

# Responses to a Nicotine Product Standard for Cigarettes among Women and Girls

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# Disclosures

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- The research that I will be discussing was funded by grants from NIH and the FDA Center for Tobacco Products.
- I do not receive any funding from tobacco or e-cigarette companies.
- The content is solely my responsibility and does not represent the official views of the NIH or the FDA.



# Tobacco Use among Women

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- The prevalence of smoking in the US is higher among men than women, but the gap has narrowed over time.<sup>1</sup>
- Women are generally less successful at maintaining long-term smoking abstinence than men (more likely to relapse).<sup>2</sup>
- Except for varenicline, current smoking cessation medications are less effective in women.<sup>3,4</sup>
- Men may be more sensitive to the pharmacological effects of nicotine, while women are more sensitive to sensorimotor aspects of smoking.<sup>5,6</sup>
- Interventions that focus exclusively on replacing nicotine, while ignoring sensorimotor aspects of smoking, may be less effective in women.

<sup>1</sup>NHIS data reported annually: *Tobacco Product Use Among Adults - United States*

<sup>2</sup>Smith PH et al. *Prev Med*. 2016 Nov;92:135-140.

<sup>3</sup>McKee SA and McRae-Clark AL. *Biol Sex Differ*. 2022 Jun 27;13(1):34.

<sup>4</sup>Smith PH et al. *Nicotine Tob Res*. 2017 Mar 1;19(3):273-281.

<sup>5</sup>Perkins KA et al. *Nicotine Tob Res*. 1999 Dec;4:301-315

<sup>6</sup>Chaudhri N, et al. *Psychopharmacology (Berl)*. 2005 Jul;180(2):258-66.



# Nicotine Reduction

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- The FDA has regulatory authority over nicotine levels in tobacco, allowing it to reduce, but not eliminate, nicotine in tobacco as appropriate to protect public health.<sup>7</sup>
- The FDA has announced that it plans to move forward with a **reduced-nicotine standard** for cigarettes and other combusted tobacco products.<sup>8</sup>
- Numerous RCTs of very low nicotine content (VLNC) have demonstrated that a reduced-nicotine standard for cigarettes has the potential to reduce dependence and increase cessation.
- Given previous research showing that women are less sensitive to changes in nicotine dose, will men and women differ in their responses to VLNC cigarettes?

<sup>7</sup>H.R.1256 - Family Smoking Prevention and Tobacco Control Act

<sup>8</sup><https://www.fda.gov/news-events/press-announcements/fda-announces-plans-proposed-rule-reduce-addictiveness-cigarettes-and-other-combusted-tobacco>



# Very Low Nicotine Content Cigarettes

## Research Cigarettes

Normal Nicotine

**Nicotine  
Content  
(*mg/g*)  
variable  
15.8**

Nicotine  
Yield (ISO)  
(*mg/cig*)  
variable  
~0.73

Tar  
Yield (ISO)  
(*mg/cig*)  
variable  
~10

Reduced Nicotine

**5.2**

~0.24

~9

Very Low Nicotine

**2.4**

~0.11

~9

Very Low Nicotine

**1.3**

~0.06

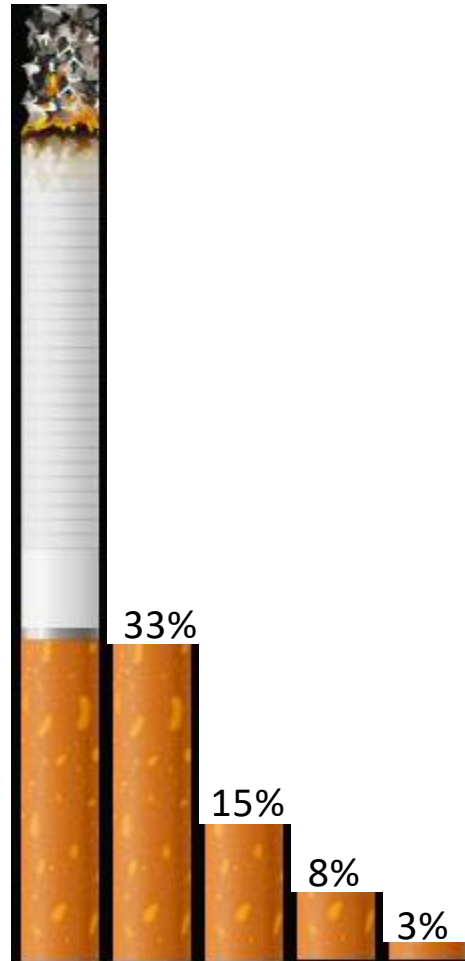
~8

Very Low Nicotine

**0.4**

~0.03

~9 (or 13)



