

# Nicotine Reduction and Smoking in Vulnerable Populations

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# Support & Disclosures

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- The content is solely my responsibility and does not necessarily represent the official views of the NIH or the FDA.



# Why Study Nicotine Reduction in Vulnerable Populations?

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- The 2009 Tobacco Control Act authorized the FDA to set product standards for cigarettes, including nicotine content. The FDA must consider the risks and benefits to the population as a whole.
- Vulnerable populations are those at elevated risk for tobacco-related health harms due to high rates of smoking and low rates of cessation.
- A reduced-nicotine standard could reduce dependence and increase the likelihood of quitting among those vulnerable to persistent tobacco use.
- However, vulnerable populations could also experience unintended negative consequences of a reduced-nicotine standard.
  - Increases in negative affect and other psychiatric symptoms
  - Increases in smoking in efforts to overcome these effects
  - Increases in alternative substance use

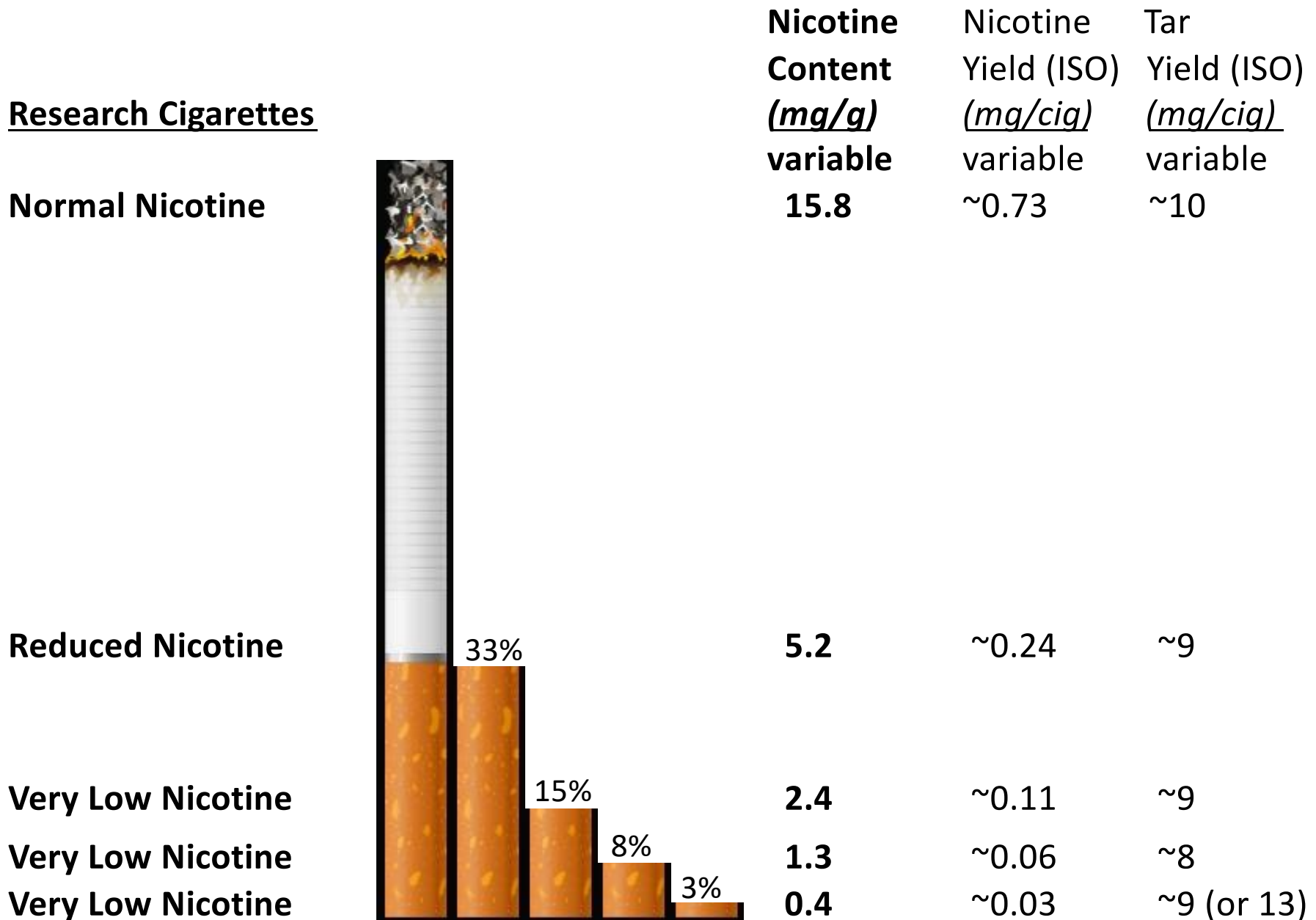


# Populations of Special Relevance to the FDA Center on Tobacco Products

|                               |   |                              |
|-------------------------------|---|------------------------------|
| Youth                         | Socioeconomically disadvantaged populations | Racial/ethnic minorities     |
| Underserved rural populations | People with MHCs                            | People with SUDs             |
| Military/veteran populations  | Pregnant women or women of reproductive age | Sexual and gender minorities |



# Very Low Nicotine Content Cigarettes



# Adults with Mental Health Conditions

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## 1. Acute exposure

- VLNC cigarettes reduce abstinence-induced craving, withdrawal and smoking in **adults with and without schizophrenia** (Tidey et al., 2013); no compensatory smoking topography (Tidey et al. 2016); cognitive effects of VLNCs reversed with NRT (AhnAllen et al. 2015)
- VLNC cigarettes reduce cigarette reinforcement in 3 vulnerable populations including **adults with affective disorders** (Higgins et al., 2017).

## 2. 6-week exposure

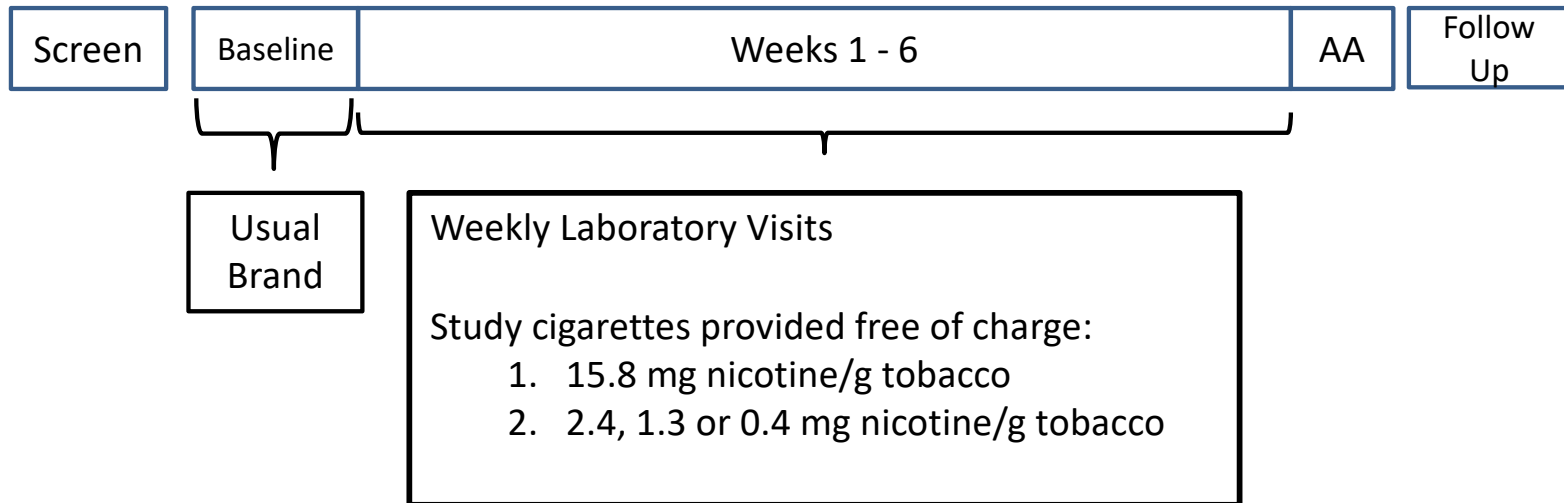
- Secondary analysis found that people with **elevated baseline depression** responded similarly to those with lower depression (Tidey et al., 2017).
- In an RCT, VLNC cigarettes reduced cigarette use and smoke intake in adults with **schizophrenia or bipolar disorder** (Tidey et al., 2019).

## 3. 12-week exposure

- In an RCT, VLNC cigarettes reduced smoking, breath CO and dependence in 3 vulnerable populations including **adults with affective disorders** (Higgins et al., 2020).



