The impact of menthol and mint e-liquid bans on menthol cigarette smokers

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BACKGROUND, RATIONALE, AND CONTEXT

One of the key challenges of tobacco regulation is weighing the risks and benefits of potential policies across different populations, including users and non-users. Tension arises between policies intended to prevent adolescent and young adult (AYA) tobacco initiation and those intended to reduce harm among current tobacco users. Specifically, menthol flavored e-liquid restrictions aimed at reducing AYA vaping may unintentionally discourage menthol cigarette smokers from switching to potentially less harmful products.

Adult menthol cigarette smoking. In 2017, the U.S. adult smoking rate reached an all-time low of 14%. Yet, cigarette smoking remains a leading cause of premature death in the U.S., responsible for nearly 480,000 deaths annually. An estimated 30% of all cancer deaths are attributable to cigarette smoking. Despite declines in the overall cigarette smoking rate, research indicates that rates of *menthol cigarette* smoking are remaining constant or even increasing. Nearly one-third of the cigarettes sold in the U.S. include menthol as a characterizing flavor. Priority populations, including racial/ethnic minorities and LGBTQ+, disproportionately smoke menthol cigarettes. For example, over 80% of black smokers prefer menthol cigarette brands, in part due to tobacco industry marketing. Menthol flavoring in cigarettes masks the harshness or bitterness of tobacco, enhances the reinforcing effects of nicotine, and is associated with poorer cessation outcomes, especially among black smokers. *Encouraging menthol cigarette smokers, who are unable to quit using nicotine, to switch to potentially less harmful products, like e-cigarettes, could improve public health outcomes*.

Adolescent and young adult vaping. Although the cigarette smoking rate is declining, use of e-cigarettes or vaping devices is increasing, especially among AYA. The 2019 *Monitoring the Future* survey reported over 25% of high school seniors indicated past 30-day vaping, a substantial increase from 2017. Vaping devices with disposable pods containing nicotine e-liquids, like JUUL (see Figure 1), account for a large proportion of the e-cigarette market share and are disproportionately used by AYA. These devices are available in many e-liquid flavors including menthol and mint. A recent Truth Initiative® survey found that mint was the second most popular JUUL pod flavor among AYA. *Therefore, tobacco control policies banning or restricting sales of flavored e-liquids, including mint, could potentially reduce AYA vaping.*

Tobacco product regulation. In November 2018, the FDA commissioner announced a plan for reducing AYA tobacco initiation by restricting or eliminating flavored tobacco products including

flavored e-liquids (e.g., fruit, candy). However, menthol and mint e-liquid flavors were excluded from the policy because they may help current smokers transition to potentially less harmful products. Then, in September 2019, the FDA announced in response to the continued increase in AYA vaping that it would enforce the premarket approval process for all non-tobacco flavored e-liquids, including menthol and mint. This enforcement discretion would require e-liquid companies to provide data showing that the availability of each flavored e-liquid would be beneficial for the protection of public health or else it would not be approved for sale. The timeline for this updated FDA enforcement action is unclear and likely to face legal challenges from the tobacco industry and vaping small businesses. In the absence of federal regulation, states and local agencies are enacting their own e-cigarette restrictions. Michigan, New York, Washington, and Oregon banned all flavored e-liquids including menthol and mint while Massachusetts and San Francisco, CA banned all e-cigarette products.

If a regulatory agency's primary goal is to reduce AYA vaping, then eliminating all e-liquid flavors including menthol and mint would likely be the ideal policy approach. The Campaign for Tobacco-Free Kids® and other advocacy groups have expressed their support for including menthol and mint in all e-liquid policy bans or sales restrictions. Alternatively, although not suitable for AYA, vaping devices, like JUUL, may be appealing substitution products for current smokers who are unwilling or unable to quit using nicotine but want to stop smoking. From a harm reduction perspective, switching from combusted tobacco (cigarettes) to non-combusted products (e-cigarettes) will likely result in a net positive public health impact. Yet, e-liquid flavor bans or sales restrictions that include menthol may unintentionally discourage menthol cigarette smokers from switching to e-cigarettes. If a goal of regulation is also to maximize switching to potentially less harmful products, then allowing menthol and mint e-liquids to remain on the market, as initially proposed by the FDA, may be a better approach; but, this policy may not lead to reductions in AYA vaping due to the availability of the youth-appealing mint flavor.

