



Very Low Nicotine Content Cigarettes in the Context of Non-Combusted Nicotine Products: Findings and Implications for Public Health Policy

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Tobacco Online Policy Seminar (TOPS) series
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Disclosures

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“The cigarette should be conceived not as a product but as a package. The product is nicotine...Think of the cigarette pack as a storage container for a day’s supply of nicotine...Think of a cigarette as a dispenser for a dose unit of nicotine. Think of a puff of smoke as the vehicle of nicotine.” (Philip Morris, 1972)

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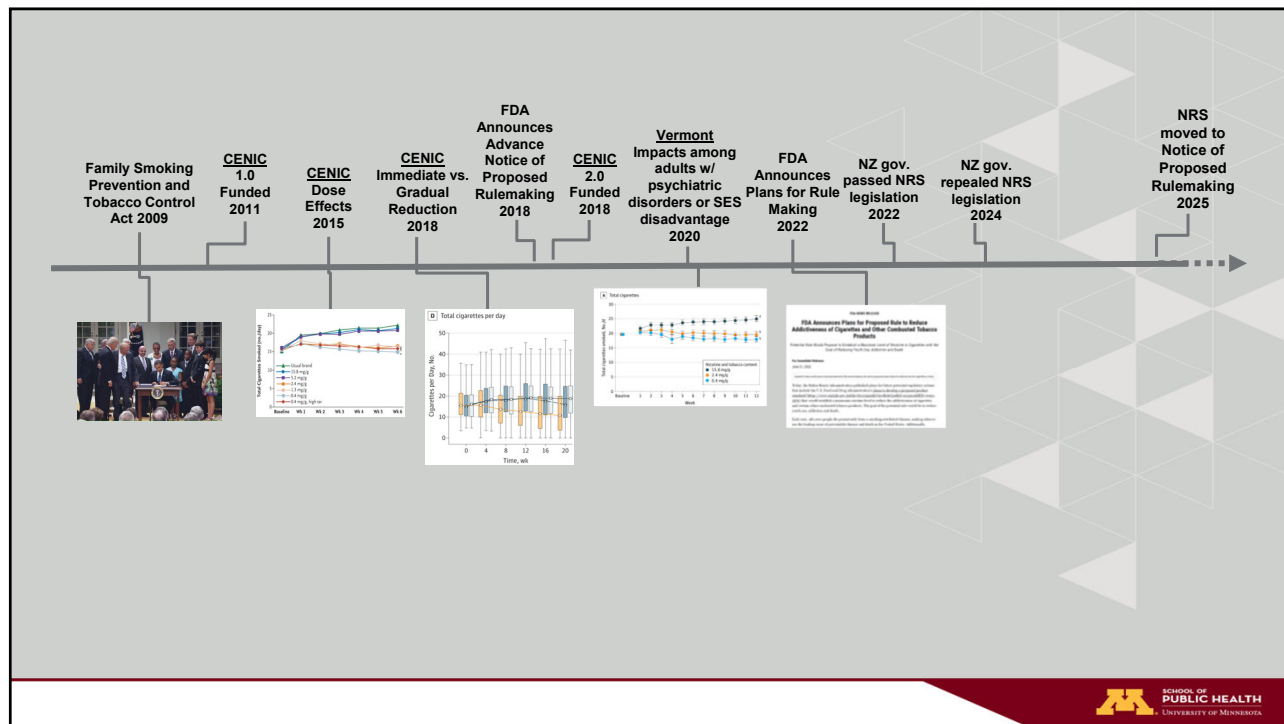
The NEW ENGLAND
JOURNAL of MEDICINE

