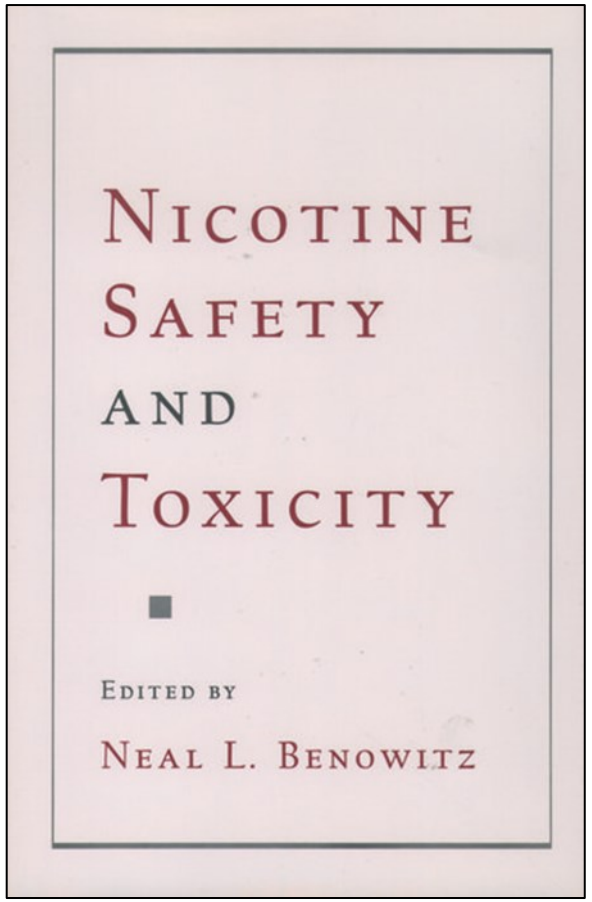
Risks and Benefits of Consumer Nicotine Delivery Systems

Welcome to the 2024, 27th Nicotine and Tobacco Conference

THEME THIS YEAR:

Risks and Benefits of Consumer Nicotine Delivery Systems: Emerging Evidence and Open Questions



August 1998

…and behind the curtain the real work gets done, so we need to thank…

- Avery Roberson
- Zack Olson
- Courtney Usher
- Michelle Forster
- Asia Abad

Adrian
5-days old
today

August 1998 rationale

- ***Nicotine as a replacement therapy:***
  - ***Smoking cessation***
  - ***Possibly for long-term maintenance of non-smoking***

- ***Potential vs. medical disorders:***
  - ***Ulcerative colitis, Alzheimer's disease, Parkinson's disease, Tourette's syndrome, attention deficit disorder, spasticity, and sleep apnea***

October 2024 rationale

- ***2009:** Congress integrates tobacco harm reduction into FDA umbrella (FDA-CTP)*
- ***2009-2024:** Wide array of consumer nicotine products developed*
- ***2024:** Tobacco harm reduction remains controversial*
  - *Risks and harms?*
  - *Benefits?*
  - *Short-term and long-term impacts?*
- ***NTSC 2024:** We hope to update the science on the risk and benefits of nicotine in different user groups including adults who smoke and non-smoking youth*

Moderator: Neal Benowitz
Session 2: Safety and Toxicity of Nicotine Delivery Devices

1. Neal Benowitz *UCSF*	**A) Nicotine Pharmacology and Safety Concerns** **B) Cardiovascular Toxicity of Nicotine: Implications for Harm Reduction**
2. Suchitra Krishnan-Sarin *Yale University*	**Youth Addiction and Mental Health**
3. Michael Ussher *University of London*	**Vaping During Pregnancy: A Systematic Review of Health Outcomes**
< Break >	

Session 2: Safety and Toxicity of Nicotine Delivery Devices

4. Steve Cook *University of Michigan*	**The Past is Prologue: Epidemiology of Exposure and Harm**
5. Cindy Chang *FDA-CTP*	**Biomarkers of Potential Harm by Tobacco Product Use**
6. Panel Discussion	**Kevin Gray** *MUSC* **Jed Rose** *Rose Research Center* **Ted Wagener** *Ohio State*

Suchitra Krishnan-Sarin
Yale University

Youth Addiction and Mental Health

Youth Nicotine Delivery Device Use: Addiction and Mental Health

Suchitra Krishnan-Sarin, PhD

Albert E. Kent Professor of Psychiatry, and Public Health
Yale University

Relevant Funding and Disclosures

Yale TCORS (Tobacco Center Of Regulatory Science)

U50DA036151; Krishnan-Sarin/O'Malley, PI)

ENACT (End Nicotine Addiction in Children and Teens) Initiative

20YVNR35460041; Krishnan-Sarin, PI)

