



**UW Center for
Tobacco Research and Intervention**

UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH

The real-world impact of three alternate nicotine delivery products on combustible cigarette use

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Public Health Need

- Reduce commercial combustible cigarette use
 - Leading preventable cause of death and disease in the U.S.
 - Commercial tobacco kills more than 8 million people in the world every year – and cigarette smoking is the most common form of tobacco use
- Public health strategies
 - Prevention
 - Taxation
 - Cessation
 - Regulatory



Cessation Strategies

- Even with evidence-based smoking cessation pharmacotherapy and counseling, only 1 in 5 people who smoke sustain abstinence
 - Pharmacotherapies tend to be nicotine agonists (i.e., nicotine replacement therapy, varenicline, bupropion) and focus on reducing abstinence-based withdrawal, including cravings, and on reducing the reward value of nicotine
 - Counseling focuses on developing coping skills (e.g., avoiding smoking cues and contexts, developing strategies to cope with negative affect and cravings) and social support
- Are we missing something?

Cues and Classical Conditioning

- After repeated pairings between an unconditioned stimulus (UCS; nicotine) and conditioned stimuli (CS; behavioral and sensory cues associated with smoking), the drug-associated cues themselves acquire hedonic or motivational significance, making them conditioned reinforcers
- Smoking cessation counseling typically focuses on avoiding cues to smoke or trying to find an alternate oral stimulus such as chewing gum or sucking on a straw
- Are we adequately addressing the conditioned reinforcement of smoking-related cues that sustain smoking behavior?

U.S. Regulatory Strategies

- Focus on regulating nicotine *per se*
 - Nicotine is the addictive agent



- Allow sale of nicotine delivery systems that present modified risk
 - E-cigarettes



- Reduce the nicotine content in combustible cigarettes to non-addictive levels
 - Very low nicotine cigarettes (VLNCs)



Alternative Products

- VLNCs
 - Minimal nicotine
 - Identical cues and behavioral experience identical to smoking conventional cigarettes (e.g., lighting the cigarette, hand to mouth motion, the visual and sensory experiences of inhaling and exhaling smoke albeit without the same “throat hit”)
- E-cigarettes
 - Nicotine
 - Some similar cues and behavioral experiences (e.g., hand to mouth motion, inhalations) but not all (e.g., no lighting, no smoke off the end of the device)

Aims and Hypotheses

- Aim 1: Examine the ability of VLNCs and e-cigarettes to serve as a substitute for smokers' usual brand cigarettes compared to each other and to no alternative product use
 - Hypothesis 1: VLNCs and e-cigarettes will reduce the number of conventional cigarettes smoked compared to no study product
 - Hypothesis 2: E-cigarettes will serve as a better substitute than VLNCs
- Aim 2: Determine whether these effects are influenced by steady-state nicotine
 - Hypothesis 3: An active nicotine patch will enhance the ability of VLNCs and e-cigarettes to serve as a substitute

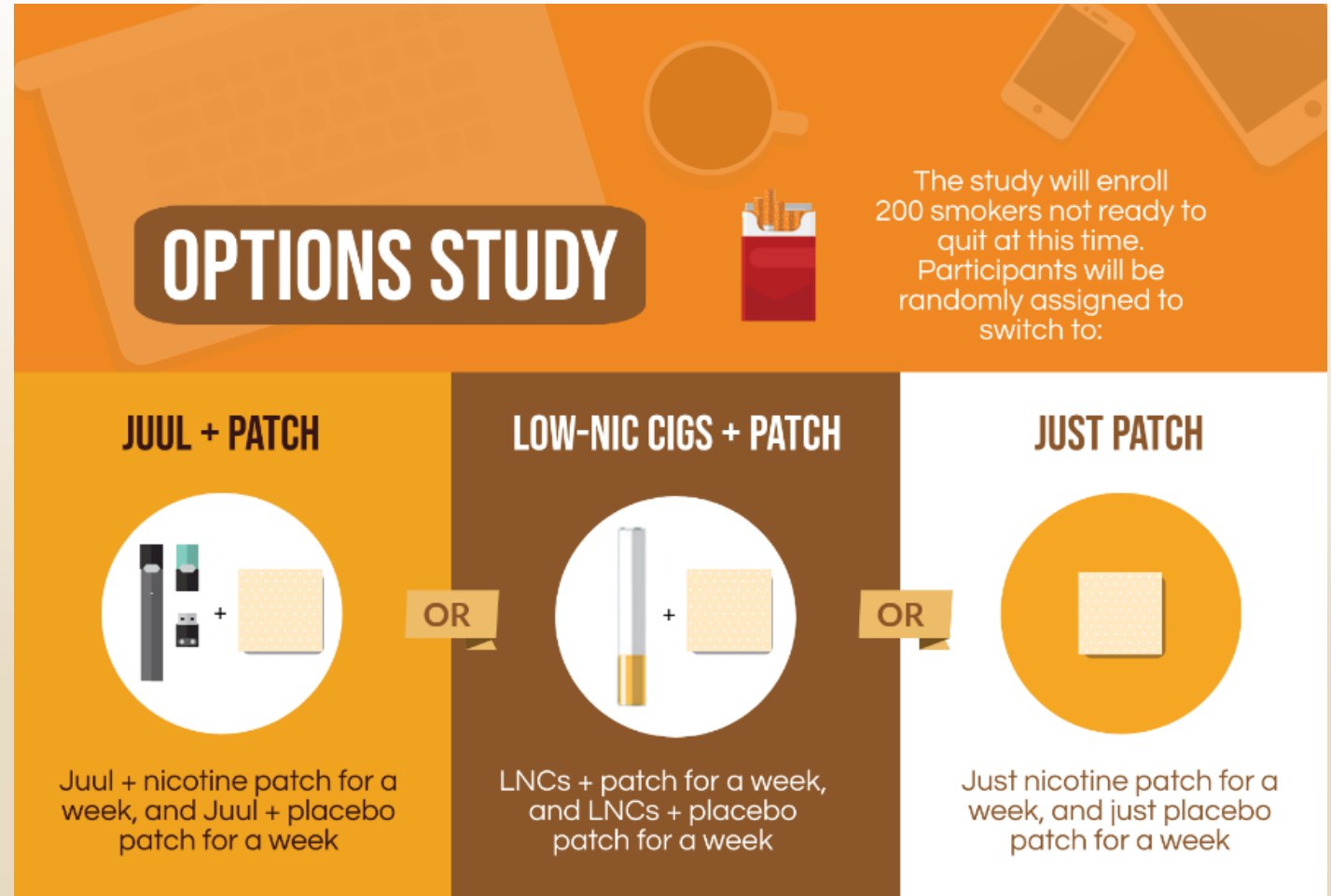
Exploratory Analyses

- Moderators of effects
- Complete abstinence from usual brand cigarettes
- Time to first usual brand cigarette
- Proportion of replacement
- Which real-time reported experiences with vaping and smoking VLNCs promote alternate product use

