

September 10, 2024 - Washington, DC

GLP-1R agonists but not DPP-4 inhibitors reduce alcohol intake in mice, rats, and humans

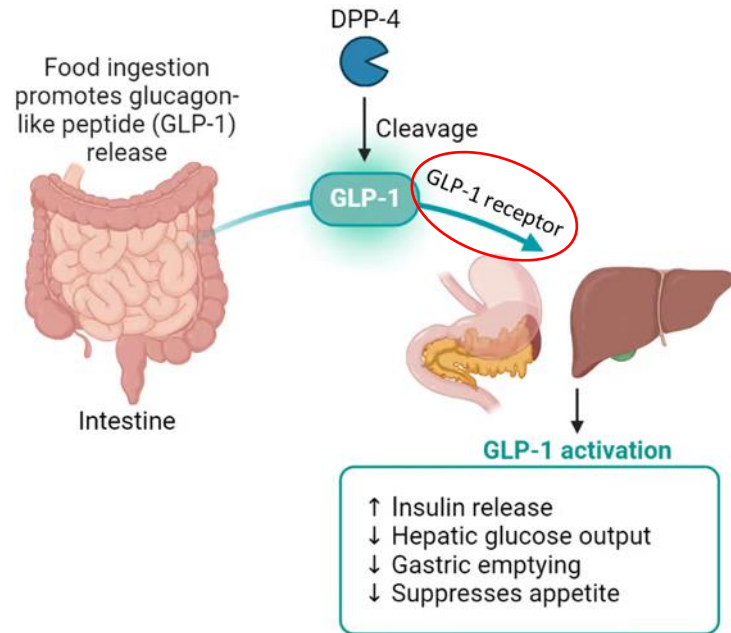


Mehdi Farokhnia, MD, MPH
NIDA and NIAAA, NIH



No conflicts of interest. Nothing to disclose.

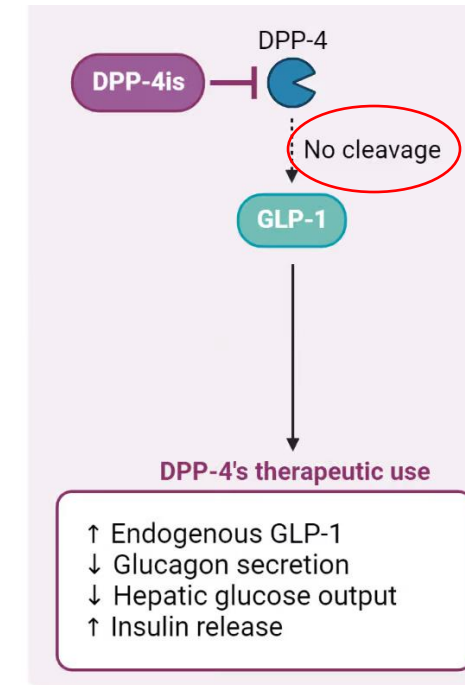
Pharmacotherapeutic approaches to target the GLP-1 system