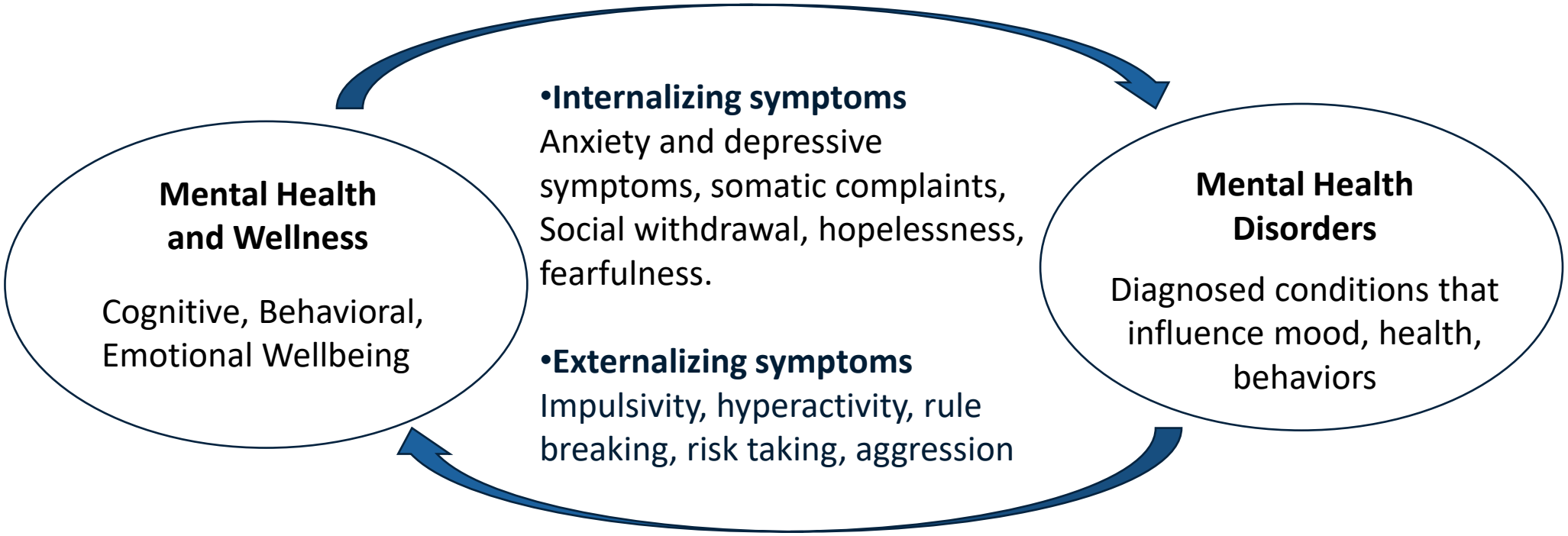
NIH National Institute on Drug Abuse

FDA

American Heart Association.

No relevance to current work : Free investigational drug from Novartis, Stalicla for alcohol drinking research;

Mental Health vs. Mental Health Disorders



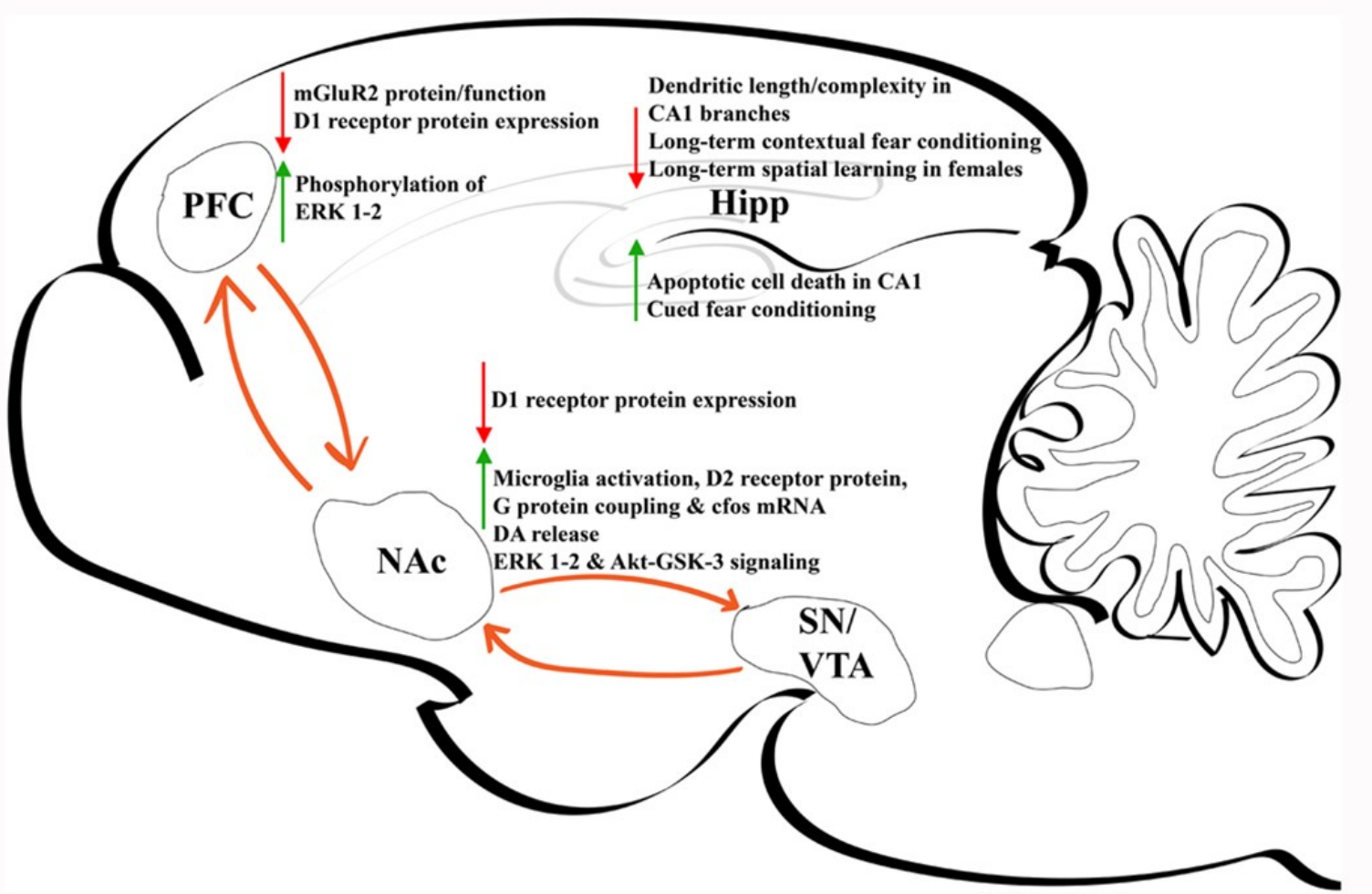
Nicotine & Adolescence: Preclinical findings

Leslie, 2020; Castro, Lotfipour, Leslie, 2023; Yuan, Cross, Loughlin, Leslie, 2015