# 6-Week Use of VLNCs in Adults with Lower vs. Higher Depressive Symptoms

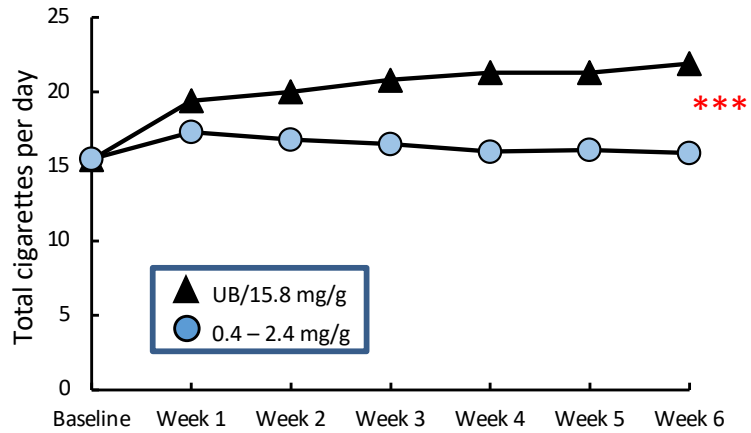


Measures: Total cigarettes per day, nicotine & toxicant exposure, dependence, craving, withdrawal, mood, psychiatric symptoms, cognitive performance, topography, quit attempts, effects of 24-hr abstinence

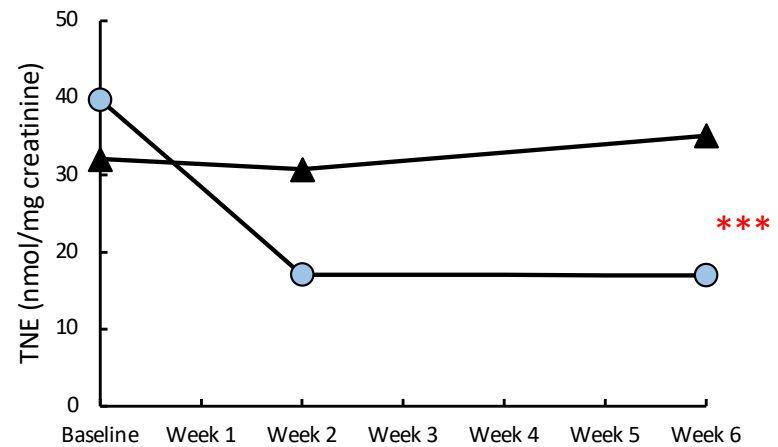
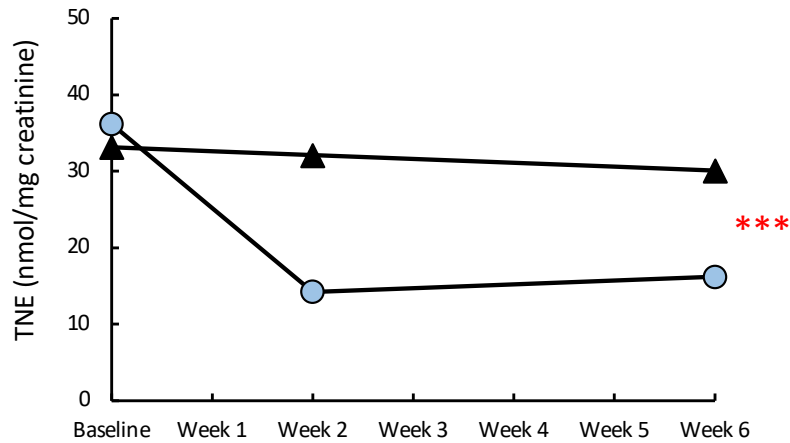
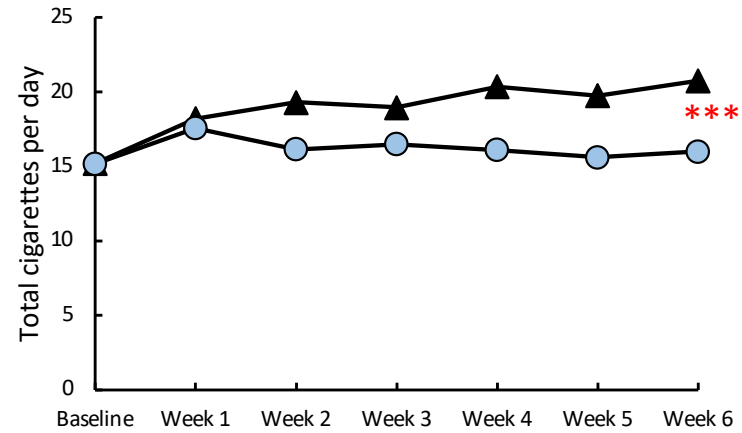
Secondary analysis of Donny et al. 2015 *NEJM*  
Tidey et al. 2017 *Nicotine Tob Res*

# Effects on CPD and Nicotine Exposure

Lower BL depressive symptoms



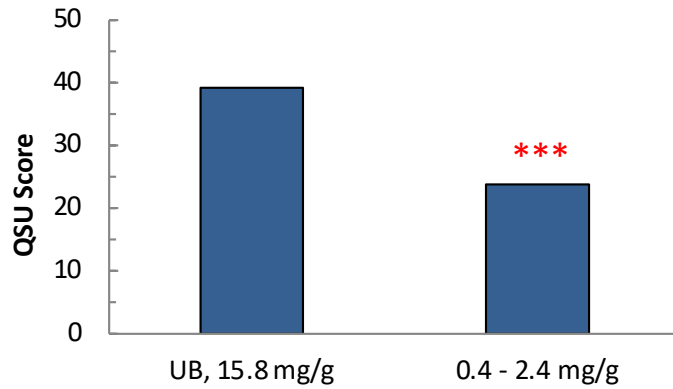
Higher BL depressive symptoms



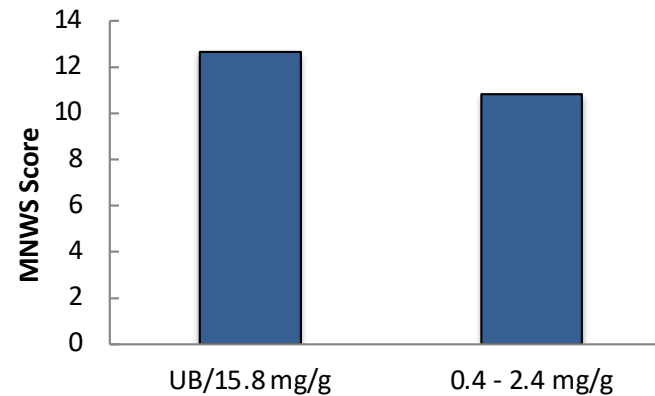
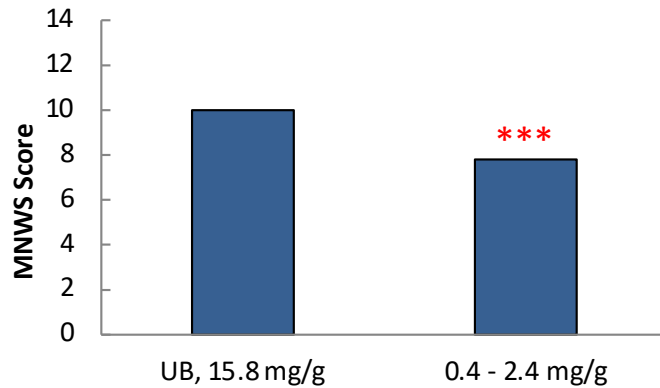
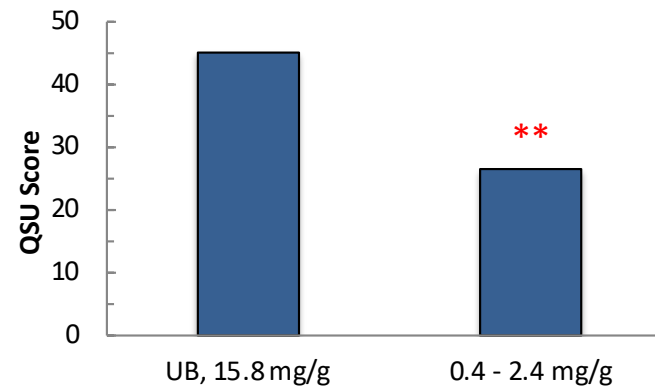