GLP-1 receptor agonism

Exenatide
Lixisenatide
Albiglutide
Dulaglutide
Liraglutide
Semaglutide

**FDA approved for
diabetes & obesity*

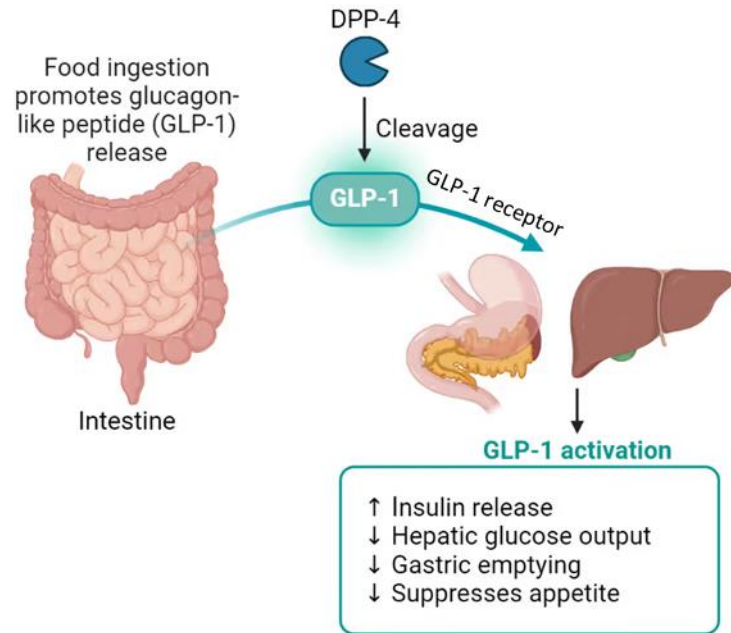


DPP-4 inhibition

Sitagliptin
Linagliptin
Alogliptin
Saxagliptin

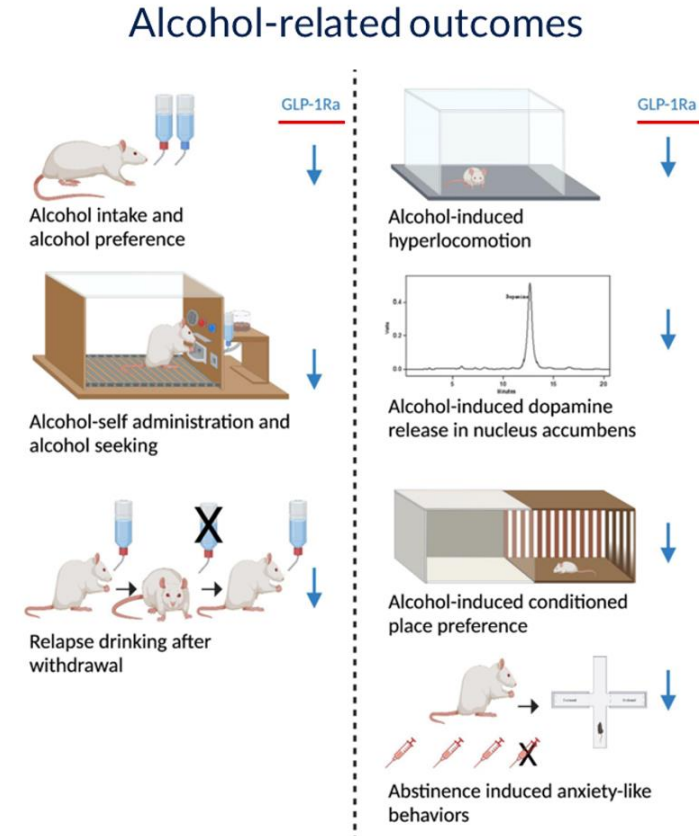
**FDA approved for
diabetes*

GLP-1R agonists reduce alcohol intake in rodents

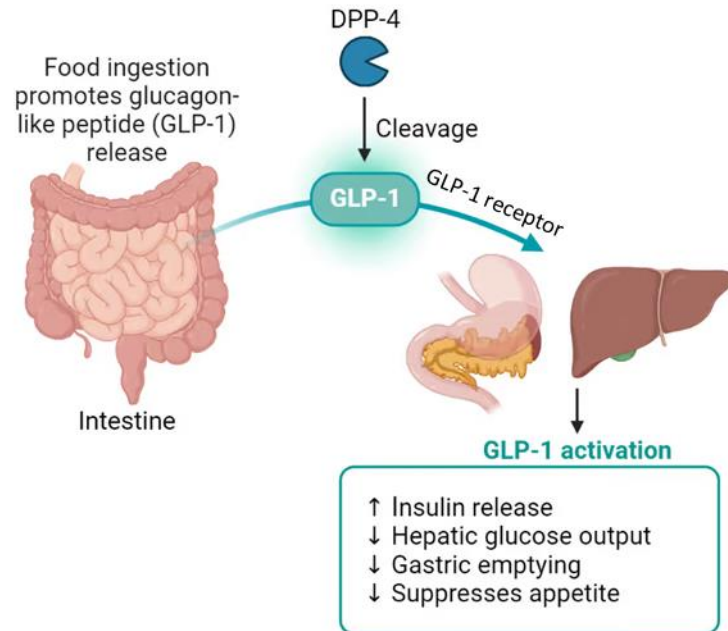


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GLP-1R agonists reduce alcohol intake in rodents



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Front Neurosci. 2020 Dec 23;14:599646. doi: 10.3389/fnins.2020.599646. eCollection 2020.

Long-Acting Glucagon-Like Peptide-1 Receptor Agonists Suppress Voluntary Alcohol Intake in Male Wistar Rats

Vincent N Marty¹, Mehdi Farokhnia^{2 3 4}, Joseph J Munier¹, Yatendra Mulpuri¹, Lorenzo Leggio^{2 3 5 6 7 8}, Igor Spigelman¹

JCI Insight. 2023 Jun 22;8(12):e170671. doi: 10.1172/jci.insight.170671.

The glucagon-like peptide-1 (GLP-1) analogue **semaglutide** reduces alcohol drinking and modulates central GABA neurotransmission

Vicky Chuong^{1 2}, Mehdi Farokhnia¹, Sophia Khom^{3 4}, Claire L Pince^{1 2}, Sophie K Elvig², Roman Vlkolinsky³, Renata Cn Marchette², George F Koob², Marisa Roberto³, Leandro F Vendruscolo⁵, Lorenzo Leggio¹

COMPLETED ⓘ

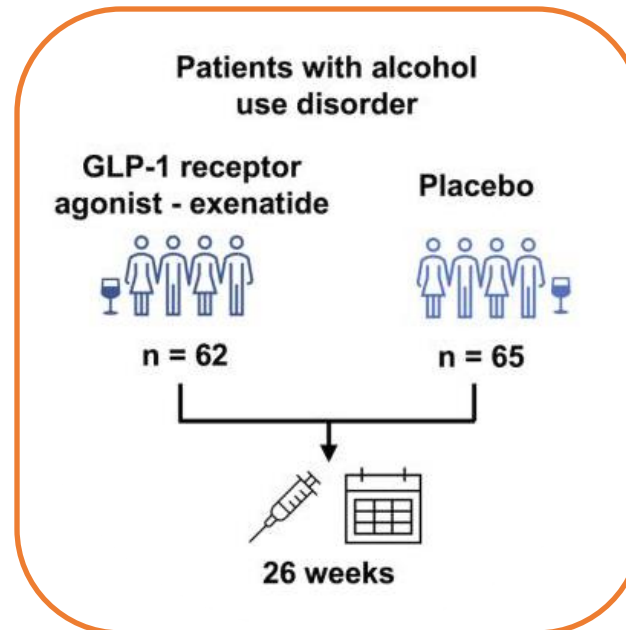
Does Treatment With GLP-1 Reduce Alcohol Intake in Patients With Alcohol Dependence? (EXALT)

ClinicalTrials.gov ID ⓘ **NCT03232112**

Sponsor ⓘ Anders Fink-Jensen, MD, DMSci

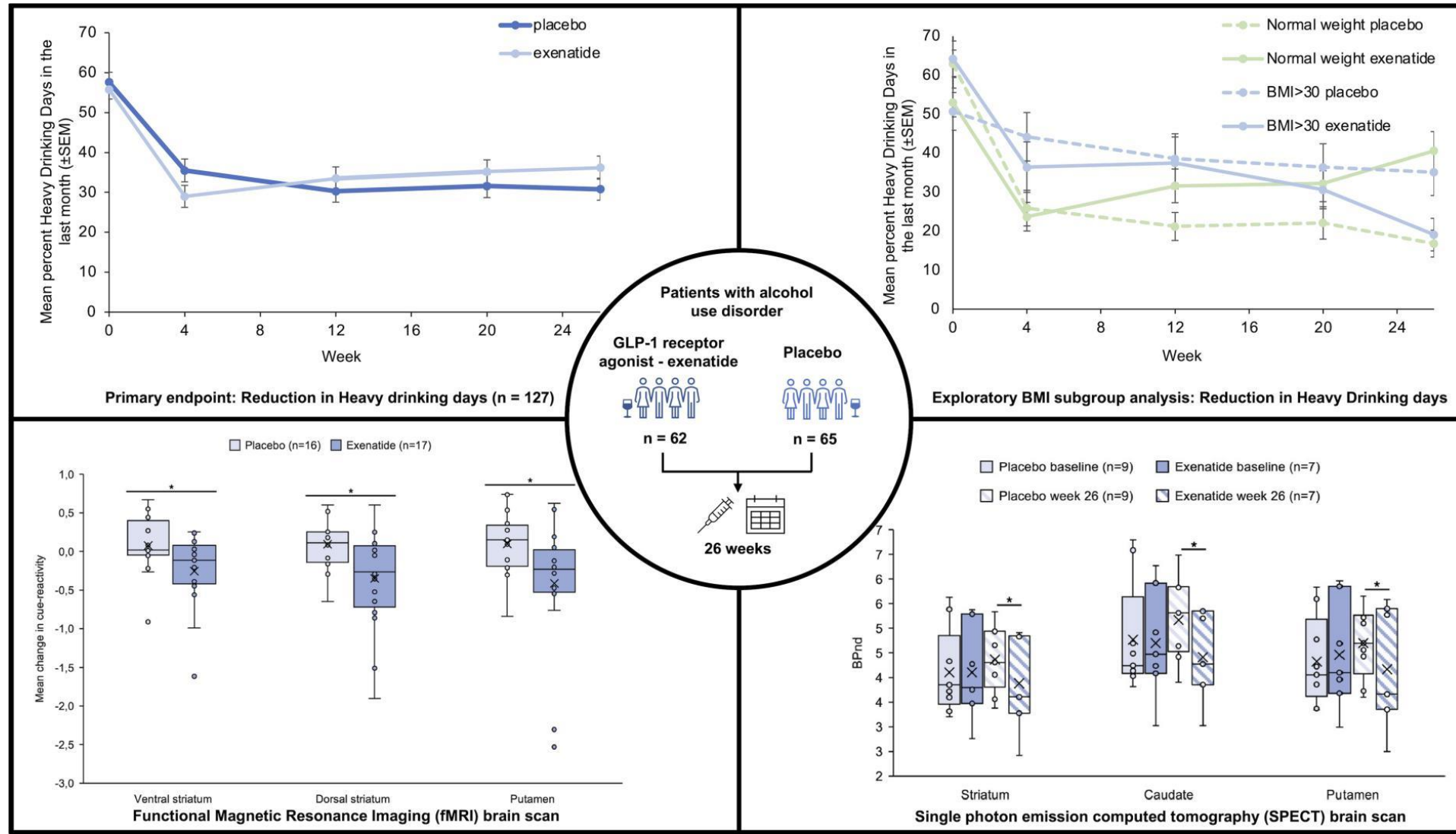
Information provided by ⓘ Anders Fink-Jensen, MD, DMSci, Psychiatric Centre Rigshospitalet (Responsible Party)