# Spectrum VLNC Trials

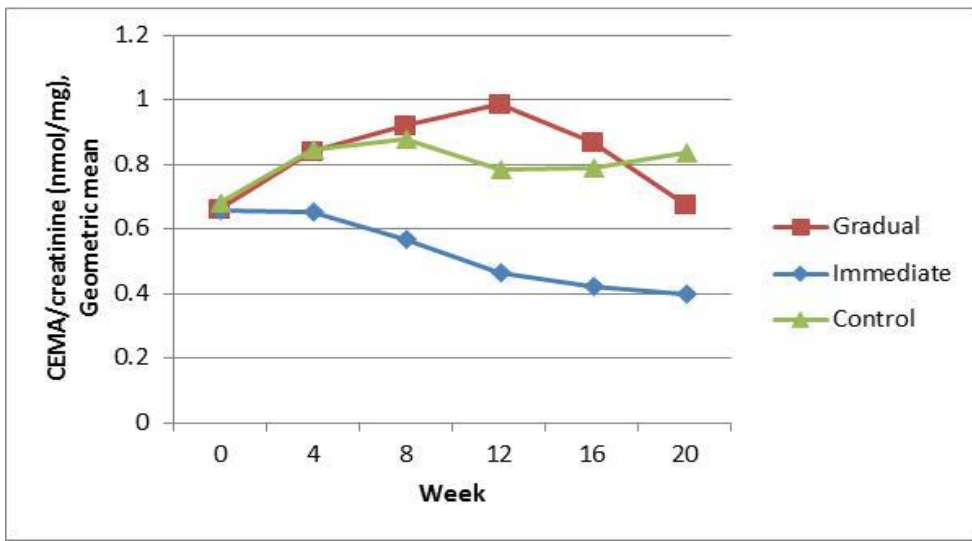
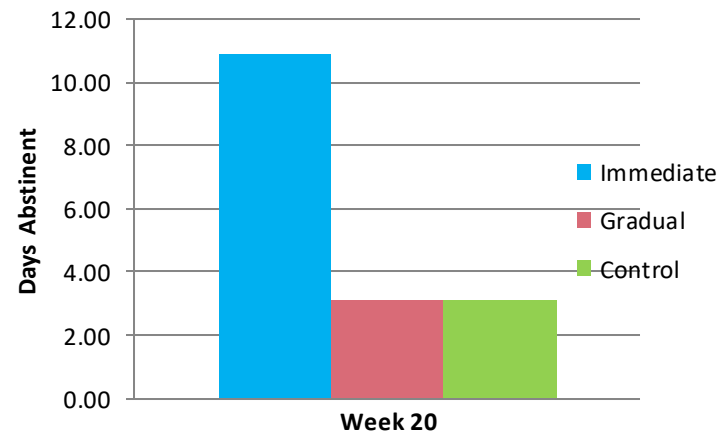
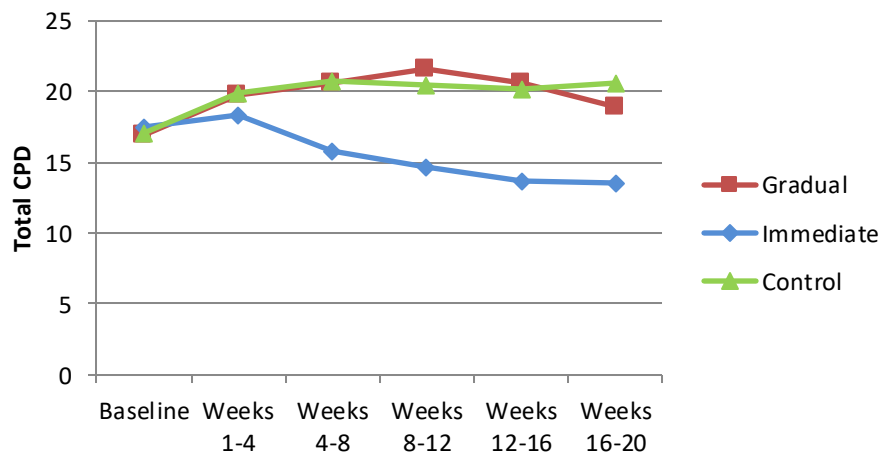
| Study          | Participants      | N    | Duration         | Results  |
|----------------|-------------------|------|------------------|--|
| Donny 2015     | General pop       | 840  | 6 wks            | VLNCs $\leq$ 2.4 mg/g reduced CPD and biomarkers; no mood disturbance or compensatory smoking                  |
| Hatsukami 2018 | General pop       | 1250 | 20 wks           | Immediate reduction group reduced CPD and biomarkers; gradual reduction group did not                          |
| Shiffman 2018  | Non-daily         | 238  | 10 wks           | VLNCs (0.4 mg/g) reduced CPD   |
| Smith 2019     | General pop       | 240  | 7 wks            | VLNCs (0.4 mg/g) and NRT each reduced CPD, but VLNCs + NRT did not outperform VLNCs only.                      |
| Tidey 2019     | SMI               | 58   | 6 wks            | VLNCs (0.4 mg/g) reduced CPD and CO; no compensatory smoking or symptom increases.                             |
| Higgins 2020   | Affective Dis     | 257  | 12 wks           | VLNCs $\leq$ 2.4 mg/g reduced CPD, biomarkers, and dependence; no compensatory smoking; mild mood disturbance. |
| Higgins 2020   | Opioid Use Dis    | 260  | 12 wks           |  |
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| Hatsukami      | General pop       | 438  | 12 wks           | Under review   |



