

Nicotine Reduction and Smoking

The potential impact and necessity of nicotine product standards for cigarettes?

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Disclosures

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- **Lots of collaborators**: Dorothy Hatsukami, Neal Benowitz, Joe McClernon, Andrew Strasser, Jen Tidey, Suzanne Colby, Rachel Denlinger-Apte, Tracy Smith, Cassidy White, Joe Koopmeiners, Sharon Murphy, Steve Hecht, and all other faculty and staff associated with CENIC past and present.



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TOBACCO COMPANY PLC



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CIGARETTES

**TOBACCO SERIOUSLY
DAMAGES HEALTH**

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CIGARETTES ARE ADDICTIVE AND DEBILITATING.
IF YOU DON'T SMOKE, DON'T START.

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The Tobacco Endgame

Eradicating a Worsening Epidemic

MPOWER provides a roadmap for the Tobacco Endgame



Monitoring
tobacco use
and prevention
policies



Protecting
people from
tobacco smoke



Offering
help to quit
tobacco use



Warning
about the
dangers of
tobacco



Enforcing
bans on tobacco
advertising,
promotion and
sponsorship



Raising
taxes on
tobacco for
effective
tobacco control

14% of Americans currently smoke cigarettes



Cigarette smoking remains high among certain groups







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Whether to push or pull? Nicotine reduction and non-combusted alternatives - Two strategies for reducing smoking and improving public health



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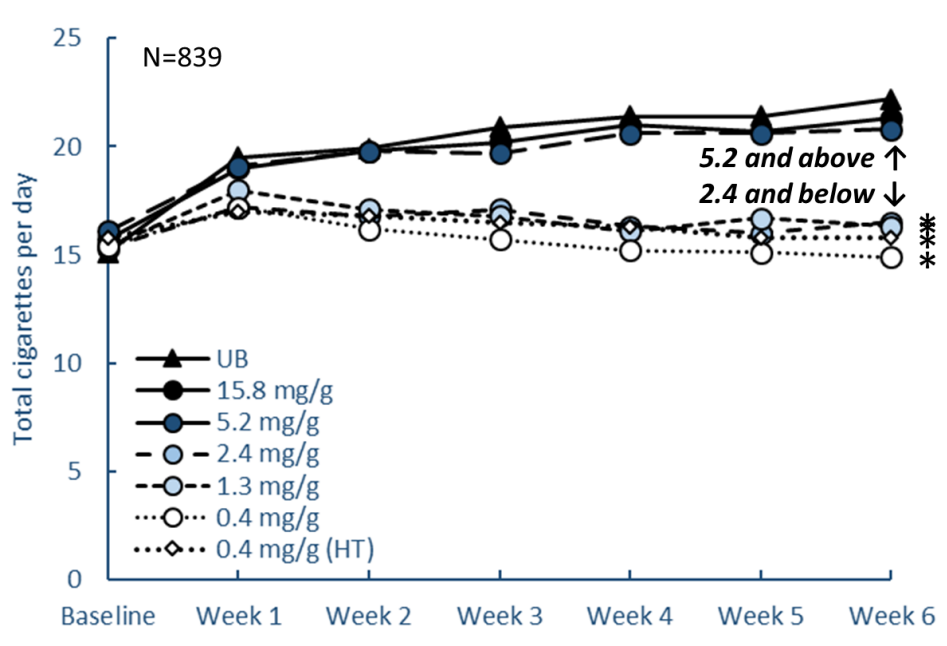
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Rationale for reducing nicotine

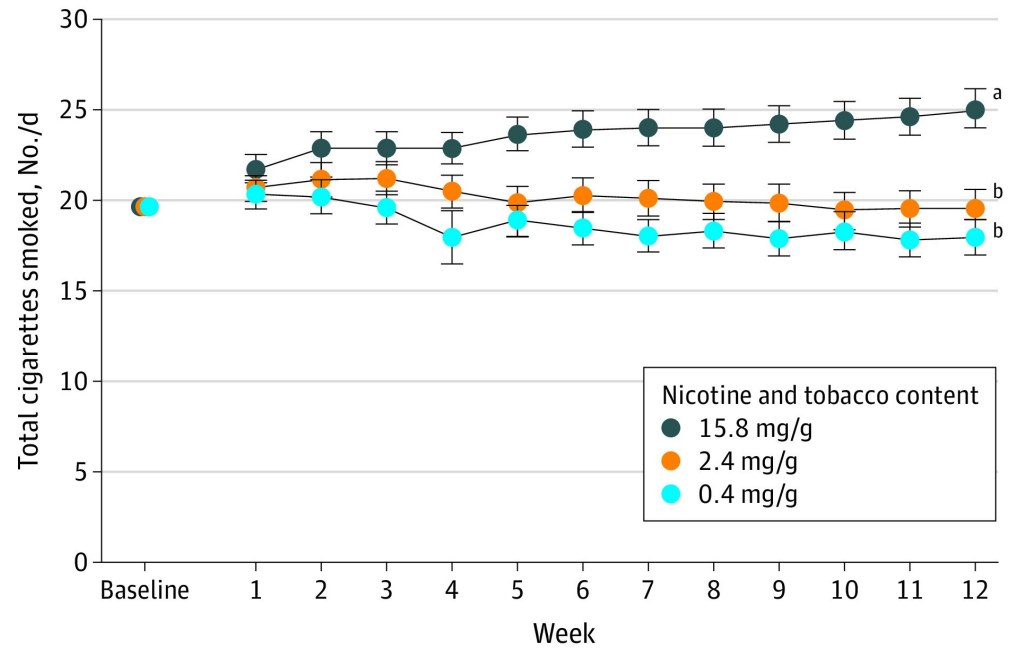
- Nicotine, through its neuropharmacological actions, motivates behavior. Currently, the primary target behavior is smoking.
- Cigarettes, as a means of nicotine delivery, are deadly
- Reducing nicotine in cigarettes will likely render them less reinforcing/addictive.
- If true, reducing nicotine could ...
 - Reduce initiation in naïve individuals
 - Increase cessation in current smokers
 - Reduce relapse in ex-smokers
- By changing behavior, nicotine reduction can improve health

Reducing nicotine *decreases* the number of cigarettes smoked



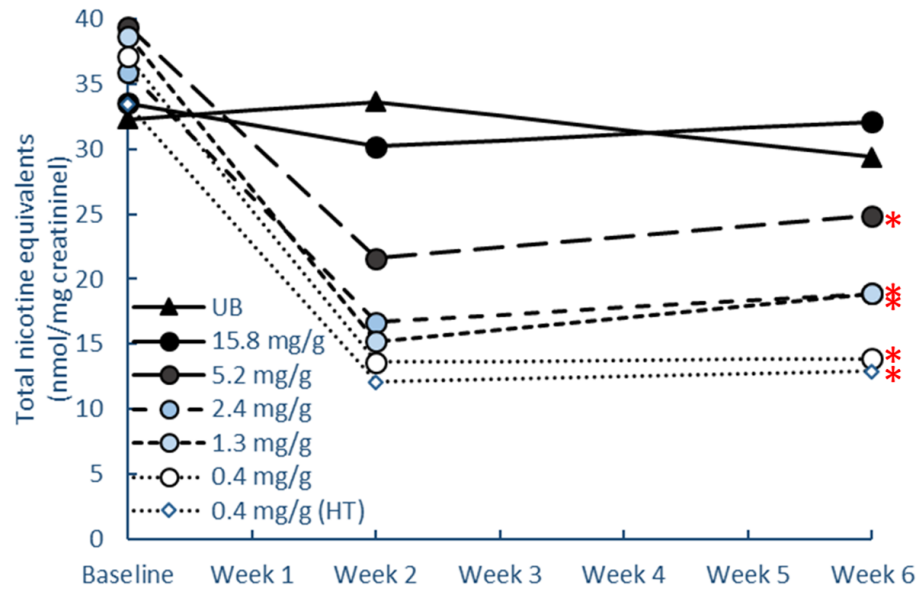
*indicates significant ($p < .0125$) difference compared to 15.8 mg/g (controlling for BL)