Comments and Questions

Mixed Design Study

- Between-subjects factor
 - VLNCs
 - E-cigarettes
 - No product
- Within-subjects factor:
 - Active nicotine patch
 - Placebo patch



Visit Schedule and Events



****Follow-up phone call 3 months after Visit 1**

Study Products

- VLNC Group – NIDA’s reduced nicotine cigarettes with 0.03 (± 0.01) mg of nicotine with a tar yield of 9 ± 1.5
 - Menthol or non-menthol VLNCs
- E-cigarette Group – Juul e-cigarette and 4 weeks of pods. Each Juul pod of e-liquid contains 0.7 ml nicotine by volume (5% nicotine by weight)
 - Virginia Tobacco or Menthol pods
- Patches – 8 patches/Switch Week
 - Active patch dosing was based on the package insert
 - >10 cigs/day = 21 mg patch and ≤ 10 cigs/day = 14 mg patches
 - Staff and participants were blind to patch type

Inclusion Criteria

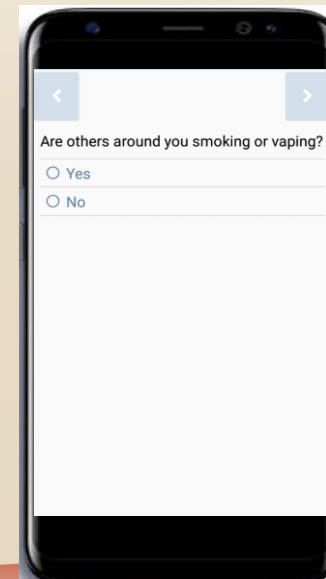
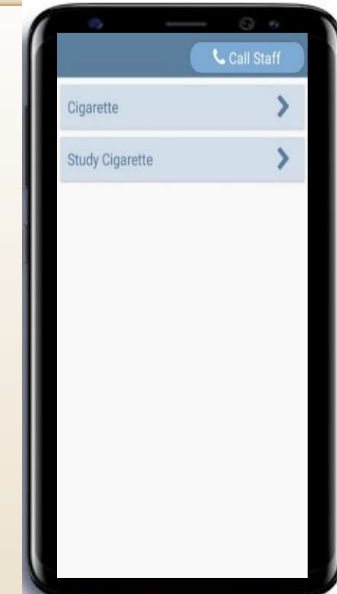
- ≥ 21 years old
- Able to read English
- No plans to quit smoking in the next 30 days
- Not currently taking smoking cessation medication
- Willing and medically able to use nicotine patches, VLNCs, and e-cigarettes
- Not currently in treatment for psychosis or bipolar disorder
- Smoking ≥ 5 cigarettes per day for the past 6 months
- Exhaled carbon monoxide (CO) > 5 ppm
- No e-cigarette use within the last month
- Not currently pregnant or breastfeeding

Visit Assessments

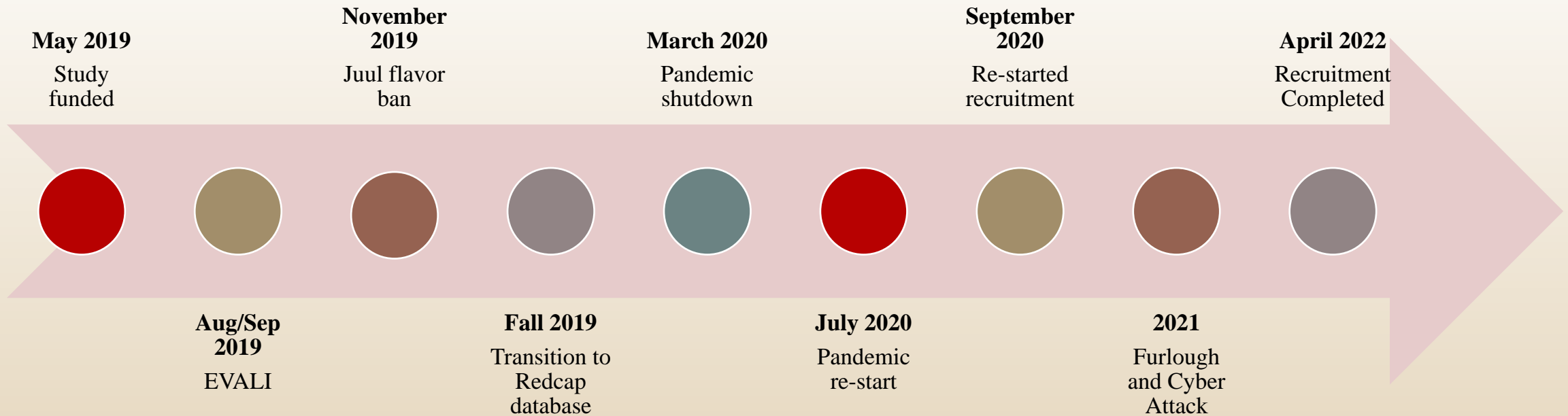
- Biomarkers
 - CO < 6 ppm = abstinence from combustible products
 - Cotinine <100 ng/mL (NicCheck) = abstinence from nicotine
 - Total nicotine equivalents (IntelliQuit) = abstinence from nicotine
- Self-report
 - Affect
 - Withdrawal
 - Craving
 - Adverse events
 - Timeline followback of cigarettes, study product, and patch use