# Effect of Immediate vs Gradual Reduction in Nicotine Content of Cigarettes on Biomarkers of Smoke Exposure

## A Randomized Clinical Trial

Dorothy K. Hatsukami, PhD; Xianghua Luo, PhD; Joni A. Jensen, MPH; Mustafa al'Absi, PhD; Sharon S. Allen, MD; Steven G. Carmella, BA; Menglan Chen, MS; Paul M. Cinciripini, PhD; Rachel Denlinger-Apte, MPH; David J. Drobes, PhD; Joseph S. Koopmeiners, PhD; Tonya Lane, MEd; Chap T. Le, PhD; Scott Leischow, PhD; Kai Luo, PhD; F. Joseph McClernon, PhD; Sharon E. Murphy, PhD; Viviana Paiano, MS; Jason D. Robinson, PhD; Herbert Severson, PhD; Christopher Sipe, MS; Andrew A. Strasser, PhD; Lori G. Strayer, MPH; Mei Kuen Tang, BS; Ryan Vandrey, PhD; Stephen S. Hecht, PhD; Neal L. Benowitz, MD; Eric C. Donny, PhD





# Outcomes from RCTs of VLNC Cigarettes

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- People who smoke who are randomly assigned to VLNC cigarettes for 6+ weeks show significant smoking reductions compared to those who are randomly assigned to NNC cigarettes.
- These effects extend to several vulnerable populations, including people with affective disorders, serious mental illness, opioid use disorders, socioeconomic disadvantage, and youth/young adults.
- There has been no indication of compensatory smoking or increases in other substance use; mild to no mood disturbance across studies.



# Women vs. Men: Potential Outcomes

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- If women are less sensitive to the pharmacological effects of nicotine, will they continue to smoke VLNC cigarettes at the same rate as they did NNC cigarettes? If so, we might see higher CPD and breath CO levels in women assigned to VLNCs compared to men.
- If women are less sensitive to nicotine, they may have fewer problems with strict adherence to VLNCs (less “cheating”). If so, we might see lower levels of nicotine exposure (cotinine/TNE) in women.
- This might be particularly apparent in vulnerable populations, which on the whole may have more difficulty with VLNC adherence due to more severe nicotine dependence.



# Effects of VLNCs in Women vs. Men

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- Women were less sensitive to the effects of nicotine content on positive subjective effects and relief of abstinence-induced negative affect than men.<sup>9,10,11</sup>
- No dose x gender interactions on subjective effects, craving, or withdrawal.<sup>12</sup>
- Women tended ( $p = .06$ ) to have a larger decrease in TNE during a 20-week immediate nicotine reduction trial than men.<sup>13</sup>

<sup>9</sup>Perkins KA, Karelitz JL. *Nicotine Tob Res.* 2015 Apr;17(4):443-8.

<sup>10</sup>Perkins KA, et al. *Nicotine Tob Res.* 2018 Sep 4;20(10):1258-1264.

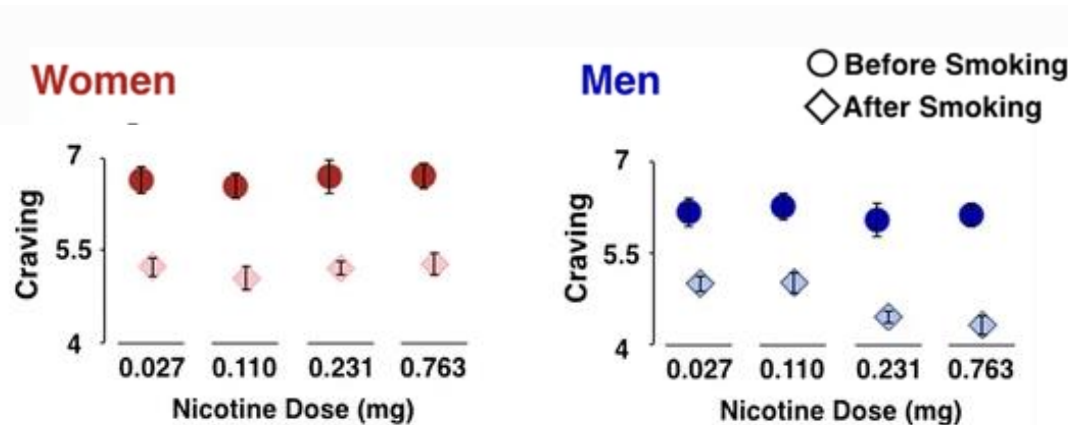
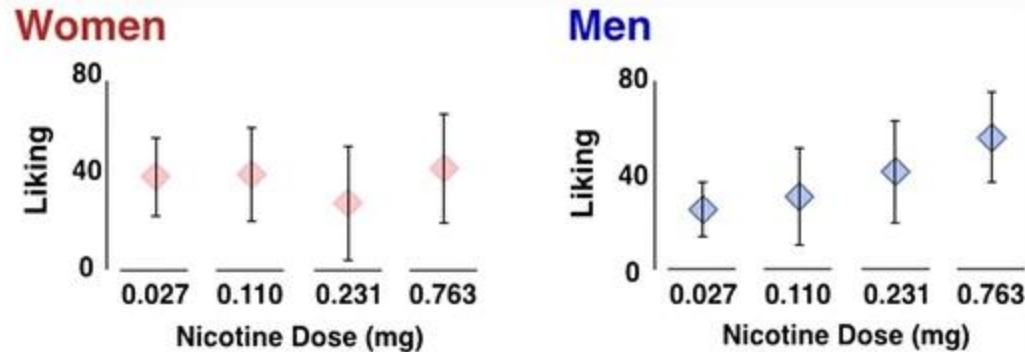
<sup>11</sup>Faulkner P, et al. *Psychopharmacology.* 2018 Jan;235(1):193-202.