Donny et al. NEJM. 2015

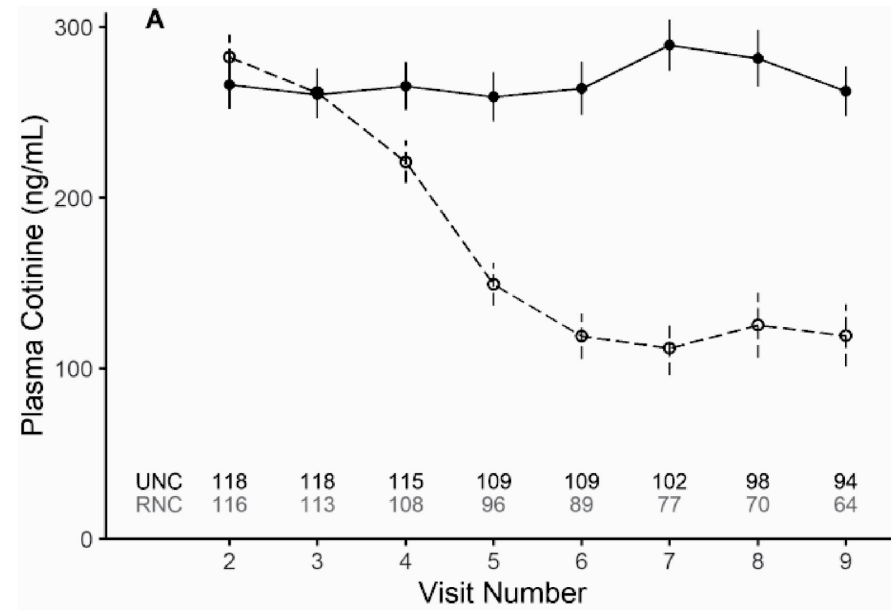


Higgins et al 2020 JAMA Netw Open

Reducing nicotine *decreases* nicotine exposure

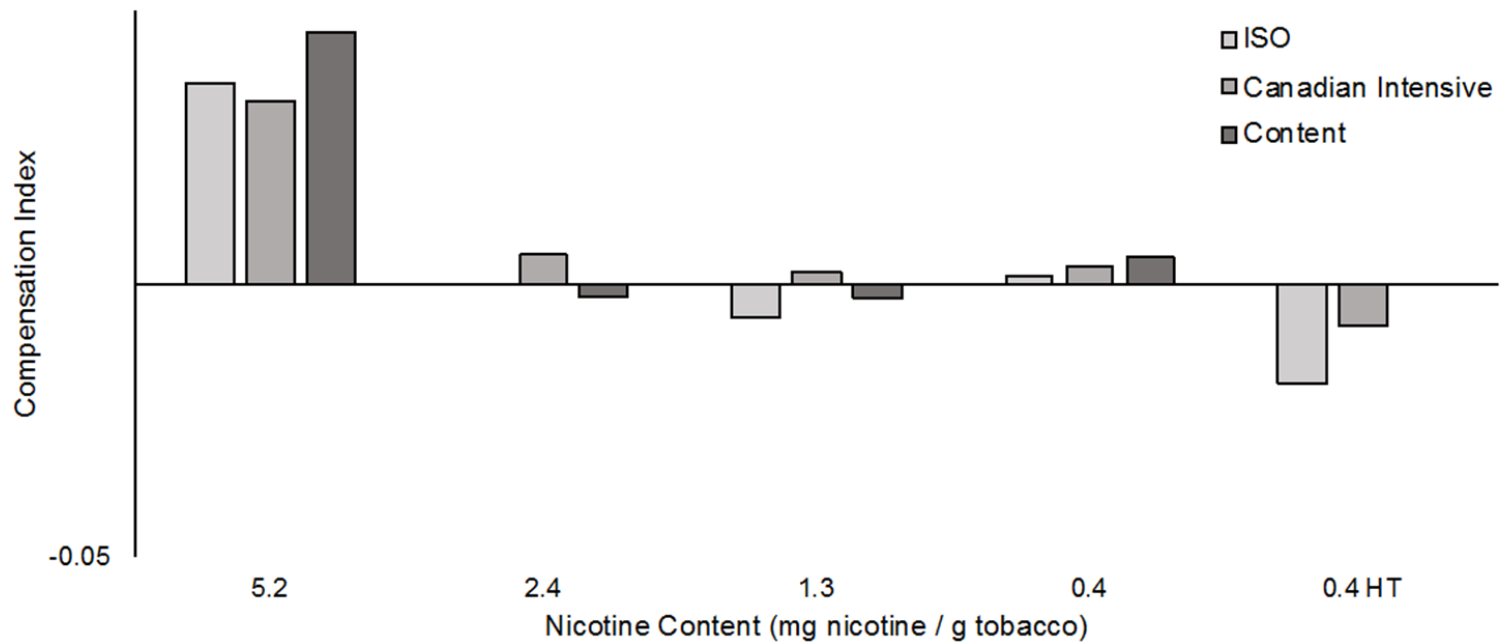


Donny et al. NEJM. 2015



Krebs et al 2021 NTR

Reducing nicotine *does not* lead to compensatory changes in how people smoke



Smith et al., CEBP 2020

Reducing nicotine *does not* lead to compensatory changes in how people smoke

“What my thoughts were and what the reality was was two totally different ideas. You know my thought was they’re going to be nasty. You’re not going to even taste anything. I’m going to smoke like a freight train to try to make up for the nicotine my body is craving and it ended up that it didn’t even come out that way.”

*Participant from open label hotel study
Denlinger-Apte et al. DAD. 2021*

Reducing nicotine is likely to *increase* cessation

In the largest trial of non-treatment seekers to date, immediate reduction to 0.4 mg/g increased odds of abstinence at Week 20 (OR: 3.22)

Hatsukami et al 2018

Reducing nicotine is likely to *increase* cessation

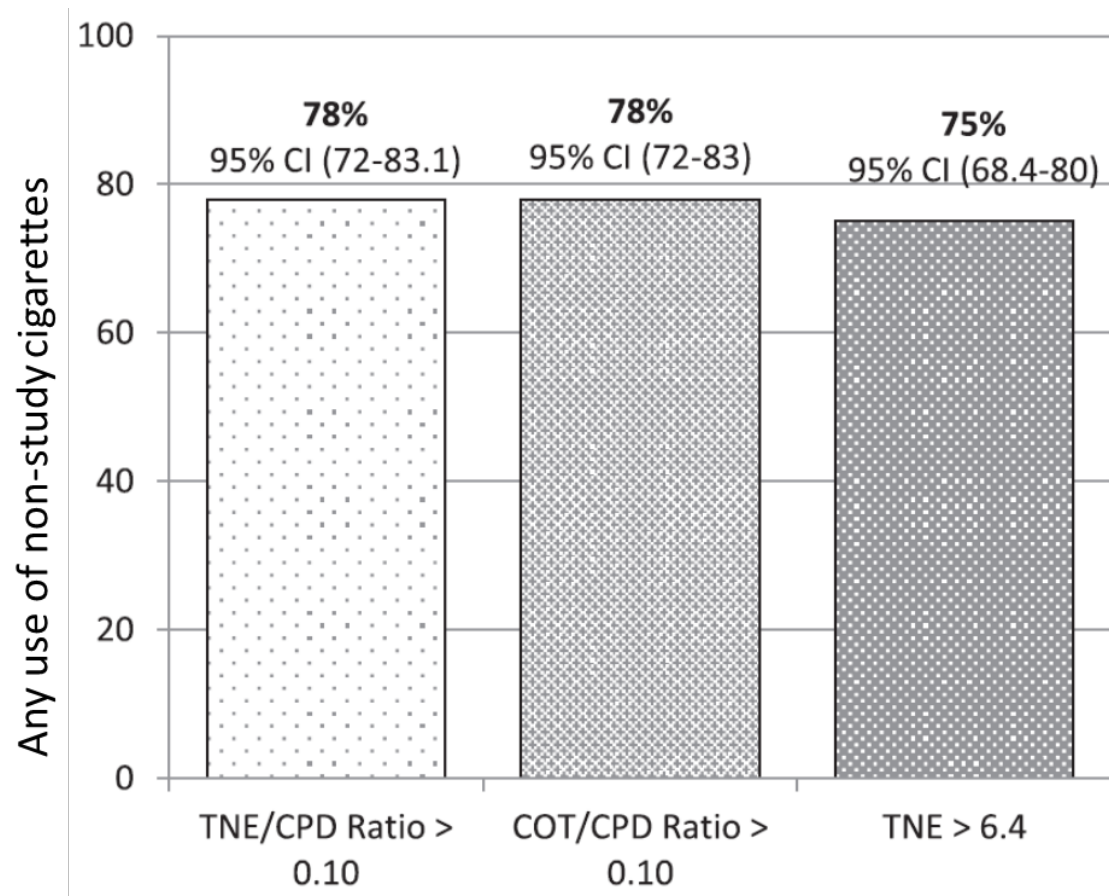
“And so I’ve been able to cut down on smoking. I don’t seem to be as needy on the cigarettes.”

“It makes me want to just go ahead and quit. Put them down.”

“I actually finally feel like the cigarettes aren’t controlling me.”