Ecological Momentary Assessment

- Each use of their own cigarettes or any study product in real time
- After randomly selected product use events, more detailed assessments of their use contexts, including the modified Cigarette Evaluation Questionnaire (mCEQ)

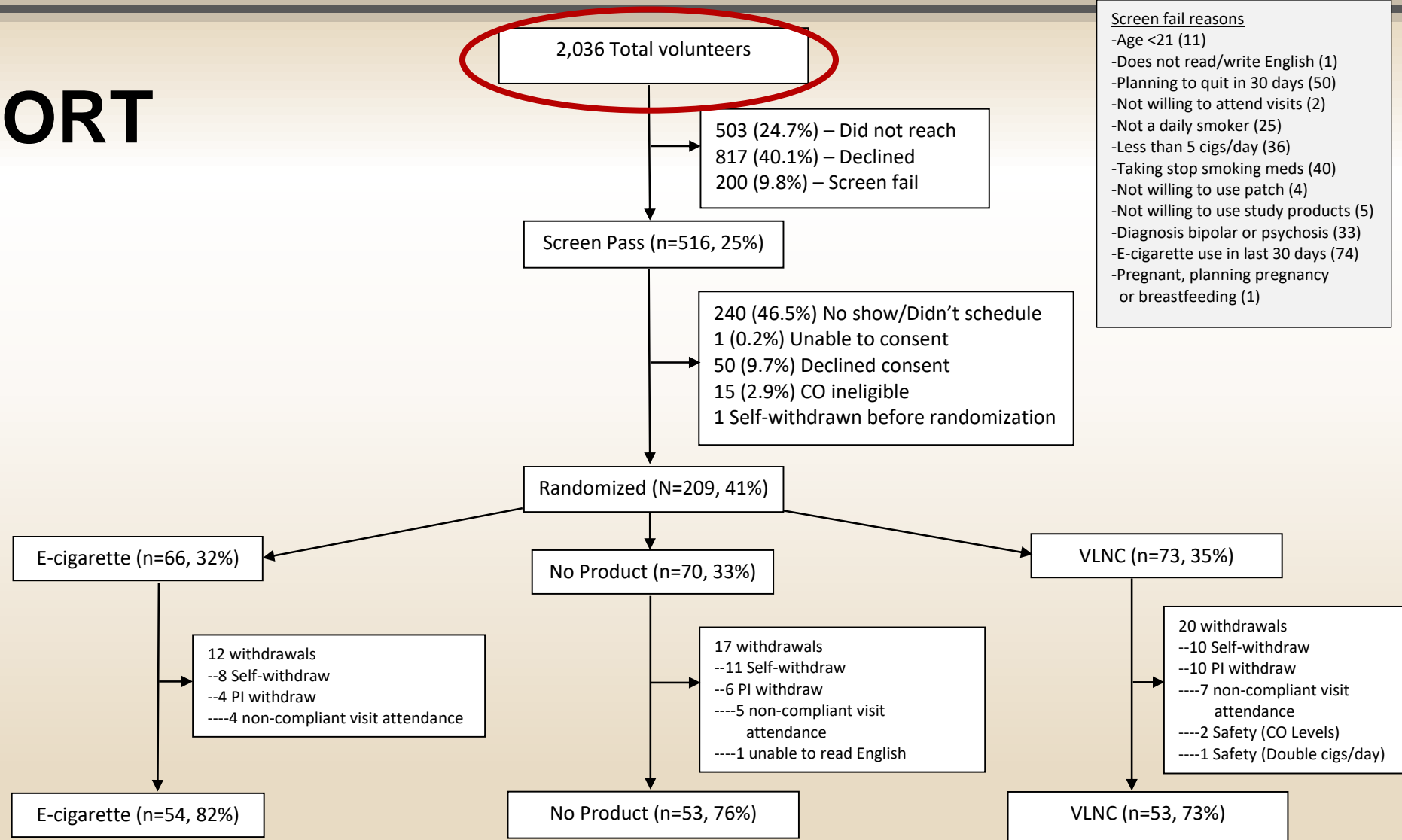


Study Implementation Timeline



Comments and Questions

CONSORT



- Screen fail reasons**
- Age <21 (11)
 - Does not read/write English (1)
 - Planning to quit in 30 days (50)
 - Not willing to attend visits (2)
 - Not a daily smoker (25)
 - Less than 5 cigs/day (36)
 - Taking stop smoking meds (40)
 - Not willing to use patch (4)
 - Not willing to use study products (5)
 - Diagnosis bipolar or psychosis (33)
 - E-cigarette use in last 30 days (74)
 - Pregnant, planning pregnancy or breastfeeding (1)