<sup>12</sup>Streck JM, et al. *Nicotine Tob Res.* 2020 May 26;22(6):878-884.

<sup>13</sup>Carroll DM, et al. *Drug Alcohol Depend.* 2021 Aug 1;225:108756.



# Effects of VLNCs in Women vs. Men



Faulkner P., et al.  
*Psychopharmacology*. 2018  
Jan;235(1):193-202

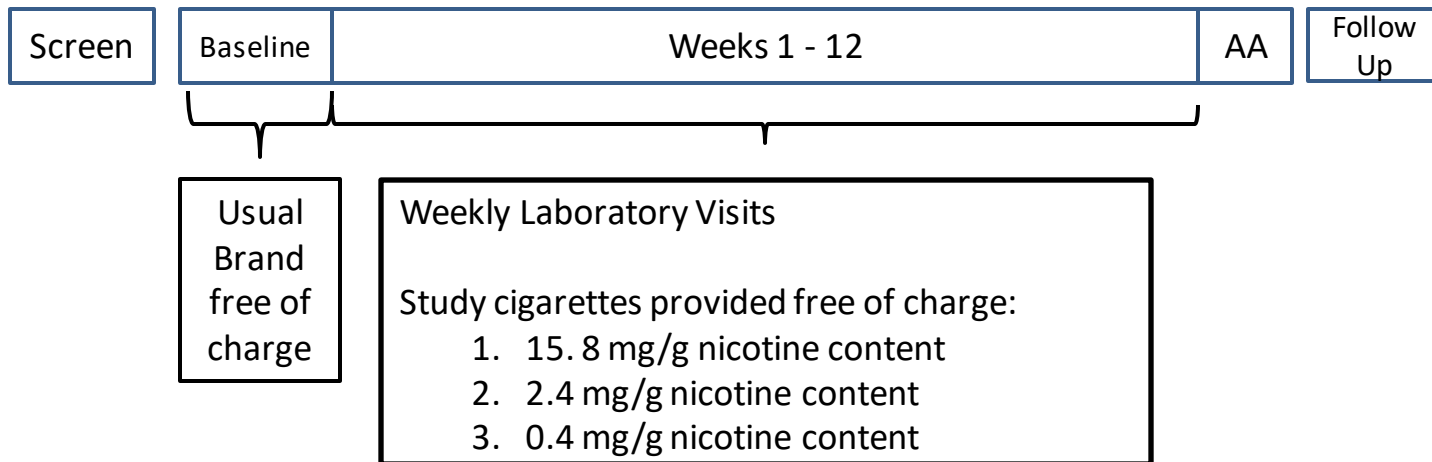


Original Investigation | Substance Use and Addiction

# 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



### 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)

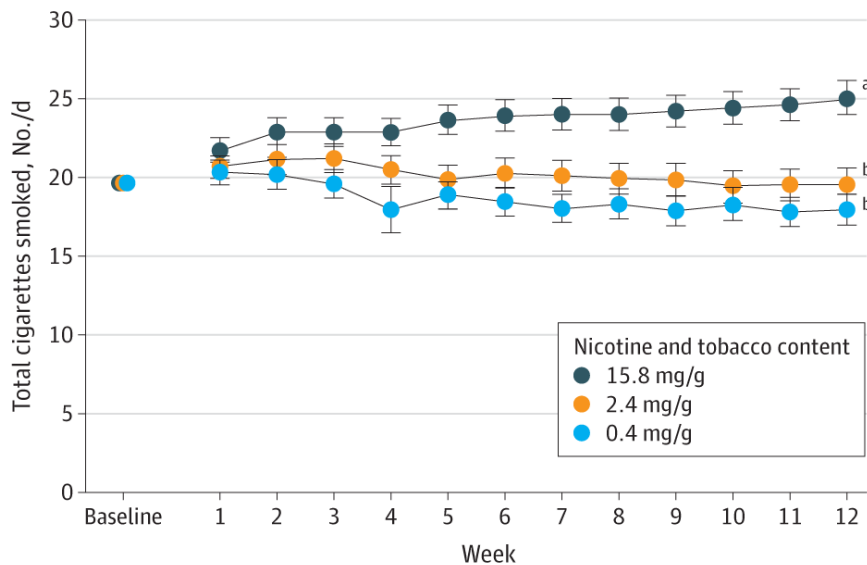


Original Investigation | Substance Use and Addiction

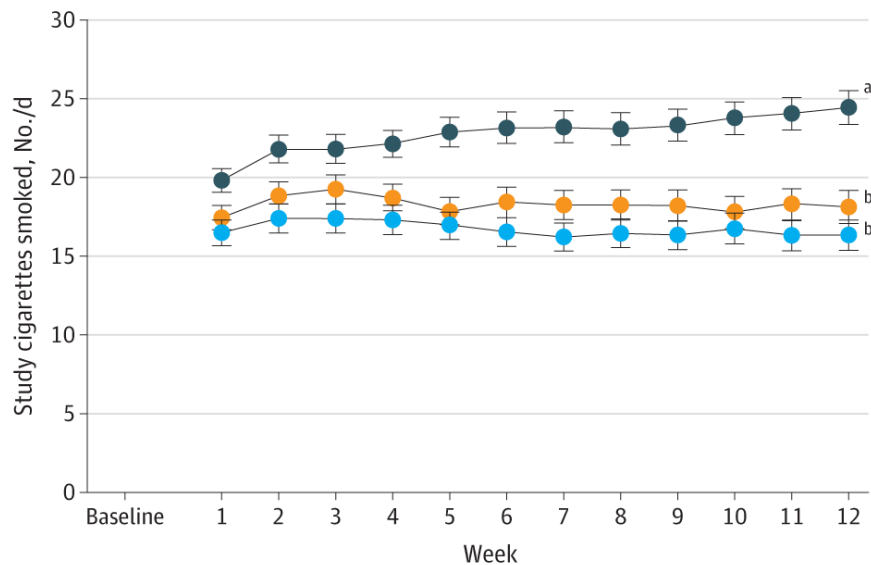
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**A** Total cigarettes