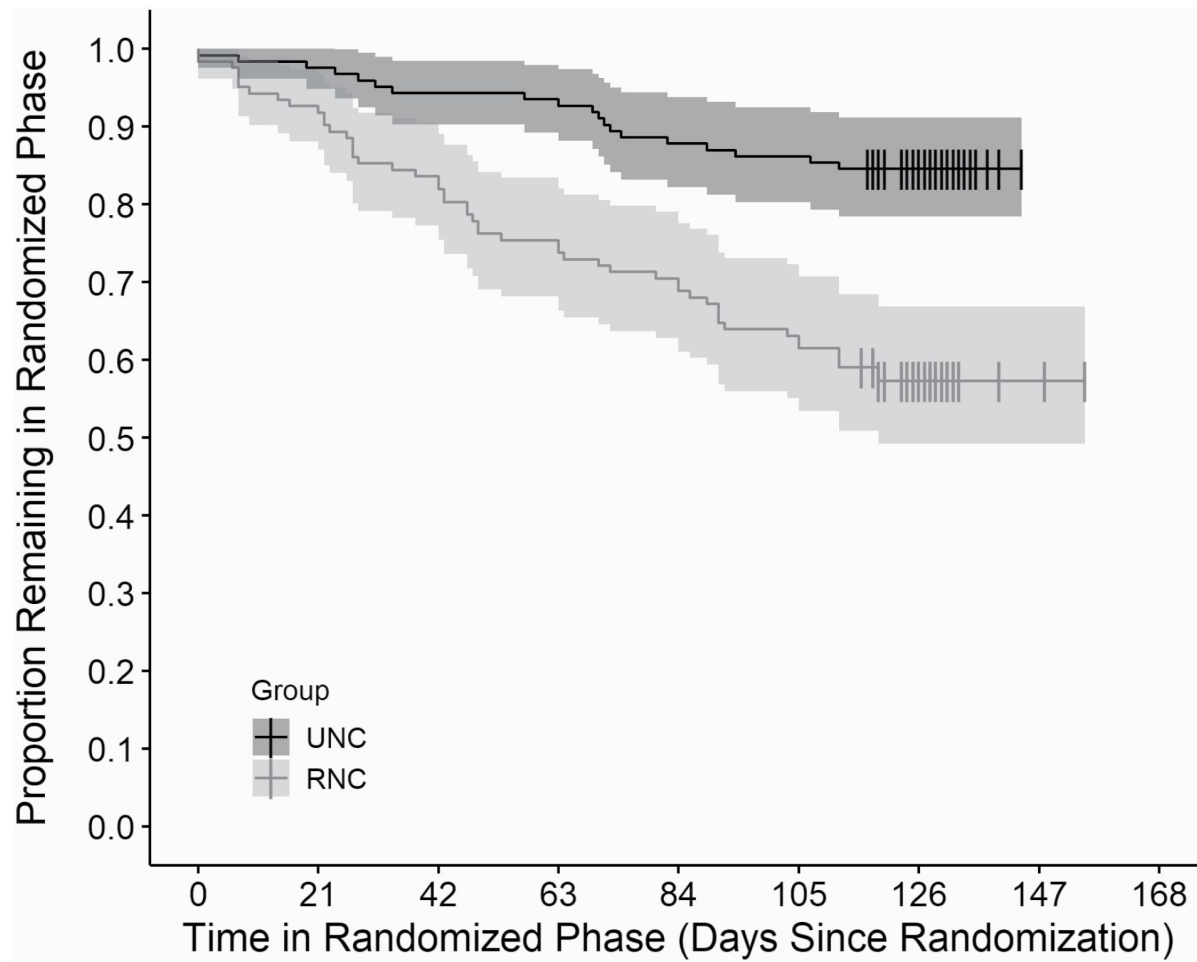
*Participant from open label hotel study
Denlinger-Apte et al. DAD. 2021*

However, reducing nicotine *leads to non-adherence*



Nardone et al., 2016

However, reducing nicotine *leads to non-adherence and dropout*



Krebs et al 2021 NTR

Implications of non-adherence/non-completion

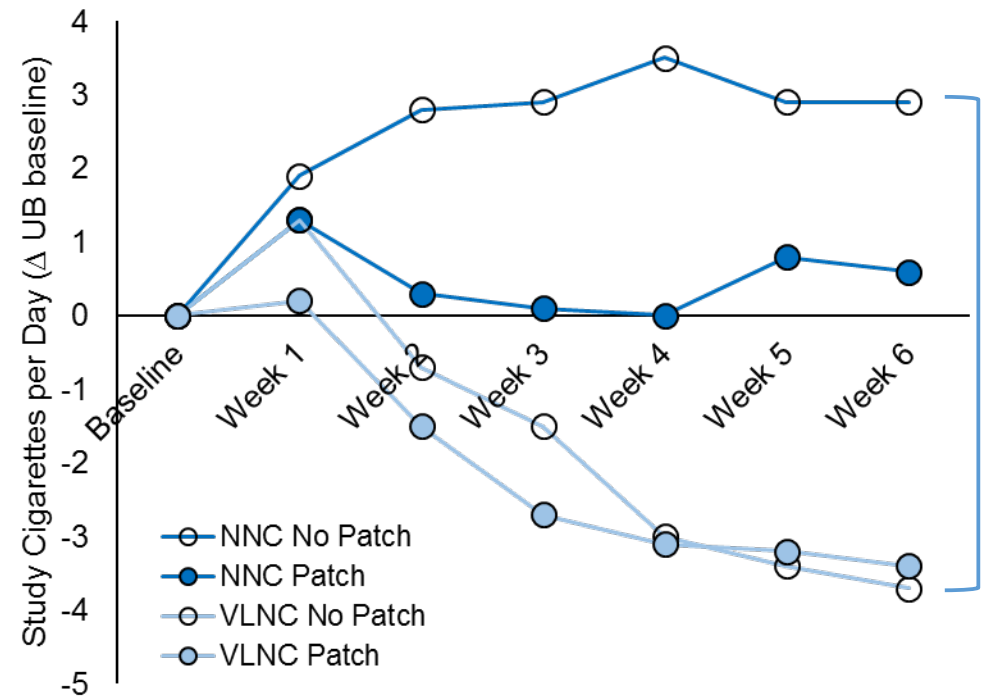


What role do alternatives sources of nicotine play?

- Nicotine replacement
 - Design: 2x2
 - Cigarette nicotine content
 - Very Low (“VLNC,” 0.4 mg/g)
 - Normal (“NNC,” 15.8 mg/g)
 - Transdermal nicotine
 - 14-21 mg patch (dose reductions PRN)
 - No patch

What role do alternatives sources of nicotine play?

- Nicotine replacement
 - VLNC cigarettes reduced smoking

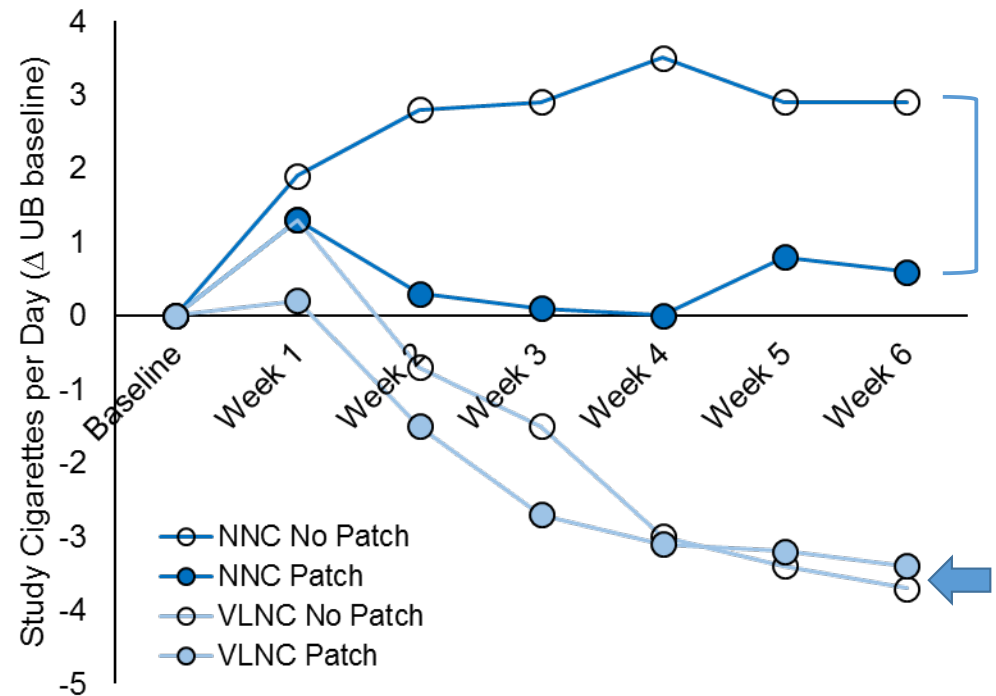


Smith et al., 2019

What role do alternatives sources of nicotine play?