Menthol vs mint e-liquid flavors. Given the strong interest in eliminating e-liquid flavors that are appealing to AYA, a highly relevant regulatory question is whether menthol and mint e-liquids are two distinct flavors with differential policy implications. Menthol and mint e-liquids are often classified together as 'menthol/mint', including in the 2019 *National Youth Tobacco Survey*, which reported 'menthol/mint' as the second most popular flavor among AYA. However, this combined classification creates an underlying assumption that menthol and mint e-liquids are equally appealing to AYA. Conversely, the recent survey by Truth Initiative® found that among 18-21 year olds only **2%** reported using menthol JUUL pods compared **32%** who reported using mint JUUL pods, indicating that menthol and mint e-liquids may have differential use and appeal among AYA. *Including mint in e-liquid flavor bans or sales restrictions to discourage AYA use but allowing menthol e-liquids to remain on the market as potential substitution products for menthol cigarette smokers may be an optimal policy approach.* However, this is currently unknown. The focus of this proposal is to determine how menthol and mint e-liquid flavor restrictions intended to reduce AYA vaping may affect adult menthol cigarette smokers.

Policy impact on racial minority smokers. Over 80% of black smokers prefer menthol cigarette brands. Black smokers have poorer cessation outcomes, likely at least partially due to smoking menthol cigarettes, and lower lung-cancer survivorship. A recent survey reported that relative to

white smokers, minority smokers had lower odds of switching to e-cigarettes, so e-liquid flavor regulations aimed at reducing AYA vaping could also have the unintended consequence of further discouraging minority smokers from switching to potentially less harmful products.

Behavioral Economics. Behavioral economics is an ideal framework for answering tobacco regulatory questions because it applies economic constructs such as product substitution and demand elasticity to individual product choice and decision-making. In behavioral economics, "price" is typically indicated in dollars but changes in price are also considered to be analogous to changes in effort required to obtain the product. The Cigarette Purchase Task (CPT) is an example of a behavioral economic assessment for smoking. In the task, participants are asked to indicate how many cigarettes they would purchase as the price of these products increases. From these data, a number of measures can be calculated including demand intensity (consumption at the lowest price) and demand elasticity (sensitivity to increases in price). A variation of the CPT is a cross-price task, which can be used to examine how changing the price of one commodity affects consumption of another commodity.

The Experimental Tobacco Marketplace (ETM) task is an extension of the cross-price task and allows researchers to examine the effects of cigarette price increases on alternative product purchasing within a complex tobacco marketplace. In this paradigm, participants use account balances to buy tobacco products from an online store. Across multiple task iterations, the price of cigarettes increases while the prices of the other tobacco products remain constant. Assessing cigarette substitution across multiple tobacco products is more informative to tobacco regulatory science than simple cross-price tasks because it more closely simulates real world decision-making from retailers selling multiple tobacco products. Recently, we conducted a pilot study using the ETM to examine the impact of a menthol cigarette ban on tobacco product purchasing.

OBJECTIVES

We are proposing a four condition ETM study to determine if banning mint but not menthol e-liquids is sufficient for encouraging menthol smokers to switch to potentially less harmful products. This proposal will also contribute vital information on how black smokers may be affected by menthol and mint e-liquids bans or sales restrictions in order to avoid potential unintended consequences in this group.