SOUNDING BOARD FREE PREVIEW

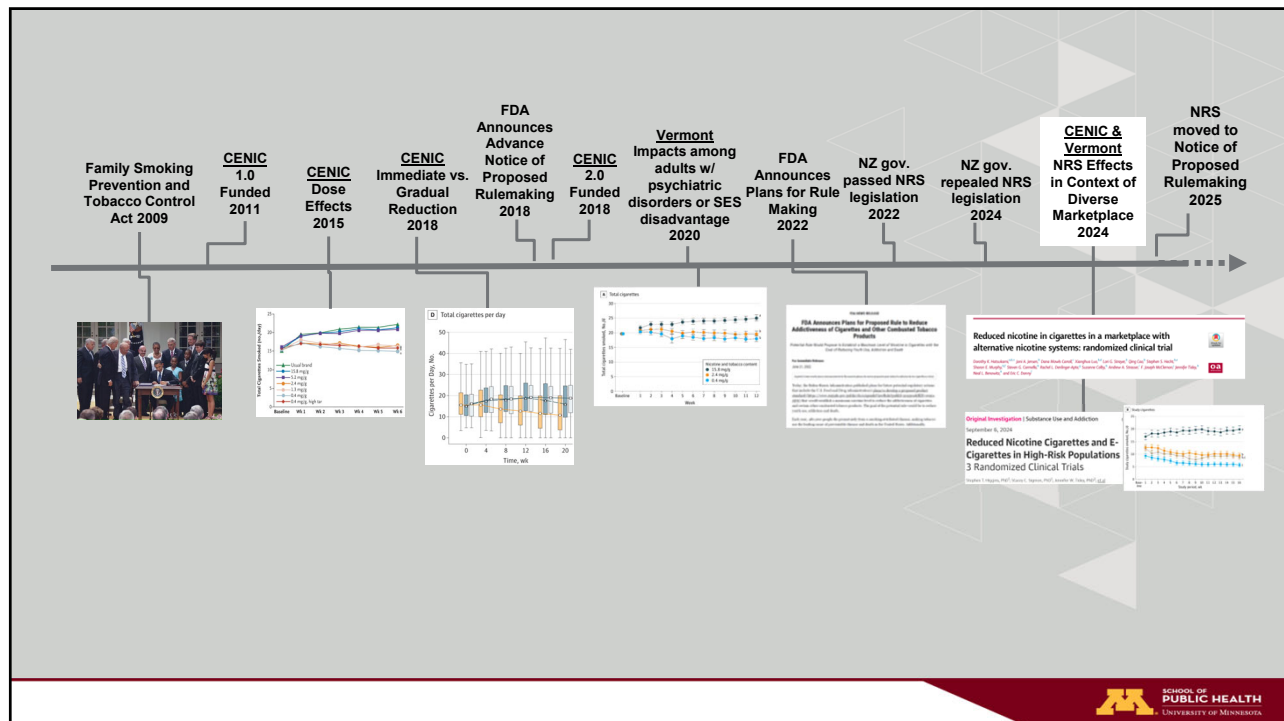
Establishing a Nicotine Threshold for Addiction -- The Implications for Tobacco Regulation

Neal L. Benowitz, M.D., and Jack E. Henningfield, Ph.D.

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“The Marketplace Study”




Reduced nicotine in cigarettes in a marketplace with alternative nicotine systems: randomized clinical trial

Deborah K. Hatsukami^{1,2,3,4}, Joni A. Jensen⁵, Dana Mowle Carroll⁶, Xianghui Luo^{1,2}, Lori G. Staryan⁷, Qing Cao⁸, Stephen S. Hecht^{1,2}, Sharon E. Murphy^{1,2}, Steven G. Carmella⁹, Rachel L. Denlinger-Ayala⁹, Suzanne Colby⁹, Andrew A. Stussman⁹, F. Joseph McClellan⁹, Jennifer Tisdley⁹, Neil L. Benowitz¹⁰, and Eric C. Dorsey¹¹

