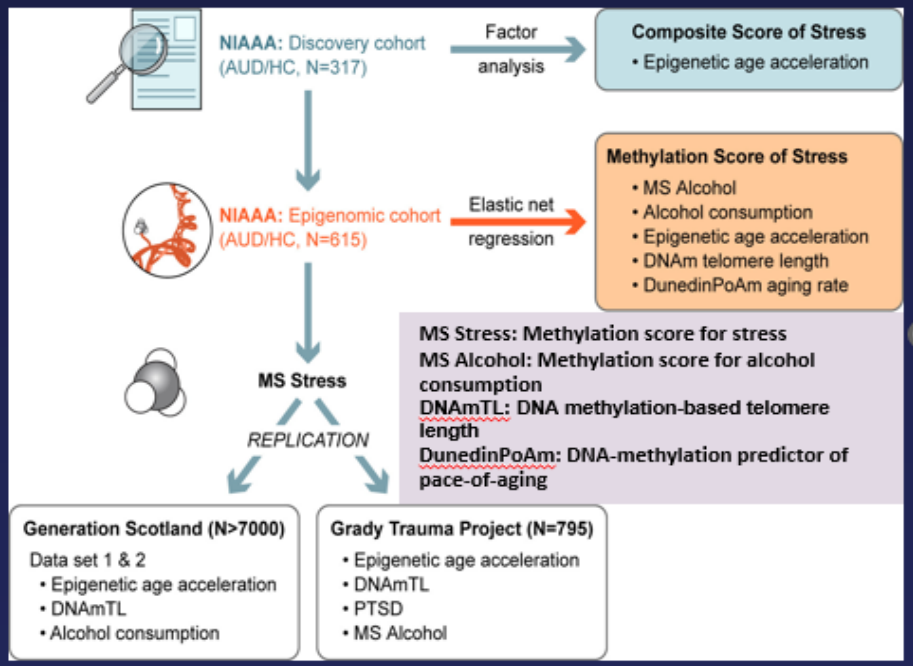
Significant smell difference between non-drinking and heavy drinking individuals



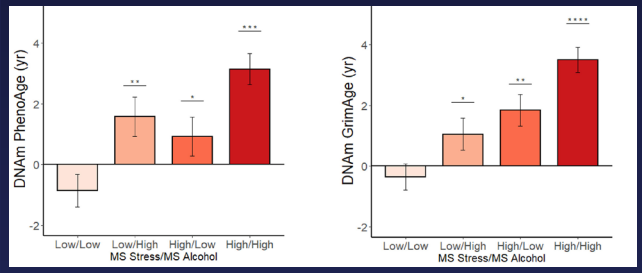
Agarwal K, Luk JW, Manza P, McDuffie C, To L, Jaime-Lara RB, Stangl BL, Schwandt ML, Momenan R, Goldman D, Diazgranados N, Ramchandani VA, Joseph PV. Chemosensory Alterations and Impact on Quality of Life in Persistent Alcohol Drinkers. Alcohol Alcohol. 2023 Jan 9;58(1):84-92. PMID: 36208183

Additive Effects of Stress and Alcohol Exposure on Accelerated Epigenetic Aging in Alcohol Use Disorder

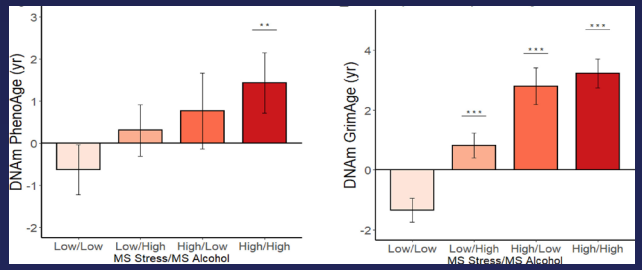
Stress contributes to premature aging and susceptibility to alcohol use disorder (AUD), and AUD itself is a factor in premature aging. To better understand the interrelationships between stress, AUD, and premature aging, this study used high density methylome arrays and telomere length assays in a deeply phenotyped sample of patients from the NIAAA intramural program. The present study showed that the combination of stress and heavy alcohol use additively accelerated epigenetic cellular age by about 4.5 years, and the finding was replicated in external samples from the Grady Trauma project and Generation Scotland. Epigenetic age correlates highly with chronological age but accelerated epigenetic age due to factors such as combined stress and AUD likely increases the risks of morbidity and mortality.