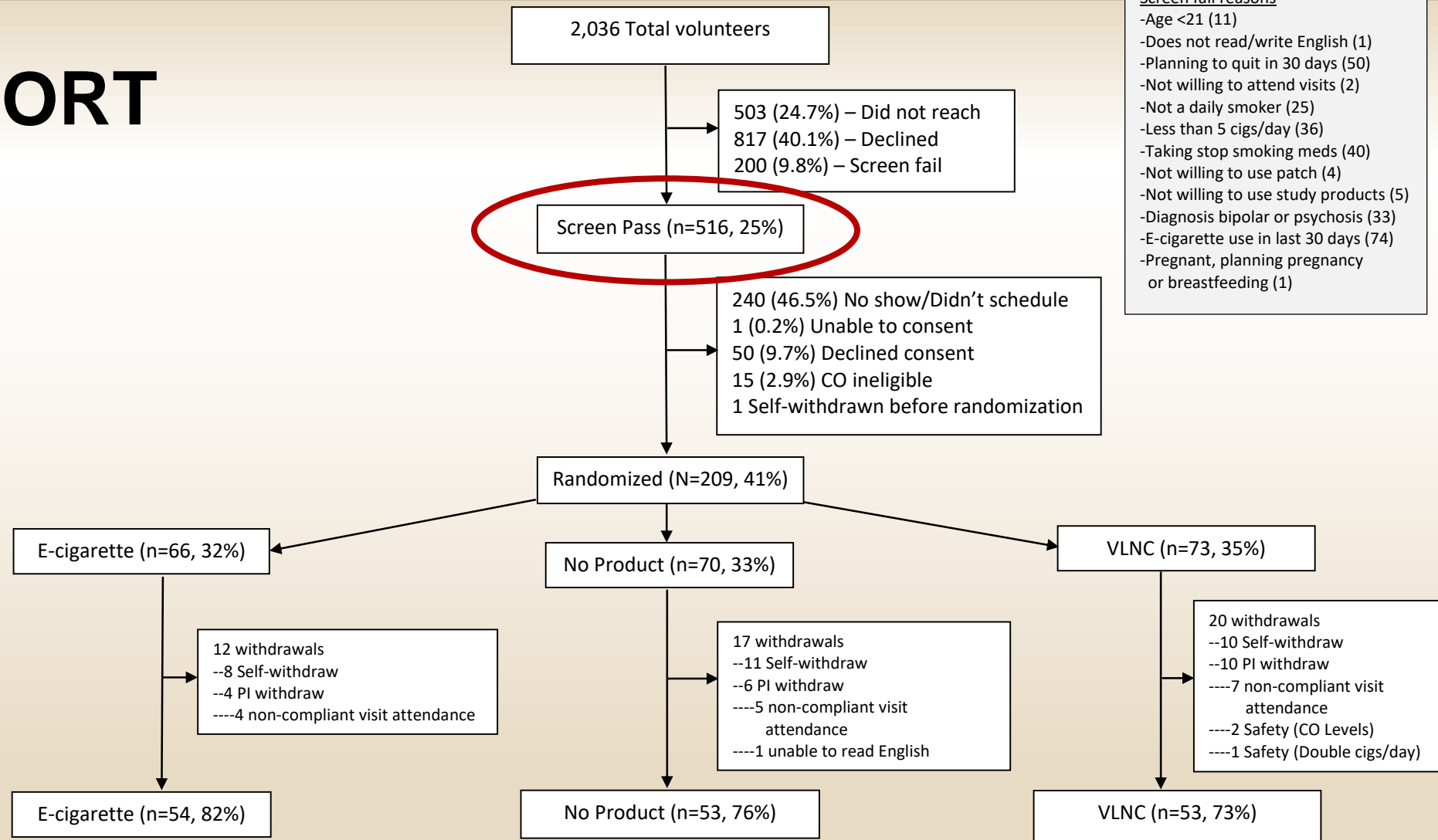
SELF-WITHDRAWAL REASONS BY GROUP

- 8 E-cigarette self-withdrawals**
- 4 Too much time/visits
 - 2 Cannot come during clinic hours/other
 - 1 No longer interested
 - 1 Does not want to use study products