Aim 1: To determine how the availability of menthol e-liquids affects combusted tobacco purchasing in menthol cigarette smokers. *Hypothesis 1: Non-menthol cigarette purchasing will be greatest when only tobacco e-liquids are available, indicating that the availability of menthol e-liquids is important for encouraging menthol cigarette smokers to switch to potentially less harmful products.*

Aim 2: To establish if the availability of mint e-liquids is beneficial to menthol cigarette smokers. *Hypothesis 2: Non-menthol cigarette purchasing will not differ by more than 10% when only menthol e-liquids are available compared to when menthol and mint e-liquids are available, indicating that banning mint e-liquids would not discourage menthol cigarette smokers from switching to potentially less harmful products.*

Exploratory Aim: To evaluate the effect of menthol and mint e-liquid restrictions among black menthol cigarette smokers. *The effects of the e-liquid marketplace manipulation will be replicated among black smokers.*

METHODS AND MEASURES

Overall Study Design

We propose to conduct a within-subjects, multi-session virtual lab study and validation field assessment to determine how the availability of menthol and mint e-liquids affects product purchasing among menthol cigarette smokers. Adult daily menthol cigarette smokers (N=80) will be recruited for this study. After initial eligibility is assessed, participants will complete six virtual sessions (1 baseline, 4 experimental, and 1 follow-up), with three in-person components, and one field assessment to evaluate their tobacco use.

Design and Setting

Participants will be recruited from Winston-Salem, NC and the surrounding area using advertisements on public transit, community flyers, and social media. In a recent trial conducted in Winston-Salem enrolling daily cigarette smokers using similar recruitment methods (U54DA031659; PI: Donny), over 60% of participants were menthol cigarette smokers and 31% identified as black or African American. In-person lab visits to drop off biosamples and pickup study products will be conducted at the Wake Forest Tobacco Control Center of Excellence located in Biotech Place in the Innovation Quarter.

Subject Selection Criteria

We anticipate recruiting up to 100 participants to achieve 80 completers. Equal numbers of black and white participants will be enrolled.

Inclusion criteria:

1. 21+ years of age
2. Self-report smoking at least 5 cigarettes per day for the past year
3. Self-report smoking menthol cigarette brands > 80% of the time
4. Breathe carbon monoxide (CO) level > 8 ppm or positive urine NicCheck
5. Willingness to use other tobacco products during the study
6. Speak, comprehend, and read English sufficiently to complete study procedures
7. Have home access to a computer, smart phone, or tablet with a web camera and internet access

Exclusion criteria:

1. Currently seeking treatment to quit smoking
2. Self-reported serious medical or psychiatric condition(s) including cardiovascular and chronic respiratory diseases
3. Body temperature > 100.4 F

4. Cold, flu or COVID-19 symptoms including fever, cough, and runny nose in the past 30 days
5. Currently pregnant, breastfeeding or intending to become pregnant for the duration of the study or unwilling to agree to use adequate protection to avoid pregnancy
6. CO reading > 80 ppm
7. Enrollment stratum (Non-Hispanic, white or Black/African American)

Individuals who report smoking non-menthol flavored cigarettes will be excluded since the purpose of the trial is to understand how menthol and mint e-liquid flavor restrictions affect menthol cigarette smokers. We plan to enroll equal numbers of white and African-American/Black participants so we will exclude individuals once the stratum is full (i.e. 40 enrolled). Those with unstable medical or psychiatric conditions are excluded as these symptoms could affect a participant's ability to complete the study. We will exclude those indicating immediate readiness to stop smoking, as participation in this study may not lead to reductions in smoking. We will exclude pregnant people, those trying to become pregnant and those currently breastfeeding due to the potential harmful effects of tobacco use on developing fetuses and infants. Because participants are required to complete portions of the protocol independently during the virtual lab sessions, they will need to be able to independently read and comprehend the study materials.

Those who report past 30 day cold, flu or COVID-19 symptoms will be temporarily excluded as a safety precaution. They will be able to re-screen once they have been symptom-free for more than 30 days.

Telephone Screening Survey

Interested individuals will complete a telephone screening interview. The screener will assess: current cigarette smoking; cigarette flavor preference; past 30 day use of tobacco products; pregnancy/breastfeeding; current health status, and intention to quit smoking. The interviewer will record the potential participant's responses in REDCap, web-based data collection platforms hosted by Wake Forest School of Medicine. The phone screening data will be used to establish preliminary eligibility. It will not be used for research purposes. Identifying information will be stored separately in a password-protected Excel spreadsheet on the Tobacco Control Center of Excellence server.