- Chronic nicotine exposure during adolescence
  - Substance Use
    - Greater sensitivity to, and use of alcohol, cannabis, cocaine
  - Cognition
    - Changes in cognition; for example, decreased contextual fear learning
  - Mood
    - Increases in anxiety and depression like behaviors.
  - Emotional Regulation
    - Neuronal and molecular alterations in regions critical for emotional regulation
- Adolescents vs Adults
  - Adolescents more sensitive to nicotine's acute behavioral effects, reward, anxiogenic effects
  - Adults more sensitive to nicotine's aversive effects and have more nicotine withdrawal

Nicotine Changes the Adolescent Brain: Preclinical findings

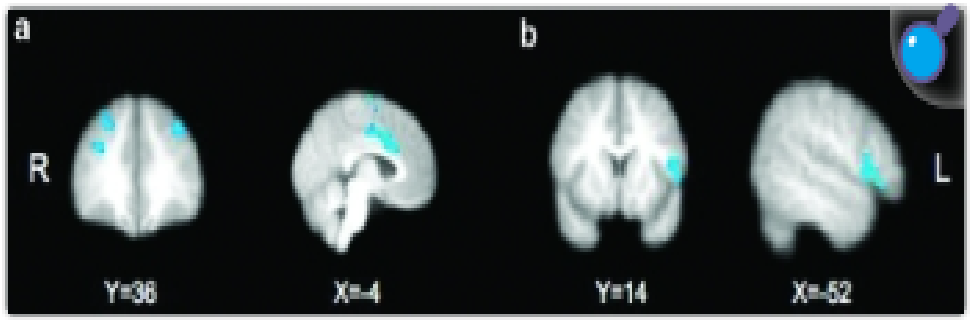
Castro, Lotfipour, Leslie, 2023



- Nicotine exposure changes
- In neurochemical system s in prefrontal cortex, nucleus accumbens, substantia nigra, ventral tegmental area (nACH, DA, GABA, Glutamate)
- In pruning and growth (e.g. white vs. grey matter), and neuronal connections

Nicotine & Response Inhibition: Adolescent Smoking vs. Not

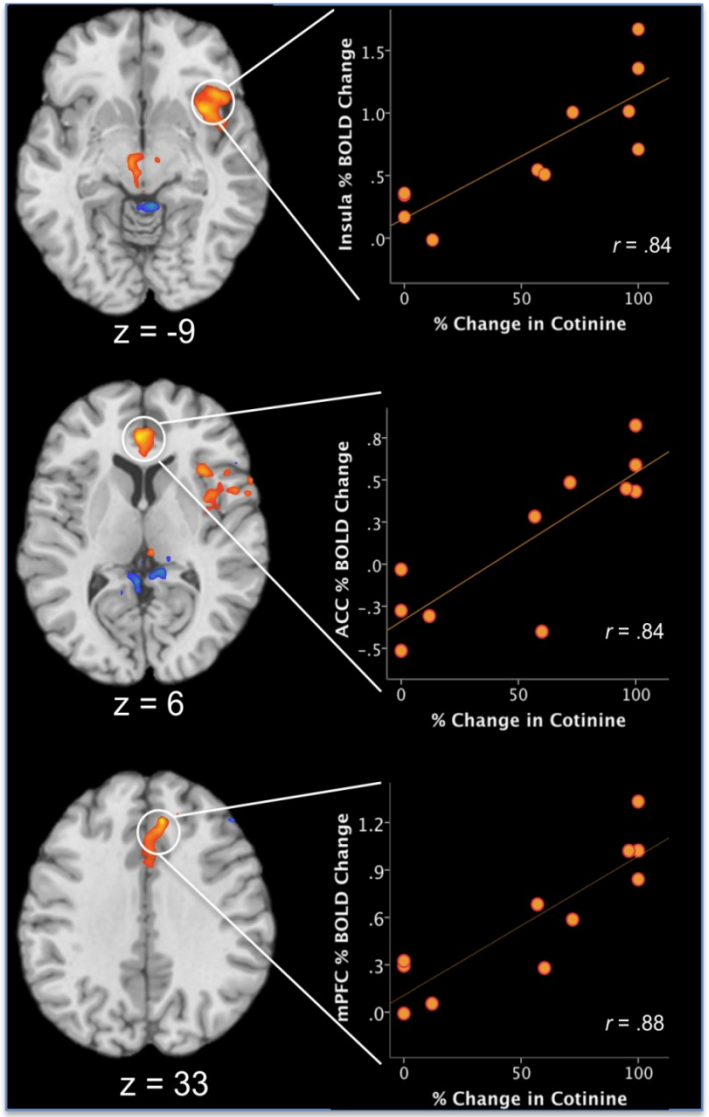
Adolescent heavy smokers. Vs nonsmokers, had lower neural activation in cortical regions in response to a Stop-Signal task (Galvan, Poldrack, Baker, McGlennen, London, 2011)



Heaviness of Smoking Index and neural activation. In smokers, HSI was negatively correlated with left and right MFG (x=−34, y=36, z=38; x=30, y=36, z=44), cingulate gyrus (x=0, y=14, z=28), supplementary motor cortex (x=0, y=−2, z=62), orbitofrontal cortex (x=−26, y=56, z=2), and right superior frontal gyrus (x=24, y=−2, z=66) in the Successful Stop>Baseline contrast (a), and with left IFG (x=−52, y=14, z=14) in the Successful Stop>Go contrast (b). There were no significant correlations with the Successful Stop>Unsuccessful Stop contrast.