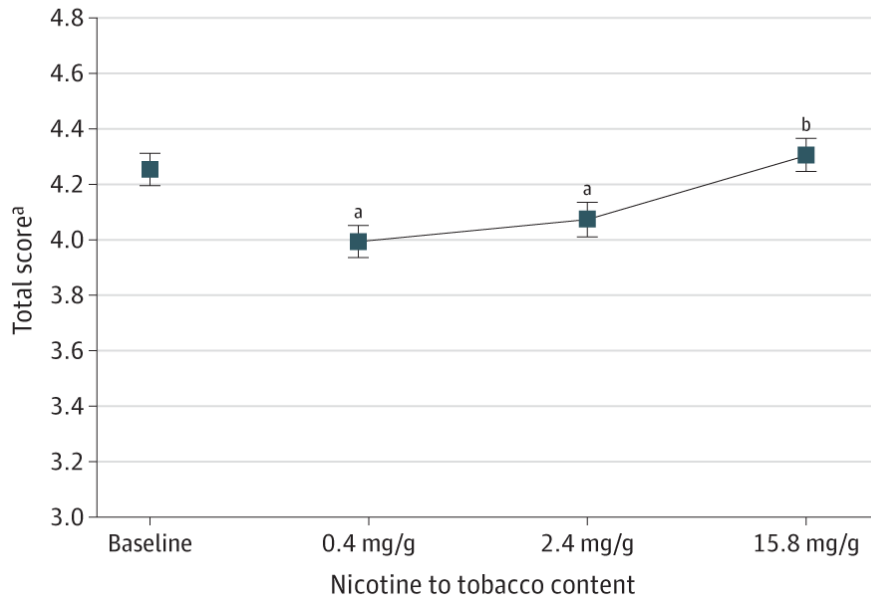


**B** Study cigarettes

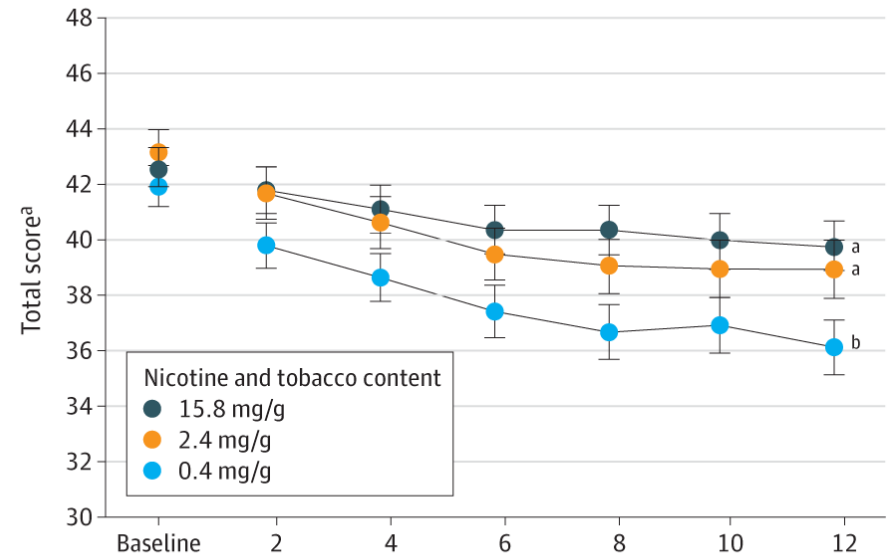


# Effects on Dependence

**A** Fagerström test for nicotine dependence

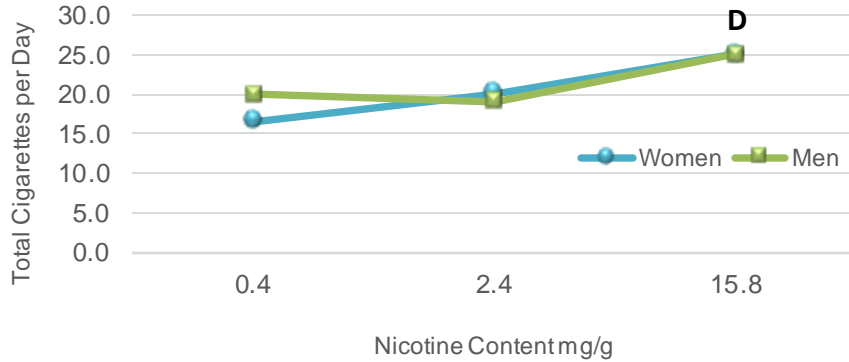


**B** Wisconsin inventory of smoking dependence motives

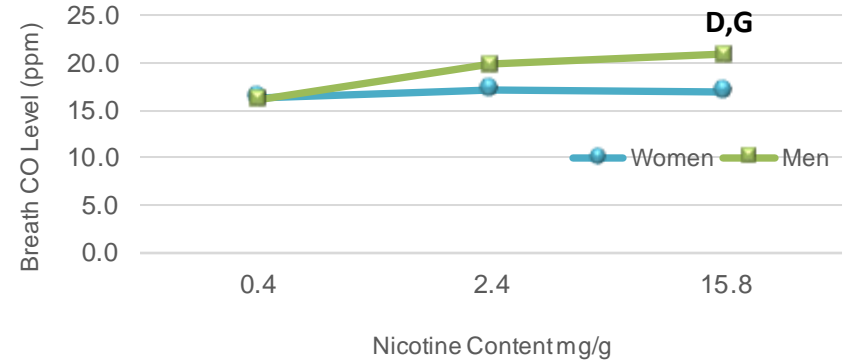