Last Update Posted ⓘ 2021-06-04

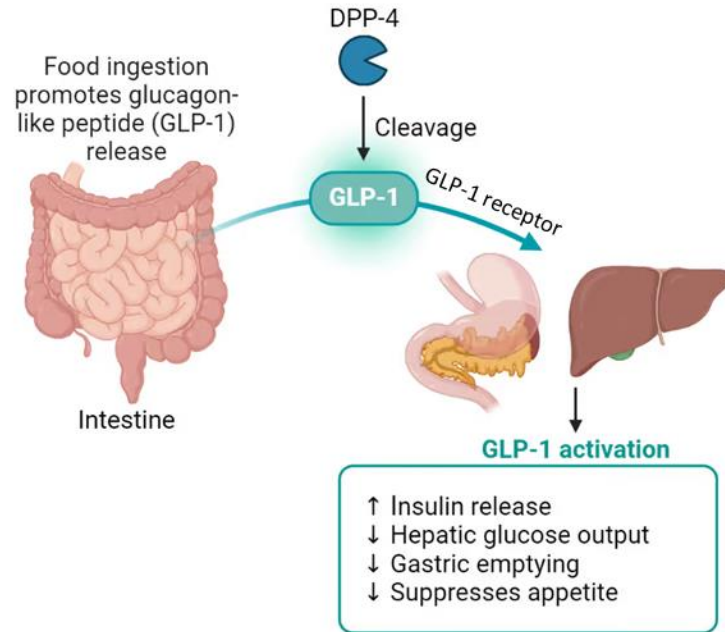


Exenatide once weekly for alcohol use disorder investigated in a randomized, placebo-controlled clinical trial

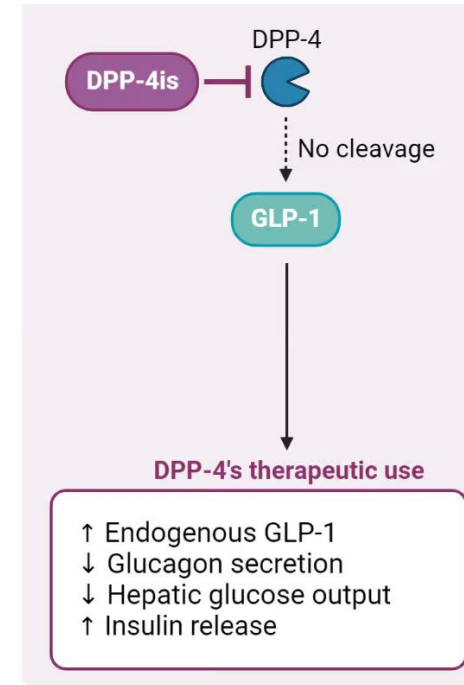
Mette Kruse Klausen, ... , Tina Vilsbøll, Anders Fink-Jensen



Could stimulating the GLP-1 system reduce alcohol intake?



GLP-1 receptor agonists



DPP-4 inhibitors



Effect of DPP-4Is on binge-like and dependence-induced alcohol drinking in male and female mice and rats

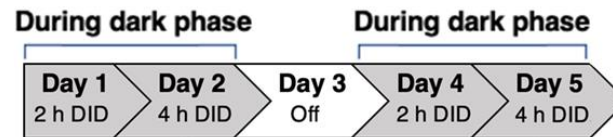
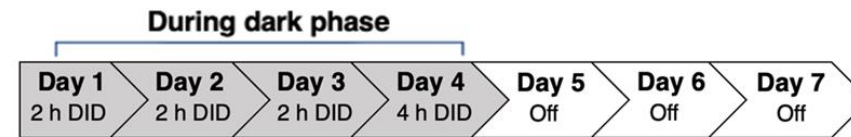
- Linagliptin (peripherally restricted)
- Omarigliptin (brain penetrant)