Check for updates 

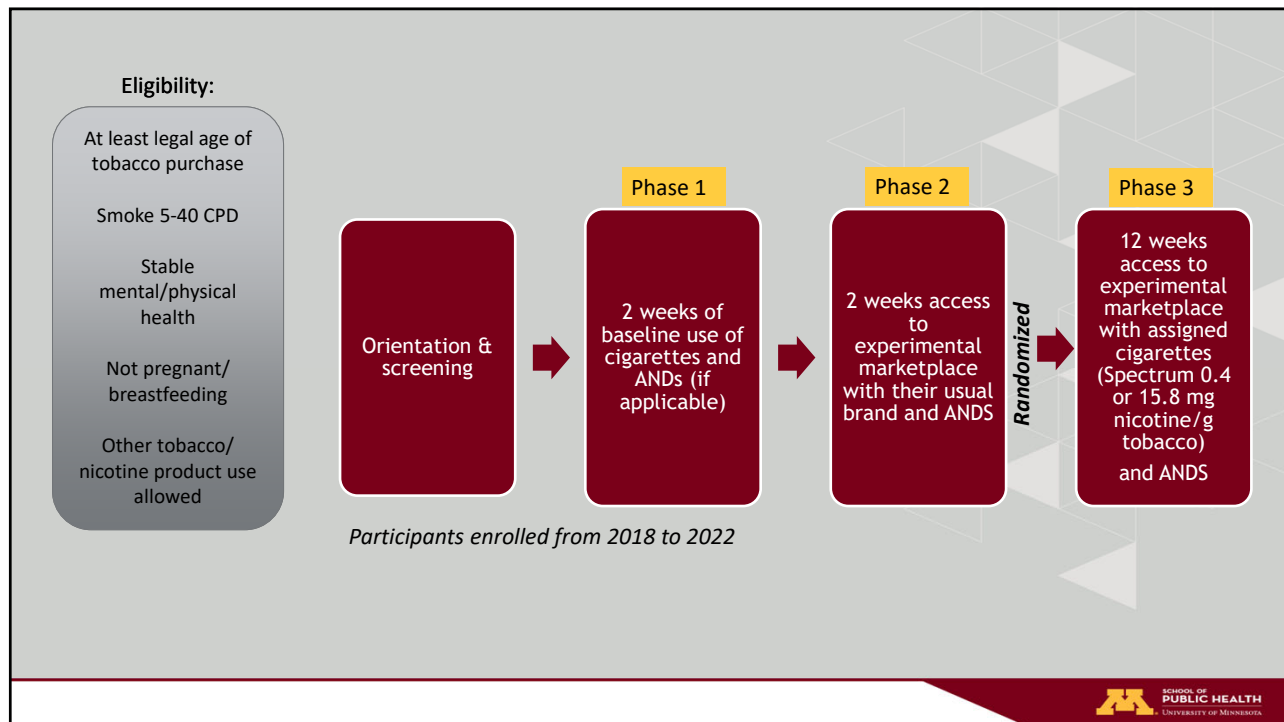
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Main objective

- To examine the effects of VLNC vs. NNC cigarettes on smoking behavior and toxicant exposure in a marketplace containing non-combusted ANDS simulating the real-world environment.
 - ANDS: E-cigarettes, snus, snuff/“dip”, nicotine pouches, medicinal nicotine

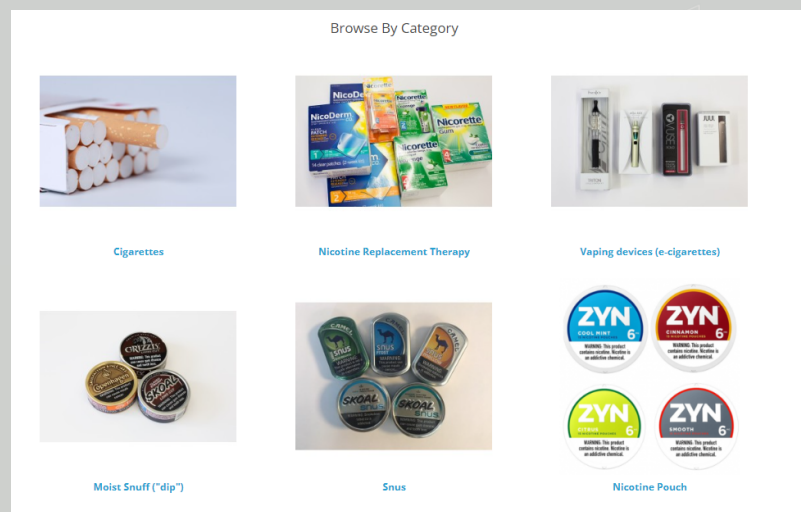
In other words, will mimicking a nicotine product standard reduce harm from smoking when compared with the status quo diverse marketplace?