Nicotine & Cognitive Interference & Abstinence: Adolescent Smokers

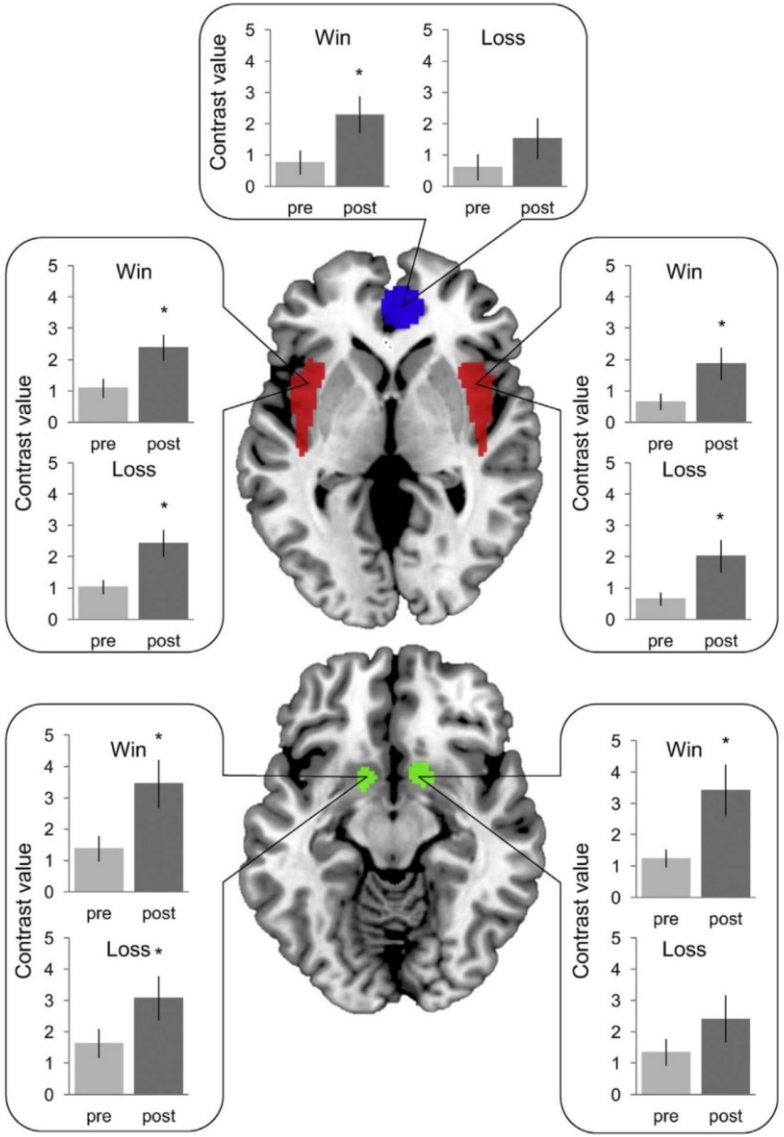
Stroop-related cognitive efficiency improves with abstinence (Krishnan-Sarin et al., 2013; Yip et al., 2016)

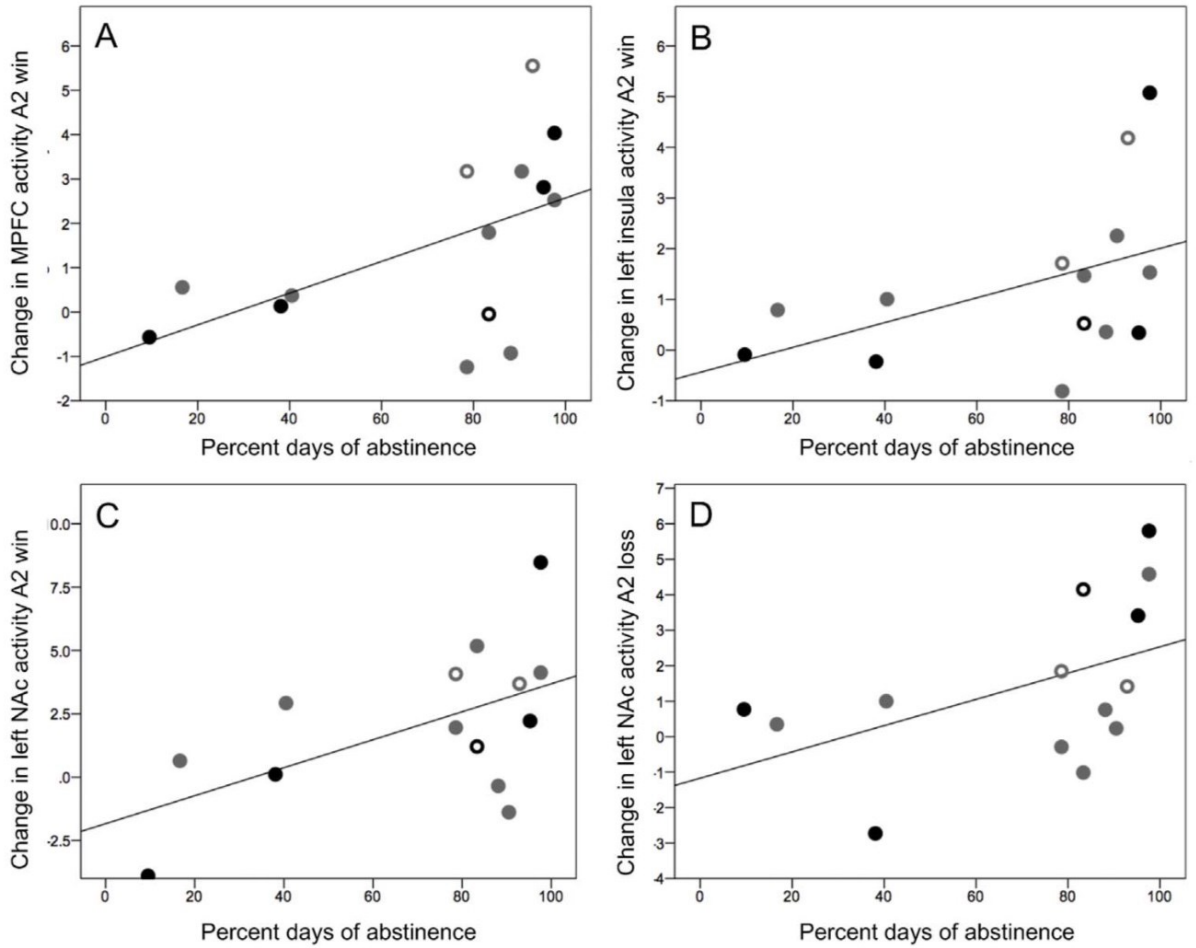


Greater percent drop in cotinine levels at EOT abstinence was positively correlated with Stroop-related reductions in anterior cingulate and insula suggesting improved cognitive efficiency with abstinence.