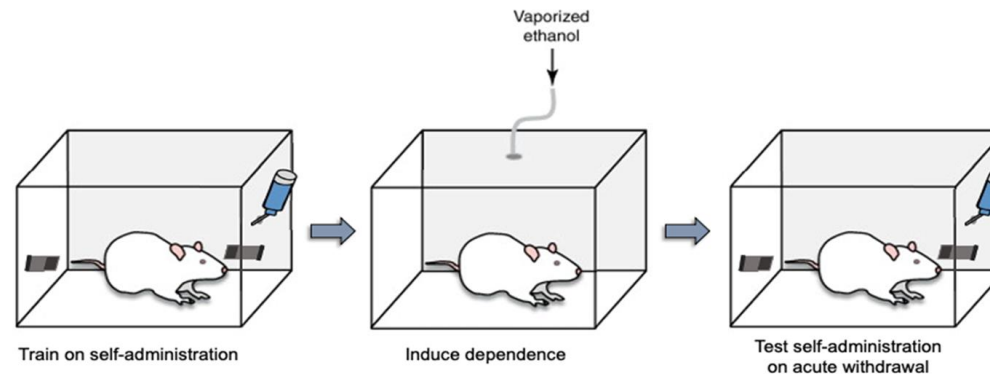
Nicolaus Bruns



Claire Pince



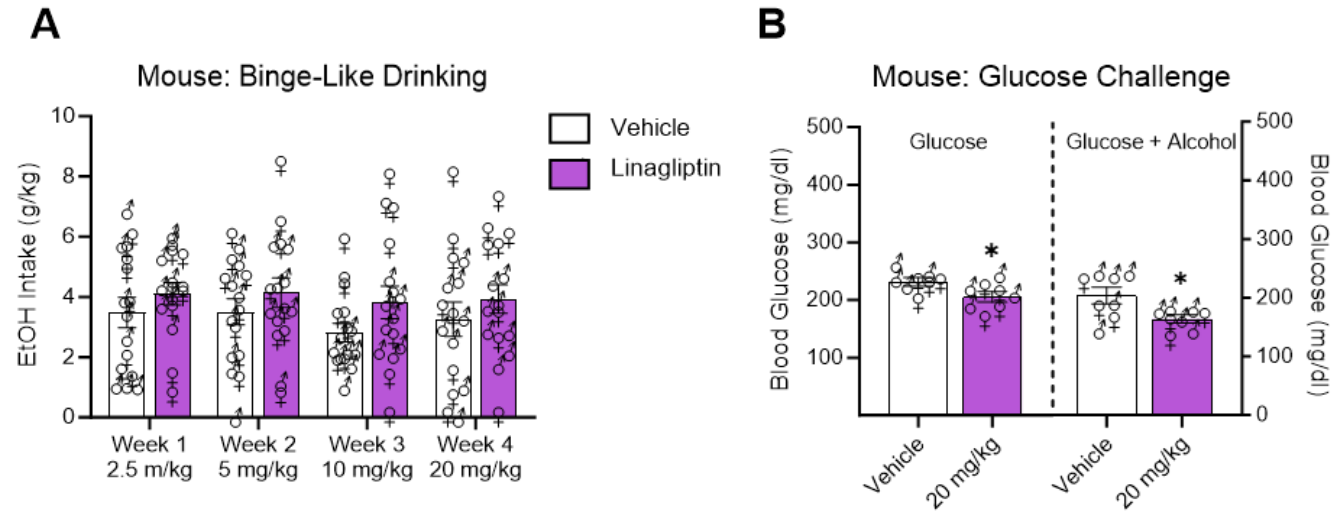
*Collaboration with
Koob & Vendruscolo
labs (NIDA IRP)*



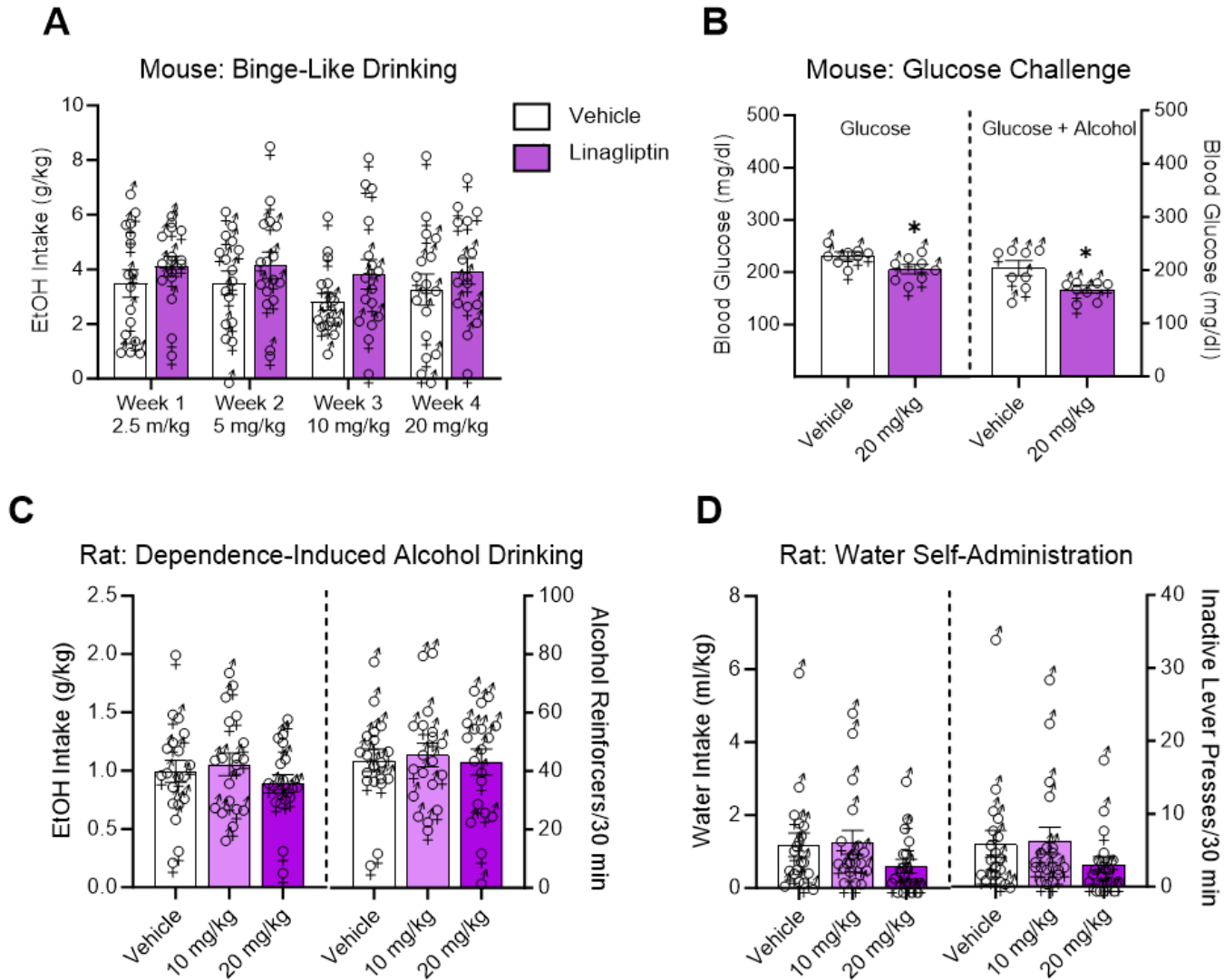
Linagliptin had no effect on alcohol drinking in mice or rats



Linagliptin had no effect on alcohol drinking in mice or rats



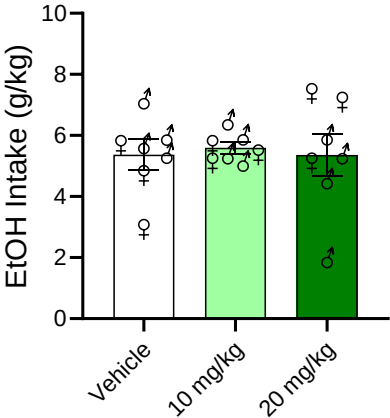
Linagliptin had no effect on alcohol drinking in mice or rats



