Real World Experience of Alcohol and Tobacco in a National Health System: The Veterans Aging Cohort Study

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COI

- I have funding from multiple federal sources including several NIH institutes. (mainly NIAAA) and the Veterans Health Administration

- The opinions expressed are my own

Challenges in Understanding Role of Alcohol and Tobacco in Cancer

- Sample size required
- Self reported measures of exposure
- Time delay between exposure and cancer presentation
- Covariance, Confounding, and Interaction

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Sample Size: U.S. Veterans Healthcare System an Exceptional Real-World Laboratory

- Largest integrated healthcare system in USA
  - 827 community-based outpatient clinics
  - 151 hospitals/medical centers
  - 126 nursing homes
  - 13.2 million in care, ~ 6 million annually
- National, paperless, EMR since 1998
- Largely captured, longitudinal aging population
- Cancer registry
- Smoking and alcohol use data
- Pharmacy fill data
- Excellent mortality ascertainment
- Links to
  - National Death Index
  - Medicare and Medicaid data
  - Million Veteran Study genetics/omics for >1 million

Sample Size: VACS EHR-based Cohorts

- Full national sample
- N~13.2 million
- All Veterans receiving care in the VA system

VACS-*National*

- HIV study
- 60,000 PWH, 120,000 PWoH
- 1 PWH:2 PWoH demographically-matched

VACS-*HIV*

- 4,352 PWH; 4,561 PWoH
- Consented survey substudy
- 1 PWH:1 PWoH
- 9 VA sites
- Patient & provider surveys
- Linkage to EHR

VACS-*HIV Survey*

- 1,730 PWH, 926 PWoH
- Consented biomarker substudy
- 2 PWH:1 PWoH
- Banked specimens, select labs, DNA
- Linkage to EHR + Survey

VACS-*HIV Biomarker*

- 534 PWH at VACS Survey Sites
- Consented biomarker substudy
- Tripartite with KPNC (284 PWH), SHCS (451 PWH)
- Banked specimens, select labs, DNA
- Linkage to EHR + MASH specific patient survey and pharmacist surveys

MASH

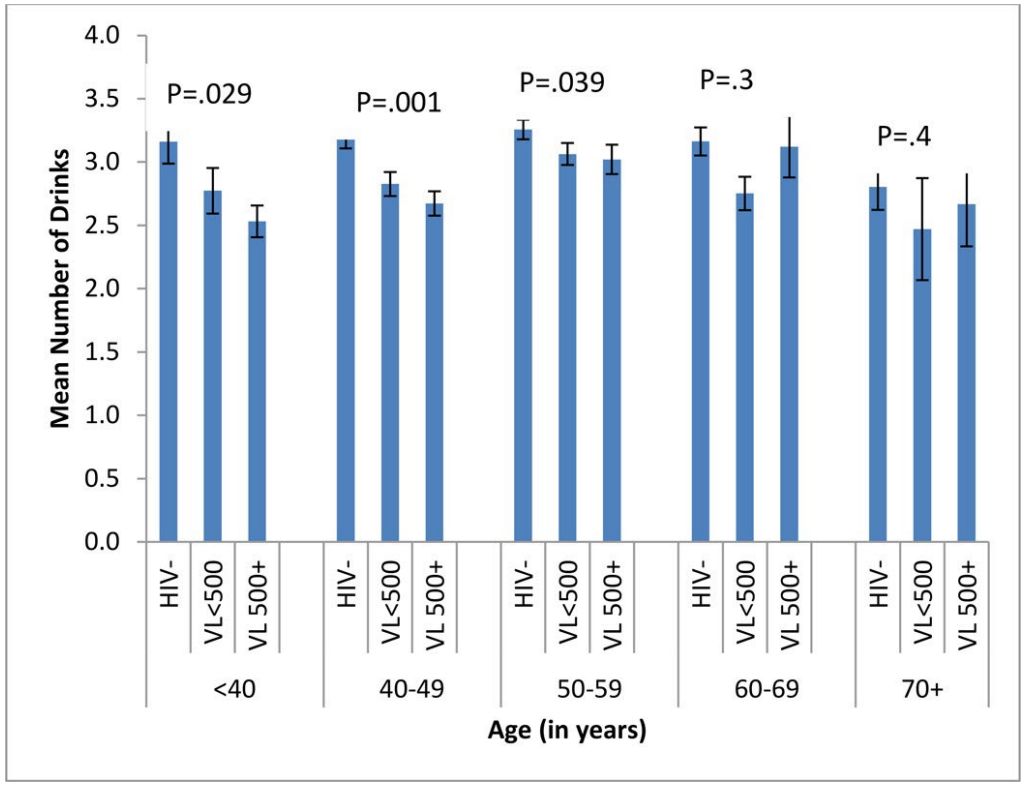
VACS
Veterans Aging Cohort Study

PWH = Persons with HIV (HIV+) PWoH = Persons without HIV (uninfected)