# Craving & Withdrawal During Abstinence

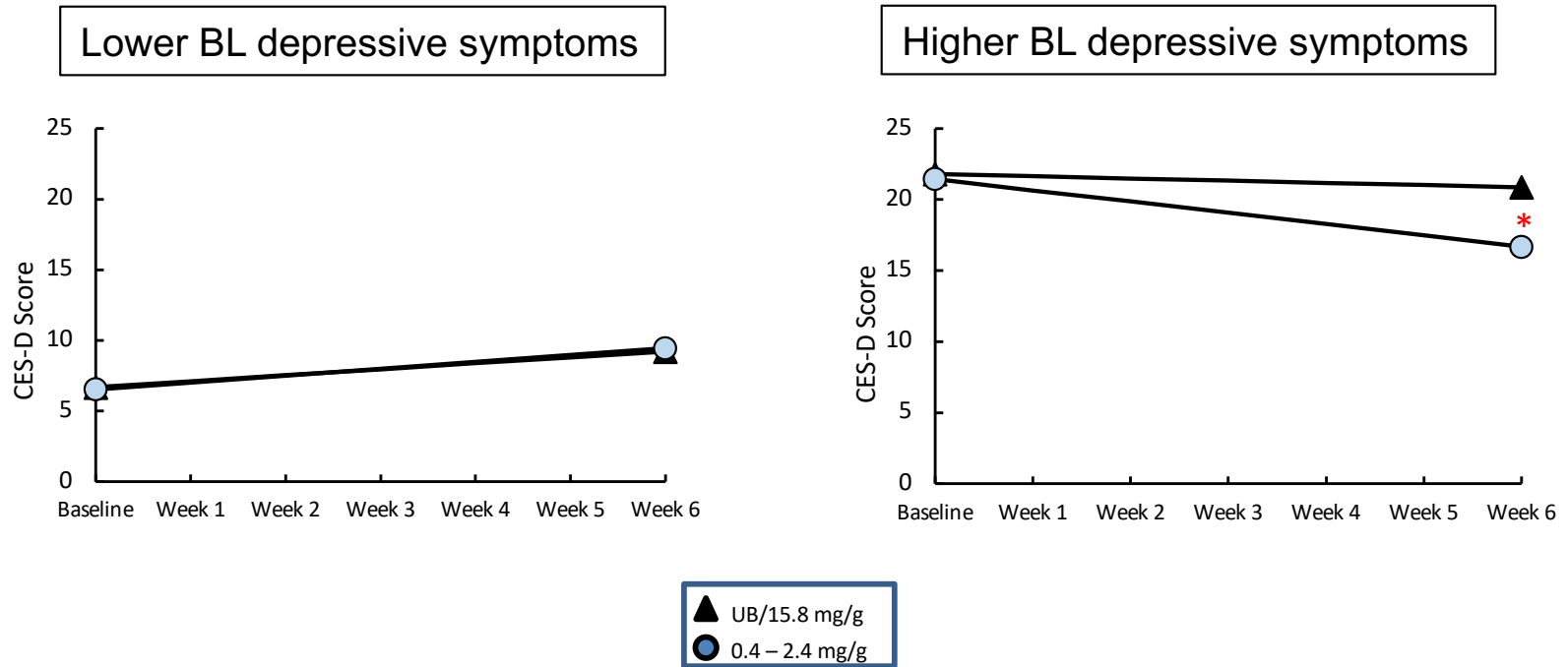
Lower BL depressive symptoms



Higher BL depressive symptoms

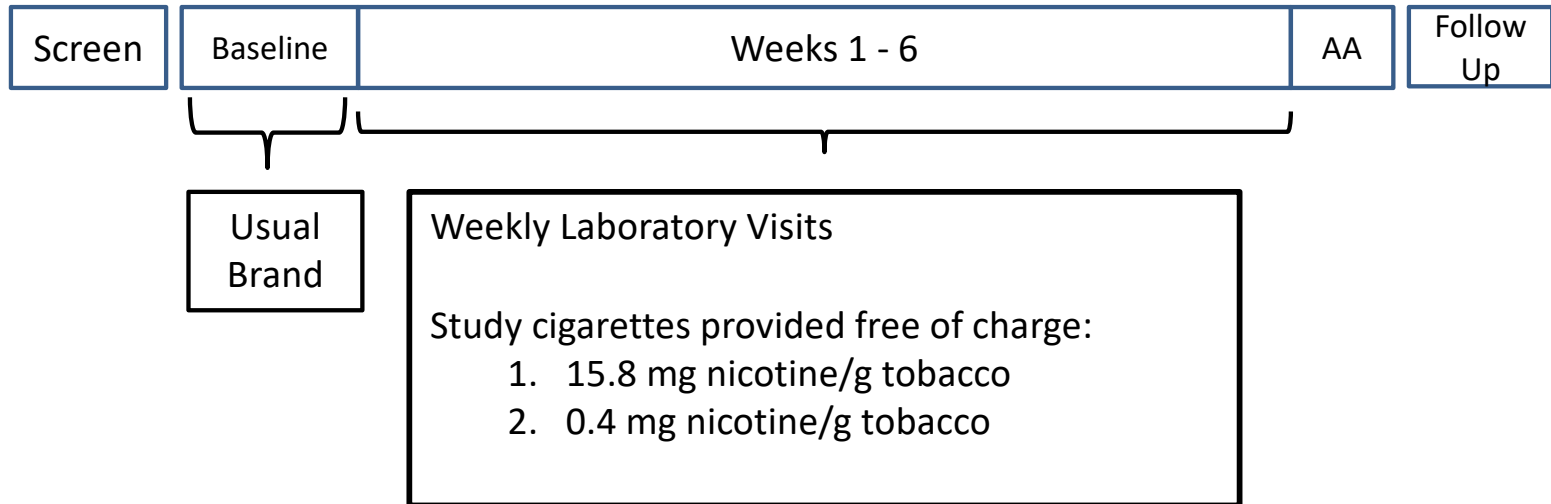


# Effects on Depression



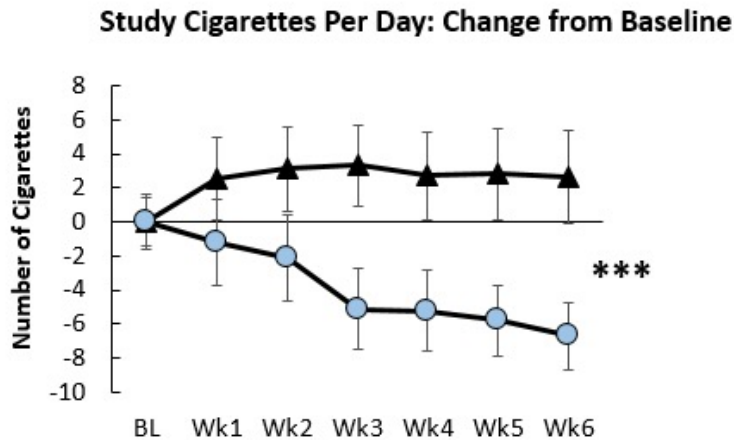
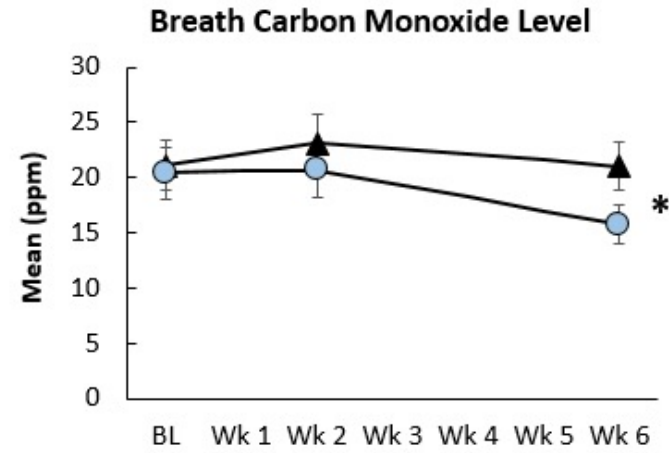
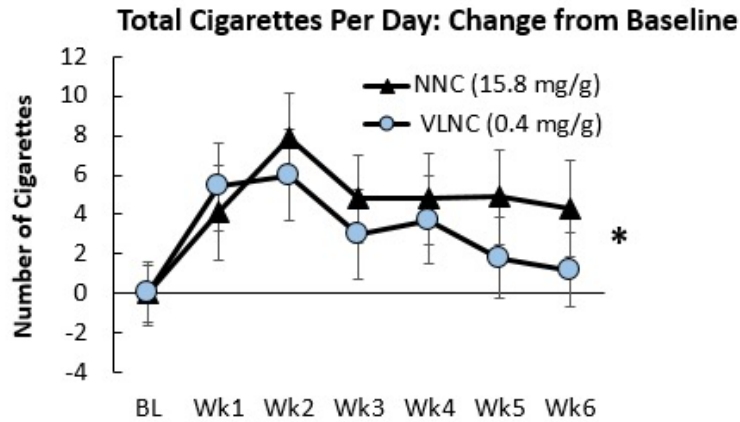
Tidey et al. 2017 *Nicotine Tob Res*

# 6-Week Use in Adults with Schizophrenia or Bipolar Disorder

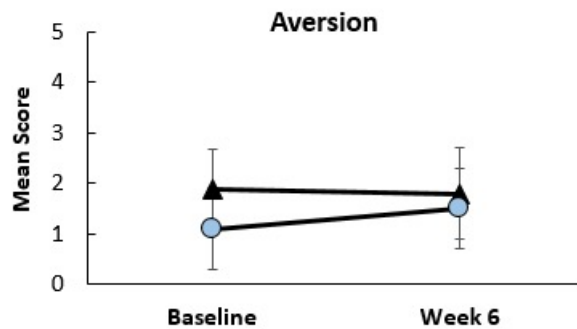
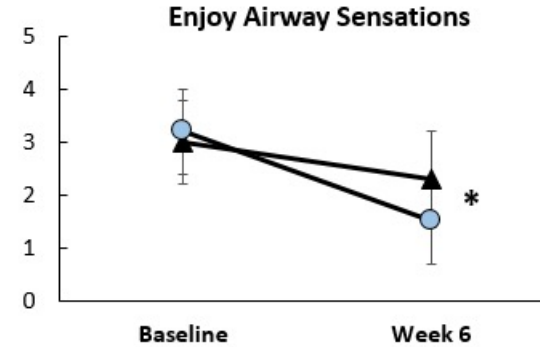
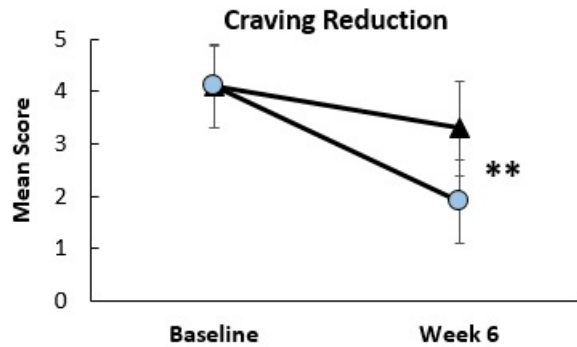
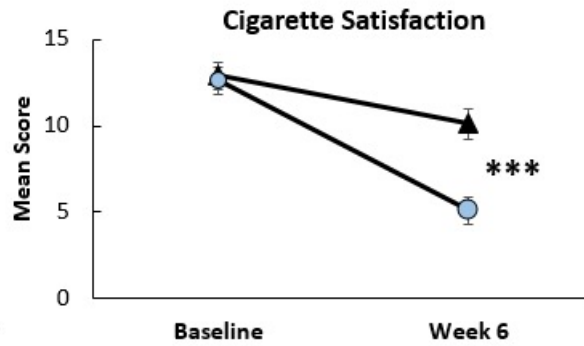