# Women vs. Men

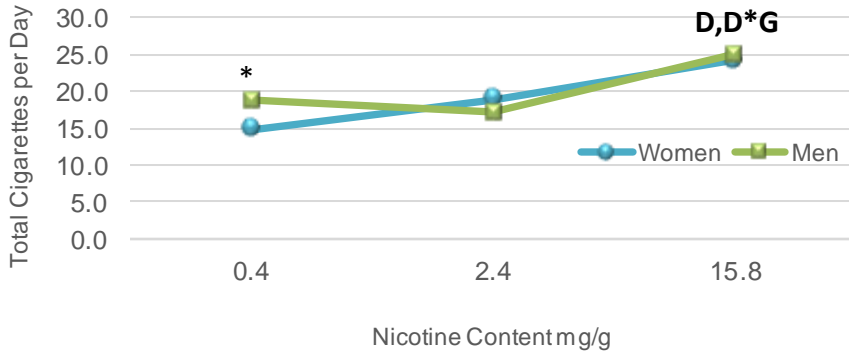
## Total CPD at Week 12



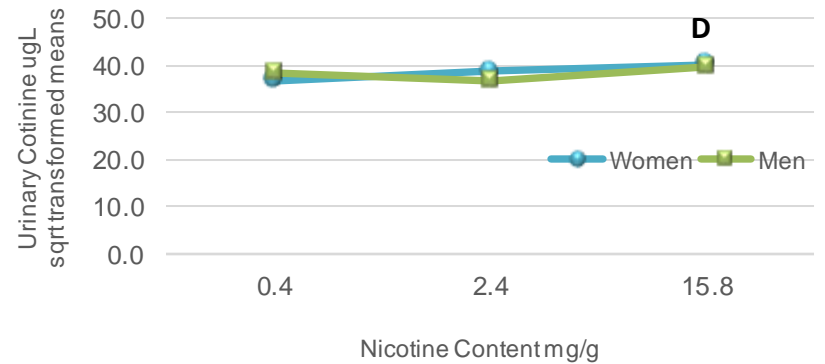
## Breath CO Level at Week 12



## Study CPD at Week 12



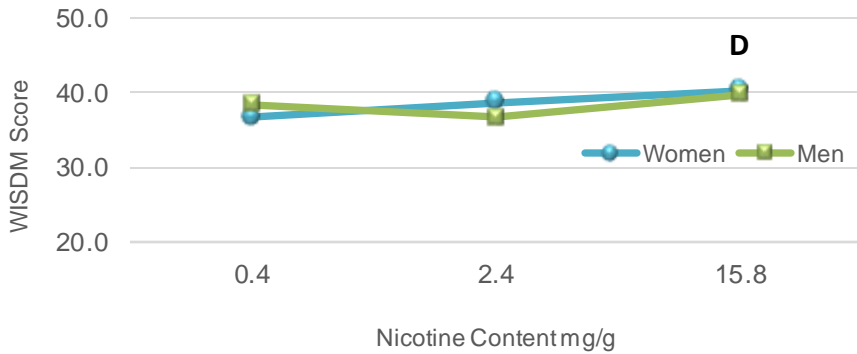
## Urinary Cotinine



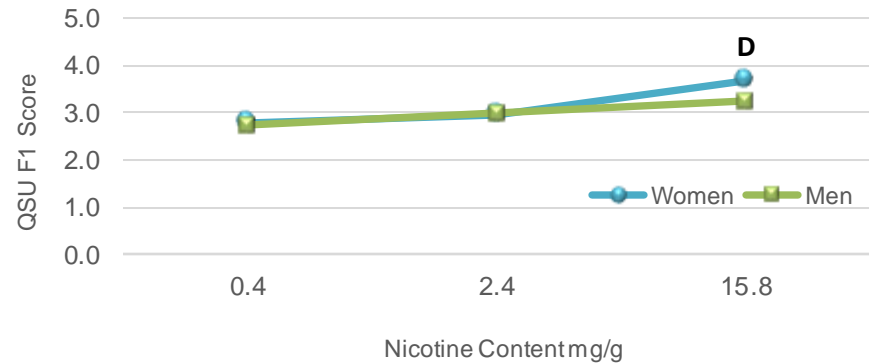