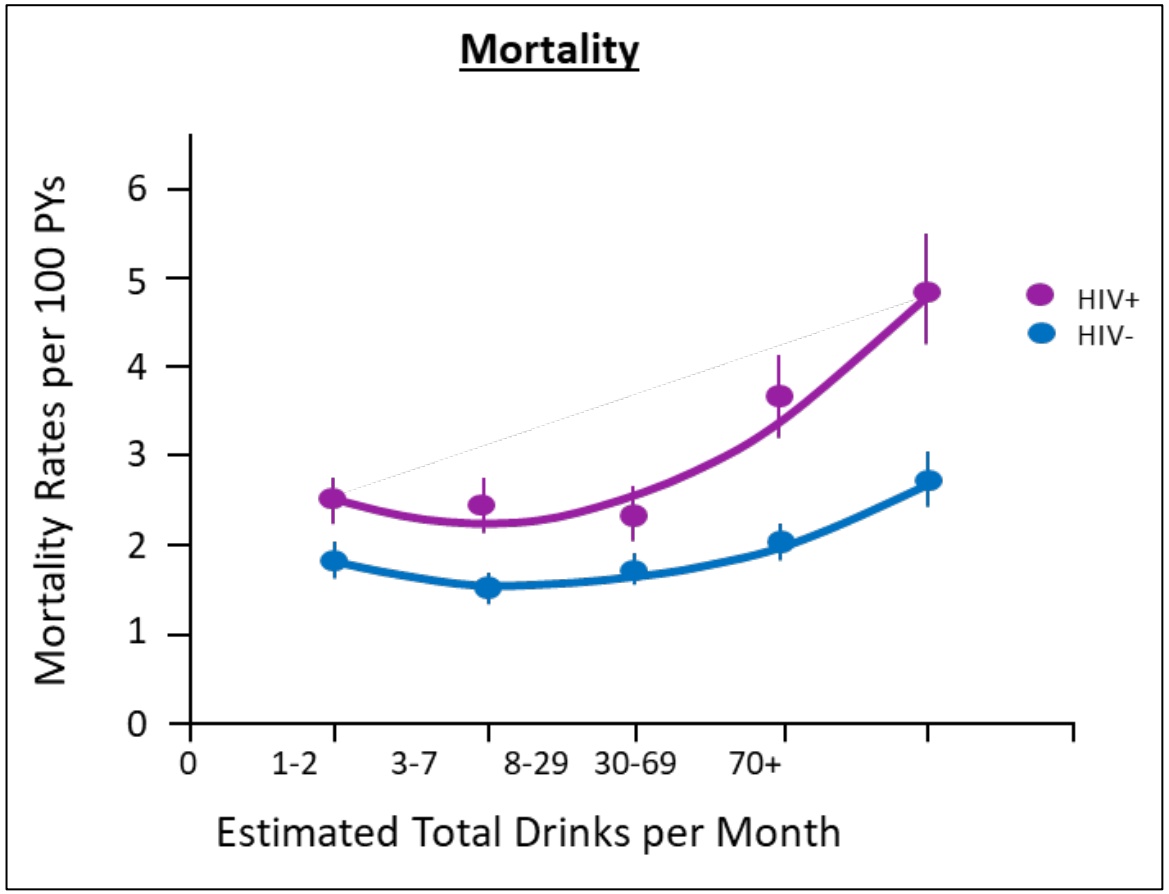
Alcohol Interacts with Comorbid Diseases Like HIV

David Feillen

Kathy McGinnis



Drinks to Feel a "Buzz"



VETERANS AGING COHORT STUDY

McGinnis, et al. AIDS Behav (2016). PMID: 26936030
Justice et al. DAD (2016). PMID: 26861883

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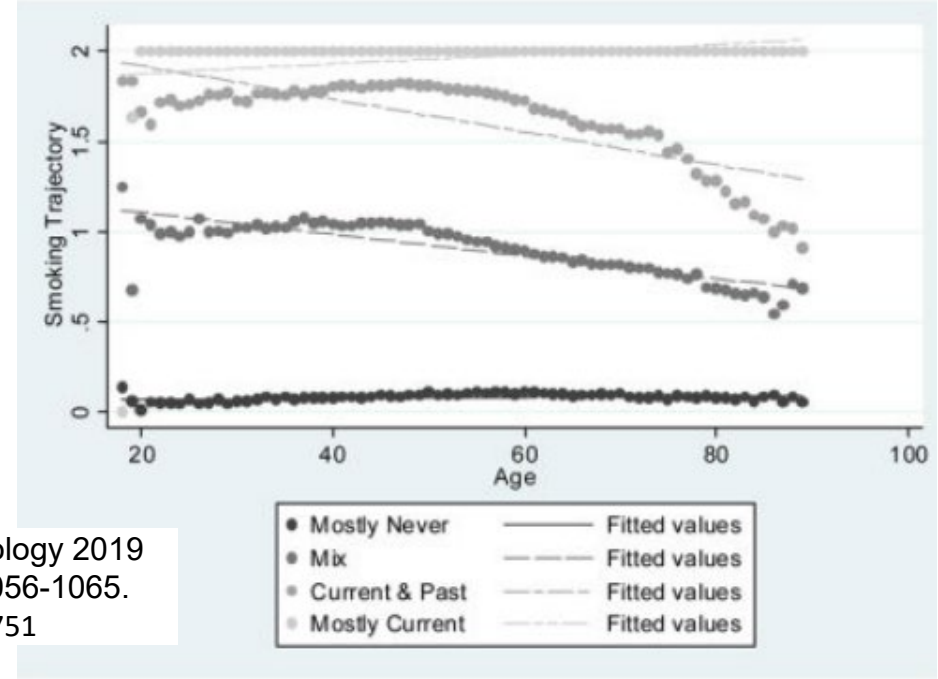
Self Reported Smoking