Measures: Total cigarettes per day, nicotine & toxicant exposure, dependence, craving, withdrawal, mood, psychiatric symptoms, topography, quit attempts, effects of 24-hr abstinence

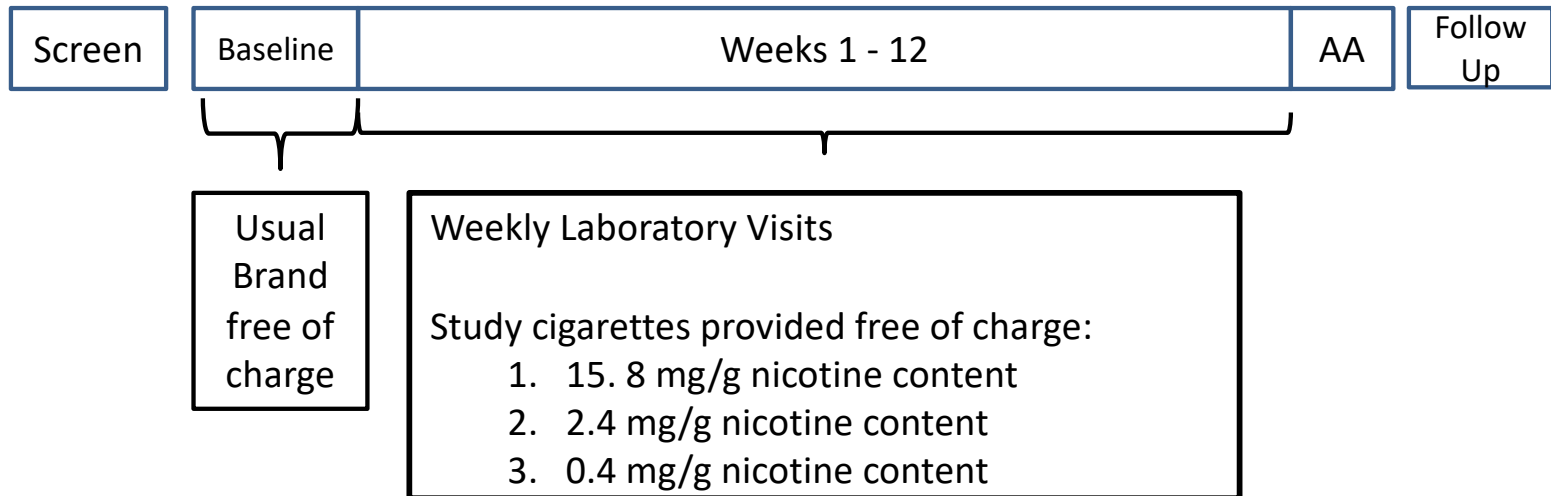
# Effects on Smoking



# Product Appeal



# 12-Week Use in Adults from 3 Vulnerable Populations



## 3 Vulnerable Populations (n = 775):

- 1: Disadvantaged women of childbearing age (n = 258)
- 2: Adults receiving treatment for OUD (n = 260)
- 3: Adults with current or lifetime depression or anxiety disorders (n = 257)

Measures: Total cigarettes per day, nicotine & toxicant exposure, dependence, craving, withdrawal, mood, psychiatric symptoms, cognitive performance, topography, quit attempts, effects of 24-hr abstinence

Higgins et al., 2020; *JAMA Network Open*

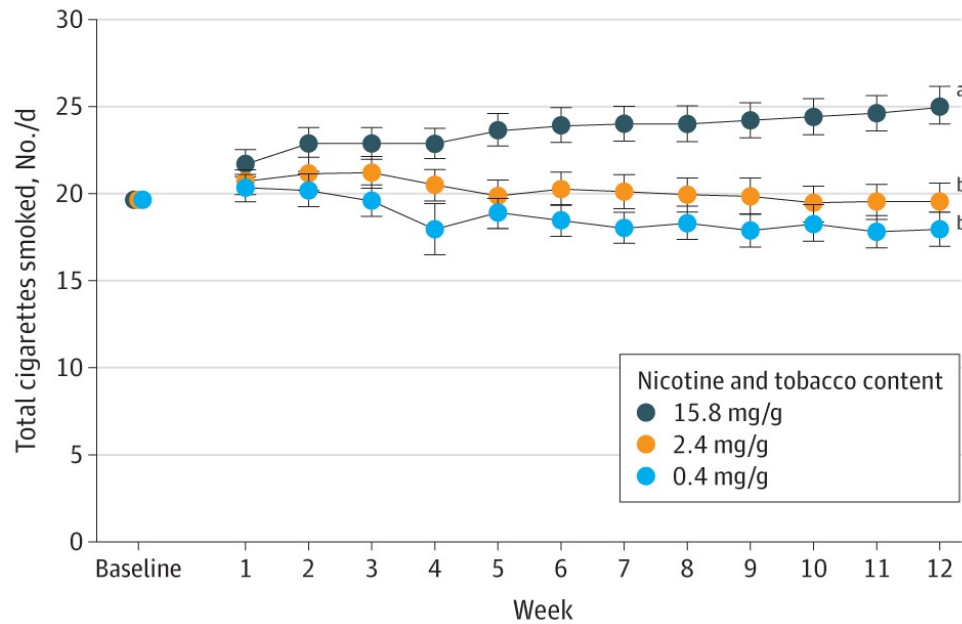


Original Investigation | Substance Use and Addiction

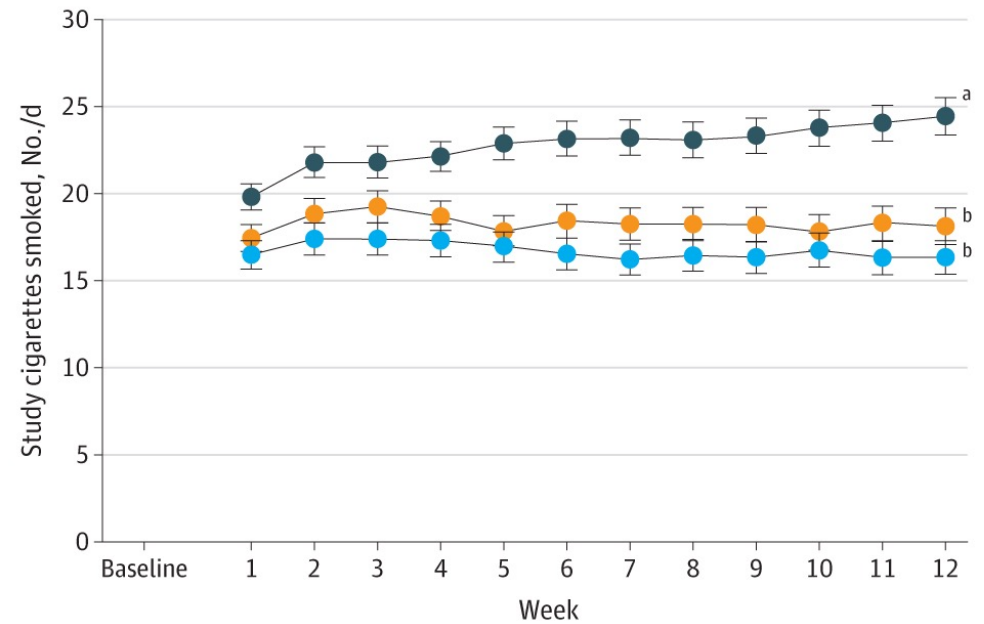
# Changes in Cigarette Consumption With Reduced Nicotine Content Cigarettes Among Smokers With Psychiatric Conditions or Socioeconomic Disadvantage: 3 Randomized Clinical Trials

Stephen T. Higgins, PhD; Jennifer W. Tidey, PhD; Stacey C. Sigmon, PhD; Sarah H. Heil, PhD; Diann E. Gaalema, PhD; Dustin Lee, PhD; John R. Hughes, MD; Andrea C. Villanti, PhD; Janice Y. Bunn, PhD; Danielle R. Davis, PhD; Cecilia L. Bergeria, PhD; Joanna M. Streck, BA; Maria A. Parker, PhD; Mollie E. Miller, PhD; Michael DeSarno, MS; Jeff S. Priest, PhD; Patricia Cioe, PhD; Douglas MacLeod, MS; Anthony Barrows, BA; Catherine Markesich, BA; Roxanne F. Harfmann, BA