Potential participants will be instructed to show a valid, state issued photo ID during the virtual screening visit. Acceptable forms of identification include a Driver's License, State Photo ID Card, State Voter ID Card, Passport, or Military ID. If the potential participant does not have a valid, state issued photo ID, the interviewer can provide them with information on obtaining one. Participants will be given the option of receiving study information or visit reminders by phone, email, and/or text message.

A participant must complete their Virtual Visit 1 within 30 days of completing the Telephone Screening Survey. If the participant is not able to attend the virtual screening visit in that timeframe, they will need to complete the telephone recruitment questionnaire again but will maintain the same Subject ID number in the participant screening database.

Interventions and Interactions

Virtual Visit 1

Research staff will schedule video calls (e.g., WebEx or Zoom) with the participants. At their scheduled call time, research staff and participants will complete the consenting procedures (more information available below) and electronically sign the consent form via DocuSign. Participants will complete one verbal assessment with research staff via REDCap to collect their identifying information. Participants will then be sent a link to complete the eligibility surveys. Research staff and participants will remain on video while the participant completes the REDCap survey. This will enable participants the ability to ask questions and share computer screens, if needed.

The following forms will be administered verbally by research staff via REDCap:

1. Identifying Information Form will include the participant's Subject Identifier, name, address (including the county of residence), email address, phone number, age, and date of birth.
2. Tobacco Use History and Exposure Questionnaire, which measures variables such as smoking amount, cigarette brand, age of initiation of smoking, number of quit attempts, duration of quit attempts and duration of smoking.

The following screening surveys will be self-administered via REDCap:

1. Brief Medical History Questionnaire to query current diagnoses, symptoms and past health problems.
2. Concomitant Medications Form will assess current medication usage.
3. Demographic History Questionnaire, which will assess age, gender, ethnicity, race, education, income, marital status, living situation, and employment history.
4. Contemplation Ladder[34] to assess intention to quit smoking.
5. Fagerstrom Test for Cigarette Dependence[35] (FTCD) to assess nicotine dependence levels.

In the event that the REDCap websites are not functioning, the virtual visits will be rescheduled to a later date and time.

Eligibility Determination

Research staff will determine eligibility after reviewing all criteria, sans the expired breath carbon monoxide reading and pregnancy test. Researchers will pay ineligible participants $20 for their time spent completing the screening surveys. Eligible participants will complete additional surveys and will receive an extra $10 for their time.

The following baseline assessments for eligible participants will be administered as an interview and entered into REDCap by the interviewer:

1. Timeline Follow Back (TLFB) Questionnaire,[36] which will assess past 14-day tobacco and nicotine product use. If a participant's reported cigarette use on the TLFB conflict with their reporting on the Tobacco Use History and Exposure Questionnaire, the RA will point out

the discrepancy to the participant and ask whether they would like to modify their responses on the Tobacco Use History and Exposure Questionnaire or clarify why they are discrepant (e.g., participants had an upper respiratory infection in the past week that resulted in atypical smoking behavior).

The following surveys will be self-administered using REDCap:

1. Tobacco Policy Questionnaire (adapted from International Tobacco Control (ITC) – Four Country survey) which assess support for various tobacco control policies, including banning menthol flavoring in cigarettes and e-cigarettes.
2. Minnesota Nicotine Withdrawal Scale a measure of nicotine withdrawal symptoms
3. Questionnaire of Smoking Urges-Brief – Usual Brand Cigarette, which measures the urge to smoke
4. Cigarette Evaluation Scale, which measures responses to cigarettes (e.g., reward, satisfaction)
5. Perceived Health Risks Scale, a measure of the perceived addictive potential and other health risks associated with cigarettes, e-cigarettes and nicotine gum
6. Tobacco Product Interest Scale, a visual analog scale assessing interest in use of various tobacco and nicotine products

In-Person Lab Visit 1

After completing Virtual Visit 1, participants will complete the COVID screener within 24 hours of their Lab visit via email or phone. Research staff will wear personal protective equipment including face masks and gloves. The participants will be required to wear facemasks when interacting with the staff. If participants do not have a mask, one will be provided to them to use for the remainder of the study. Temperature checks will be conducted immediately upon arrival using a thermal heat scanner.