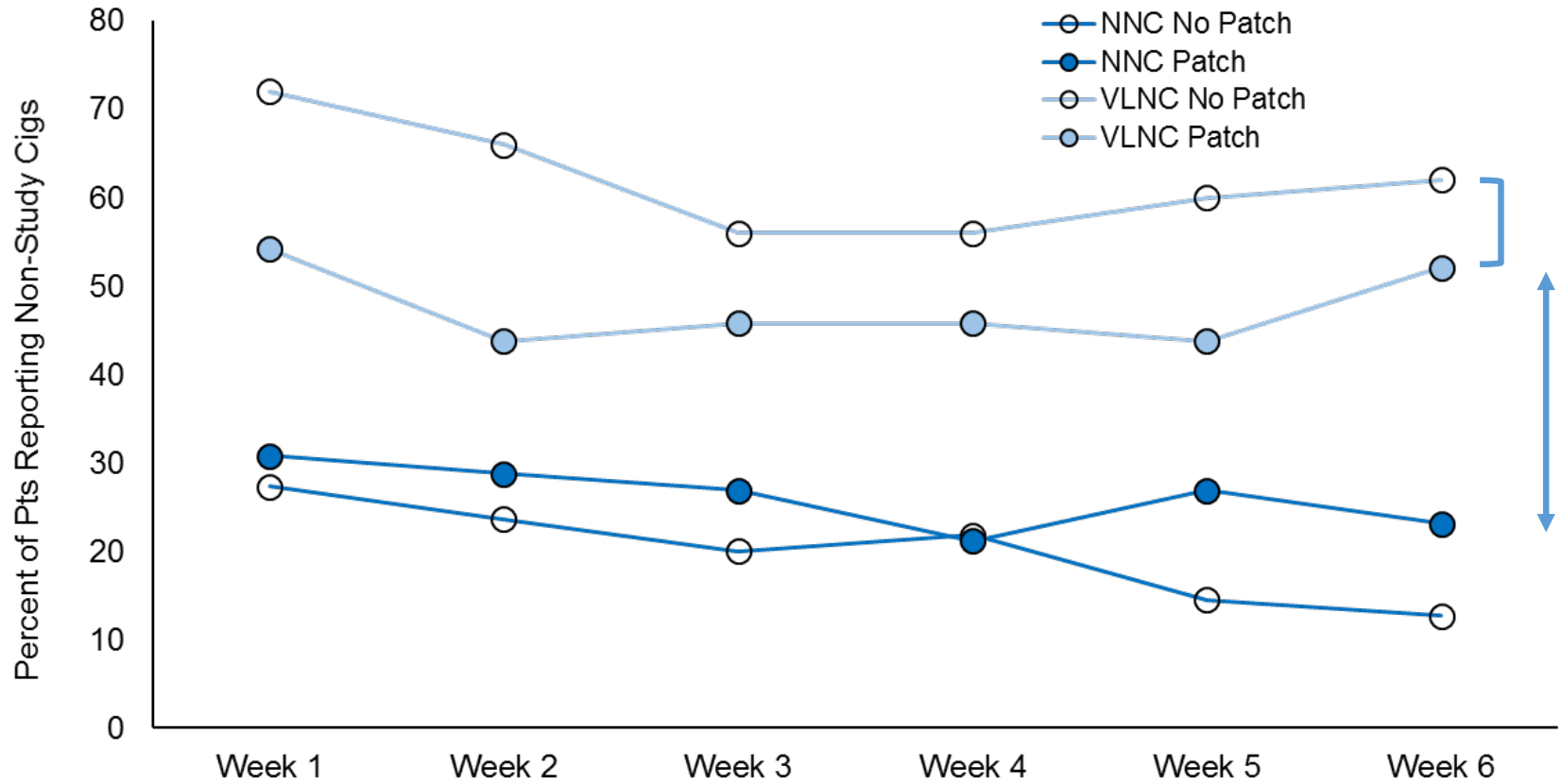
- Nicotine replacement

- VLNC cigarettes reduced smoking
- Patch reduced smoking of NNC cigarettes, but added little to the effect of VLNCs
 - Other studies have found small effect of patch on VLNC use (Donny et al., 2009; Hatsukami et al., 2013)



Smith et al., 2019

What role do alternatives sources of nicotine play?

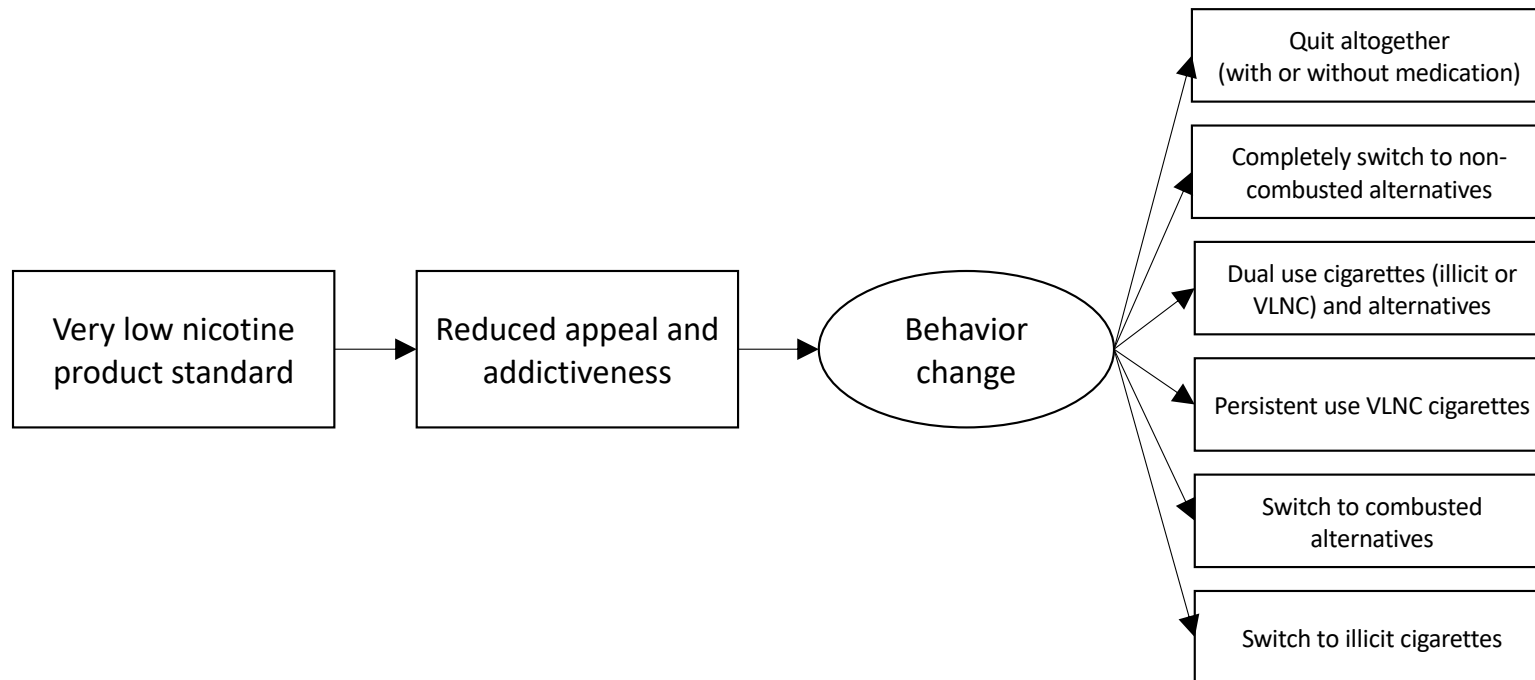




All behavior is choice

-Herrnstein, 1970

What role do alternatives sources of nicotine play?

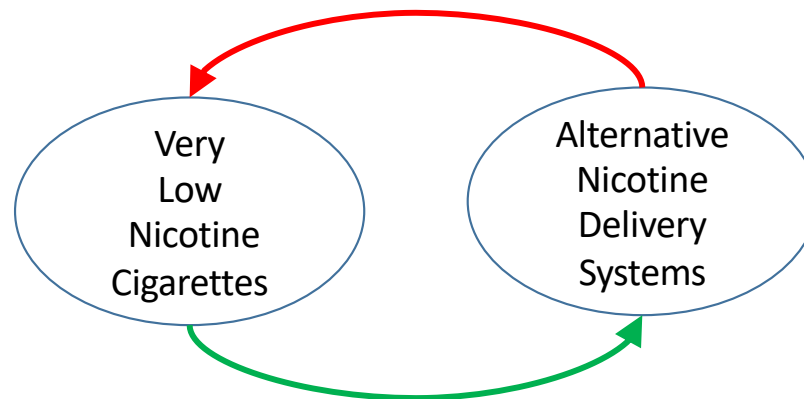


What role do alternatives sources of nicotine play?

Nicotine reduction was associated with an increase in days using alternative products (most commonly e-cigarettes)

AND

Use of alternative products was associated with increased number of days abstinent from cigarettes



What role do alternatives sources of nicotine play?

- Focus of current trials: Nicotine reduction in the context of alternative sources of nicotine


Marketplace Research Study

123456789 My Account Wish List (0) Shopping Cart Checkout

Currency

Search 0 item(s) - \$0.00

Featured




Your usual brand of cigarettes

The cigarettes you usually smoke. ..

\$6.00

ADD TO CART




Very low nicotine content cigarettes (VLN cigs)

Cigarettes that contain the same ingredients and chemicals as normal nicotine cigarettes, while cont..

\$6.00

ADD TO CART




Heat not burn tobacco device (iQOS)

An electronic device that heats tobacco sticks called HeatSticks enough to release nicotine-co..

\$7.00

ADD TO CART



Vaping Device (JUUL)

The JUUL vaping device uses e-liquid pods that contain nicotine salts derived from tobacco leaves. E..