Self report may be subject to under reporting
- Use decreases with age (Figure)
- Social desirability bias
- Abstainer bias

Cotinine gold standard (Table)
- Only measures recent use
- ICD codes terrible
- Self report (survey or EHR) good



Addiction Biology 2019 Sep;24(5):1056-1065. PMID: 30284751

Table 2. Smoking from clinical reminder, survey, and ICD codes compared with cotinine (≥30 and ≥10) as reference standard ($n = 318$), FY 2019

	Percent						
	Prevalence	Agreement	Sensitivity	Specificity	PPV	NPV	Kappa
Cotinine ≥30	42		—	—	—	—	—
Clinical reminder	39	91	86	95	92	90	.81
Survey	38	92	85	97	95	90	.83
ICD-10	24	77	51	97	92	73	.50
Cotinine ≥10	46		—	—	—	—	—
Clinical reminder	39	90	82	97	95	86	.79
Survey	38	91	82	99	98	86	.81
ICD-10	24	74	48	97	93	69	.46

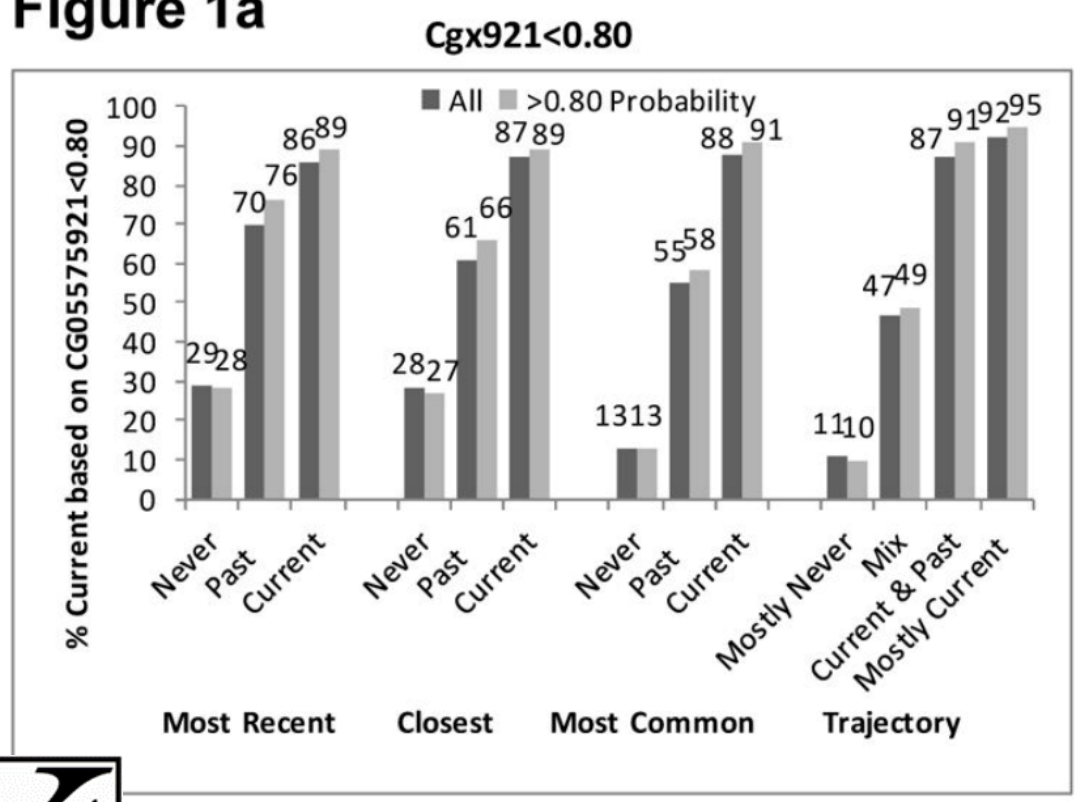
ICD: International Classification of Disease.

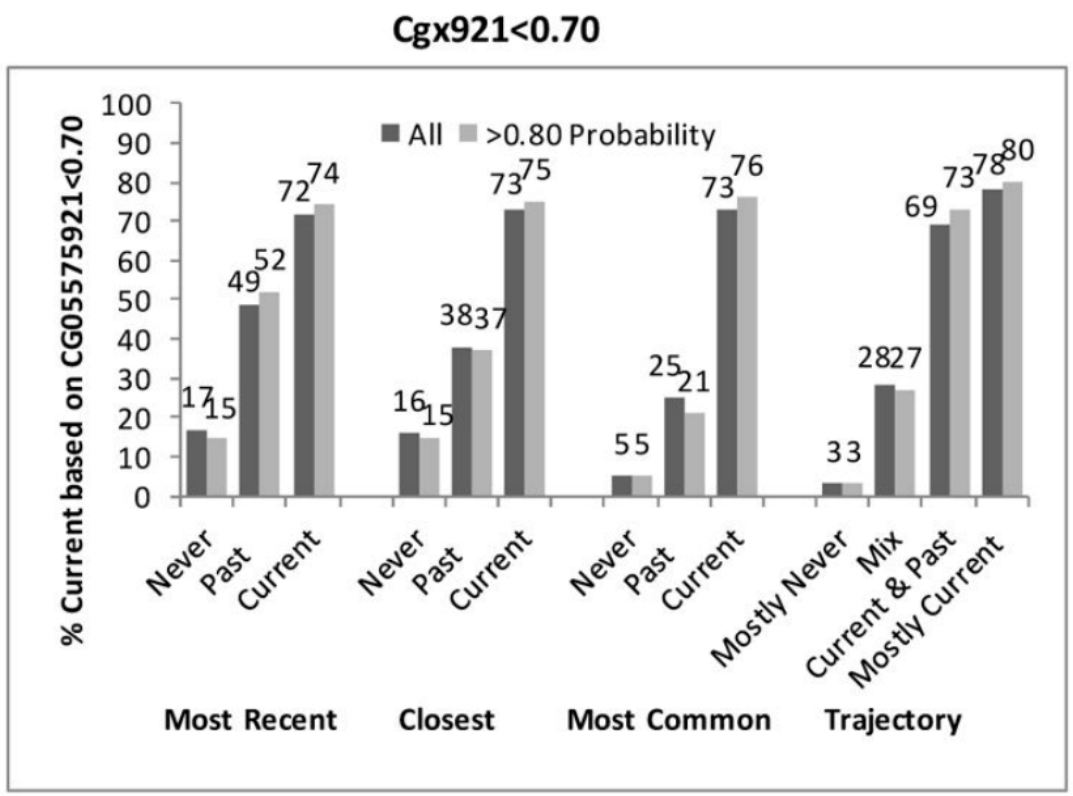
Jamiaopen. eCollection 2022 Jul. PMID: 37252267