Omarigliptin had no effect on alcohol drinking in mice or rats

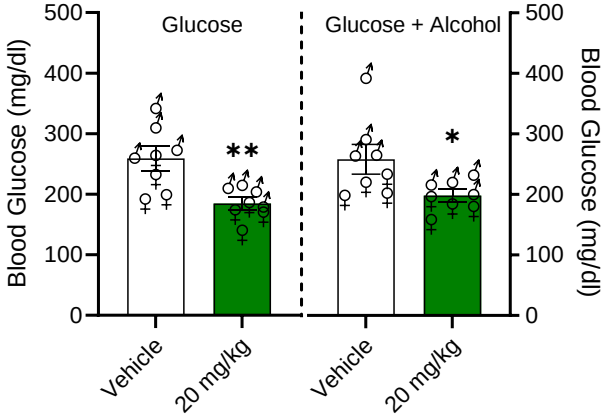
A

Mouse: Binge-Like Alcohol Drinking



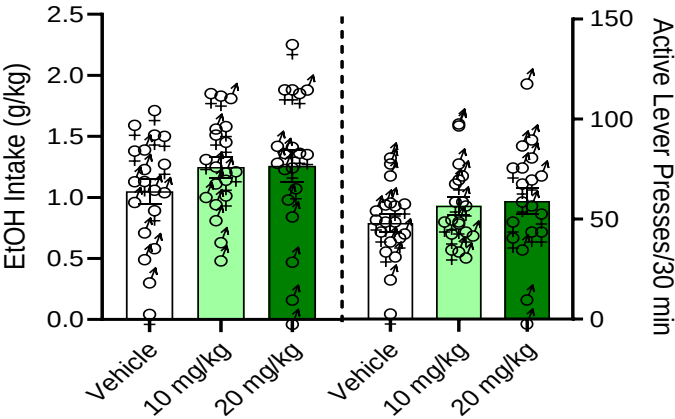
B

Omarigliptin Glucose Challenge



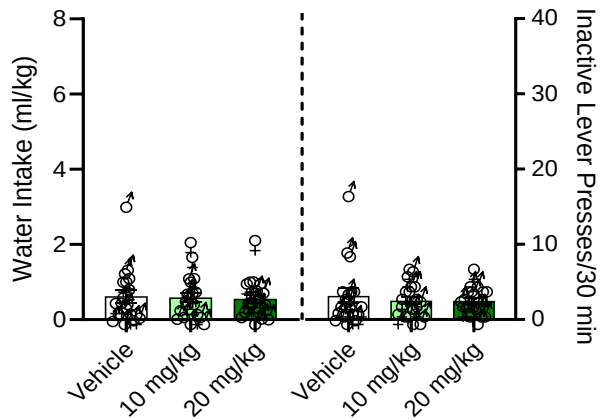
C

Rat: Dependence-Induced Alcohol Drinking



D

Rat: Water Self-Administration



Receipt of GLP-1 medications and change in alcohol use: Real-world electronic health records data



GLP-1 receptor agonists:

Exenatide
Lixisenatide
Albiglutide
Dulaglutide
Liraglutide
Semaglutide

DPP-4 inhibitors:

Sitagliptin
Linagliptin
Alogliptin
Saxagliptin

Veterans Aging Cohort Study (VACS)



Christopher Rentsch

- ~13.5 million veterans ever received care in the Department of Veterans Affairs, the largest integrated healthcare system in the US
- New initiators of GLP-1RAs or DPP-4Is who received ≥ 2 doses over ≥ 60 consecutive days and had an AUDIT-C score > 0 at baseline (washout: ≥ 180 days)

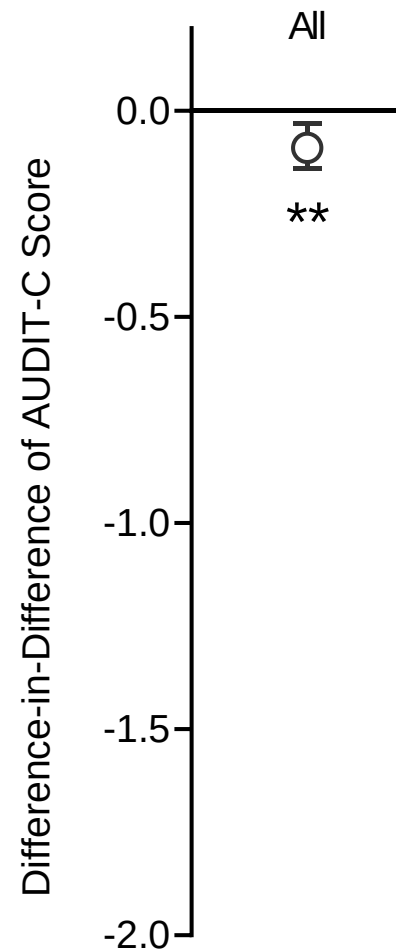
AUDIT-C

					SCORE
How often do you have a drink containing alcohol?					
Never (0 points)	Monthly or less (1 point)	Two to four times per month (2 points)	Two to three times per week (3 points)	Four or more times per week (4 points)	
How many alcoholic drinks do you have on a typical day where you are drinking?					
1-2 (0 points)	3-4 (1 point)	5-6 (2 points)	7-9 (3 points)	10 or more (4 points)	
How often do you have 6 or more alcoholic drinks on a single occasion?					
Never (0 points)	Less than monthly (1 point)	Monthly (2 points)	Weekly (3 points)	Daily or almost daily (4 points)	
TOTAL SCORE (a sum of the three questions, with scores ranging from 0-12 points)					
Non-drinkers (0 points)		Drinkers (1-3 points for females, 1-4 points for males)		At risk drinkers (≥ 4 for females, ≥ 5 for males)	