- 11 No Product self-withdrawals**
- 3 Too much time/visits
 - 3 Other
 - 2 No longer interested
 - 2 Cannot come during clinic hours
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- 10 VLNC self-withdrawals**
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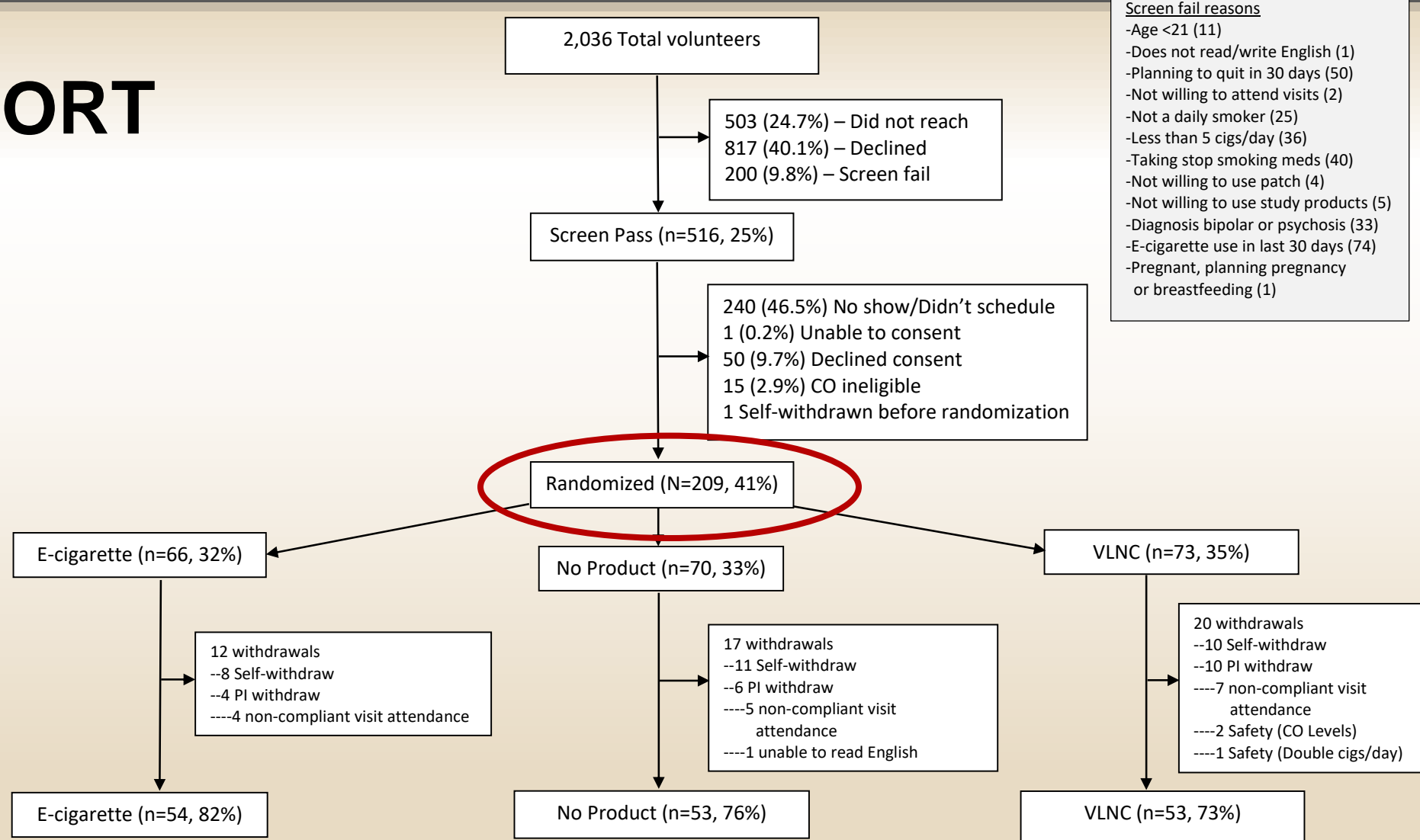
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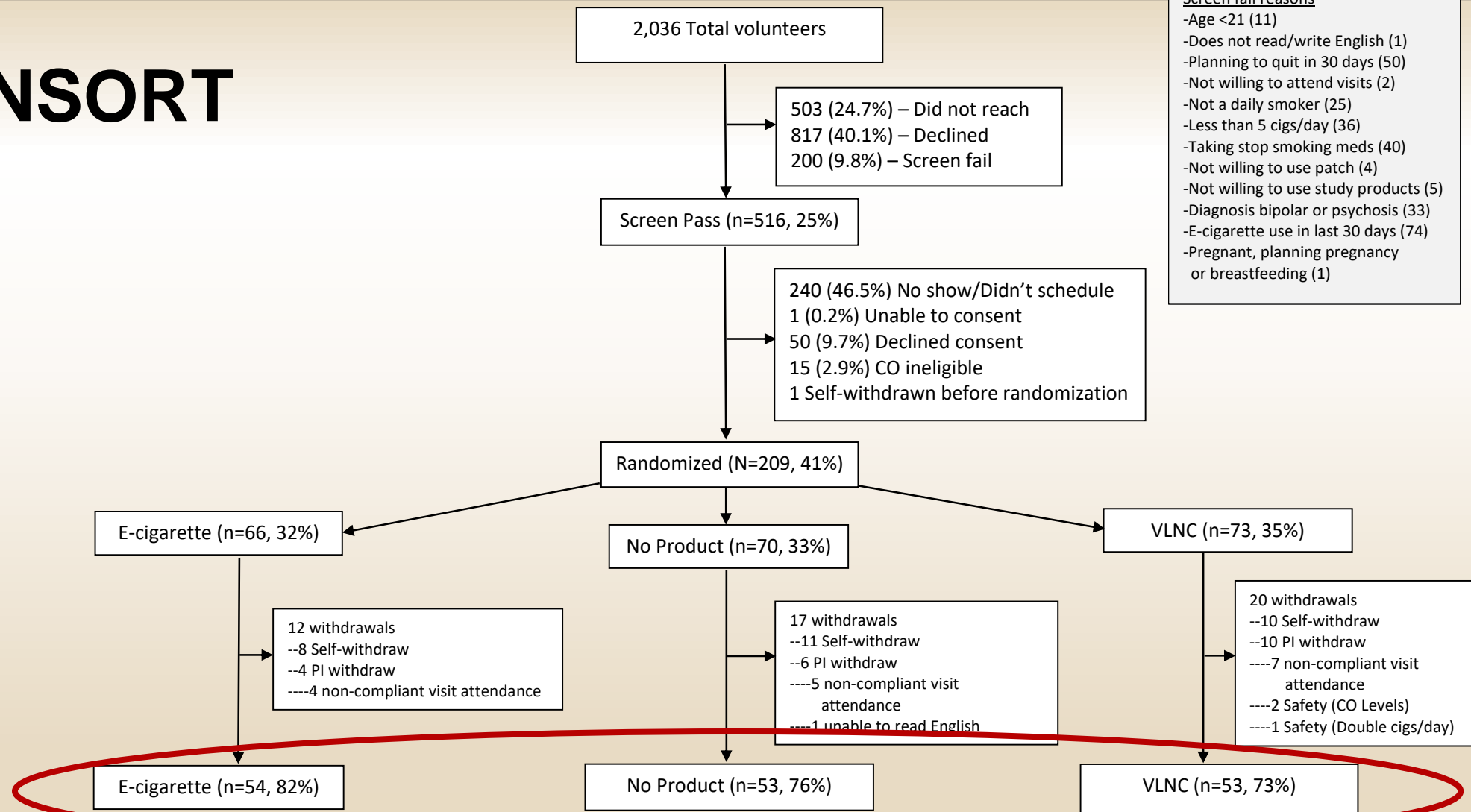
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Study Sample (N=160)

- Age: 52 years (SD=12)
 - Withdrawn participants were significantly younger (M=47, SD=11, p=.02)
- Gender:
 - Men = 39%, Women = 60%, Trans/non-binary = 1%
- Race:
 - African American/Black = 22%, White = 71%, American Indian/Alaska Native = 1%, Multiple Races = 4%
- Hispanic: 3%
- Sexual orientation:
 - Gay/Lesbian = 6%, Heterosexual = 80%, Bisexual = 9%
- History of mental illness: 59%

Smoking Characteristics

- Cigarettes per day = 16.8 (SD=9.3)
- Baseline CO = 19.5 (SD=14.0)
- Baseline cotinine = 4.5 (SD=2.5, Range=0-14)
- Baseline total nicotine equivalents = 54.1 (38.3)
 - Highly correlated with cotinine (r 's=.75-.84)
- Motivation to quit smoking = 3.9 (SD=1.8, Range 1-7)
- FTCD = 4.9 (SD=2.1)
- Smoke menthol = 56.3%