VETERANS AGING COHORT STUDY

Methylation Sites May Be an Option for Unbiased Measurement

Figure 1a





VETERANS AGING COHORT STUDY

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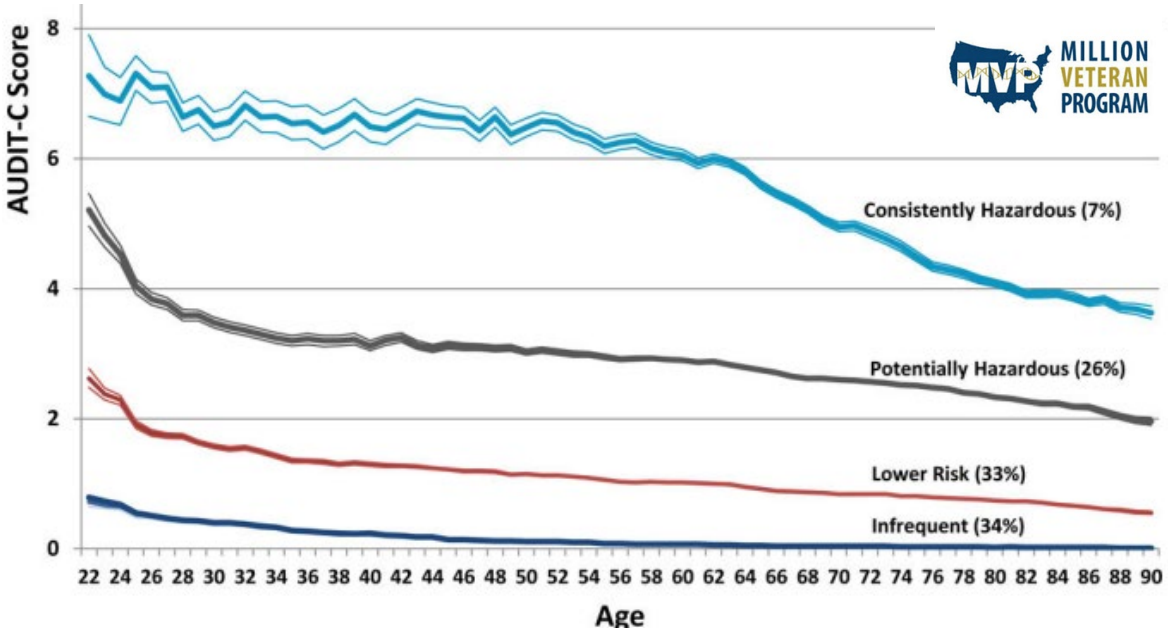
Measuring Alcohol Use--Even Trickier