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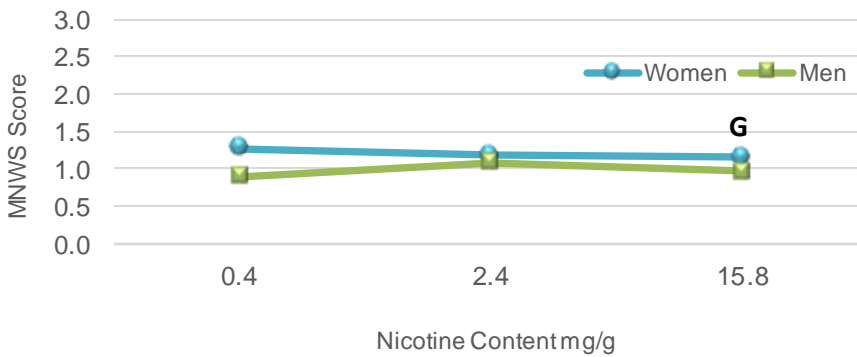
## Cigarette Dependence (WISDM)



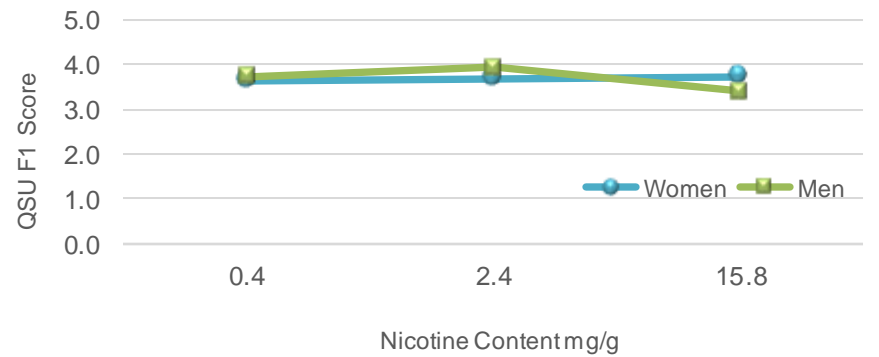
## Craving for Study Cigs (QSU F1)



## Nicotine Withdrawal (MNWS)



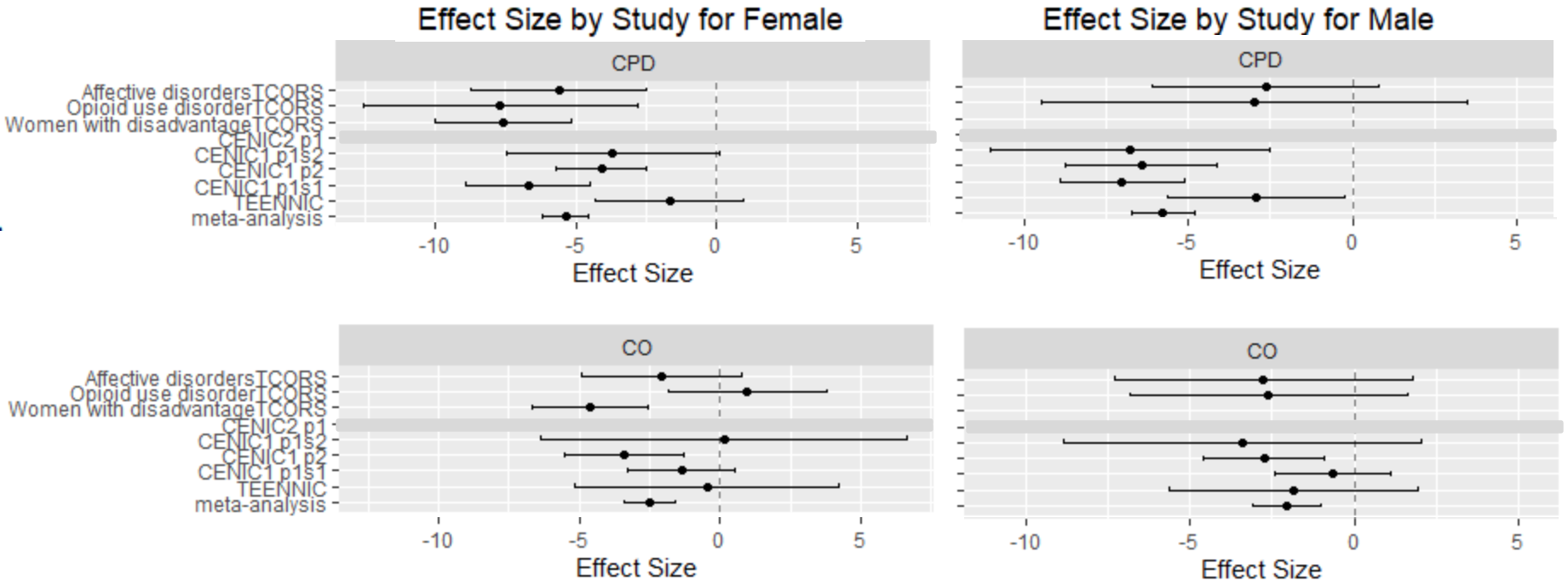
## Craving for Usual Brand (QSU F1)