NIAAA Cohort



Replication Study (Grady Trauma Project)



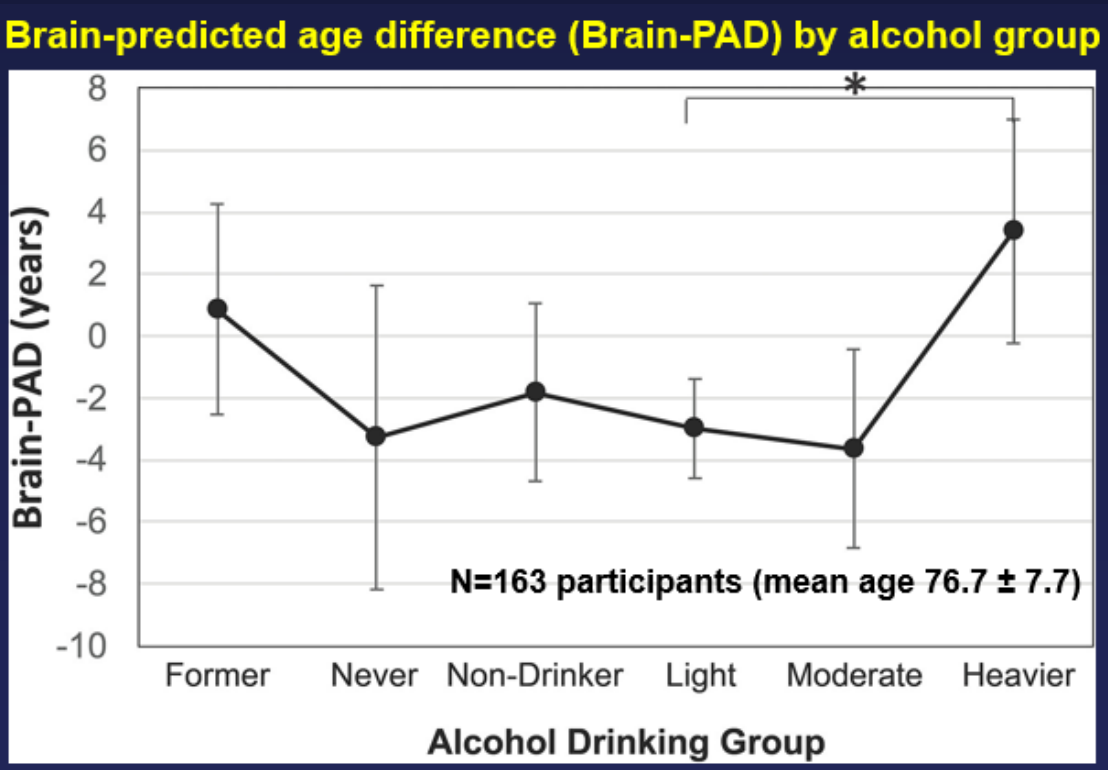
PhenoAge: Composite estimate of phenotypic age

GrimAge: Composite of DNA methylation - based markers linked to health- and lifespan. Relative to other measures of epigenetic aging, GrimAge is the strongest predictor of various age-related pathology.

Jung J, McCartney DL, Wagner J, Yoo J, Bell AS, Mavromatis LA, Rosoff DB, Hodgkinson CA, Sun H, Schwandt M, Diazgranados N, Smith AK, Michopoulos V, Powers A, Stevens J, Bradley B, Fani N, Walker RM, Campbell A, Porteous DJ, McIntosh AM, Horvath S, Marioni RE, Evans KL, Goldman D, Lohoff FW. Additive Effects of Stress and Alcohol Exposure on Accelerated Epigenetic Aging in Alcohol Use Disorder. Biol Psychiatry. 2023 Feb 15;93(4):331-341. PMID: 36182531

Heavy Drinking Associated with Older Neuroimaging-Derived Predicted Brain Age Difference Among Community-Dwelling Older Adults

Evidence indicates that alcohol misuse among older adults contributes to accelerated aging in certain brain regions and impaired cognitive function, learning, memory, and motor function. In this study, researchers found that heavier drinkers (defined here as >14 drinks per week) showed older brain predicted age differences (brain-PAD) than light drinkers (by about 6 years). Brain- PAD is the difference between the brain-predicted age and chronological age based on neuroimaging data. The brain-PAD among light and moderate drinking older adults did not differ from their nondrinking counterparts, suggesting no protective benefit of alcohol on brain aging. These results support the growing body of evidence that alcohol misuse contributes to accelerated neurodegeneration among older adults.



Funk-White M, Wing D, Eyler LT, Moore AA, Reas ET, McEvoy L. Neuroimaging-Derived Predicted Brain Age and Alcohol Use Among Community-Dwelling Older Adults. Am J Geriatr Psychiatry. 2023 Feb 20:S1064-7481(23)00217-8. PMID: 36925380.

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