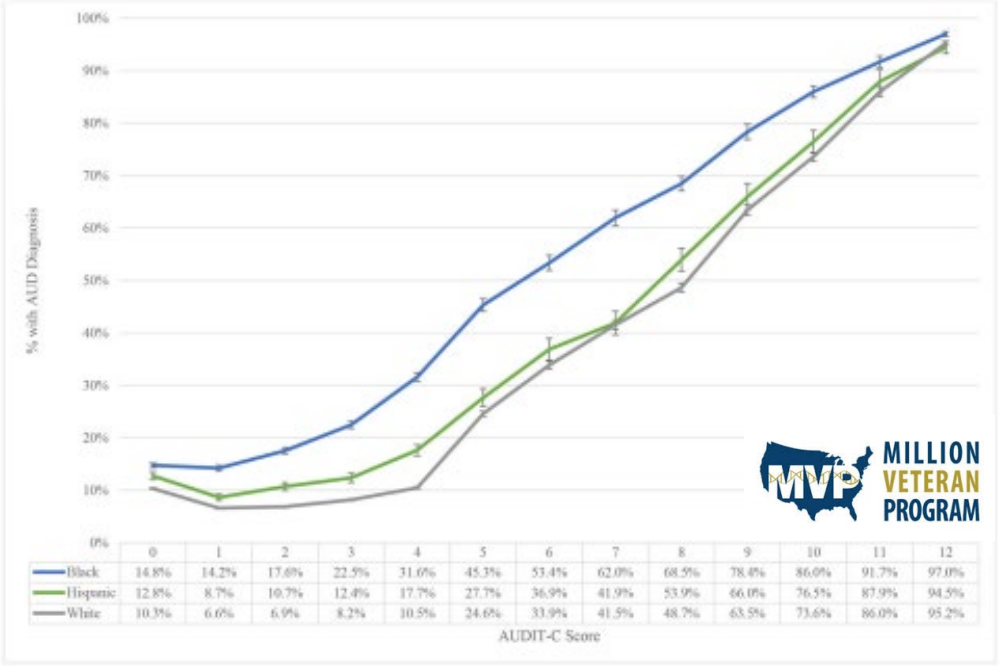
Self report subject to under reporting

- Social desirability bias
- Use decreases with age (Figure)[1]
- Abstainer bias worse with age



Phosphatidyl ethanol (PEth) gold standard

- Only recent use (past 21 days)
- Demonstrates differential social desirability bias[2]
  - Among PWH, highest mortality among those reporting abstinence and PEth ≥8 ng/mL (5.69 per 100 PY, 95% CI 3.78–8.56)
  - Comparable with high-risk AUDIT-C and PEth ≥8 ng/mL (6.12 per 100 PY, 95% CI 3.82– 9.85)
  - Results similar after full adjustment and among PWoH



ICD Codes demonstrate racial bias[3]

1. Alcohol Clin Exp Res. 2019 March ; 43(3): 465–472.
2. J Acquir Immune Defic Syndr. 2018 February 01; 77(2): 135–143.
3. Am J Psychiatry. 2023 June 01; 180(6): 426–436.

Challenges in Understanding Role of Alcohol and Tobacco in Cancer

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Time Delay Between Exposure and Cancer: Risk Takes 10-20 Years to Resolve

HCC Risk Among Never Drinkers Vs. Just Quit Drinking

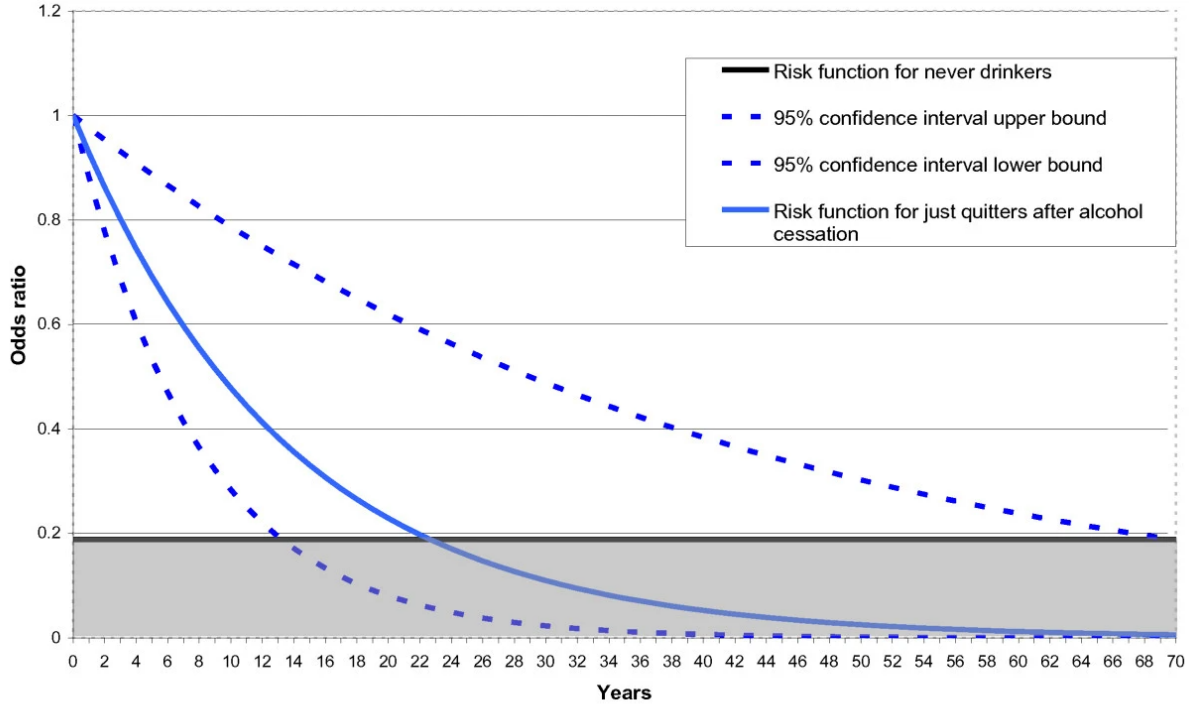

Illustration: Risk decline of liver cancer post cessation of alcohol consumption compared to just quitters.