Participants will provide carbon monoxide (CO) readings at least 6-feet away from other people, including the research staff, while they have their masks off. NicCheck Strips, which assess cotinine levels in urine, will also be used to confirm smoking status if participants have an expired breath CO reading less than or equal to 8 ppm. Participants with child-bearing potential will complete a urine pregnancy test. Participants will also be given the opportunity to sample the alternative tobacco and nicotine products that will be available during the ETM. Products include: fruit, dessert, mint, menthol, and tobacco flavored e-liquids; non-menthol preferred brand cigarettes; and mint, fruit and cinnamon flavored nicotine gum. Product sampling will occur at least 10-feet from other people, including the research staff. The sampling phase allows participants to draw upon personal experiences when completing the ETM task during Virtual Visits 2-5. This increases the study's validity by reducing the likelihood that they will purchase products from the ETM that they will not use during the field assessment and increases the likelihood of adherence to only using study products.

For the cigarettes and e-liquids, they will be instructed to take puffs ad lib for up to 2 minutes. For nicotine gum, they will be instructed to keep the product in their mouth for up to 2 minutes.

Virtual Visits 2-5

1. Participants will complete Virtual Visit 2 between 1 and 21 days after completing In-Person Lab Visit 1. Virtual Visits 2-5 will ideally be conducted four days in a row to reduce online task fatigue. However, visits may be scheduled up to 7 days apart.

The following assessments will be administered as an interview and entered into REDCap by the interviewer:

1. Timeline Follow Back (TLFB) Questionnaire, which will assess tobacco and nicotine product use since their last virtual visit.

The following surveys will be self-administered using REDCap:

1. Minnesota Nicotine Withdrawal Scale
2. Questionnaire of Smoking Urges-Brief – Usual Brand Cigarette

Participants will complete the ETM task on the computer. If the participant needs assistance with navigating the online marketplace the research staff may screen share and allow the participant to verbally select the items that they would like to purchase. The products available on the ETM include:

- Menthol and non-menthol cigarettes (matched to the participant's preferred brand)
- Fruit, dessert, mint, menthol and tobacco e-liquids (e.g., Suorin iShare)
- Mint, fruit, and cinnamon nicotine gum (e.g., Nicorette).

Participants will undergo one of four marketplace conditions during Virtual Visits 2-5, with the order of administration randomized across participants.

- Marketplace Condition 1 includes only tobacco e-liquids.
- Marketplace Condition 2 includes menthol and tobacco e-liquids.
- Marketplace Condition 3 includes mint menthol, and tobacco e-liquids.
- Marketplace Condition 4 includes fruit, dessert, mint, menthol, and tobacco e-liquids.

Staff will instruct participants to complete the ETM task as if they are purchasing the products from a retailer, and that one iteration of the task will be randomly selected and will determine which products they will use during the field assessment. In reality, we will randomly assign which condition is used 1, 2, 3, or 4 but will assign products based on when menthol cigarettes were not available each to simulate a menthol cigarette ban.

For each marketplace condition, participants will complete 10 iterations of the ETM task in ascending order. The prices for menthol cigarettes on the ETM will be set at: $0.12, $0.25, $0.50, $1.00, $2.00, $4.00, $8.00, and $16.00 and $32.00 per cigarette. During one task iteration, menthol cigarettes will be eliminated from the marketplace to simulate a menthol cigarette ban. The costs for the other products will reflect average prices in NC and will not change during the task. For each task iteration, participants will receive individually-tailored account balances approximately equal to the money they would spend on cigarettes for seven days. They can

purchase as many or few products as their account balance allows. Participants are not required to buy products from the ETM or can buy nicotine gum if they prefer to abstain. If they do not buy products from the ETM and do not use tobacco products during the field assessment (biochemically-verified), then they will receive their ETM account balance at Virtual Visit 6. This payment is delayed to reduce the likelihood that they will use this money to buy their preferred brand menthol cigarettes, thus decreasing the validity of the ETM task.