\$10.00

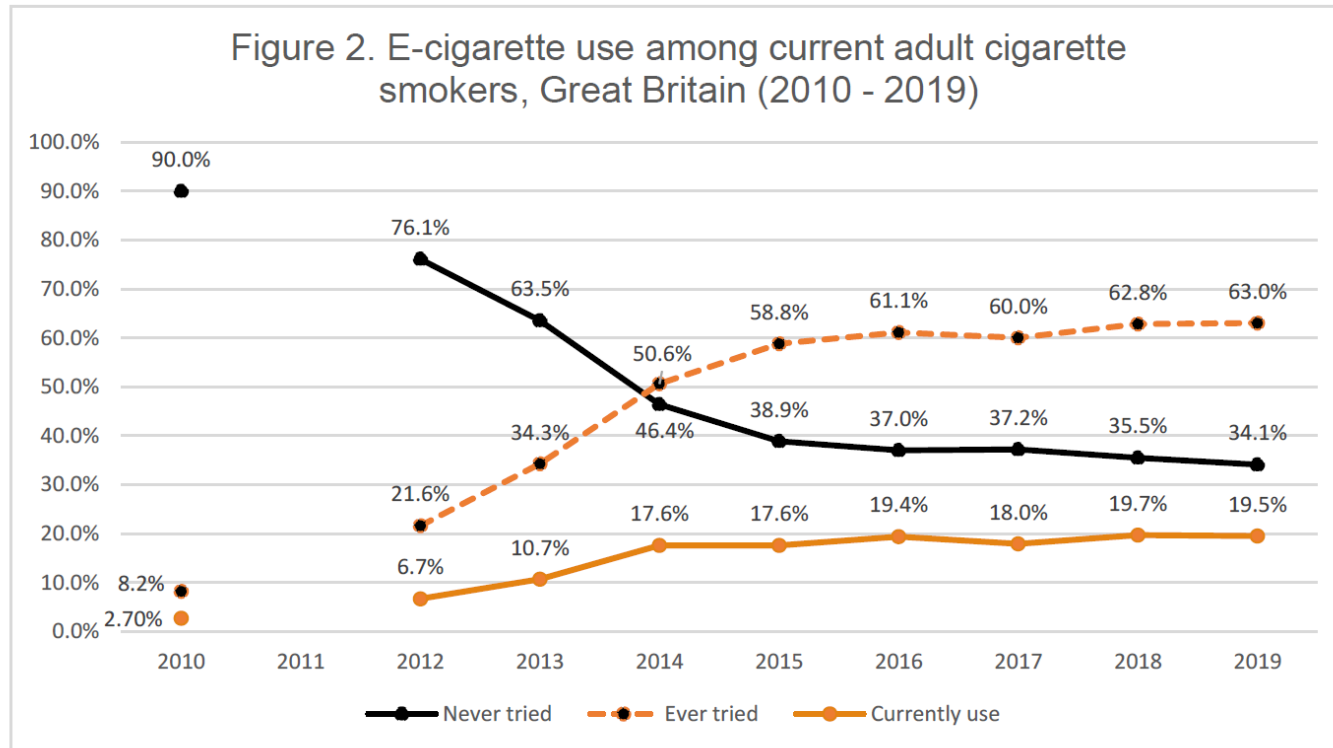
ADD TO CART

WARNING: This product contains nicotine. Nicotine is an addictive chemical.

Is nicotine reduction *necessary*?
Are less harmful alternatives *sufficient*?



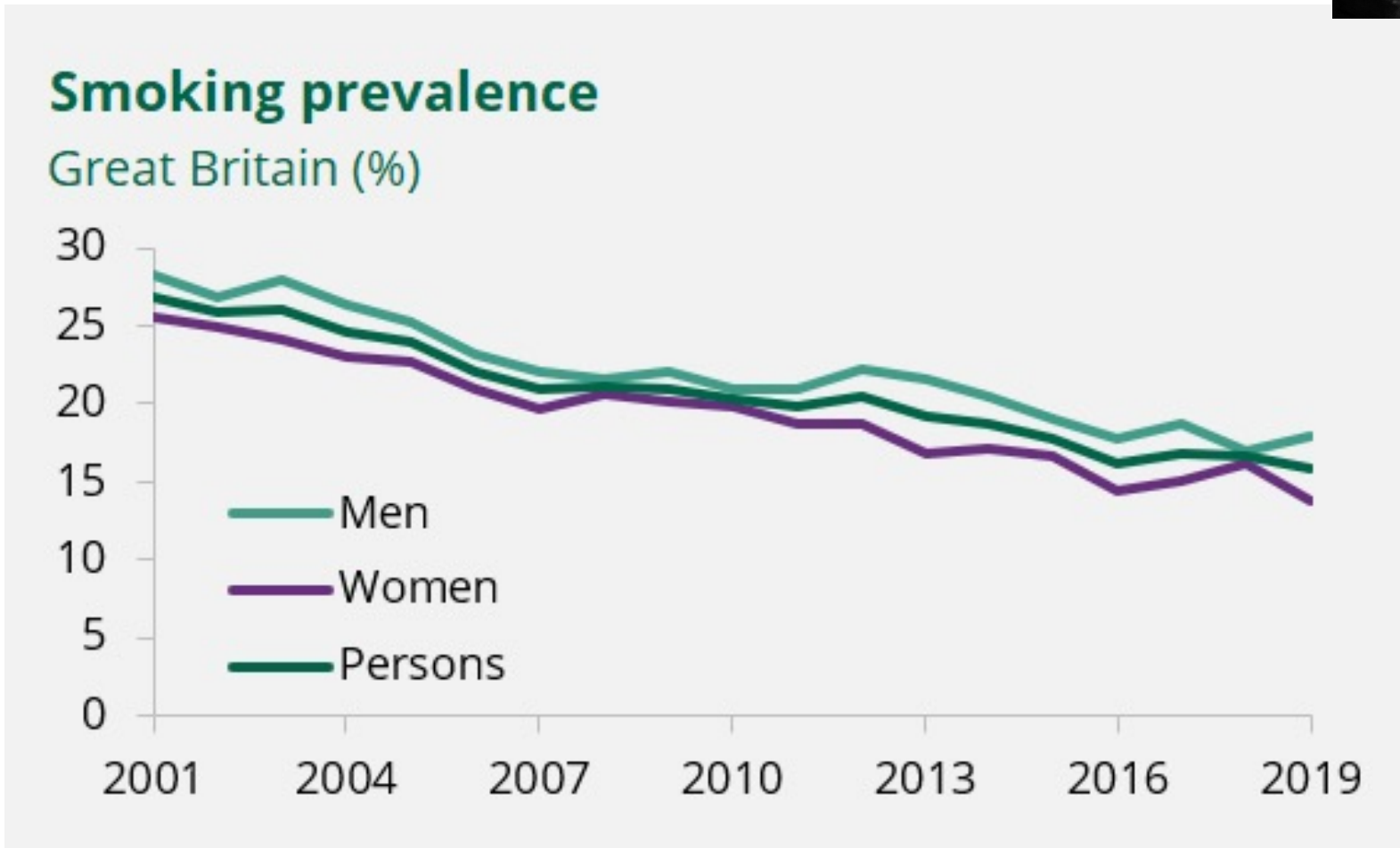
Alternatives may not be enough



Unweighted base: GB adult smokers (2010, n=2297; 2012, n=2093; 2013, n=1895; 2014, n=1776; 2015, n=2037; 2016, n=1704; 2017, n=1632; 2018, n=1633, 2019, n= 1777).