Nicotine & Reward & Abstinence: Adolescent Smokers

Blunted response to non-drug rewards improves following treatment and is correlated with abstinence (Garrison et al., 2017)





Tobacco Initiation in Children: Changes in Neurocognitive Performance and Cortical Area

Dai, Doucet, Wang, Puga, Samson, Xiao, Khan, 2022

- ABCD; Wave 1: 2016-2018; Wave 2: 2018-2021
- 11 729 participants at wave 1 (9.9 [0.6] years old)
- 116 children reported ever use of tobacco products at wave 1.
  - 80 - use of e-cigarettes or cigarettes.
  - 10 - cigars
  - 12 - smokeless tobacco
  - 5 - pipes
  - 8- nicotine replacement
- Initiating tobacco use in late childhood was associated
  - Lower general cognitive performance with sustained effects at 2-year follow-up.
  - Lower cortical volume (frontal, parietal, temporal) cortices with sustained effects at 2-year follow up

E-cigarette & Youth: Depressive symptoms

Moustafa, Testa, Rodriguez, Pianin, Audrain-McGovern, 2021

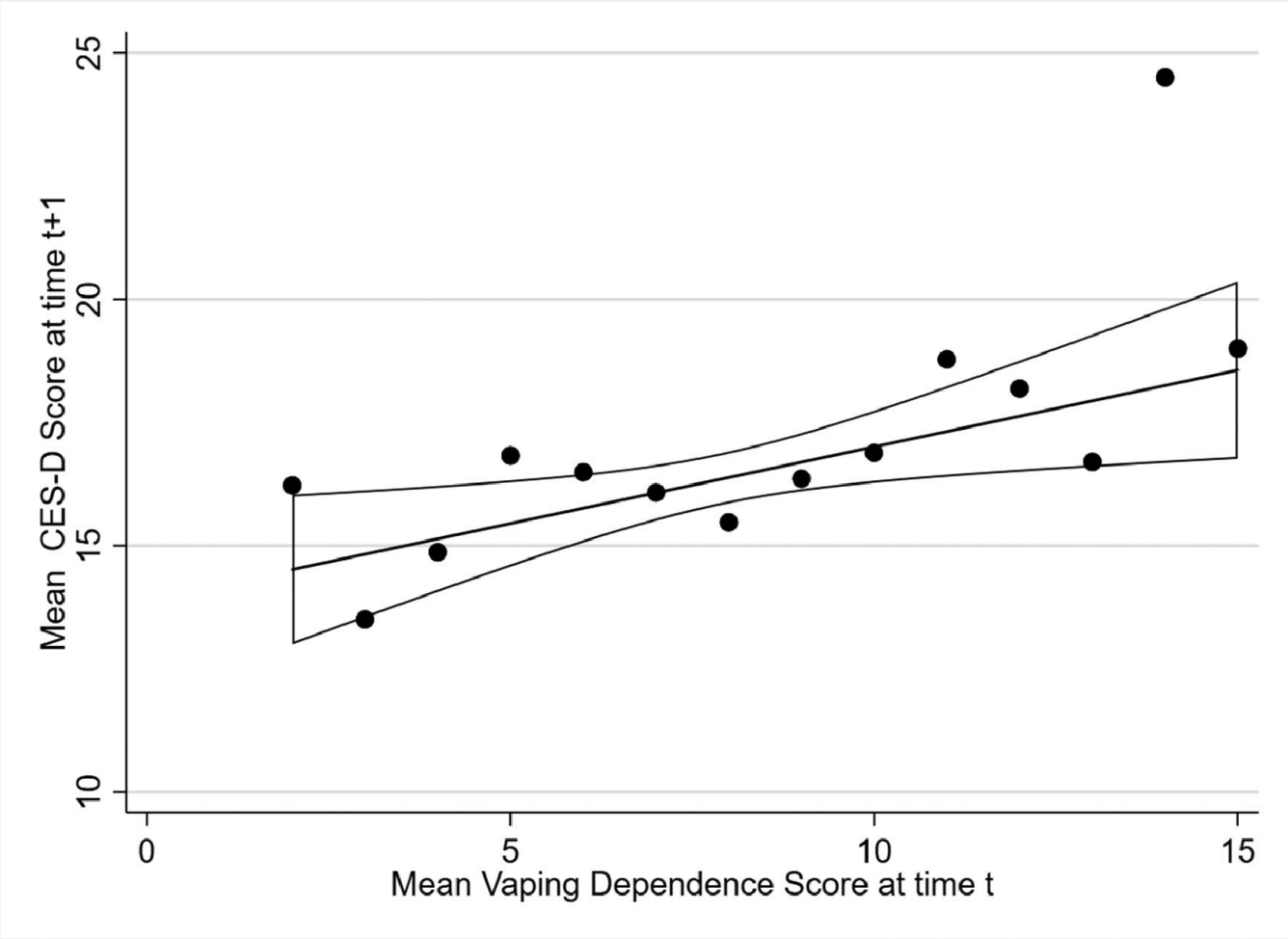
	E-cigarette use							
	Baseline level				Linear trend			
	b	SE	z-value	p-value	b	SE	z-value	p-value
Baseline depression					0.01	0.00	4.26	<0.0001
Sex	−0.04	0.08	−0.56	0.57	0.00	0.03	0.04	0.97
Black race	−0.05	0.11	−0.45	0.66	−0.14	0.05	−2.87	0.004
Other race	−0.05	0.13	−0.36	0.72	−0.09	0.05	−1.76	0.08
Ethnicity	−0.24	0.09	−2.58	0.01	0.08	0.04	2.28	0.02
Peer e-cigarette use	0.17	0.02	9.09	<0.0001	−0.02	0.01	−2.49	0.01
Household e-cigarette use	0.19	0.10	1.90	0.06	−0.07	0.04	−1.69	0.09
Marijuana use	0.54	0.10	5.30	<0.0001	0.05	0.05	0.97	0.33
Alcohol use	0.23	0.09	2.46	0.02	0.13	0.04	2.89	0.004
Positive expectations	0.12	0.01	9.78	<0.0001	0.01	0.01	−1.89	0.06
Cigarette smoking	0.31	0.05	5.77	<0.0001	−0.07	0.02	−2.78	0.005
Perceived benefits	0.10	0.01	1.14	0.25	0.01	0.01	0.45	0.66