Participants will be instructed to use only the products purchased from the ETM during the subsequent 7-day period after Virtual Visit 5 and told that we will assess adherence by self-report, product accountability, and biochemical verification. The field assessment validates the ETM task by having participants use the products in the real world, simulating the different regulatory environments. Actual product use enables us to measure their subjective experiences such as withdrawal, craving, or product satisfaction as well as assess changes in carbon monoxide exposure, a biomarker of harm, when using products other than menthol cigarettes. We will conduct between-subjects analyses comparing these secondary outcomes by marketplace condition.

In-Person Lab Visit 2

In-Person Lab Visit 2 will be completed up to 48 hours after completing Virtual Visit 5. Participants will complete the COVID screener within 24 hours of their Lab visit via email or phone. Research staff will wear personal protective equipment during the visit including face masks and gloves. The participants will be required to wear facemasks when interacting with the staff. Temperature checks will be conducted immediately upon arrival using a thermal heat scanner.

Participants will provide CO readings be at least 6-feet away from other people, including the research staff, while they have their masks off.

Participants will be given the products they purchased during the ETM task and will be instructed to only use these products for the next seven days. They will also be given a urine collection cup and instructions for sample collection.

Virtual Visit 6

Participants will complete Virtual Session 6 seven days after completing In-Person Lab Visit 2. They will bring a first morning void urine sample, which will be banked for future biomarker analysis (e.g., total nicotine equivalents).

The following baseline assessments will be administered as an interview and entered into REDCap by the interviewer:

1. Timeline Follow Back (TLFB) Questionnaire which will assess past tobacco and nicotine product use since Virtual Visit 5.

The following surveys will be self-administered using REDCap:

1. Tobacco Policy Questionnaire
2. Minnesota Nicotine Withdrawal Scale

3. Questionnaire of Smoking Urges-Brief – Usual Brand Cigarette
4. Product Evaluation Scale
5. Perceived Health Risks Scale
6. Tobacco Product Interest Scale

Participants will complete the ETM task under the same marketplace condition from which they received their field assessment products. Exploratory pre-post field assessment analyses will examine how actual use of the products affects subsequent purchasing of those products.

Research staff will conduct in-depth interviews with the participants to assess the following constructions: 1) decision-making during the ETM task; 2) use of alternative products during the field assessment; 3) product risk perceptions and; 4) opinions regarding possible tobacco control policies.

In-Person Lab Visit 3

In-Person Lab Visit 3 will be completed up to 48 hours after completing Virtual Visit 6. Participants will complete the COVID screener within 24 hours of their Lab visit via email or phone. Research staff will wear personal protective equipment during the visit including face masks and gloves. The participants will be required to wear facemasks when interacting with the staff. Temperature checks will be conducted immediately upon arrival using a thermal heat scanner. Participants will bring a first void urine sample and all of their used/unused products.

Participants will provide CO readings at least 6-feet away from other people, including the research staff, while they have their masks off.

All participants will be emailed a cessation manual and local smoking cessation resources.

Product adherence

To verify self-reported tobacco use, all used and unused products will be collected and counted at In-Person Lab Visit 3. Discrepancies between consumption stated on the TLFB versus consumption based on the products returned will be addressed. Non-adherence (i.e., using products not purchased from the ETM) will be assessed via the TLFB and qualitative interview with the importance of honest self-reporting emphasized. If participants report not using combusted tobacco, then CO readings < 6 ppm will verify their self-report.

Compensation

Participants will be paid $155 for completing the study. They will earn $30 for completing Virtual Visit 1, $15 per visit for completing Virtual Visits 2-6 plus a $50 bonus for completing the study.

Participants that do not meet enrollment criteria at Virtual 1 will earn $20 for attending the visit. Participants that start but do not complete the study will receive payments for the virtual visits attended. They will not receive the $50 completion bonus.