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ANDS and the Experimental Marketplace

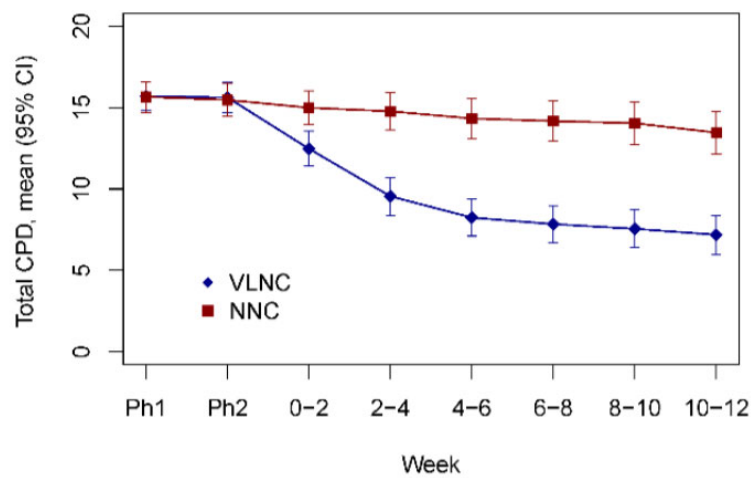


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Pause for questions

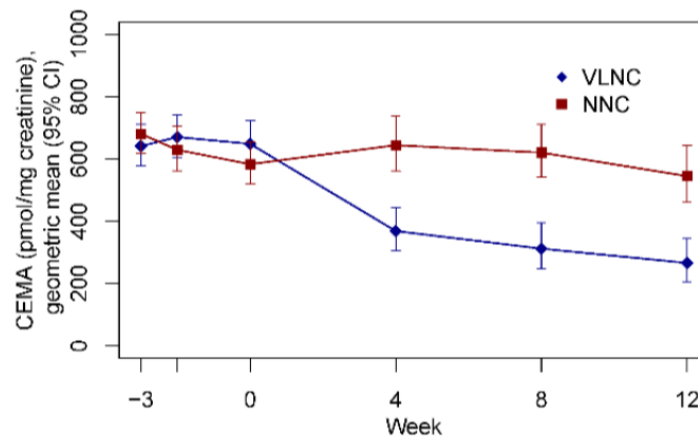
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Results: Cigarettes per day (Primary endpoint)



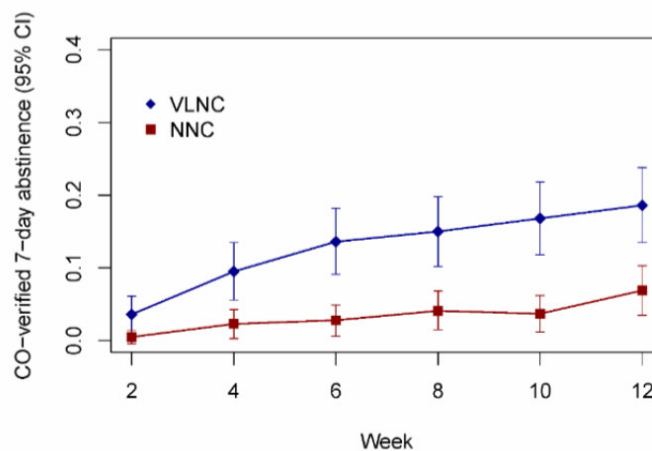
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Results: Urinary CEMA, biomarker of acrylonitrile (respiratory toxicant)