**A** Total cigarettes

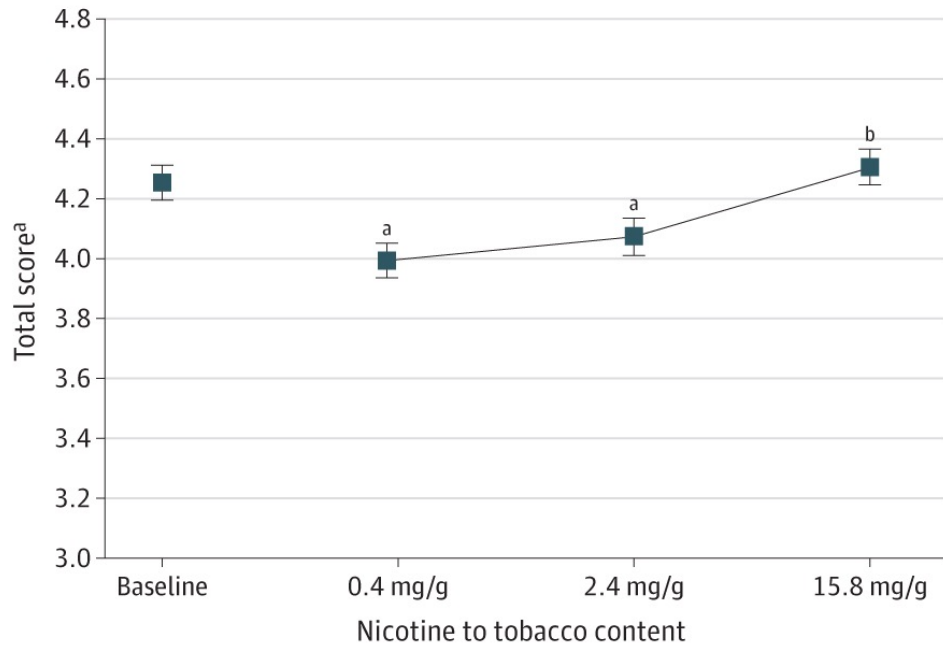


**B** Study cigarettes

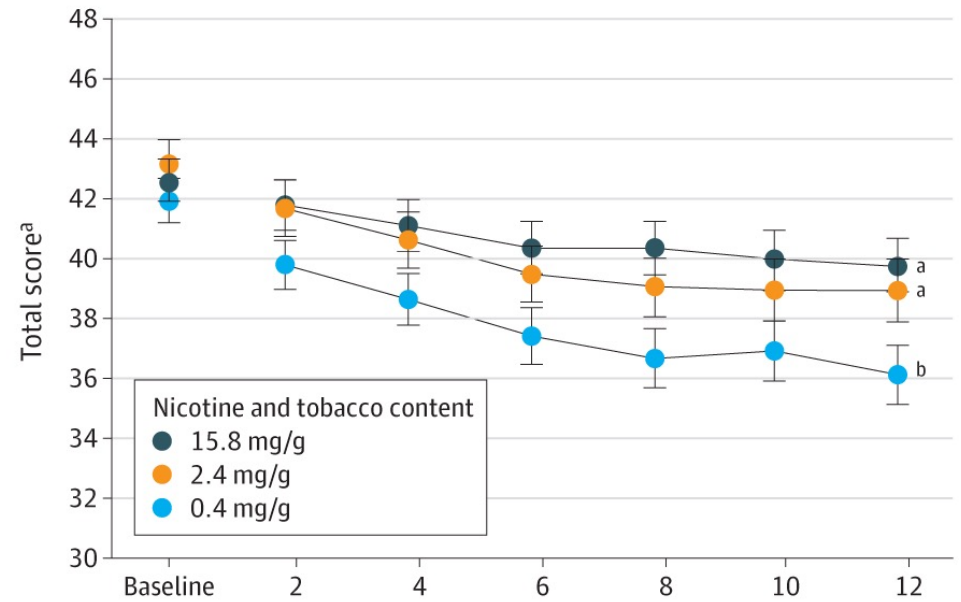


# Effects on Dependence

**A** Fagerström test for nicotine dependence



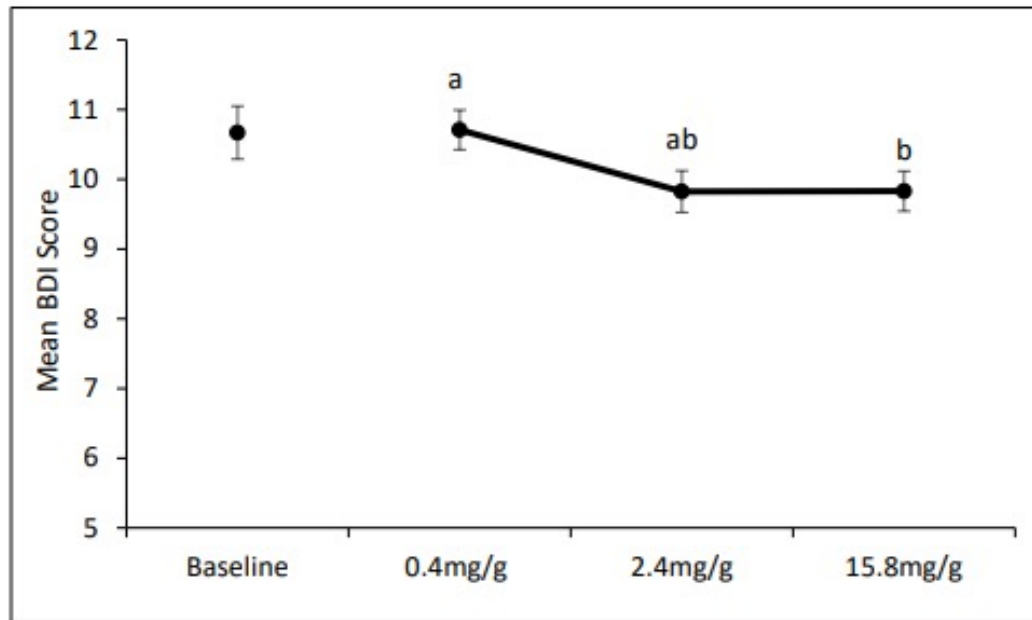
**B** Wisconsin inventory of smoking dependence motives





# Effects on Depression

**eFigure 6.** Beck Depression Inventory Score by Dose



eFigure 6. Panel shows Beck Depression Inventory (BDI) Scores for each of the three nicotine-content-cigarette doses (0.4, 2.4, and 15.8 mg/g). Data points are collapsed across participants, populations, and 12-week study period; error bars represent  $\pm$  SEM. Data points not sharing a superscript letter differed significantly by dose.

# Adults Who Use Other Substances

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## 1. Acute exposure

- VLNC cigarettes reduce cigarette reinforcement in 3 vulnerable populations including **adults with OUD** (Higgins et al., 2017).

## 2. 6-week exposure

- Secondary analysis found that **current cannabis use** did not moderate the effects of VLNCs on smoking, nicotine dependence, craving, or nicotine exposure; VLNCs did not increase cannabis use (Pacek et al. 2016).
- Secondary analysis in **alcohol users** found no evidence of compensatory alcohol use or binge drinking (Dermody et al. 2016).

## 3. 12-week exposure

- In an RCT, VLNC cigarettes reduced smoking, breath CO and dependence in 3 vulnerable populations including **adults with OUD** (Higgins et al., 2020).

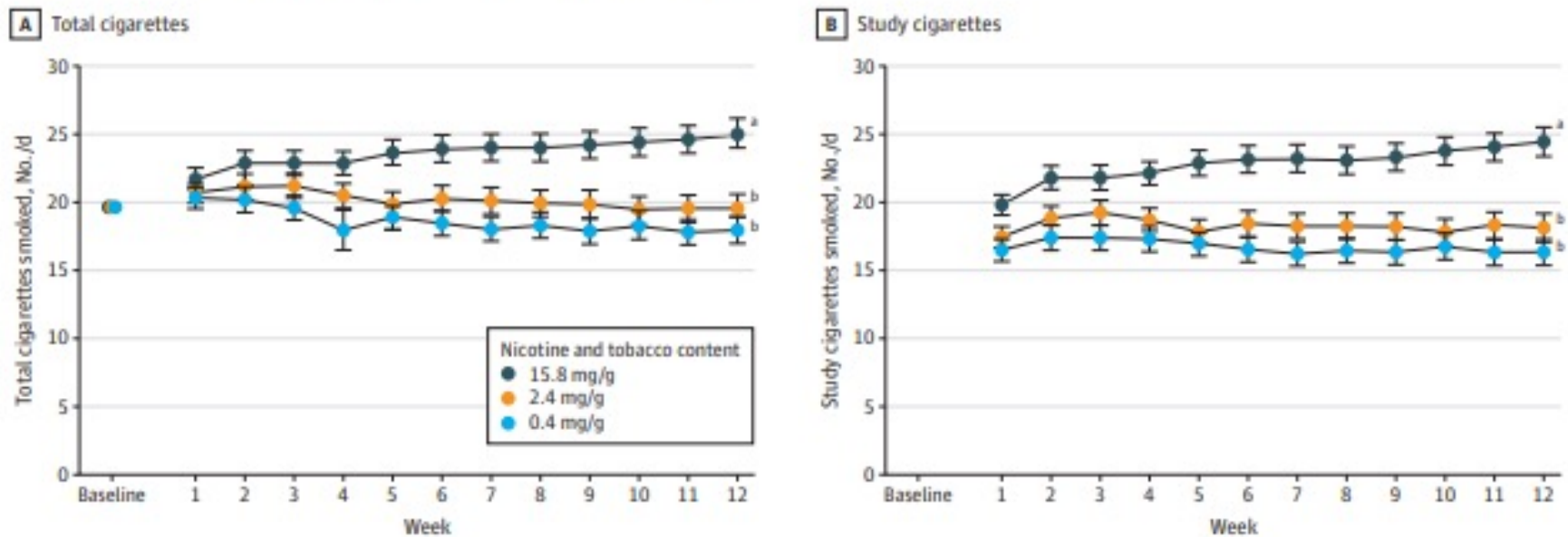
## 4. 20-week exposure

- Secondary analysis found that **baseline drinking and SMAST score** did not moderate the effects of VLNCs on Week 20 CPD or CO; smaller reduction in TNE among higher alcohol users; VLNCs reduced daily alcohol use and binge drinking (Dermody et al. 2021).