ANALYSIS PLAN

Primary Outcome

- Total amount of non-menthol cigarettes purchased when menthol cigarettes are not available.

Secondary Outcomes

- Total amount of tobacco e-liquid purchased when menthol cigarettes are not available.
- Total amount of menthol e-liquid purchased when menthol cigarettes are not available.
- Total amount of mint e-liquid purchased when menthol cigarettes are not available.
- Total amount of dessert and fruit e-liquid purchased with menthol cigarettes are not available

Exploratory Outcomes

- Mean Perceived Health Risk Scale scores
- Mean Product Evaluation Scale scores
- Mean Minnesota Nicotine Withdrawal Scale scores
- Mean Questionnaire on Smoking Urges scores
- Mean Tobacco Product Interest scores
- Mean Tobacco Policy Questionnaire scoresTotal amount of non-menthol cigarettes purchased when menthol cigarettes are not available by race
- Total amount of tobacco e-liquid purchased when menthol cigarettes are not available by race.
- Total amount of menthol e-liquid purchased when menthol cigarettes are not available by race.
- Total amount of mint e-liquid purchased when menthol cigarettes are not available by race.
- Total amount of dessert/fruit e-liquid purchased when menthol cigarettes are not available by race.
- Themes emerging from the qualitative interviews

Sample Size/Estimation/Analysis

Power calculation

Based on prior ETM studies in which the effects of increasing cigarette price were observed in 22-40 participants, a sample size of 80 will be sufficient for answering Aims 1 and 2 as well as the exploratory racial subgroup analyses. No ETM studies have examined the impact of e-liquid flavor availability on combusted tobacco purchasing, so we do not have a direct effect size estimate for our manipulation. In our pilot study, the marketplace manipulation (menthol little cigars available vs. not) resulted in a small effect size (Cohen's d = 0.31), likely because JUUL pods were overwhelmingly preferred. When comparing mean menthol/mint e-liquid purchasing vs mean tobacco e-liquid purchasing, there was a large effect size (d = 1.2). Thus, we anticipate that our proposed marketplace manipulation will be associated with at least a medium effect size (d = 0.5) for non-menthol cigarette purchasing and a sample size of 80 will be sufficient for detecting differences.

For Aim 1 comparing within-participant impact of menthol e-liquid availability on mg of nicotine purchased, our proposed sample size of 80 will have 80% power to detect differences as small as d=0.31 using a paired t-test assuming type I error set to 0.05.

Aim 2 hypothesizes that nicotine purchased will be nearly equivalent when mint e-liquid is available or not. Framing the question as an equivalence test, we set a region of equivalence to be [-0.33, 0.33] standard deviations for the difference in effect with the addition of mint. Employing a paired t-test with type I error set to 0.05, our planned sample size of 80 will have 80% power to reject the null that there is an effect outside of [-0.33, 0.33] in favor of the alternative that the effect lies in [-0.33, 0.33]. In the context of mg of nicotine, this would map to an equivalence region of [-20, 20] mg of nicotine, assuming a standard deviation of 60 mg. In other words, we are sufficiently powered to conclude equivalence between mg of nicotine purchased with and without mint available.

Statistical analysis plan

Linear mixed-effects models with fixed effects for marketplace condition ('tobacco' vs 'menthol & tobacco' vs 'menthol, mint & tobacco') and order of condition administration, and a random effect for participant (to adjust for correlation induced by repeatedly measuring the same participant) will compare the total amount of non-menthol cigarettes and e-liquids purchased at the highest menthol price (Aims 1 and 2). All products will be converted to mg of nicotine (as listed on their packaging) to standardize purchasing across products, as in previous ETM studies.[53-55] Analyses will be conducted to determine if race moderates product purchasing (Exploratory Aim).

ETM data will be used to generate demand curves for each product using an exponential demand equation. Alpha is the rate of change in demand, Q_0 is peak consumption, C is cost, and k is a constant.