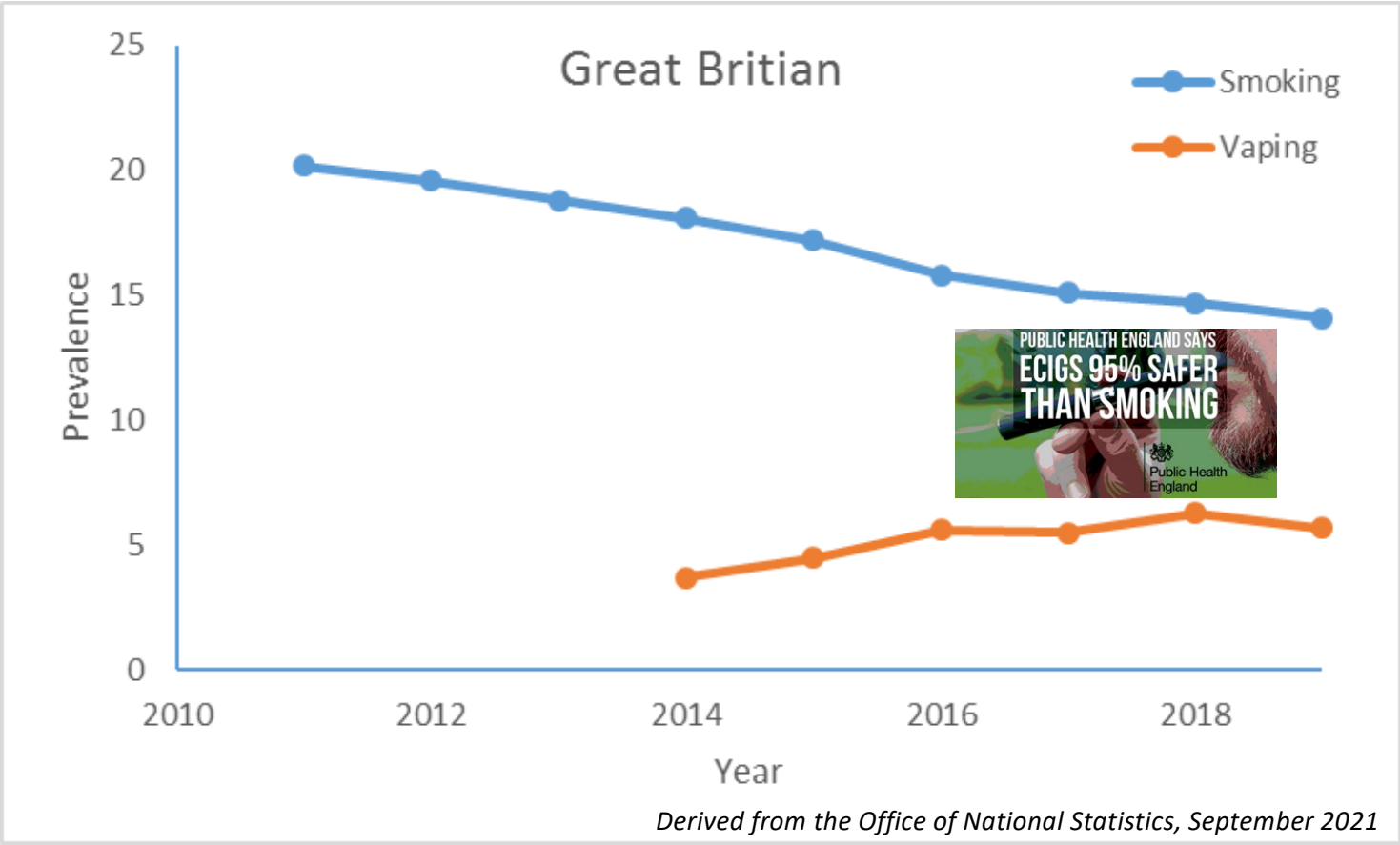
ASH, September 2019

Alternatives may not be enough





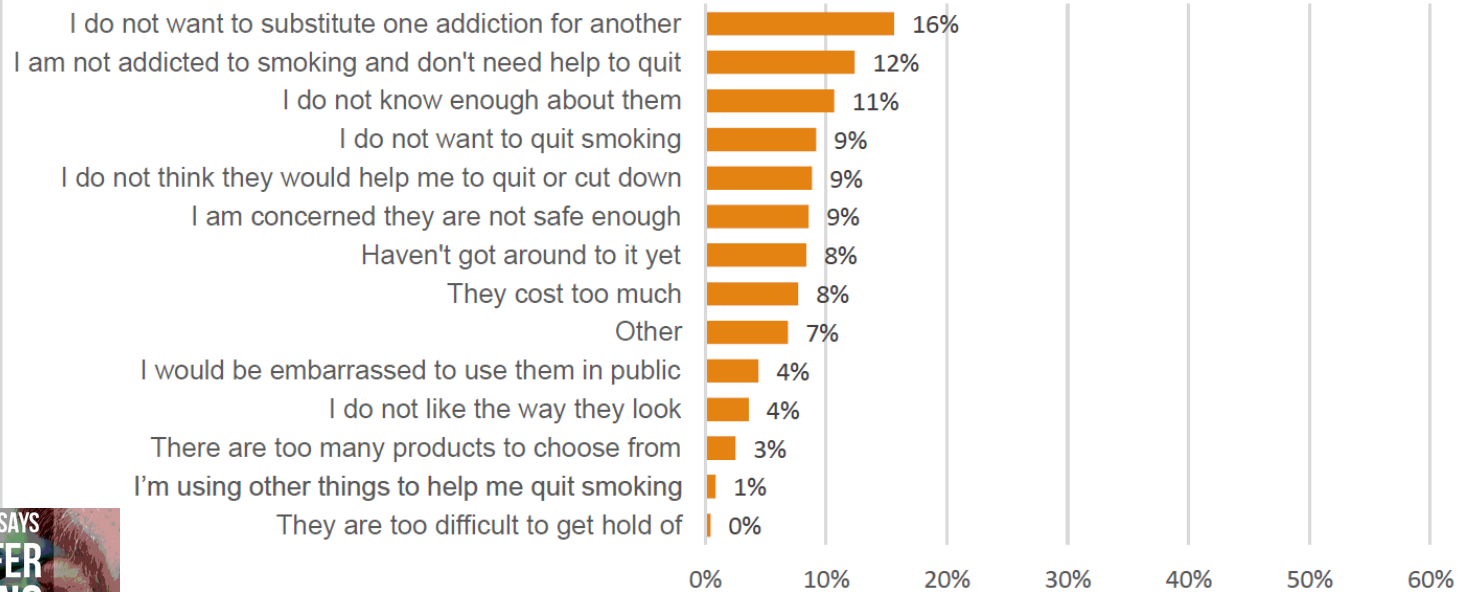
Alternatives may not be enough



Alternatives may not be enough

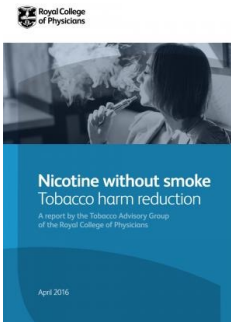


Figure 5. Main reason for not trying an e-cigarette among smokers (2019)