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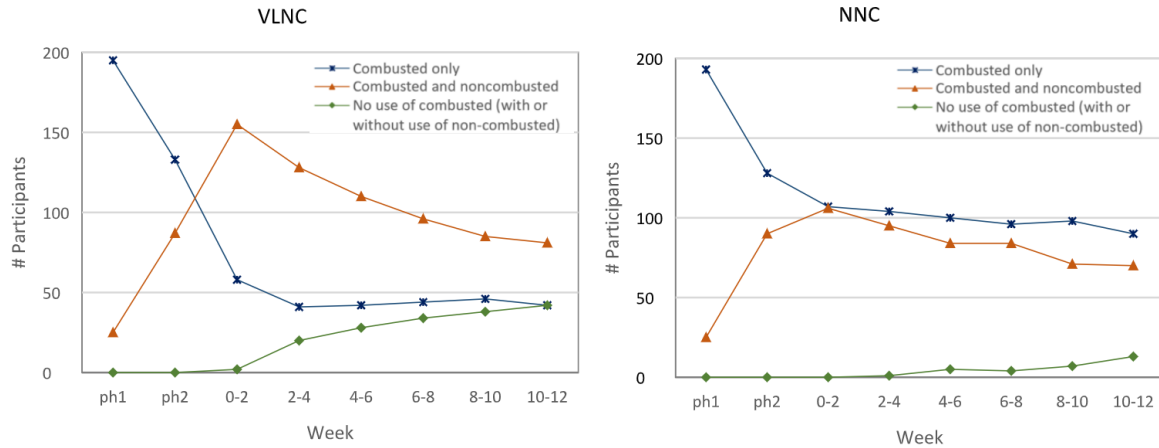
Results: Proportion of participants with CO-verified (≤ 6 ppm) smoking abstinence



VLNC: 81% used ANDS
NNC: 64% used ANDS

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Results: Patterns of use



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Pause for questions

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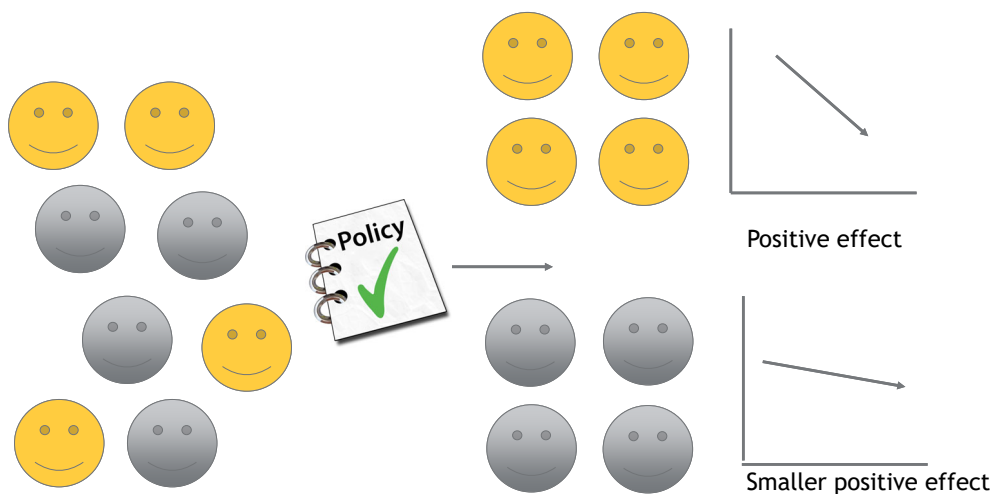
Additional key question

Will certain groups of people who smoke benefit less than others?

Focused on age, education, and racial identity.

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**Between group differences can generate hypotheses
that inform within-group studies/tailored efforts**



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Why examine moderation by these characteristics?

Provides a health equity lens.

- Slowly declining smoking prevalence among those of older age and those of lower educational attainment.
- Those who have been racialized as Black are more likely to die due to smoking.

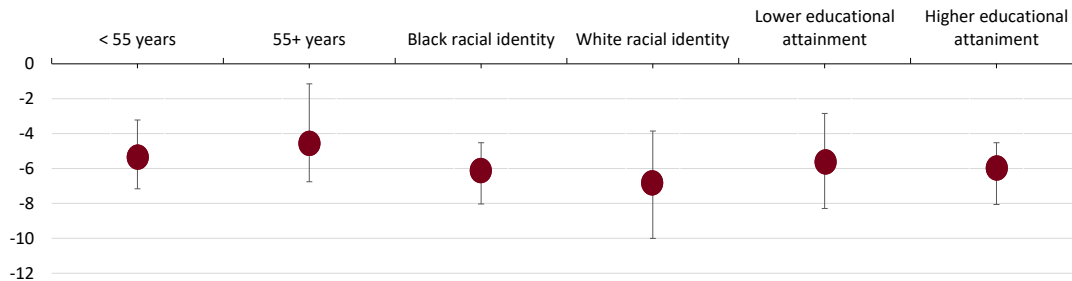
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Methods

- Secondary data analyses of the Marketplace Study (Hatsukami et al., 2024).
- Exploring for moderation.
 - Point estimates and confidence intervals and tests for interaction.