Moustafa et al., 2021

- Greater depressive symptoms at age 14 (baseline) were significantly associated with an increase in the rate of e-cigarette use progression across 36 months
- E-cigarette use at baseline - not significantly associated with depressive symptoms trend

E-cigarettes & Youth: Dependence & Depressive symptoms

Chaiton, Gan, Bondy, Cohen, Dubray, Eissenberg, Kaufman, Schwartz, 2023



Mean depression symptoms scores at subsequent 3-month follow-up by mean depressive symptom scores at previous survey among youth (aged 16–25 years) in Canada (N=1,226). CES-D, Center for Epidemiologic Studies Depression Scale

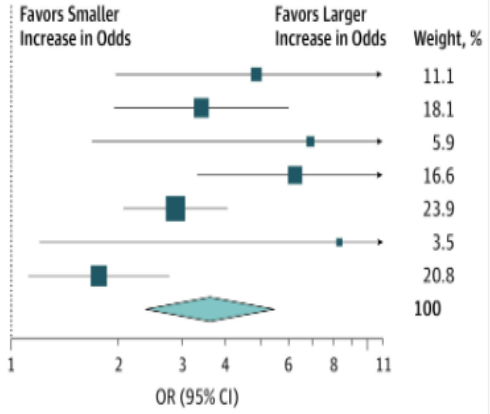
E-cigarettes and Other Tobacco Use

Soneji et al., 2017

Figure 2. Meta-analysis of Adjusted Odds of Cigarette Smoking Initiation Among Never Cigarette Smokers at Baseline and Ever e-Cigarette Users at Baseline Compared With Never e-Cigarette Users at Baseline.

Source	Probability of Cigarette Smoking Initiation, %		Unadjusted OR (95% CI)	Adjusted OR (95% CI)
	Ever e-Cigarette Users	Never e-Cigarette Users		
Miech et al,[10] 2017	31.1	6.8	6.23 (1.57-24.63)	4.78 (1.91-11.96)
Spindle et al,[9] 2017	29.4	10.6	3.50 (2.41-5.09)	3.37 (1.91-5.94)
Primack et al,[22] 2016	37.5	9.0	6.06 (2.15-17.10)	6.82 (1.65-28.22)
Barrington-Trimis et al,[8] 2016	40.4	10.5	5.76 (3.12-10.66)	6.17 (3.29-11.57)
Wills et al,[7] 2016	19.5	5.4	4.25 (2.74-6.61)	2.87 (2.03-4.05)
Primack et al,[6] 2015	37.5	9.6	5.66 (1.99-16.07)	8.30 (1.19-58.00)
Leventhal et al,[5] 2015	8.8	3.1	2.65 (1.73-4.05)	1.75 (1.10-2.78)
Total	**23.2**	**7.2**	**3.83 (3.74-3.91)**	**3.50 (2.38-5.16)**

Heterogeneity: $\tau^2 = 0.13$; $Q_6 = 13.79$; $P = .03$; $I^2 = 56\%$
Test for overall effect: $z = 6.34$; $P < .001$

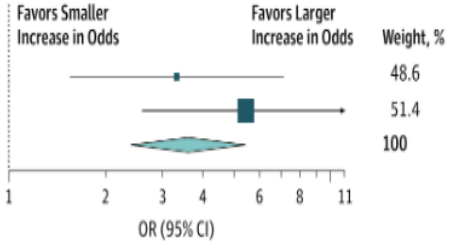


The odds ratios (OR) for the studies[5,6,7,8,9,10,22] are adjusted for a study-specific set of demographic, psychosocial, and behavioral risk factors. The size of the point estimate (black square) is proportional to the weight of the study in the random-effects meta-analysis model. The weights add to 99.9% and not 100% because of rounding. Q indicates Cochrane Q.

Figure 3. Meta-analysis of Adjusted Odds of Current (Past 30-Day) Cigarette Smoking at Follow-up Among Noncurrent Cigarette Smokers at Baseline and Current e-Cigarette Users at Baseline Compared With Noncurrent e-Cigarette Users at Baseline.

Source	Probability of Past 30-Day Cigarette Smoking, %		Unadjusted OR (95% CI)	Adjusted OR (95% CI)
	Past 30-Day e-Cigarette Users	Non–Past 30-Day e-Cigarette Users		
Unger et al,[23] 2016	26.2	7.0	4.71 (2.27-9.77)	3.32 (1.55-7.11)
Hornik et al,[24] 2016	19.0	2.0	11.18 (5.41-23.13)	5.43 (2.59-11.38)
Total	**21.5**	**4.6**	**5.68 (3.49-9.24)**	**4.28 (2.52-7.27)**

Heterogeneity: $\tau^2 = 0.00$; $\chi^2_1 = 0.83$; $P = .36$; $I^2 = 0\%$
Test for overall effect: $z = 5.37$; $P < .001$



The odds ratios (OR) for the studies[23,24] are adjusted for a study-specific set of demographic, psychosocial, and behavioral risk factors. The size of the point estimate (black square) is proportional to the weight of the study in the random-effects meta-analysis model.