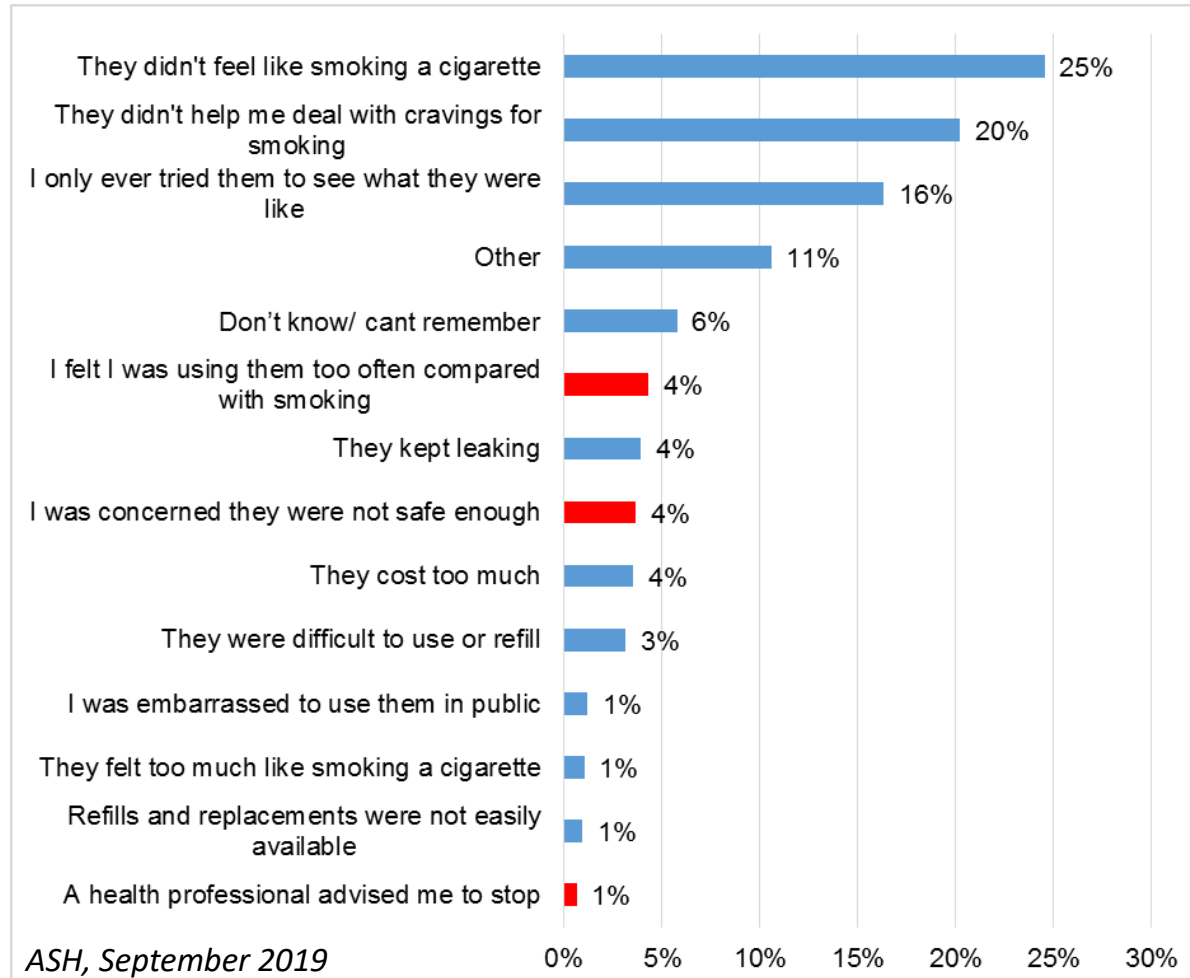


Unweighted base: GB current smokers who have not tried e-cigarettes; 2019, n=614

ASH, September 2019



Alternatives may not be enough



Royal College of Physicians



Nicotine without smoke
Tobacco harm reduction

A report by the Tobacco Advisory Group
of the Royal College of Physicians

April 2016





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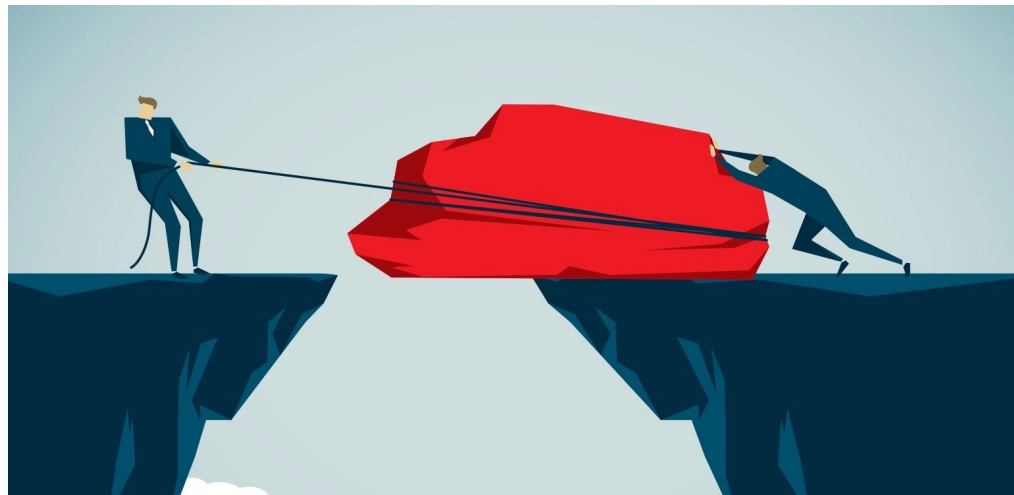
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What alternatives are necessary/sufficient in the context of reduced nicotine cigarettes?

- Flavors
- Nicotine delivery

A terminated trial – preliminary data

- Design: 2x2x2

- Cigarette nicotine content

- Very Low (“VLNC,” 0.04 mg/g)
 - Normal (“NNC,” 15.8 mg/g)



- Vaping Device (e-liquid) nicotine content

- Low (0.3%)
 - Moderate (1.8%)

- Vaping Device (e-liquid) flavor options

- Tobacco - (3) Tobacco/Menthol options
 - Range - (12) Tobacco/Menthol, Mint, Fruit, Dessert options



650 mAh and 2.4 ml tank
with a 2.2-2.4 ohm coil

3ml bottles of e-liquid
Study labels included flavor brand
name and nicotine content.

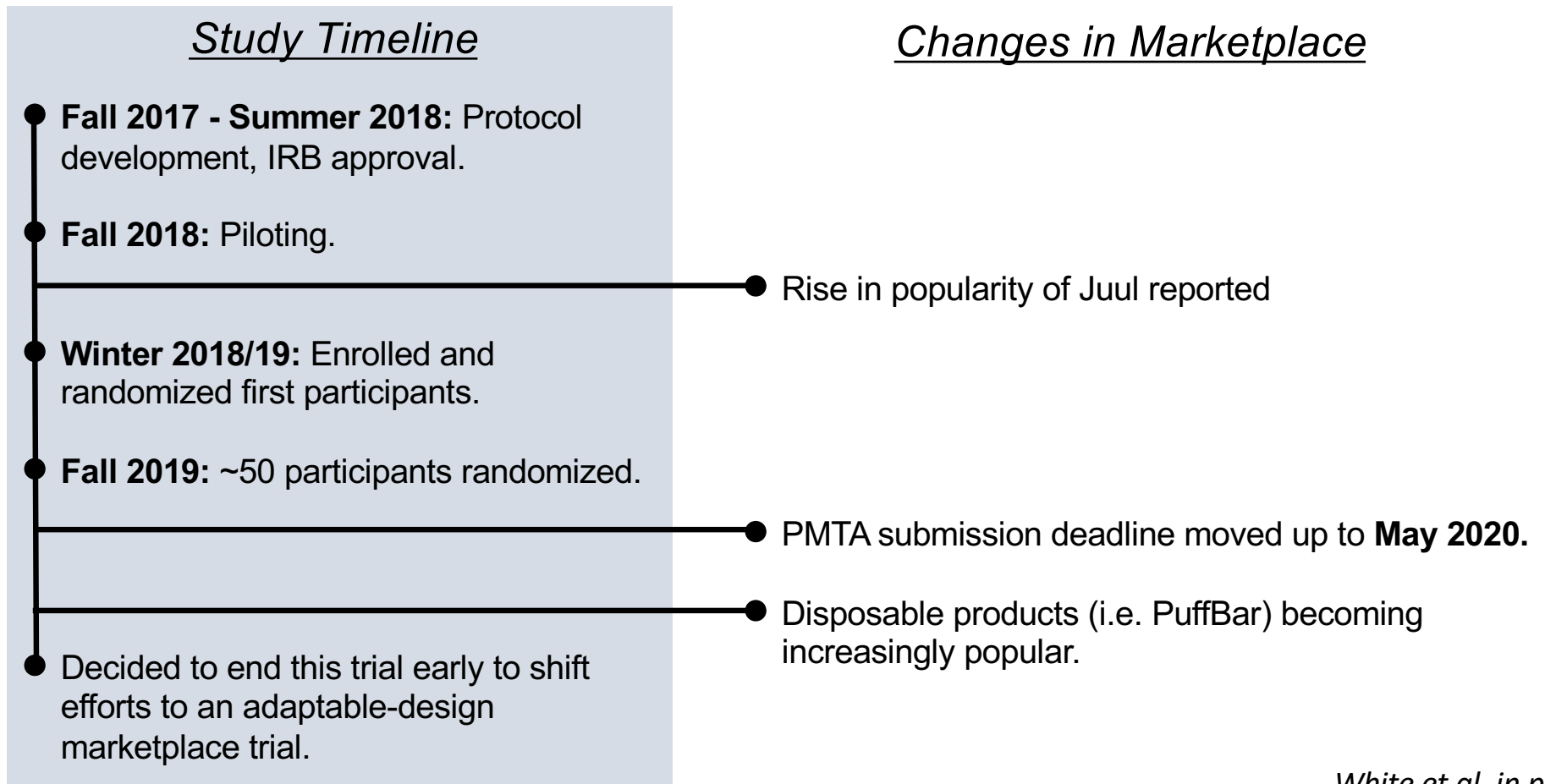


- Participants

- History of smoking 5-50 cigarettes daily for past month
 - History of using vaping device on 2+ separate occasions, but less than 15 days in past month