# VLNC Trials included in Meta-analysis

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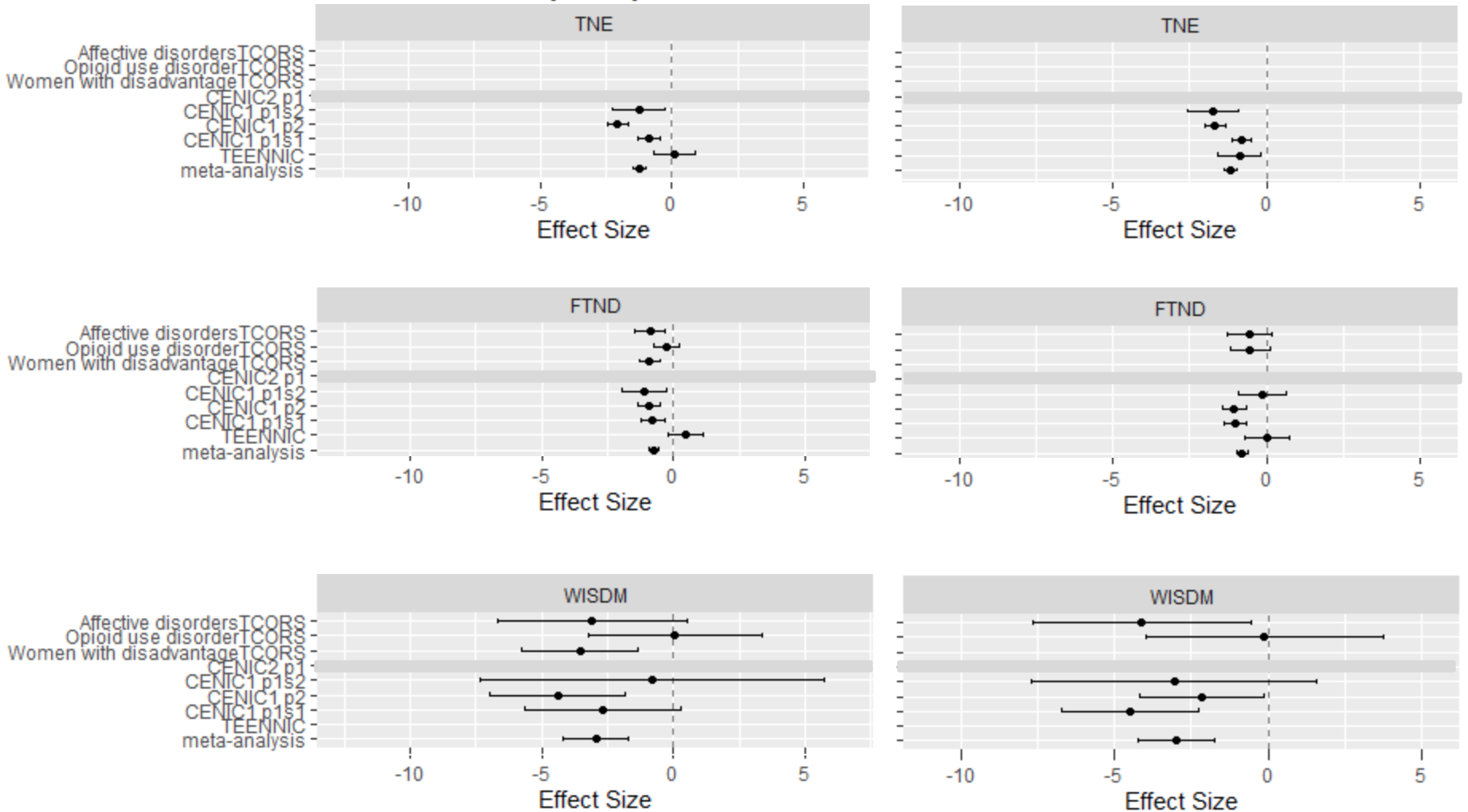
# Meta-analysis outcomes: Women vs. Men



# Meta-analysis outcomes: Women vs. Men

Effect Size by Study for Female

Effect Size by Study for Male



# Discussion

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## Limitations

- These analyses are preliminary.
- Early studies only asked participants to respond male vs. female. Current studies ask more nuanced questions regarding gender at birth vs. current gender identification.

## Conclusions

- Based on these analyses, there seems to be little to no evidence of differential responses to VLNC cigarettes over a 6+ week period in women vs. men.
- These results provide reassurance that both women and men would benefit from a reduced-nicotine standard for cigarettes.



# Acknowledgments

- Special thanks to Mike DeSarno at UVM for the secondary analysis of Higgins et al. 2020 data and Joe Koopmeiners and Ziyu Ji at UMN for conducting the meta-analysis of CENIC and UVM TCORS trials.
- CENIC team: Eric Donny, Dorothy Hatsukami (Center PIs), the amazing CENIC faculty, staff, and trainees, and our research participants.
- UVM TCORS team: Steve Higgins (Center PI), the outstanding UVM TCORS faculty, staff, and trainees, and our research participants.
- Research funding from the NIH and FDA Center for Tobacco Products