Propensity score matching and modelling

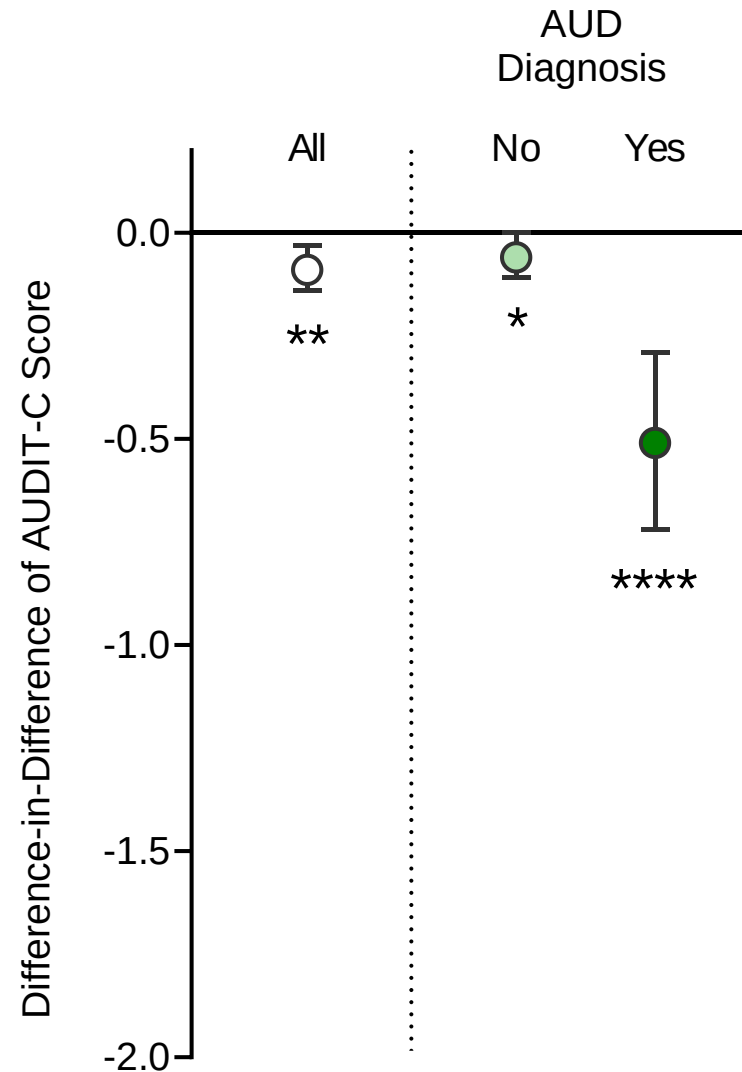
- Estimated from logistic regression including 54 covariates capturing wide range of personal and clinical characteristics
- Three separate comparisons:
 - **GLP-1RA** (n = 14,130) vs. **unexposed** (n = 12,398)
 - **DPP-4I** (n = 44,498) vs. **unexposed** (n = 40,938)
 - **GLP-1RA** (n = 11,863) vs. **DPP-4I** (n = 11,145)
- Outcome: Difference-in-Difference (DiD) in AUDIT-C
 - Overall
 - Stratified by AUD diagnosis
 - Stratified by baseline AUDIT-C score

Receipt of GLP-1RAs, compared to unexposed, was associated with decreased
AUDIT-C score, especially among those with AUD and hazardous alcohol use



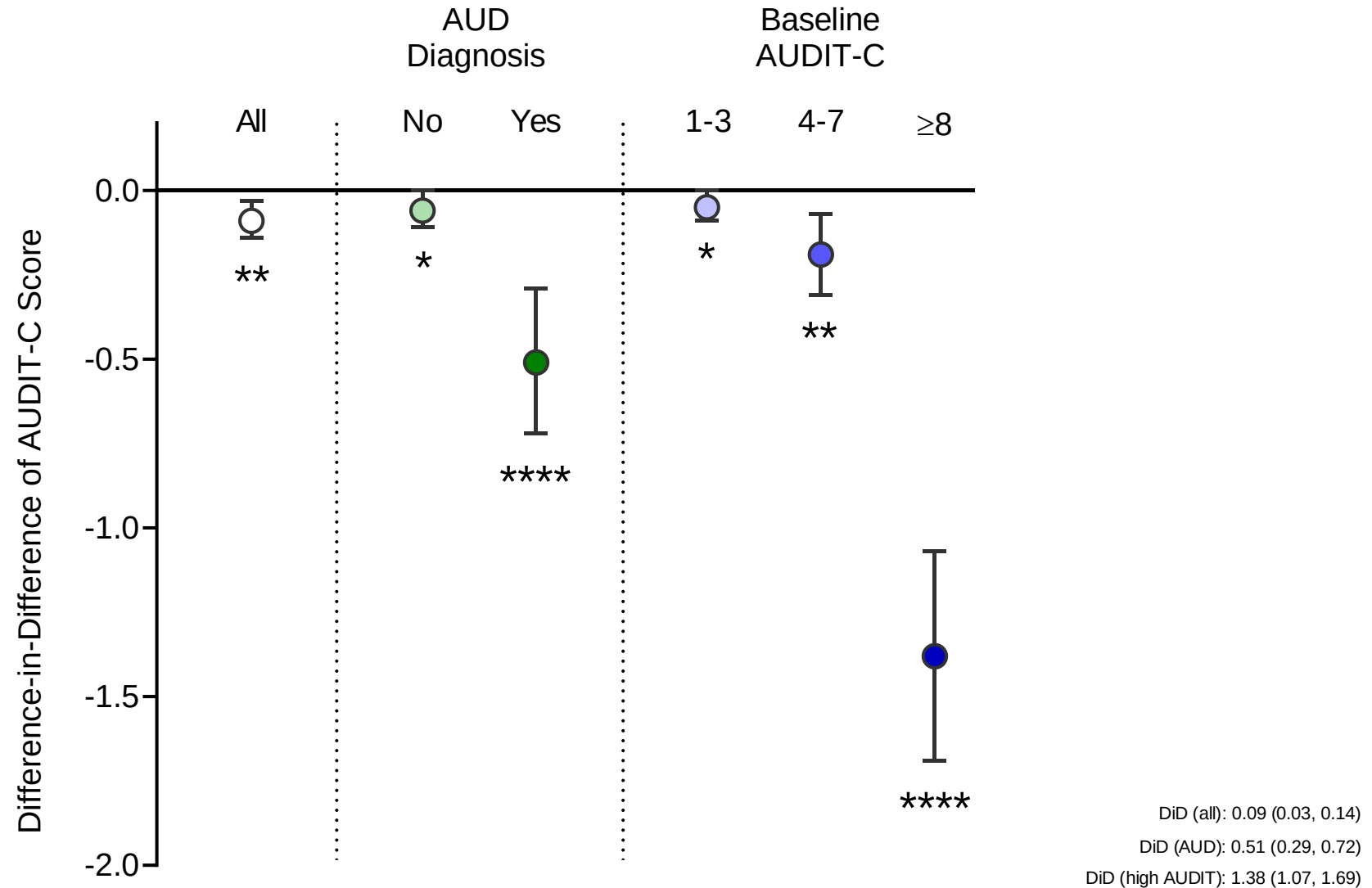
DiD (all): 0.09 (0.03, 0.14)

Receipt of GLP-1RAs, compared to unexposed, was associated with decreased
AUDIT-C score, especially among those with AUD and hazardous alcohol use