Product Use

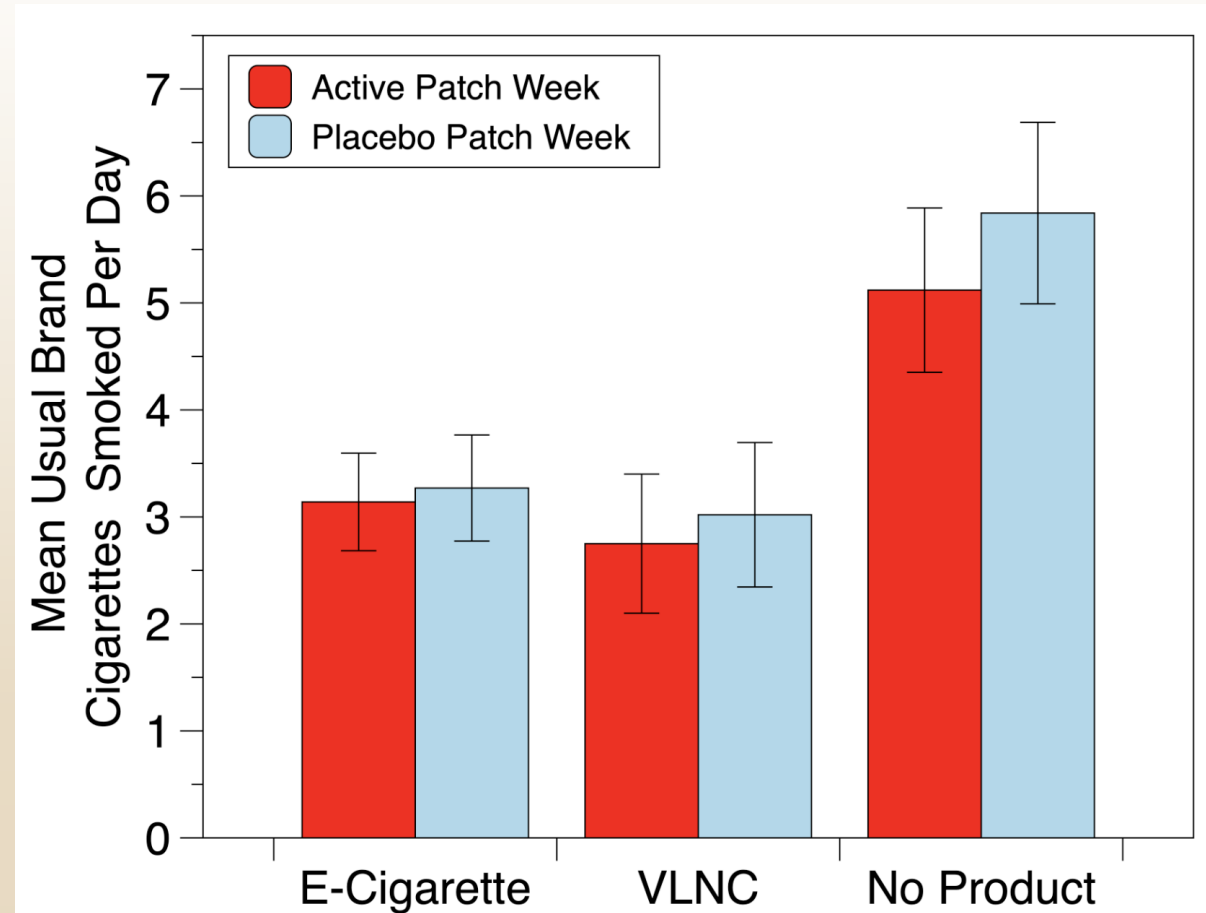
- Minimal use during the lead-in week
 - 1.78 (SD=2.13) VLNCs/day
 - 2.15 (SD=2.36) vape events (i.e., about 15 puffs or 10 minutes) per day
- Switch Week use
 - 9.37 (SD=0.85) VLNCs/day
 - 7.04 (SD=0.83) vape events/day
 - Product use declined during the second Switch Week
- Significant Patch effect ($p < .001$)
 - 8.78 (SD=.66) during placebo Switch Week
 - 7.63 (SD=.56) during active Switch Week

Hypothesis Tests

- Repeated measures ANOVA
 - Baseline cigs/day as a covariate
- Significant main effect of Product
 - $F(2, 150)=5.52, p=.005, \text{partial } \eta^2 = .07)$
 - No main effect of Patch
 - No Product x Patch interaction

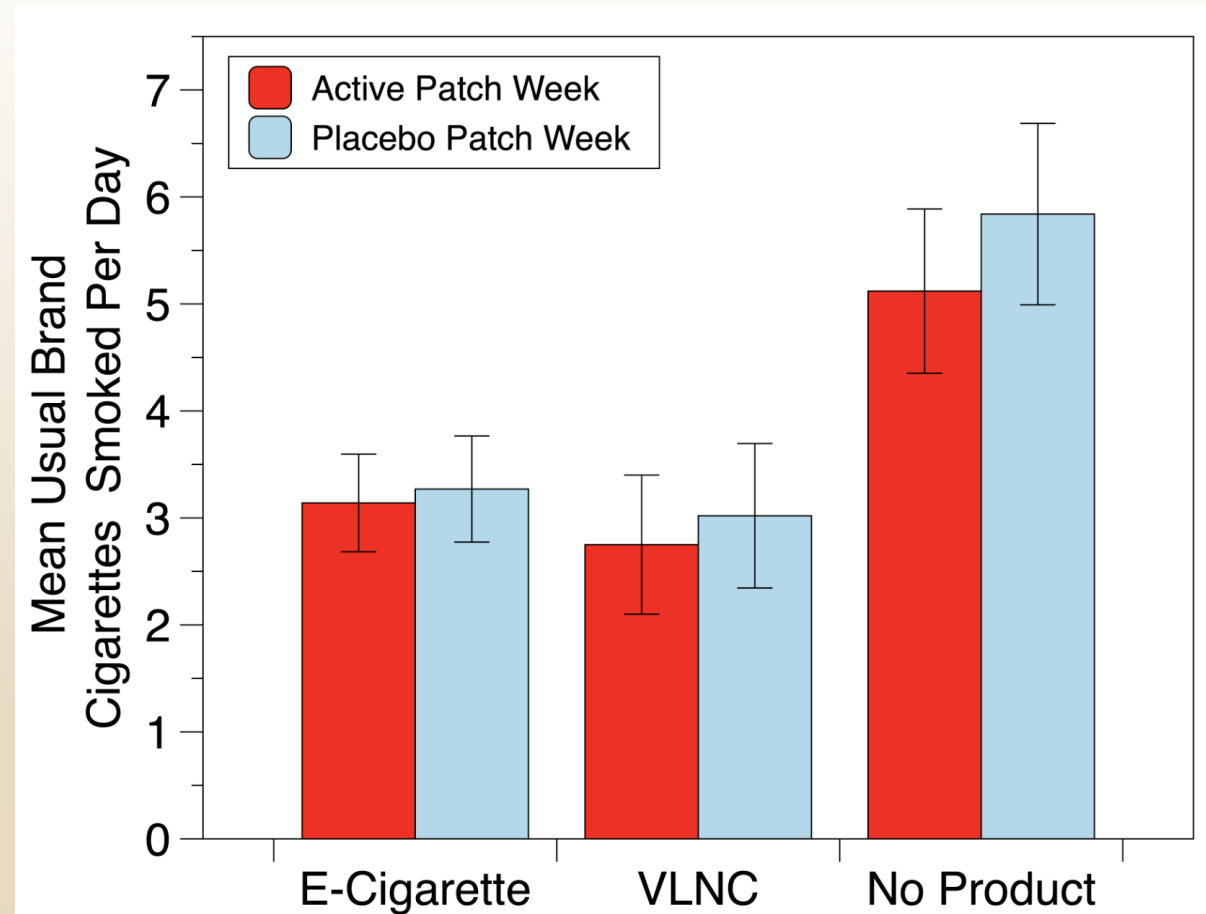
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Hypothesis Tests