BMC Cancer **11**, 446 (2011)

Challenges in Understanding Role of Alcohol and Tobacco in Cancer

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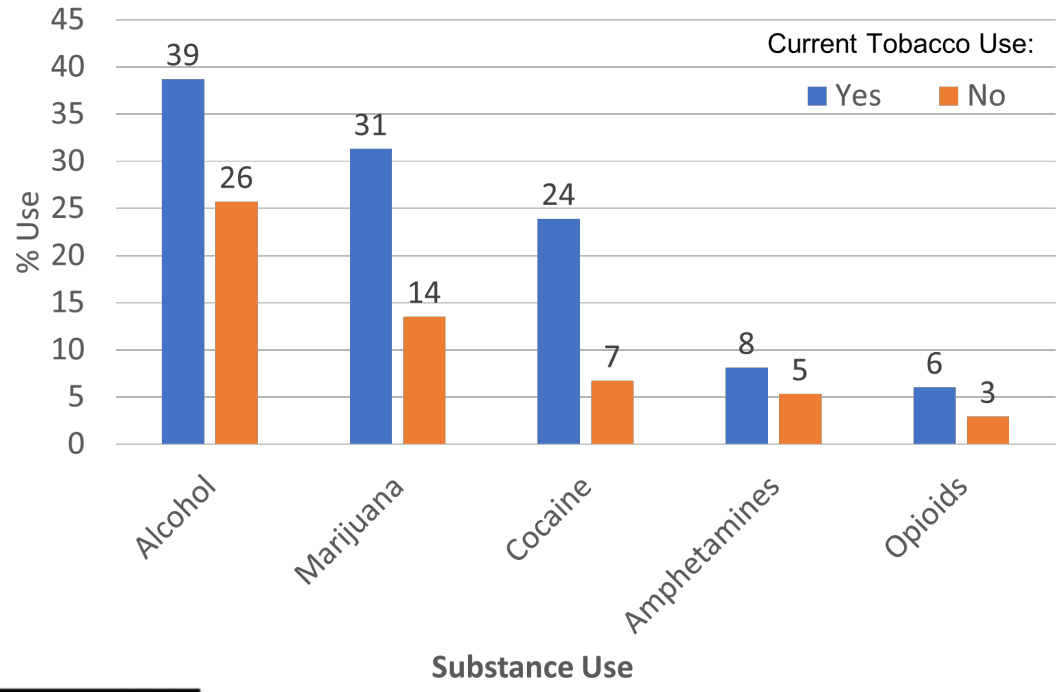
Use of One Substance Increases Use of Other Substances



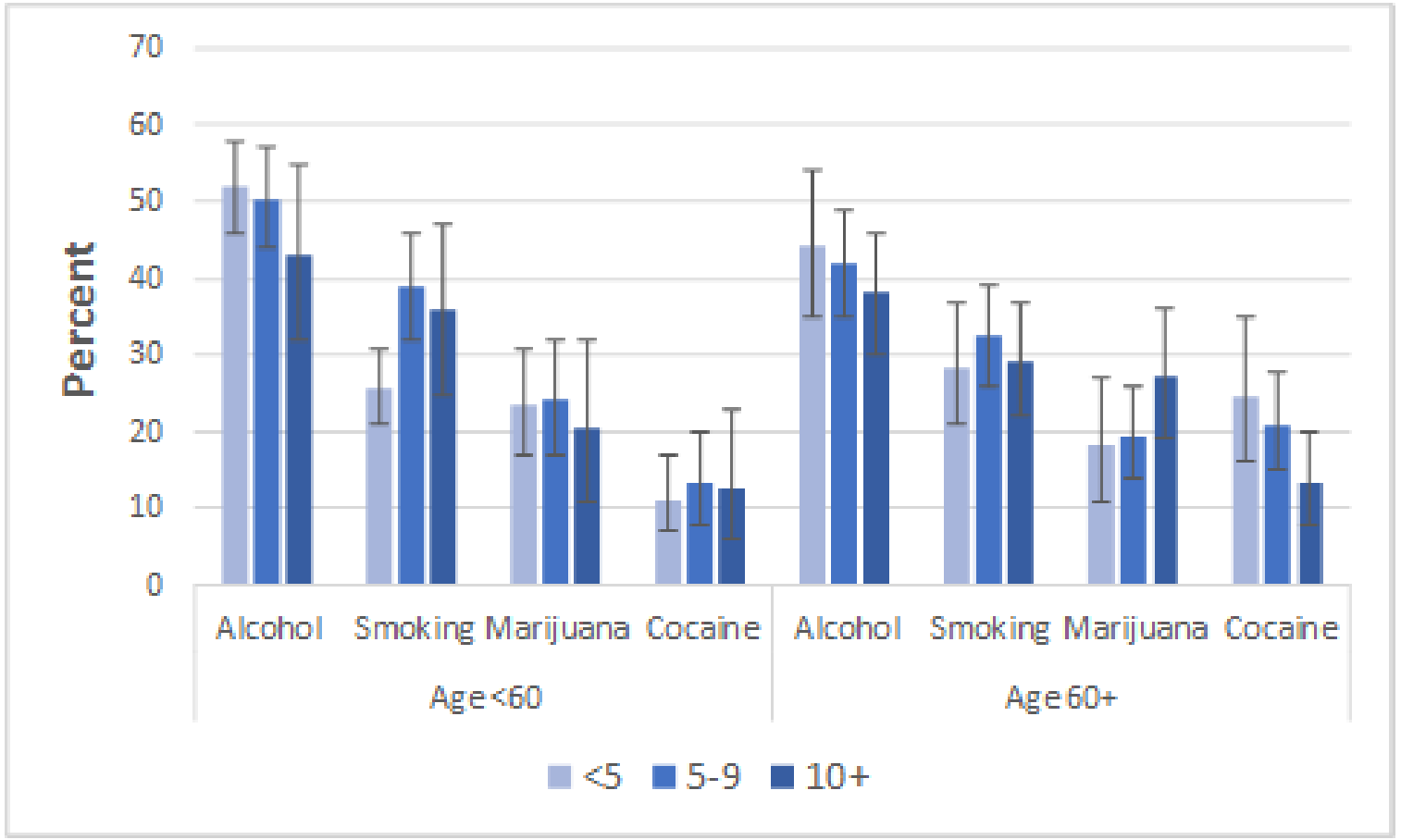
Association of tobacco use with other substance use