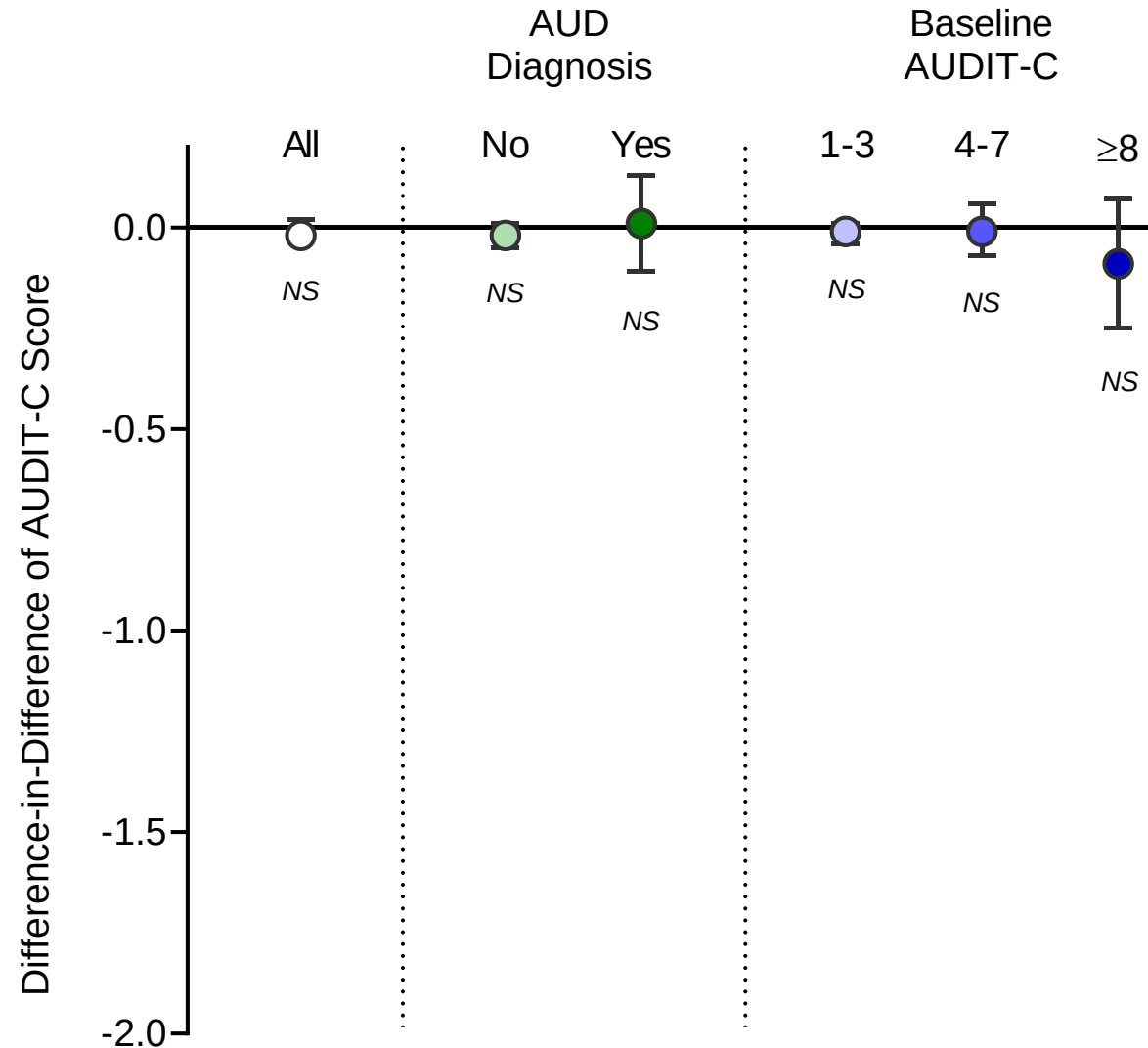


DiD (all): 0.09 (0.03, 0.14)
DiD (AUD): 0.51 (0.29, 0.72)

Receipt of GLP-1RAs, compared to unexposed, was associated with decreased
AUDIT-C score, especially among those with AUD and hazardous alcohol use

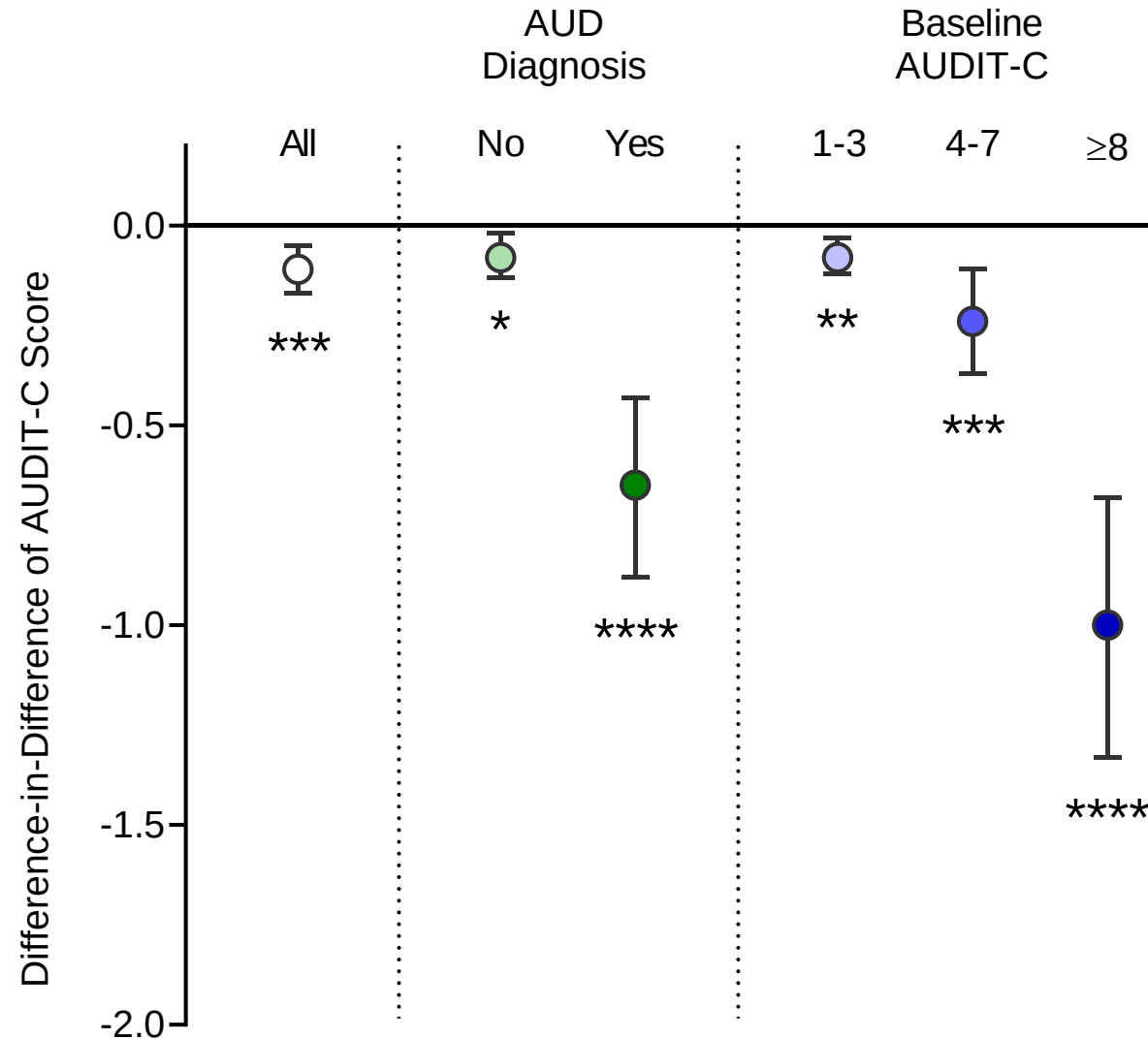


Receipt of DPP-4Is, compared to unexposed, was not
associated with decreased AUDIT-C score