- VLNCs and e-cigarettes will reduce the number of conventional cigarettes smoked compared to no study product
 - Supported
- E-cigarettes will serve as a better substitute than VLNCs
 - Not Supported
- An active nicotine patch will enhance the ability of VLNCs and e-cigarettes to serve as a substitute
 - Not Supported

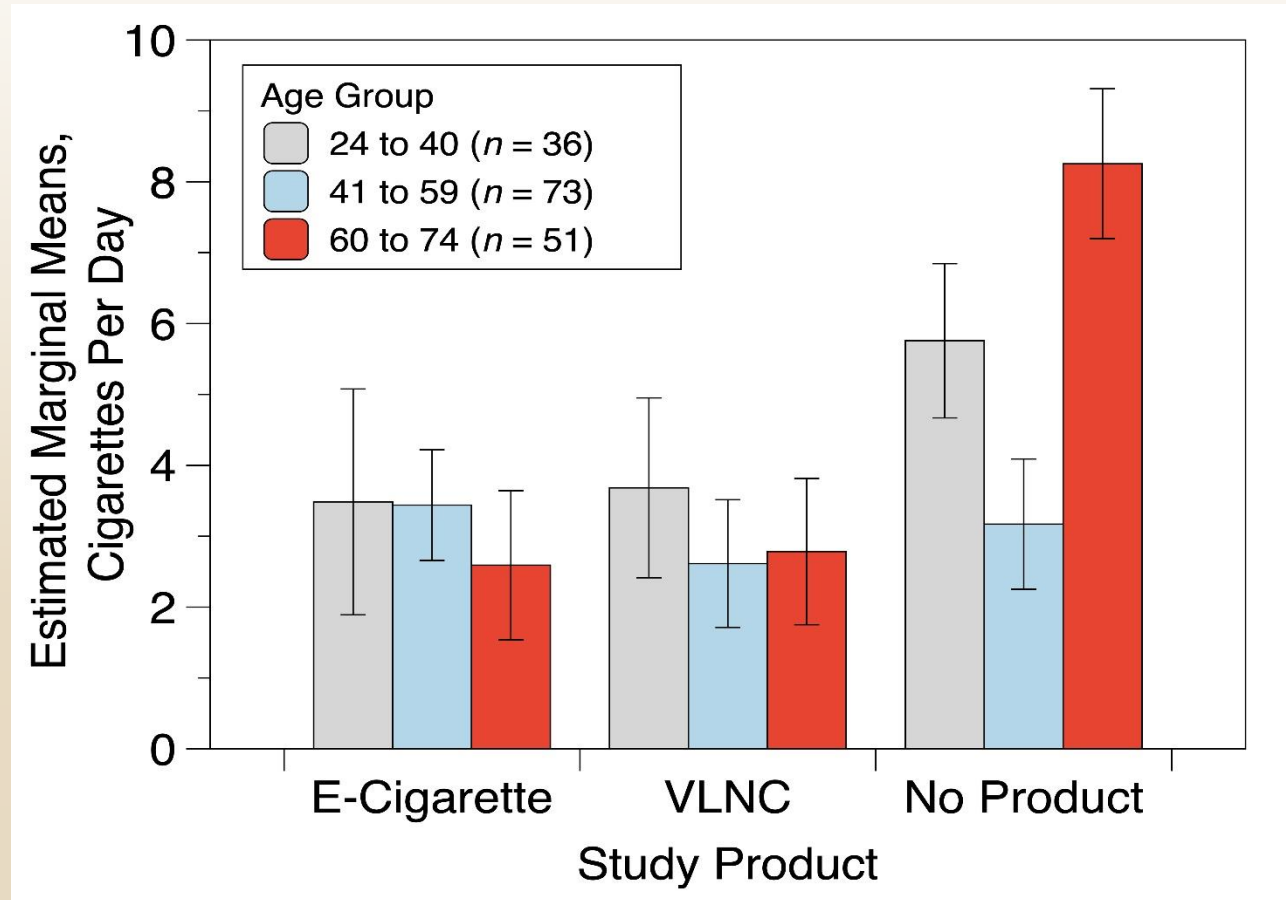


Moderators

- Age
- Race
- Sexual orientation
- Education
- Mental illness – lifetime, depression, anxiety, serious psychological distress
- Menthol use
- Time to first cigarette

Moderators

- Age x Product interaction ($F(4, 144)=2.72, p=.03$)