E-cigarettes and Other Substances

Systematic review & meta-analysis: association between e-cigarette use and use of psychoactive substances in 10–24 yo youth

Lau, Conti, Hemmati, Baldacchino, 2023

- Several longitudinal studies showed that ever e-cigarette users have an increased likelihood for subsequent use of other substances compared to never e-cigarette users.

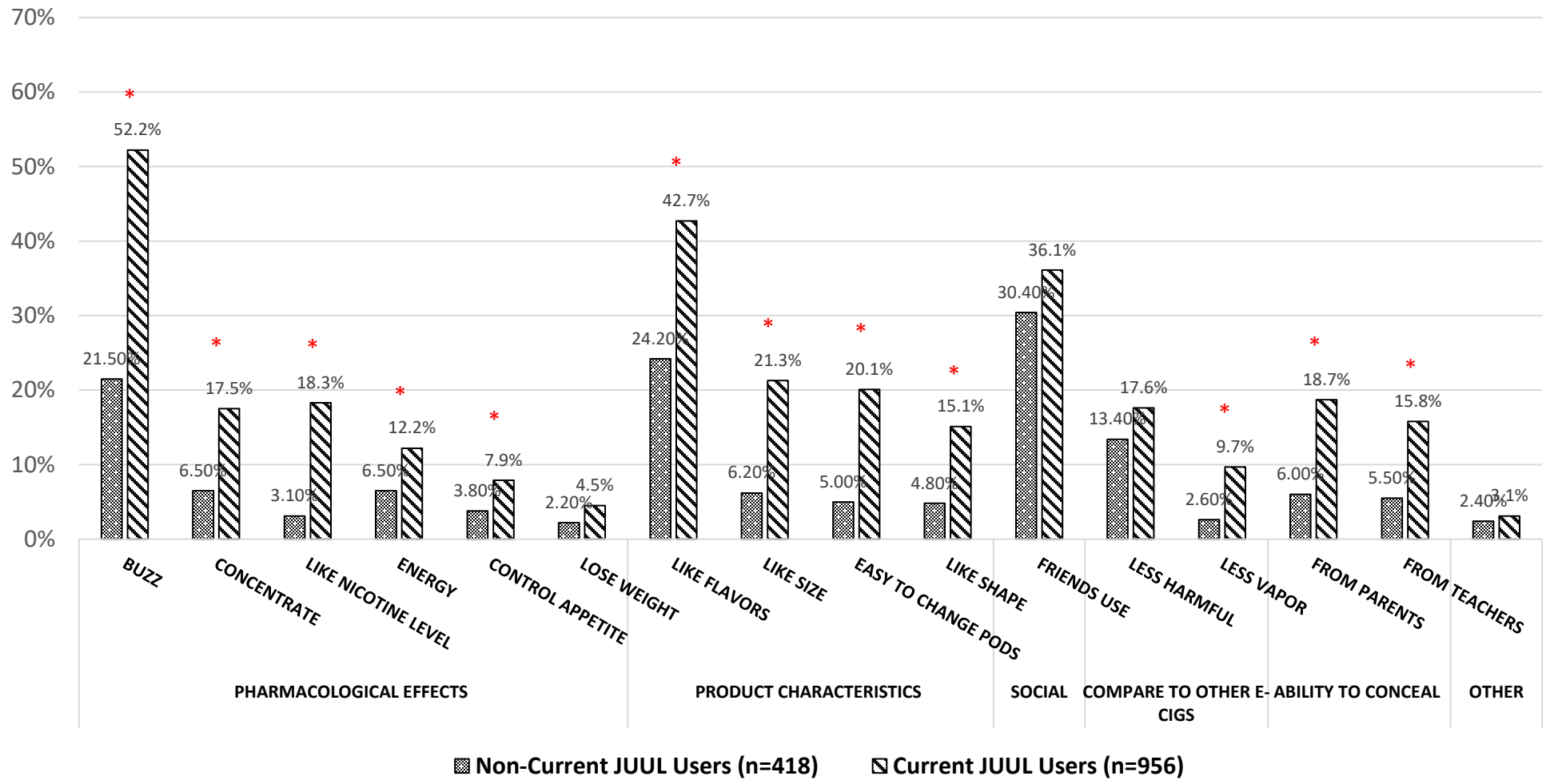
- Some of these studies examined youth who reported use of e-cigarettes but no use of other substance (i.e. cannabis, alcohol) at the first wave.

  - Bentivegna et al., 2021 : PATH waves 1,2, 3.
    - Increased cannabis smoking (OR:2.55), cannabis vaping (OR:2.05), non-prescribed Ritalin (OR:2.13), polysubstance use (OR; 2.67)
  - Seidel et al., 2022: Prospective cohort from Germany 2017-2019
    - Increased rates of trying cannabis (ARR: 1.83)
  - Sun et al., 2022: PATH waves 4.5 and 5.
    - Increased rates of past 12-month (ARR: 2.57) and 30-day (ARR: 3.20) cannabis use.
  - Lozano et al., 2017: Longitudinal cohort from Mexico 2015-2017
    - No effect of only ecig use. Use of both ecigs and cigs at wave 1 increased rates of cannabis us.

E-cigarettes & Use/Addiction in Youth: Reason for use

Youth experience positive effects of nicotine

Kong, Bold, Morean, Bhatti, Camenga, Jackson, Krishnan-Sarin 2019



E-cigarettes & Use/Addiction in Youth: Reasons for Use

Youth report tolerance & preoccupation with use (Bold et al., 2016; Kong et al.,2021)

- Tolerance Breaks

"…I've taken tolerance breaks… it's to the point where I don't ever feel anything. But I'm just so used to feeling like high or buzzed all the time."

I mean, at this point, I'm so addicted to it, and I have such a tolerance, that I don't even feel anything anymore. It's just like I kinda need to do it."

- Feeling preoccupied with obtaining e-cigarettes

"It's more just like you're kind of itching to hit a JUUL all the time.."