	N (%)	Odds Ratio (95% CI)	
		Unadjusted	**Adjusted***
Peth (>20 ng/mL)	184 (38.7%)	1.86 (1.46, 2.37)	1.80 (1.40, 2.33)
Cannabis	147 (31.3%)	2.93 (2.20, 3.89)	3.62 (2.65, 4.95)
Cocaine	112 (23.9%)	4.34 (3.05, 6.17)	3.84 (2.63, 5.60)
Opioids	28 (6.0%)	2.16 (1.22, 3.83)	2.42 (1.32, 4.44)
Amphetamines	38 (8.1%)	1.57 (0.99, 2.48)	1.57 (0.96, 2.57)

*Models adjusted for age, gender, race and ethnicity, and cohort

VETERANS AGING COHORT STUDY

Substance Use and Polypharmacy Co-Occur Among PWH



- Medications, Alcohol, Substance use in HIV Study (MASH)
- Extends VACS to include Kaiser Permanente Northern California and Swiss Cohort
- Prospectively collect data on: all medications, Self report and biomarker verified substance use

Alcohol and Smoking Independently Associated with Hepatocellular Carcinoma Adjusting for Liver Disease in >6.5 M Veterans

Figure. Ten-Year Risk of Hepatocellular Carcinoma (HCC)

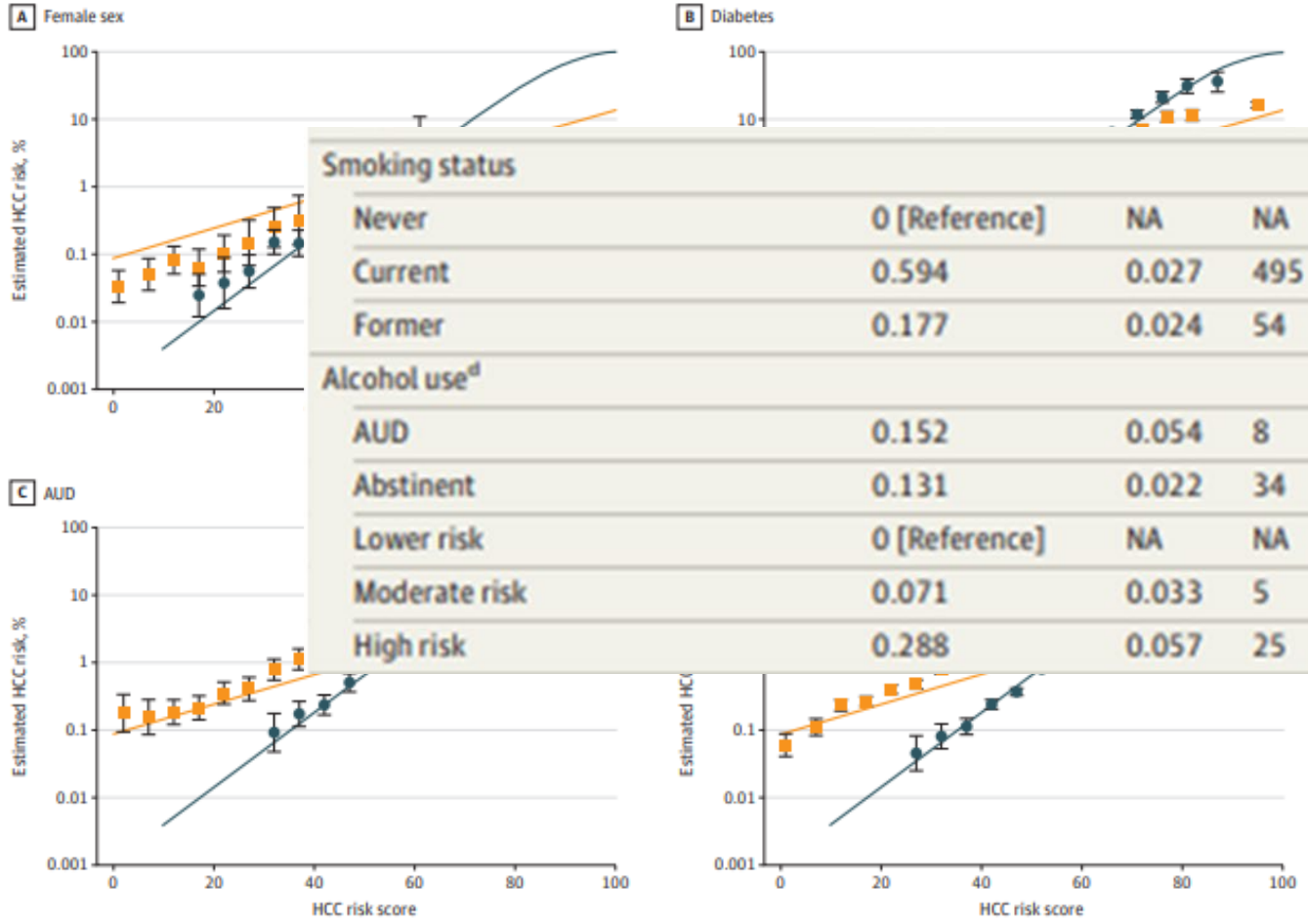


Table 3. Cox Proportional Hazards Regression Model Fit to Development Sample of Veterans With Hepatocellular Carcinoma Events During a Maximum 10-Year Follow-Up