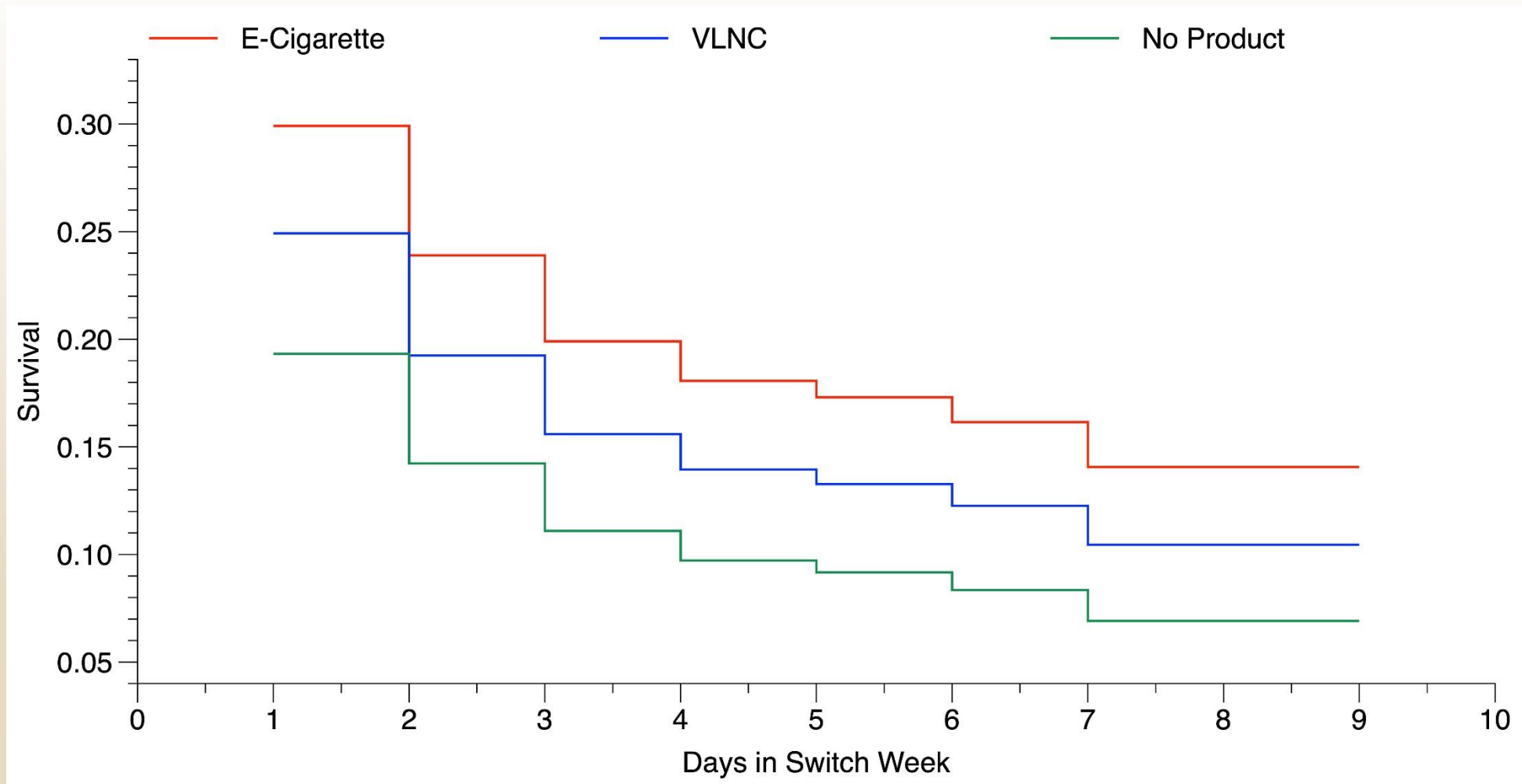


Complete Abstinence

	Percent Self-reported Abstinence for the Entire Switch Week	
	Active Patch	Placebo Patch*
E-cigarette	15.1	26.4
VLNC	11.5	11.3
No Product	5.7	11.1

*p<.05

Time to First Usual Brand Cigarette



Proportion of Switching

- Mean daily study product use during Switch Weeks/mean baseline cigarettes per day
- Significant main effect of Patch ($p < .001$)
 - 59.39% (SD=3.44) of study products relative to what they would have used of their usual brand cigarettes during placebo patch Switch Weeks
 - 52.67% (SD=3.19) during active patch Switch Weeks
- Significant main effect of Product ($p = .02$)
 - 63.83% (SD=4.53) in VLNC group
 - 48.24% (SD=4.44) in E-cigarette group

Predictors of Use Events

- 37,853 total use events and 10,969 use context assessments
- Correlates of mCEQ factors with number of alternate product use events
 - Smoking/Vaping Satisfaction, Psychological Reward, Aversion, Enjoyment of Respiratory Tract Sensations, and Cigarette Craving Reduction
- Vaping satisfaction ($r=.30$, $p=.04$) and smoking satisfaction ($r=.43$, $p=.003$) were the only predictors of e-cigarette and VLNC use
 - Only during the active patch Switch Weeks

Limitations

- Participants were not motivated to quit smoking
- Only asked to switch for 7 days
- Taste of VLNCs was not reinforcing and may have limited ability to serve as a substitute
- Limited racial and sexual orientation diversity

Conclusions

- Nicotine delivery devices (e-cigarettes) and non-nicotine smoking cue devices (VLNCs) significantly reduce the number of cigarettes smoked and were similar in their ability to substitute for participants' usual cigarettes
- Steady state nicotine from an active nicotine patch did not help participants refrain from smoking their usual cigarettes
 - This was true no matter what product they were assigned
- Behavioral factors, in addition to nicotine dependence, play a key role in sustaining smoking behavior
 - This is especially true for older smokers

Conclusions

- There is a clear need to address the impact of smoking cues and behavioral factors as part of smoking cessation treatment, especially among older smokers
- Product satisfaction plays a key role in product use, illustrating the need for appealing substitutes
- Future research is needed to disentangle the role of nicotine from the specific behavioral features and cues associated with substitution

Gratitude

- Kate Kobinsky
- Meg Feyen & Holly Prince
- Health Counselors – Renae Borkowski, Tess Kuba, Mari Marquez, Chris Ripley
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- Data Team – Julia Matthews, Adam Nunez, Todd Hayes-Birchler
- Kari Giacalone, Chris Hollenback, Katrina Bundy

Comments and Questions

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