# Adults in Treatment for OUD

Figure 2. Number of Total and Study Cigarettes Smoked per Day According to Nicotine Content



Participants with OUD:  
No difference on total CPD, dependence severity, CO  
More non-study CPD early in the trial; more e-cig, NRT and smokeless tobacco use  
Less sensitive to effects of VLNCs on nicotine intake, toxicant exposure, craving

Higgins et al., 2020; *JAMA Network Open*

# Adults with Socioeconomic Disadvantage

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## 1. Acute exposure

- VLNC cigarettes reduce cigarette reinforcement in 3 vulnerable populations including **low SES women** of reproductive age (Higgins et al., 2017).

## 2. 12-week exposure

- In an RCT, VLNC cigarettes reduced CPD, breath CO and dependence in 3 vulnerable populations including **low SES women** (Higgins et al., 2020).

## 3. 18-week gradual reduction

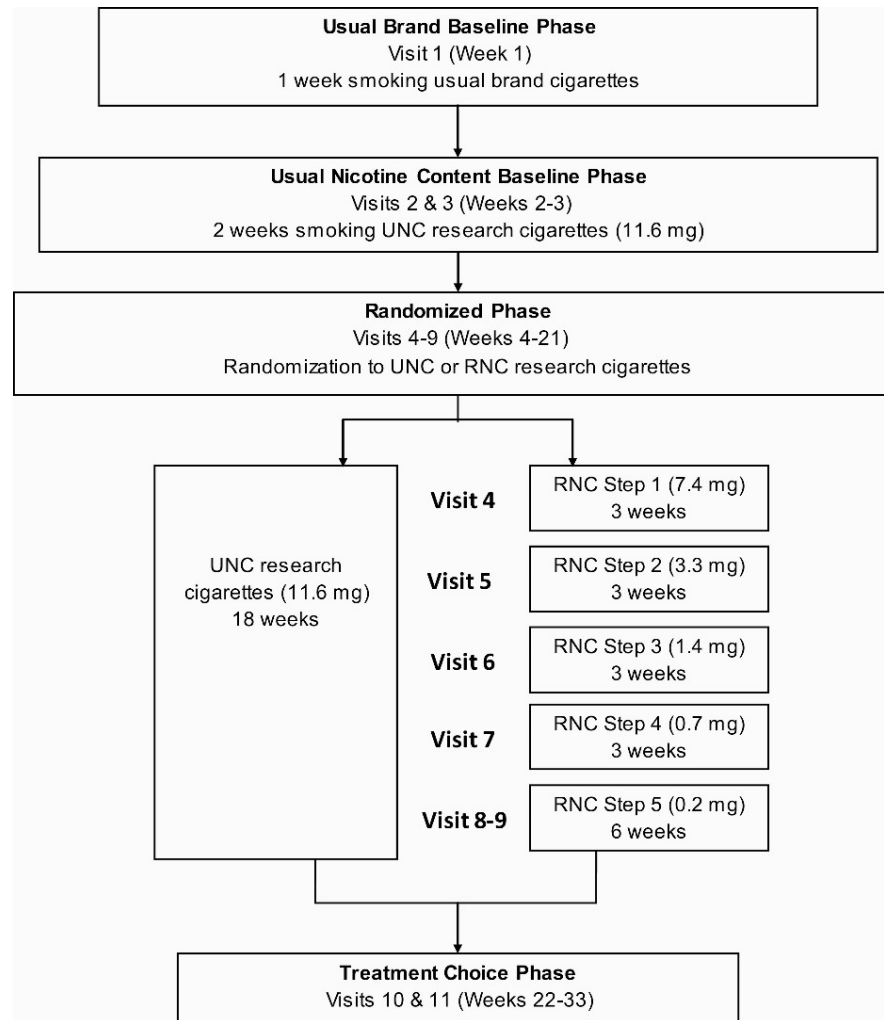
- In an RCT, **low SES adults** in the RNC group had higher attrition and lower CPD, nicotine exposure and CO. Among completers, RNC group was more likely to make a quit attempt and more likely to be abstinent (9% vs 3%) one month later (Krebs et al. 2020).

## 4. 20-week exposure

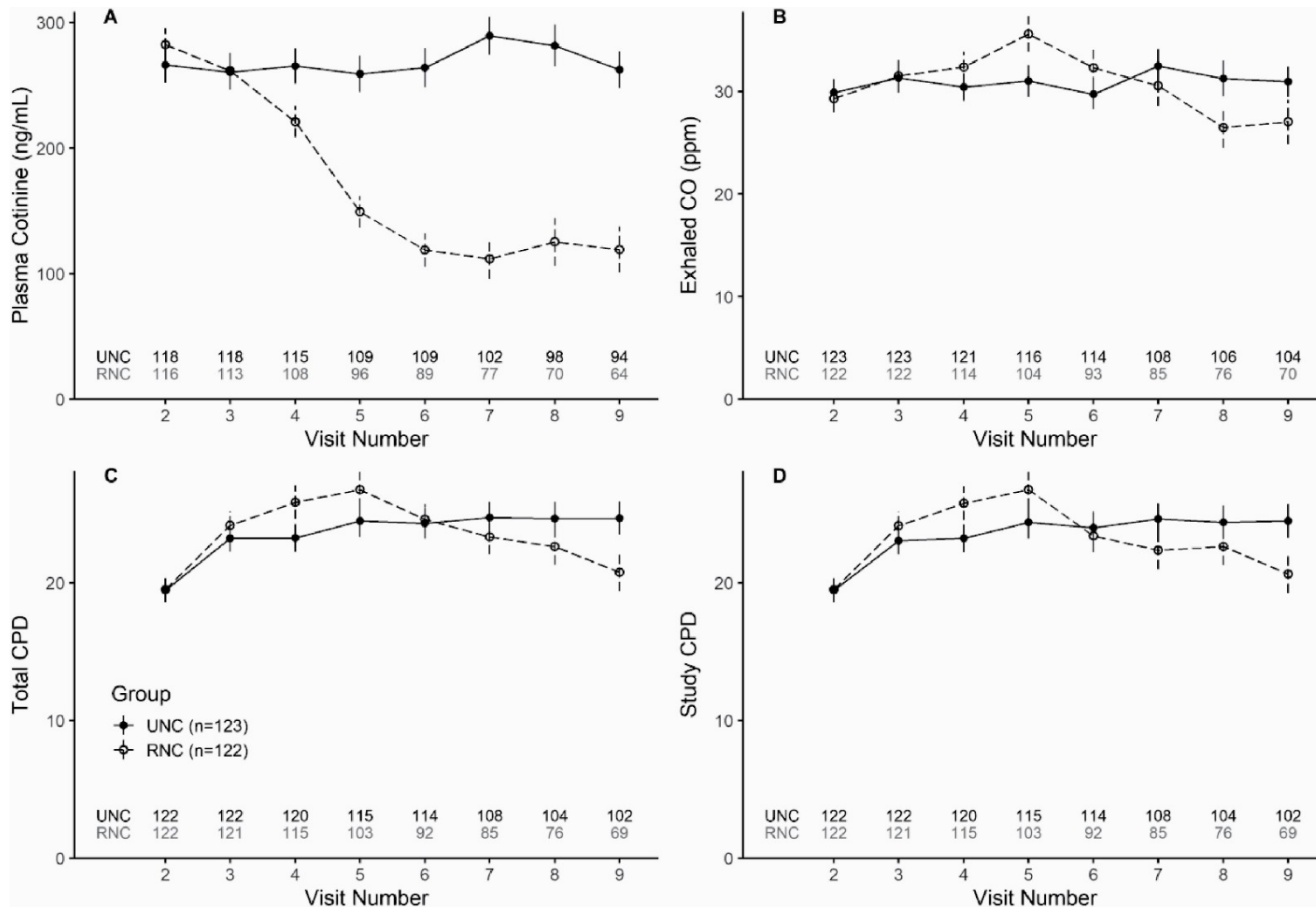
- Secondary analysis of a 20-week RCT found that regardless of **race, gender or educational attainment**, immediate reduction resulted in reductions in CPD, nicotine and toxicant exposure; Black participants had smaller reduction in TNE than White participants (Carroll et al., 2021).