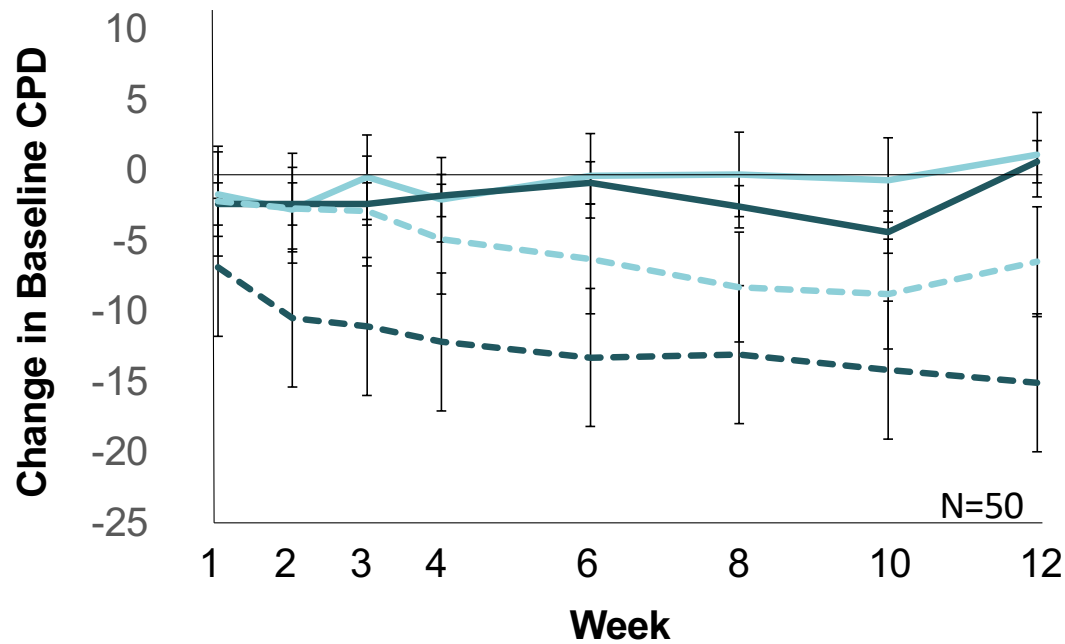
White et al, in prep

A terminated trial – preliminary data

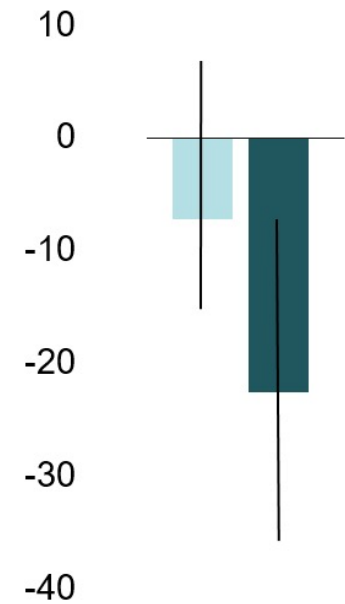


White et al, in prep

A terminated trial – preliminary data



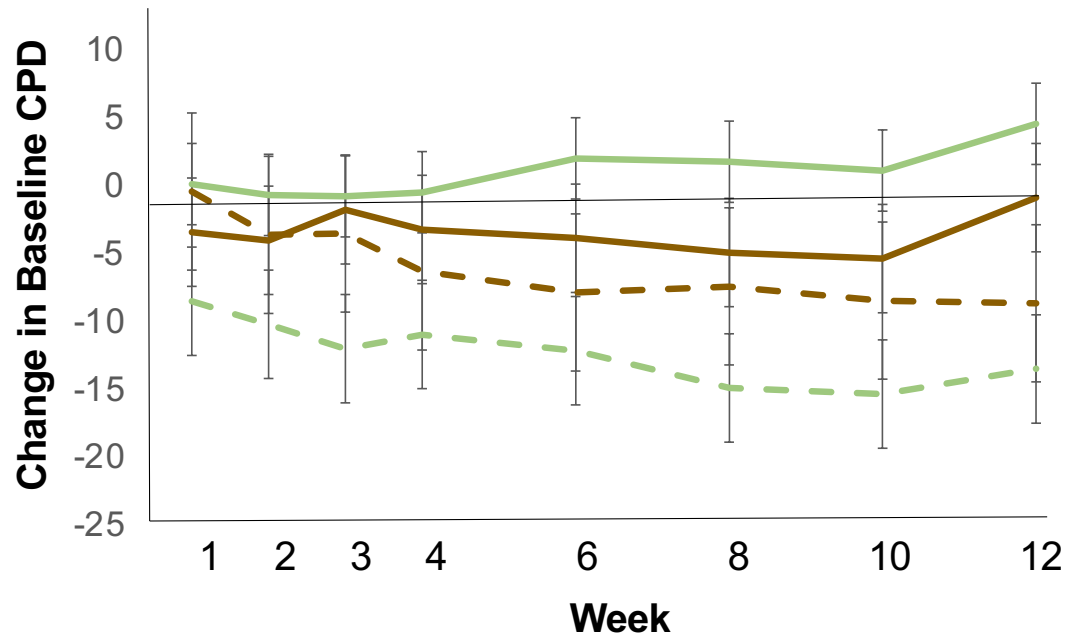
- NNC Cig + Low E-liquid
- NNC Cig + Moderate E-liquid
- - - VLNC Cig + Low E-liquid
- - - VLNC Cig + Moderate E-liquid



	Mean difference in Week 12 CPD (95% CI)	Interaction p-value
VLNC vs NNC Low E-liquid	-7.22 (-17.32, 2.87)	0.061
VLNC vs NNC Moderate E-liquid	-22.6 (-35.56, -9.64)	

Adjusted for baseline CPD, site, menthol status, and age group.

A terminated trial – preliminary data





- NNC Cig + Tobacco E-liquid
- NNC Cig + Range E-liquid
- - VLNC Cig + Tobacco E-liquid
- - VLNC Cig + Range E-liquid

A crowdsourcing study – Discrete Choice

Imagine one of the products below will be the only nicotine and tobacco product you have access to for the next week. Which product would you choose?

(1 of 18)

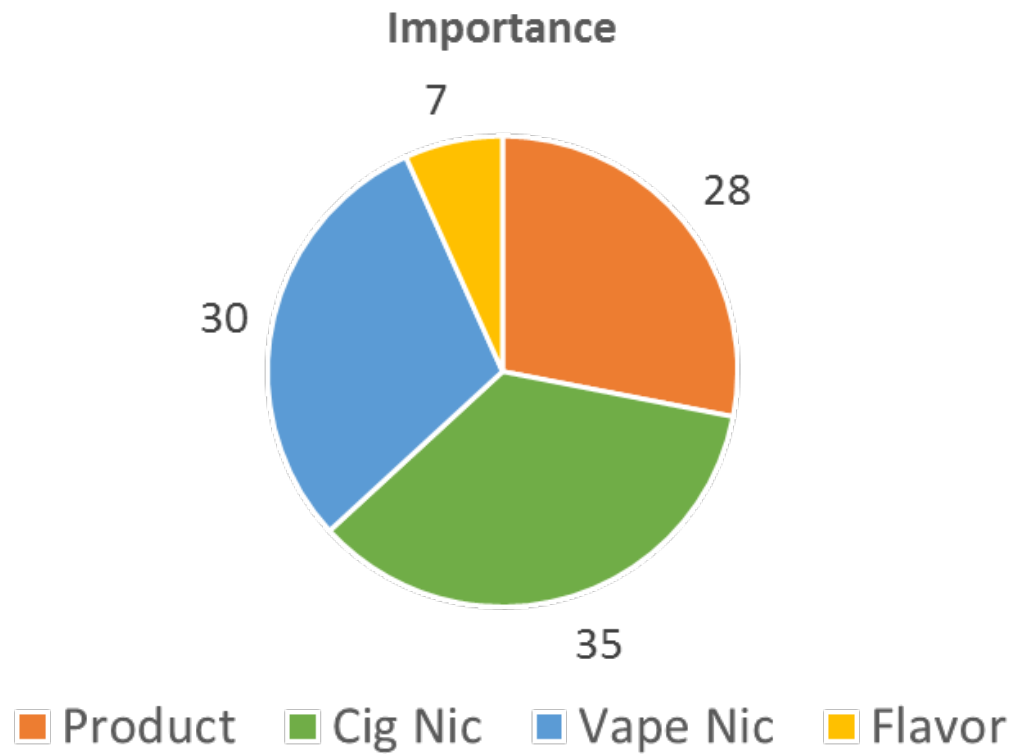
	Option 1	Option 2
PRODUCT	 Cigarettes	 Vaping Device
FLAVOR	Your choice of non-menthol or menthol.	Your choice of tobacco and menthol flavors.
NICOTINE CONTENT	Low: About <u>half</u> as much nicotine as your usual cigarettes, per puff.	Low: About <u>half</u> as much nicotine as your usual cigarettes, per puff.
	<input type="button" value="Select"/>	<input type="button" value="Select"/>

White et al, in prep

A crowdsourcing study – Discrete Choice

Product Type	Cigarettes	Vaping Device
Nicotine Content	<ul style="list-style-type: none">• Very Low: <u>95% less</u> nicotine than your usual cigarettes, per puff.• Low: About <u>half</u> as much nicotine as your usual cigarettes, per puff.• Normal: The <u>same</u> amount of nicotine as your usual cigarettes, per puff.	<ul style="list-style-type: none">• Very Low: <u>95% less</u> nicotine than your usual cigarettes, per puff.• Low: About <u>half</u> as much nicotine as your usual cigarettes, per puff.• Moderate: The <u>same</u> amount of nicotine as a your usual cigarettes, per puff.
Flavor	<ul style="list-style-type: none">• Your choice of menthol or non-menthol	<ul style="list-style-type: none">• Your choice of tobacco and menthol flavors• Your choice of tobacco, menthol, fruit and dessert flavors

A crowdsourcing study – Discrete Choice



Summary

The Science Behind Nicotine Reduction

- Nicotine levels at or below 2.4 mg/g reduce smoking and exposure to harmful constituents
- Smokers switched to very low nicotine content cigarettes do NOT compensate; moderate reductions may lead to compensation
- Immediate reduction is likely to lead to more rapid declines in smoking and improved public health, but will also present greater challenges in terms of discomfort and adherence.
- Use of very low nicotine cigarettes is likely to increase smoking cessation by reducing dependence, craving, and withdrawal and by increasing quit attempts and the probability of achieving abstinence.
- Reducing nicotine in cigarettes leads to significant non-adherence (i.e., participants use non-study cigarettes)

Summary

The Implementation of Nicotine Reduction

- Smokers are likely to demonstrate a wide range of behavioral changes following implementation of a low nicotine product standard ranging from abstinence to persistent smoking to use of alternative sources of nicotine.
- In the absence of policies (like nicotine reduction) that reduce the abuse liability of cigarettes, many smokers will fail to try and/or persist in using alternative nicotine delivery systems.
- If the goal is to maximize improvements in public health, both nicotine reduction and harm reduction approaches are likely to be necessary but neither may be sufficient to **rapidly** end the devastation caused by smoking.

Preference

a greater liking for one alternative over another or others

Choice

an act of selecting or making a decision when faced with two or more possibilities.

Thank you for listening

Decision-making

the action or process of making decisions, especially important ones

Control

the power to influence or direct people's behavior or the course of events

Habit

an acquired mode of behavior that has become nearly or completely involuntary

Addiction

a greater liking for one alternative over another or others

Drugs disrupt the circuits that give us free will.
It is really the essence of addiction.

- Nora Volkow, 168th Annual Meeting of the American Psychiatric Association