Characteristic	PE	SE	χ^2	*P* value	HR (95% CI)
Age, y					
X = (Age - 50)/5[a]	0.787	0.031	634	<.001	2.20 (2.07-2.34)
X^{2a}	−0.087	0.009	84	<.001	0.92 (0.90-0.93)
X^{3a}	0.002	0.001	6	.01	1.00 (1.00-1.00)
Sex					
Male	0 [Reference]	NA	NA	NA	1 [Reference]
Female	−0.647	0.087	55	<.001	0.52 (0.44-0.62)
Race and ethnicity[b]					
		0.039	127	<.001	0.64 (0.60-0.69)
		0.036	262	<.001	1.80 (1.68-1.94)
		NA	NA	NA	1 [Reference]
		0.045	2	.15	1.07 (0.98-1.17)
		0.036	30	<.001	1.21 (1.13-1.30)
Smoking status					
Never	0 [Reference]	NA	NA	NA	1 [Reference]
Current	0.594	0.027	495	<.001	1.81 (1.72-1.91)
Former	0.177	0.024	54	<.001	1.19 (1.14-1.25)
		0.012	37	<.001	0.93 (0.91-0.95)
		0.004	0	.63	1.00 (0.99-1.01)
		0.000	2	.16	1.00 (1.00-1.00)
Alcohol use[d]					
AUD	0.152	0.054	8	.005	1.17 (1.05-1.29)
Abstinent	0.131	0.022	34	<.001	1.14 (1.09-1.19)
Lower risk	0 [Reference]	NA	NA	NA	1 [Reference]
Moderate risk	0.071	0.033	5	.03	1.07 (1.01-1.15)
High risk	0.288	0.057	25	<.001	1.33 (1.19-1.49)
		0.014	2920	<.001	2.08 (2.02-2.13)
		0.004	231	<.001	0.94 (0.93-0.94)
		0.000	26	<.001	1.00 (1.00-1.00)
		0.013	920	<.001	0.68 (0.66-0.70)
		0.004	2168	<.001	1.19 (1.18-1.19)
		0.002	50	<.001	0.99 (0.99-0.99)
		NA	NA	NA	1 [Reference]
		0.020	1841	<.001	2.41 (2.31-2.50)
Smoking status					
Never	0 [Reference]	NA	NA	NA	1 [Reference]
Current	0.594	0.027	495	<.001	1.81 (1.72-1.91)
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Moderate risk	0.071	0.033	5	.03	1.07 (1.01-1.15)
High risk	0.288	0.057	25	<.001	1.33 (1.19-1.49)
BMI					
X = (BMI - 25)/5[a]	0.146	0.020	52	<.001	1.16 (1.11-1.21)
X^{2a}	0.030	0.015	4	.048	1.03 (1.00-1.06)
X^{3a}	−0.010	0.003	10	.002	0.99 (0.99-1.00)

jamanetworkopen.2024. PMID: 39504020.

Glucagon-like peptide-1 receptor agonists but not dipeptidyl peptidase-4 inhibitors reduce alcohol intake

Mehdi Farokhnia,[1] John Tazare,[2] Claire L. Pince,[1] Nicolaus Bruns Vi,[1] Joshua C. Gray,[3] Vincent Lo Re III,[4] David A. Fiellin,[5] Henry R. Kranzler,[6] George F. Koob,[7] Amy C. Justice,[5] Leandro F. Vendruscolo,[8] Christopher T. Rentsch,[9] and Lorenzo Leggio[1]

Mouse and rat models for unhealthy alcohol intake:
Previously showed effect of the GLP-1RA (semaglutide)
Tested two DPP-4Is (linagliptin and omarigliptin)

Compared changes in AUDIT-C between propensity-score-matched recipients of GLP-1RA, DPP-4I, & unexposed

GLP-1RA recipients had a greater reduction in AUDIT-C scores than unexposed and DPP-4I recipients

No differences between DPP-4I and unexposed

n=27,231 GLP-1RA vs. unexposed
77,911 DPP-4I vs. unexposed
28,996 for GLP-1RA vs. DPP-4I

Journal of Clinical Investigation, Published Online March 6, 2025 PMID: 40048376

EMR Cohorts Address Challenges in Understanding the Role of Alcohol and Tobacco in Cancer

Sample size

- 9 m Veterans/yr
- Other health systems

Self report

- Serial PEth
- Methylation Data

Time delay

- 20 yrs of data
- Need biomarkers/ intermediate outcomes

Covariance, Confounding, and Interaction

- Propensity adjustment
- Causal modeling

Consider a More Personalized Clinical Approach

- Get a PEth first, then, if needed address alcohol
- Use EHR decision support to create personalized messages accounting for other factors (cancer, heart disease, drug interactions)
- Substitute a positive behavior (exercise) for use of substances—especially when they are used to self medicate
- Select medications that address multiple modifiable factors (GLP-1 inhibitors for 3) but consider whether life long treatment is reasonable

VACS

Veterans Aging Cohort Study

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