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Mean difference in CPD (week 12) comparing VLNC vs NNC cigarette conditions



Takeaway: No evidence for moderation for any groups with VLNC resulting in reductions in CPD for all

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Incidence rate ratios of smoke-free days comparing VLNC vs NNC during the intervention

< 55 years	55 + years	Black racial identity	White racial identity	Lower education	Higher education
5.08 (95% CI: 2.86, 9.00)	2.27 (95% CI: 0.83, 6.35)	5.27 (95% CI: 2.01, 13.80)	4.23 (95% CI: 2.21, 8.07)	3.24 (95% CI: 0.97, 10.80)	4.57 (95% CI: 2.65, 7.89)

Takeaway: Evidence for moderation by age only; VLNC resulting in higher rate of smoke-free days in all groups

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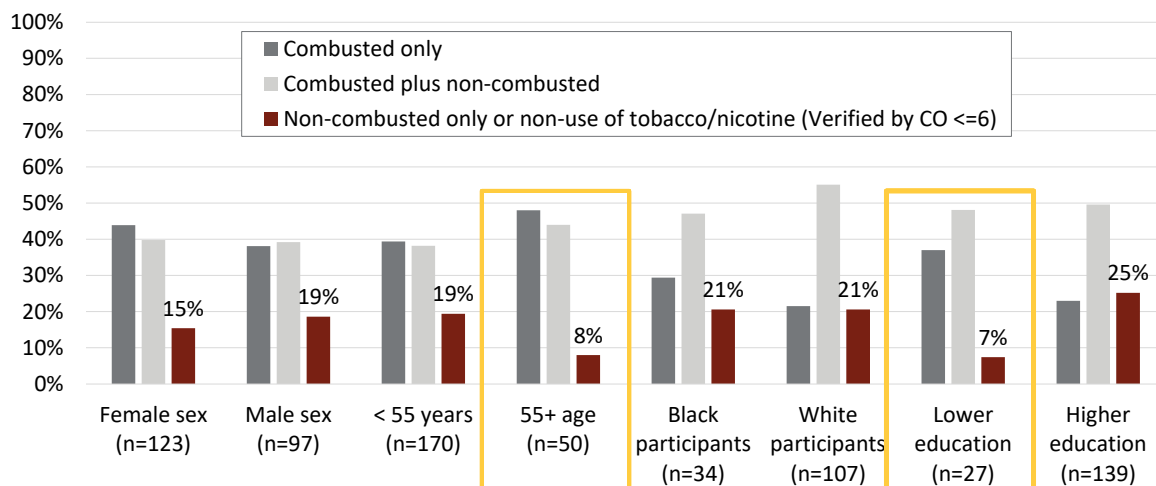
**Geometric mean ratio (VLNC : NNC) in
urinary biomarker CEMA (pmol/mg creatinine)
(week 12)**

< 55 years	55 + years	Black racial identity	White racial identity	Lower education	Higher education
0.47 (95% CI: 0.35, 0.63)	0.87 (95% CI: 0.53, 1.43)	0.49 (95% CI: 0.26, 0.91)	0.54 (95% CI: 0.39, 0.74)	0.74 (95% CI: 0.43, 1.30)	0.42 (95% CI: 0.30, 0.59)

Takeaway: Evidence for moderation by age and a signal for moderation by education

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End of study product use in VLNC condition



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Implications of moderator analyses

- Moderation by age and a signal by education.
- Majority who quit VLNC cigarettes switched to an e-cigarette. This occurred less so in those of older age and lower education.
 - In post-hoc analysis, older age and lower education groups had a ratio of ~3 for the number of close friends who use cigarettes vs e-cigarettes. Their counterparts had a ratio of ~2.
 - Social norms of tobacco product use may impact VLNC use behaviors.