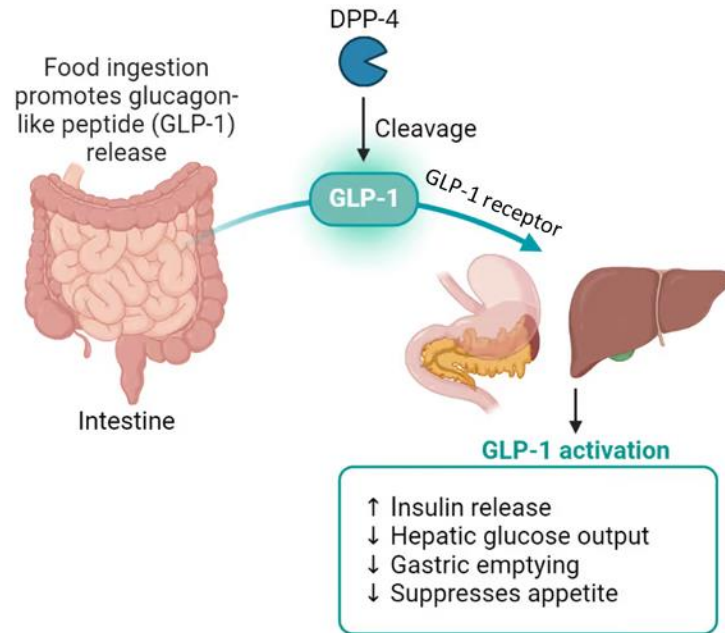
DiD (all): 0.02 (-0.02, 0.05)
DiD (AUD): -0.01 (-0.13, 0.11)
DiD (high AUDIT): 0.09 (-0.07, 0.25)

Receipt of GLP-1RAs, compared to DPP-4Is, was associated with decreased AUDIT-C score, especially among those with AUD and hazardous alcohol use

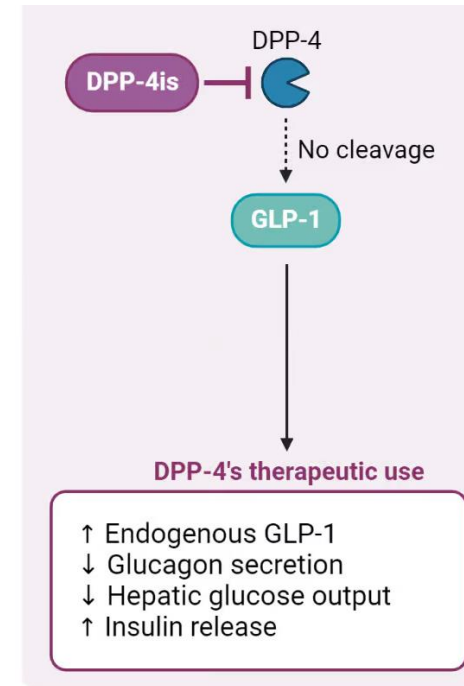


DiD (all): 0.11 (0.05, 0.17)
DiD (AUD): 0.65 (0.43, 0.88)
DiD (high AUDIT): 1.00 (0.68, 1.33)

Could stimulating the GLP-1 system reduce alcohol intake?



GLP-1 receptor agonists



DPP-4 inhibitors



Semaglutide Therapy for Alcohol Reduction (STAR)

Two Harmonized RCTs
(ongoing)

Oklahoma State University



NCT05891587

NIH Intramural Research Program



NCT06015893



- Safety/tolerability (number and severity of AEs, reaching the target dose)
- Efficacy (drinks per week, PEth, etc.)
- Experimental medicine procedures (CR, VR, MRI)



RECRUITING ⓘ

Semaglutide for Alcohol Use Disorder

ClinicalTrials.gov ID ⓘ NCT05520775

Sponsor ⓘ University of North Carolina, Chapel Hill

RECRUITING ⓘ

Effects of Semaglutide on Nicotine Intake

ClinicalTrials.gov ID ⓘ NCT05530577

Sponsor ⓘ University of North Carolina, Chapel Hill

RECRUITING ⓘ

Clinical Trial of Rybelsus (Semaglutide) Among Adults With Alcohol Use Disorder (AUD)

ClinicalTrials.gov ID ⓘ NCT05892432

Sponsor ⓘ University of Colorado, Denver

RECRUITING ⓘ

Does Semaglutide Reduce Alcohol Intake in Patients With Alcohol Use Disorder and Comorbid Obesity? (SEMALCO)

ClinicalTrials.gov ID ⓘ NCT05895643

Sponsor ⓘ Psychiatric Centre Rigshospitalet

CBS EVENING NEWS

CBS NEWS

Unexpected side effect from popular weight loss drugs studied for help with addiction treatment



Health

Life, But Better

Fitness

Food

Sleep

Mindfulness

Relationships

Weight-loss meds like Ozempic may help curb addictive behaviors, but drugmakers aren't running trials to find out

Vox

SCIENCE

Is Ozempic an anti-desire drug?

Scientists are realizing GLP-1 drugs have the potential to turn down cravings — for more than just food.

NEWS | BRAIN & BEHAVIOR

Science

Hot weight loss drugs tested as addiction treatments

Clinical trials will gauge whether GLP-1 analogs curb drug, alcohol cravings

FORBES > INNOVATION

Forbes

BREAKING

Increasing Evidence Suggests Ozempic (Semaglutide) Helps Curb Alcoholism

LIVING BETTER

npr

Ozempic seems to curb cravings for alcohol. Here's what scientists think is going on

AUGUST 28, 2023 · 5:00 AM ET

Unexpected side effect from popular weight loss drugs studied for help with addiction treatment

Weight-loss meds like Ozempic may help curb addictive behaviors, but drugmakers aren't

GLP-1 receptor agonists are promising but unproven treatments for alcohol and substance use disorders

nature medicine

Lorenzo Leggio, Christian S. Hendershot, Mehdi Farokhnia, Anders Fink-Jensen, Mette Kruse Klausen, Joseph P. Schacht & W. Kyle Simmons

Hot weight loss drugs tested as addiction treatments

Clinical trials will gauge whether GLP-1 analogs curb drug, alcohol cravings

Increasing Evidence Suggests Ozempic (Semaglutide) Helps Curb Alcoholism

Ozempic seems to curb cravings for alcohol. Here's what scientists think is going on

~ THANK YOU ~