E-cigarettes & Use/Addiction in Youth

Youth experience withdrawal symptoms and addiction (Bold et al., 2016; Kong et al., 2021

- Withdrawal symptoms
  - Negative emotions (e.g., anxious, angry, agitated)
  - Increased cravings
  - Negative physical symptoms (e.g., headaches)
  - Trouble focusing

- Addiction/Dependence

I mean, honestly, in my opinion, I don't really get anything out of it. It's mainly just like a buzz, and then like for the rest of the day I'm just kind of like stuck on doing it... like it's just an addiction that I'm trying to quit.

I mean, at this point, I'm so addicted to it, and I have such a tolerance, that I don't even feel anything anymore. It's just like I kinda need to do it."

Nicotine, it's like, at the beginning, you had it [a buzz], and now it's just like your stuck. Like, you're not doing it for the pleasure of doing it, you're doing it because you feel like you have to.

E-cigarette Dependence in Youth (PROMIS Measure)

Morean, Krishnan-Sarin, O'Malley, 2018

1. When I haven't been able to vape for a few hours, the craving gets intolerable.
2. I drop everything to go out and get e-cigarettes or e-liquid/juice.
3. I vape more before going into a situation where vaping is not allowed.
4. I find myself reaching for e-cigarettes/a vape without thinking about it.

- 997 participants ages 13-20 years who self-reported using vaping nicotine 4+ days/week

E-cigarette Dependence
• Any: 98.5% • Sometimes – Very Often: 65.2% • Often - Very Often: 31.8%

E-cigarette Withdrawal in Youth

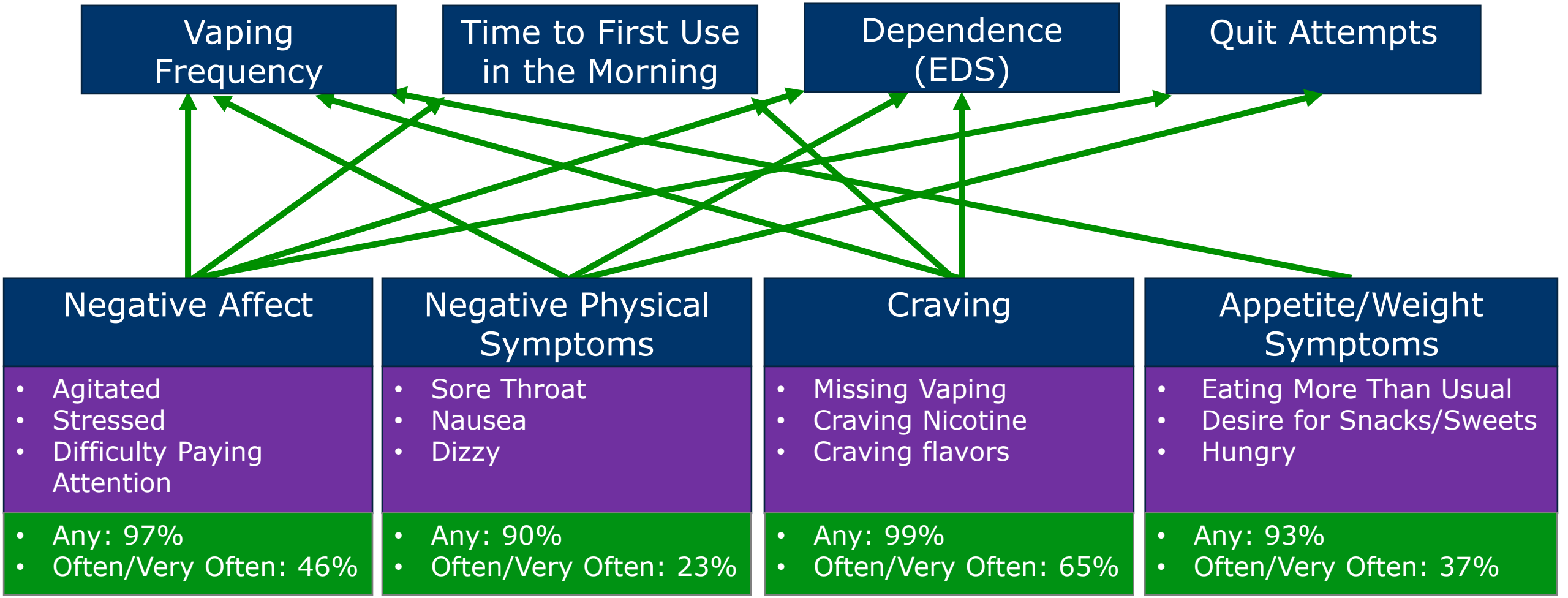
Morean, Rajeshkumar, Krishnan-Sarin, 2024

- Develop measure: Lit review, subject matter experts, cognitive interviews
- Validate measure: Survey with 997 youth and young adults ages 13-20 years who reported vaping nicotine 4 or more days/week

Negative Affect	Negative Physical Symptoms	Craving	Appetite/Weight Symptoms
• Agitated • Stressed • Difficulty Paying Attention	• Sore Throat • Nausea • Dizzy	• Missing Vaping • Craving Nicotine • Craving flavors	• Eating More Than Usual • Desire for Snacks/Sweets • Hungry
• Any: 97% • Often/Very Often: 46%	• Any: 90% • Often/Very Often: 23%	• Any: 99% • Often/Very Often: 65%	• Any: 93% • Often/Very Often: 37%

E-cigarette Withdrawal in Youth

Morean, Rajeshkumar, Krishnan-Sarin, 2024



Covariates: sex, age, ethnicity, race, SES, daily nicotine vaping, past-month use of other tobacco products

Yale SCHOOL OF MEDICINE

Mental Health vs. Mental Health Disorders

Nicotine exposure may influence daily functioning in youth by changing

- Brain structure
- Cognition
- Emotional regulation
- Stress
- Depressive symptoms
- Anxiety Symptoms
- Dependence
- Withdrawal
- Other substance use

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