# Adults with Socioeconomic Disadvantage



# Adults with Socioeconomic Disadvantage



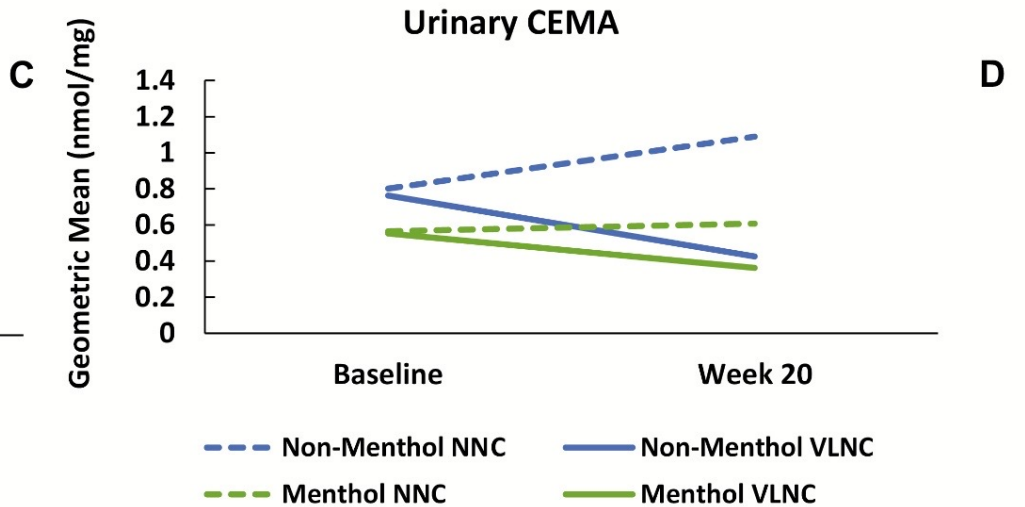
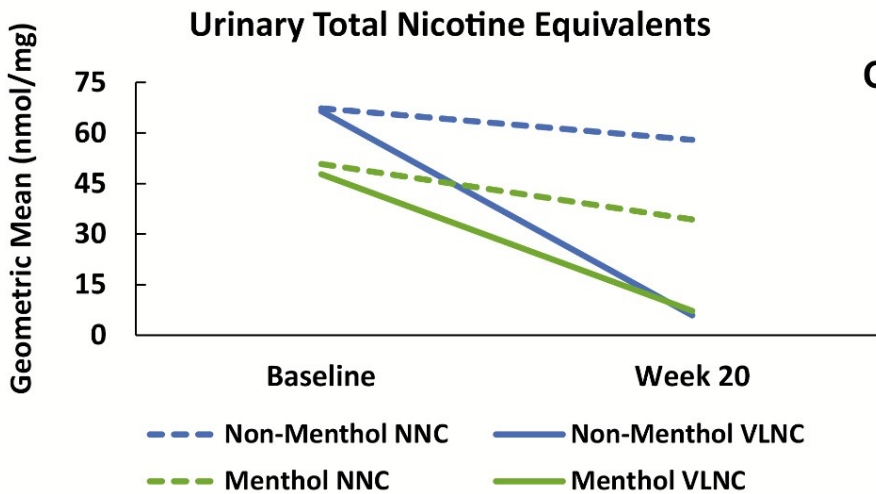
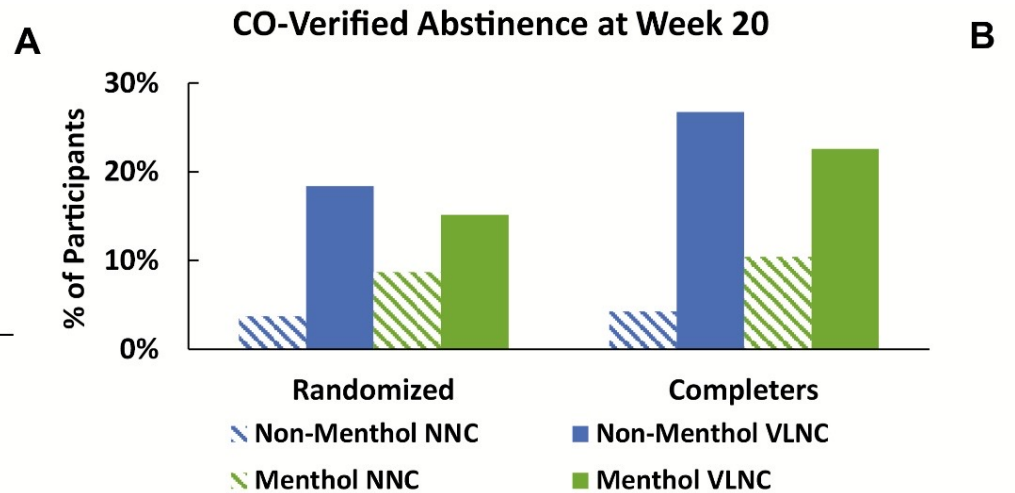
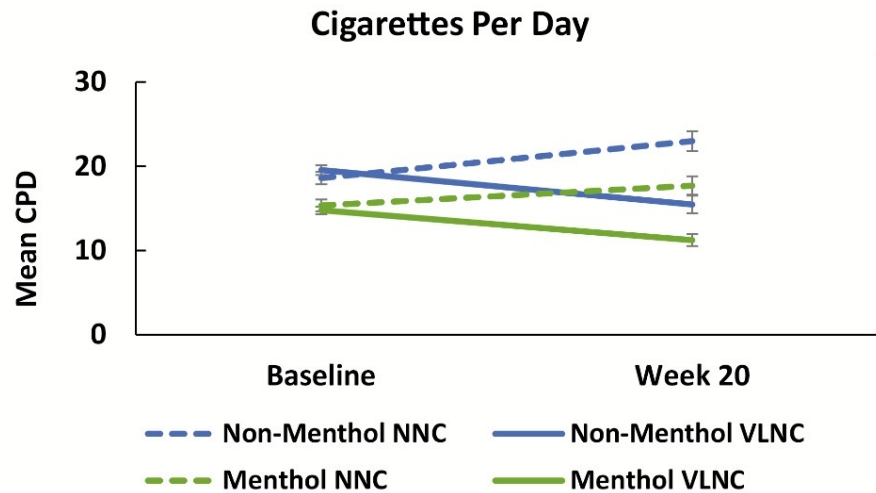
# Adults with Other Vulnerabilities

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1. Effects of VLNCs on smoking, nicotine/toxicant exposure and abstinence were smaller in **menthol smokers** than non-menthol smokers (Denlinger et al., 2019).
2. A secondary analysis found that having 0-1, 2-3 or  $\geq 4$  **cumulative vulnerabilities** (rural residence, OUD, affective disorder, low educational attainment, poverty, unemployment, physical disability) was associated with CPD but did not moderate response to VLNCs (Higgins et al., 2021).
3. Acute exposure study in **pregnant women** found that VLNCs were less satisfying, rewarding and reinforcing than UB (Heil et al., 2020).



# Menthol Smokers





# Youth and Young Adults

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## 1. Acute exposure

- VLNC cigarettes reduced abstinence-induced craving, withdrawal and negative affect in **smokers aged 15-19** (Cassidy et al., 2018); VLNCs were less reinforcing (Cassidy et al., 2019); no moderation of CO boost by menthol (Denlinger-Apte et al. 2019)
- Secondary analysis in 3 vulnerable populations found that **18-24 year-olds** were more sensitive to the effects of nicotine dose on demand than older adults (Davis et al. 2019).

## 2. 3-week exposure

- VLNC cigarettes reduced cigarettes per day in **youth ages 15-19** (Cassidy et al. 2020).

## 3. 6-week gradual reduction

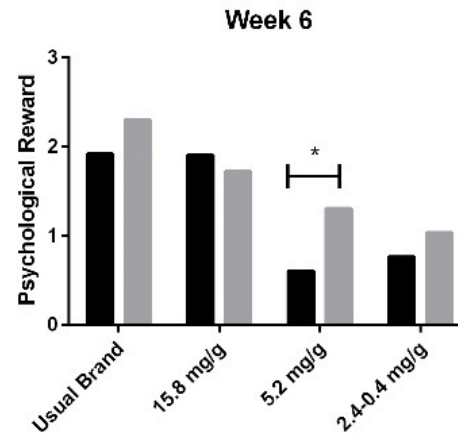
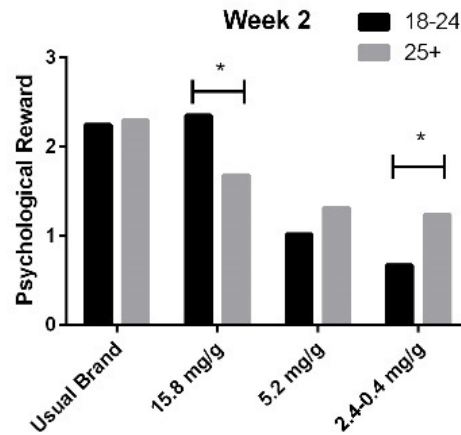
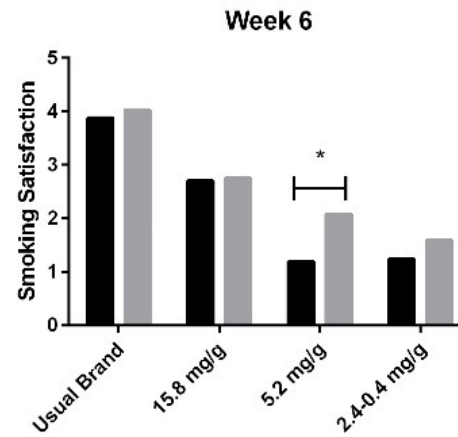
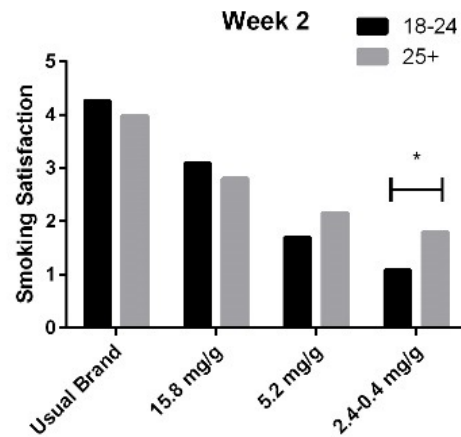
- Secondary analysis found that **18-24 year-olds** found VLNCs less satisfying and rewarding, and smoked fewer CPD, than older adults at Week 2; no differences at Week 6 (Cassidy et al. 2019).