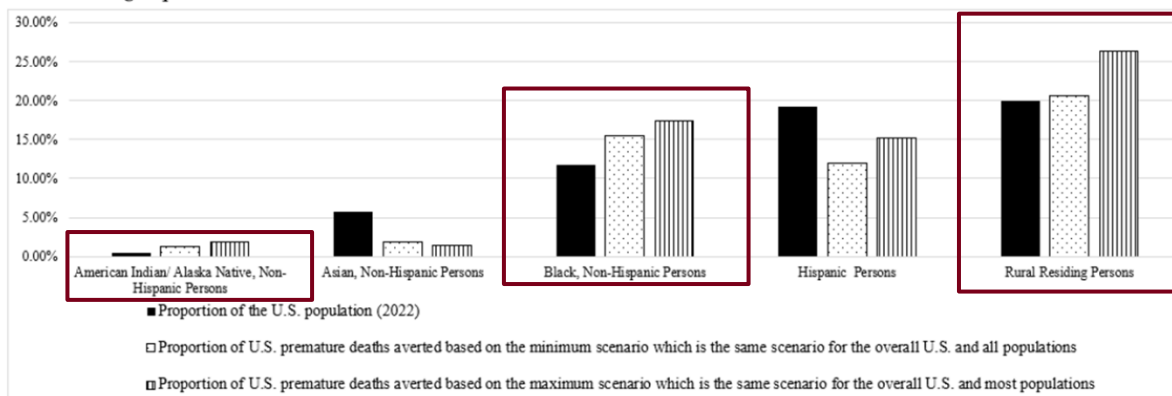


Takeaway: Those of older age and lower educational attainment may need more support (e.g., education, referral to quitting resources) to quit VLNC cigarettes.

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A pro-health equity policy

Figure 1. Proportion of the U.S. Population and of Premature Deaths Averted for U.S. Racial / Ethnic Minoritized Populations and the Rural Residing Population

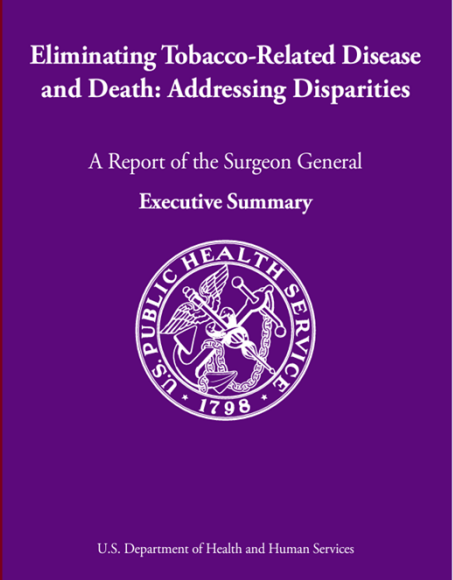


Collaboration with David Mendez, Thuy Le, Joe McClernon

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“Reducing nicotine in cigarettes and other combustible tobacco products to minimally addictive or nonaddictive levels should reduce tobacco use among many population groups experiencing tobacco-related disparities.”

--2024 Surgeon General report



U.S. Department of Health and Human Services

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Conclusions and Implications

- A nicotine reduction standard implemented in a diverse marketplace is anticipated to reduce smoking and harmful exposures.
- Older age and lower education groups may benefit less so from than their counterparts.
- Not a “silver bullet”: Dual use/exclusive smoking still common.
- Implement as part of a comprehensive plan that includes cessation education, access to medications, and surveillance (Hatsukami et al., 2022).
 - Another promising avenue aligns with the FDA CTP’s 2023 Strategic Plan, which is to educate about the relative risks of tobacco products and complete switching.

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Thank you.



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Additional slides as needed



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Will people just smoke more?