## 4. 20-week exposure

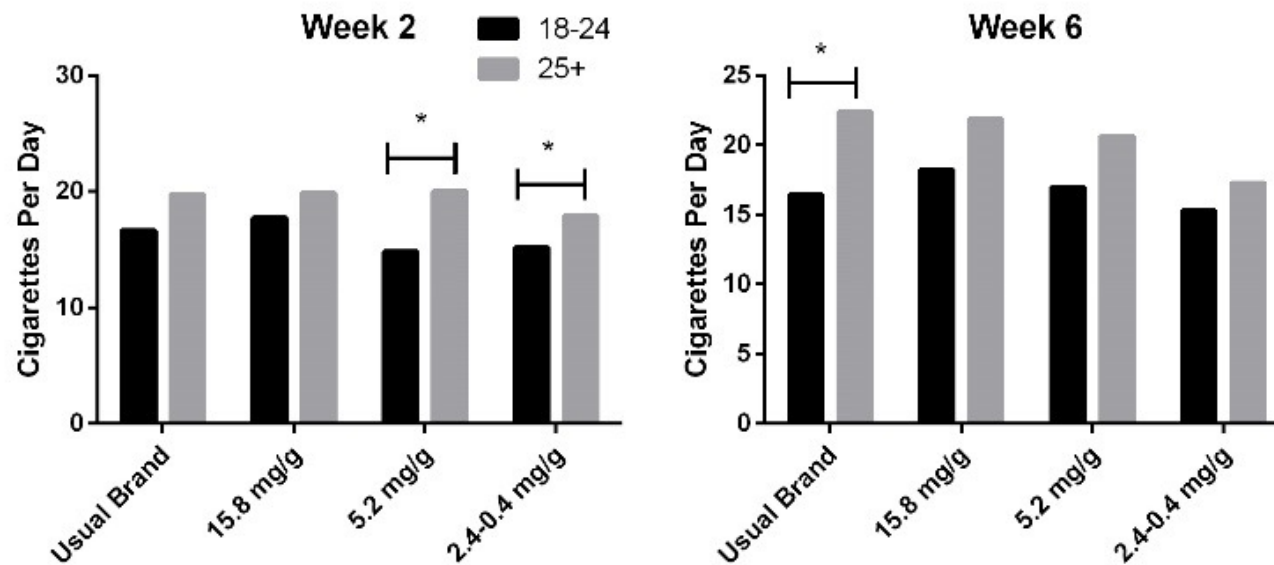
- Secondary analysis of a 20-week RCT found that **age group (18-24 vs. 25+)** did not moderate effects of immediate reduction on CPD reduction; positive subjective effects of cigarettes were lower among 18-24 year-olds (Cassidy et al. 2021).



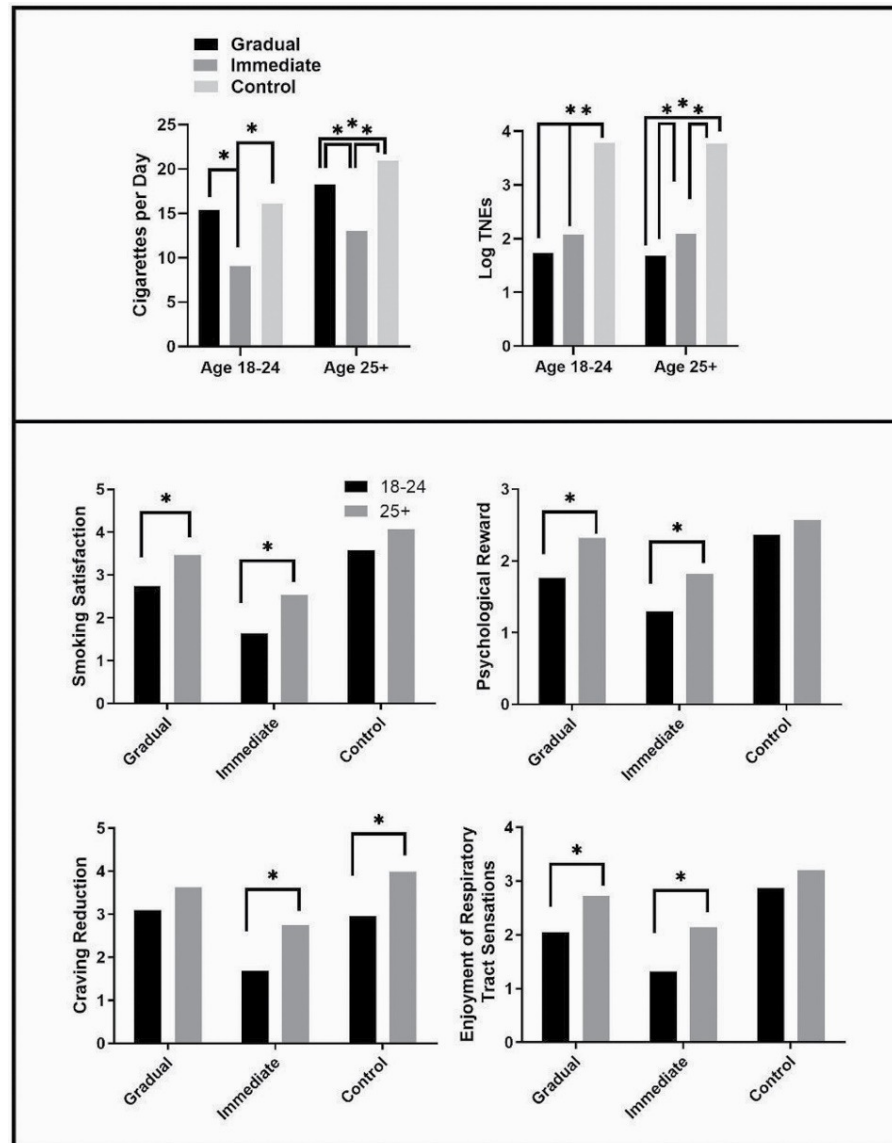
# Younger vs. Older Adults



# Younger vs. Older Adults



# Younger vs. Older Adults



# Populations of Special Relevance to the FDA Center on Tobacco Products

|   |  |   |
|---|--|---|
| <b>Youth</b><br>(Cassidy et al. 2018; 2019; 2020; 2021;<br>Davis et al. 2019) | <b>Socioeconomically<br/>disadvantaged populations</b><br>(Higgins et al. 2017; 2020; Krebs et al.<br>2020; Carroll et al. 2021) | <b>Racial/ethnic minorities</b><br>(Carroll et al. 2021)  |
| <b>Underserved rural<br/>populations</b>                                      | <b>People with MHCs</b><br>(Tidey et al. 2013; 2017; 2019; Higgins et<br>al. 2017; 2020)   | <b>People with SUDs</b><br>(Higgins et al. 2017; 2020; Dermody et<br>al. 2016; 2021; Pacek et al. 2016) |
| <b>Military/veteran<br/>populations</b>                                       | <b>Pregnant women or<br/>women of reproductive<br/>age</b> (Higgins et al. 2017; 2020; Heil et<br>al. 2020)                      | <b>Sexual and gender<br/>minorities</b>   |

# Summary: VLNCs in Vulnerable Populations

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- To date, effects of VLNCs in vulnerable populations are very similar to effects in less vulnerable populations.
  - Reduction in smoking without increasing psychiatric symptoms, substance use or compensatory smoking
- Extent of CPD reduction is ~ 4-7 CPD
  - Studies enroll non-treatment-seeking participants and provide free cigarettes
  - Some indication of increased treatment seeking and quitting
- Supplementary nicotine may help with adherence and enhance reductions in smoking
  - Study of 16-week use of VLNC cigarettes with and without e-cigarettes in 3 vulnerable adult populations is currently underway; lab study of VLNC cigs with and without e-cigs in youth/young adults is underway



# Collaborators

- CENIC team: Eric Donny, Dorothy Hatsukami, Suzanne Colby, Tonya Lane, Rachel Cassidy, Rachel Denlinger-Apte, Patricia Cioe, Joe McClernon, Neal Benowitz, Andrew Strasser, the CENIC Biostats Core and Biomarkers Core, our outstanding staff and trainees, and the rest of the CENIC team.
- UVM TCORS team: Steve Higgins, Diann Gaalema, Stacey Sigmon, Sarah Heil, Andrea Villanti, John Hughes, Jan Bunn, Dustin Lee, our outstanding staff and trainees, and the rest of the UVM TCORS team.