SRNT 2024 SYMPOSIA

SYM4-3

**MINIMAL EVIDENCE OF COMPENSATORY SMOKING DURING
CLINICAL TRIALS OF VERY LOW NICOTINE CONTENT CIGARETTES:
A MACHINE-LEARNING APPROACH**

Joseph S. Koopmeiners¹, Ziyu Ji¹, Rachel L. Denlinger-Apte², David M. Vock¹, Jack M. Wolf¹, Rachel N. Cassidy³, Suzanne M. Colby³, Eric C. Donny², Stephen T. Higgins⁴, Jennifer W. Tidey⁵, Dorothy K. Hatsukami¹. ¹University of Minnesota, ²Wake Forest University School of Medicine, ³Brown University, ⁴University of Vermont, ⁵Brown University School of Public Health.

- Analyzed data from nine trials (n= 2396) comparing participants assigned to VLNC cigarettes (0.4 mg/g) or normal nicotine content (NNC) cigarettes.
- Individual treatment effects ranged from a 30 CPD decrease to a 2 CPD increase when randomized to VLNC cigarettes. Average decrease of 6 CPD.
- Estimated <1% of PWS would smoke more when assigned to VLNC cigarettes.

Takeaway: Nearly all PWS will reduce, not increase, their smoking



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Substitution with cannabis

- Secondary analysis (Meier et al. 2023) of a 20-week VLNC study confirmed cannabis use at baseline (THC in urine). Found co-users of cigarettes and cannabis may experience small increases in cannabis (~2-3 more days per year).
- Preliminary analyses of the Marketplace Trial found no increase in cannabis use in VLNC versus NNC (personal communication: Dr. Emily Hackworth)
- No increase in cannabis use with VLNC cigarettes observed in a secondary analysis (Gaalema et al. 2022) of three VLNC trials conducted by the Vermont TCORS.

Takeaway: no concerning increases in cannabis use is expected; surveillance would be particularly important due to the dramatic changes in legalization since these studies were conducted.



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Substitution with alcohol

- Secondary analysis (Dermody et al. 2016) of a 6-week VLNC study ...
 - No evidence for increases in alcohol use overtime and instead supports that VLNC cigarettes may contribute to reductions in alcohol use overtime.
 - Regarding binge drinking, there was no differences between the VLNC and NNC conditions at end of study.
 - There was a non-significant ($p=0.08$) increase in binge drinking in the 2 weeks after assignment to VLNC cigarettes, which corresponded to the peak of withdrawal symptoms.
- Findings on overall alcohol use correspond to preliminary analyses of the Marketplace Trial (personal communication: Dr. Emily Hackworth) and a secondary data analysis (Gaalema et al. 2022) of three VLNC trials conducted by the Vermont TCORS.

Takeaway: potential for increased binge drinking in the short-term but in the longer-term no differences in binge or overall drinking.



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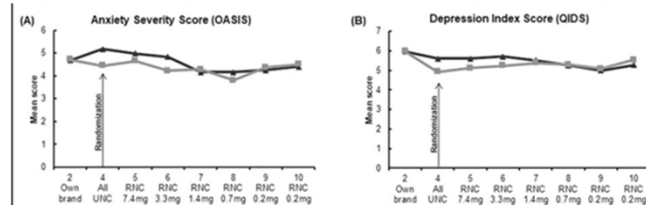
What about exacerbating mental health conditions?

PLOS ONE

RESEARCH ARTICLE

The effects of reduced nicotine content cigarettes on biomarkers of nicotine and toxicant exposure, smoking behavior and psychiatric symptoms in smokers with mood or anxiety disorders: A double-blind randomized trial

Jonathan Foulds^{1*}, Susan Veldheer^{1,2}, Gladys Pachas^{3,4}, Shari Hrabovsky^{1,5}, Ahmad Hameed⁶, Sophia I. Allen¹, Corinne Cather^{3,4}, Nour Azzouz^{3,4}, Jessica Yingst¹, Erin Hammett¹, Jennifer Modesto¹, Nicole M. Krebs¹, Courtney Lester¹, Neil Trushin¹, Lisa Reinhart¹, Emily Wasserman¹, Junjia Zhu¹, Jason Liao¹, Joshua E. Muscat¹, John P. Richie, Jr.¹, A. Eden Evins^{3,4}



Takeaway: no evidence that VLNC cigarettes caused worsening mental health problems.