Cross-price elasticity estimates will be calculated as the slope of the regression line (B_1) fit to log-transformed purchasing of each alternative product when offered at fixed prices (C) versus log-transformed menthol cigarette price (P): $\log C = B_0 + B_1 \log P$. Exploratory paired t-tests will compare product purchasing during the pre- and post-field assessment ETM task.

For the qualitative data, we will use grounded theory to develop hypotheses related to the topics of interest. Interviews will be audio-recorded and transcribed verbatim. Audio transcriptions will be reviewed for accuracy and entered into Atlas.ti or another qualitative data management software program. Two research staff members will code the first five interviews to achieve greater than 90% interrater reliability and then every 10th interview to ensure integrity. The research team will analyze the interviews using iterative analyses including qualitative research techniques of open and axial coding; major thematic categories; analytical domains; triangulation of data; comparisons within and between groups; and documenting analytical pathways. Saturation will be achieved when no new themes emerge.

HUMAN SUBJECTS PROTECTION

Recruitment Methods

Participants will be recruited by posting study information on flyers distributed in the community, Craigslist, social media channels, and Wake Forest Baptist's "BeInvolved" site. Participants will also be recruited by utilizing MyChart messaging. Members of the PI's research team will perform recruitment. Coordination of potential participants' virtual visits will be done by phone or by email.

Contact information will be stored on password-protected computers that are kept behind locked doors for which only the PI's research team will have access keys and passwords.

Recruitment will be continuous through the course of the study. If necessary, advertisements and recruitment strategies will be redesigned to target specific sub-populations if recruitment falls short of a representative demographic balance.

Participants that have previously performed research with the PI and co-investigator research team and have agreed to be re-contacted for future studies may be contacted for recruitment purposes by email or phone according to their previously stated preference.

Informed Consent

Prior to Virtual Visit 1, participants will be briefly screened over the phone to determine initial eligibility. For this process alone, we will seek a waiver of signed informed consent. This part of the research procedure presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

Before beginning the informed consent process during Virtual Visit 1, participants will need to show a valid, state issued photo identification. The interviewer will confirm the age and identity of the participant via video (e.g., WebEx, Zoom). The interviewer will then present a PowerPoint via screen share of the main takeaways of the informed consent form. Participants will be asked follow up questions to ensure comprehension of the informed consent form.

In order to ensure adequate informed consent, participants will be asked to read the first several lines aloud to determine literacy. If the interviewer determines that the participant is not literate, they will be dismissed from the study but will receive $20 for attending the screening visit. The participant will be instructed to read several open-ended questions aloud and discuss the answers with the researcher. Only after the participant and the researcher are fully satisfied that the participant understands the purpose of the study, the confidentiality of the data, the procedures, the risks/benefits and his/her rights as a research participant will the consent form be signed electronically via DocuSign and the participant undergo screening procedures. The participant will be emailed a signed electronic copy of the consent document for their records.

Confidentiality and Privacy

Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. To help ensure subject privacy and confidentiality, only a unique study identifier will appear on the data collection form. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a linkage file, stored separately from the data. The linkage file will be kept secure, with access limited to designated study personnel. Following data collection subject identifying information will be destroyed *(*three years after closure of the study; paper documents will be shredded, electronic documents will be securely deleted using software that will delete and overwrite sensitive disk space*),* consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff. Data and records will be

kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

Data Safety and Monitoring

The principal investigator and co-investigators will be responsible for the overall monitoring of the data and safety of study participants. The principal investigator and co-investigators will be assisted by other members of the study staff.

Potential risks of participation

1. Survey Questionnaires: The interviews will include questions about medical history, tobacco use, and questionnaires about mood. Answering these personal questions could make the participant feel uncomfortable.
2. Breach of Confidentiality: The risk of the interview is loss of privacy if other people find out the results.
3. Smoking Cigarettes: All cigarettes are detrimental to a person's health and can lead to severe or fatal medical problems including:
    a. Cardiovascular diseases: Coronary heart disease, heart attack, stroke, peripheral vascular disease, reduced blood circulation, abdominal aortic aneurysm
    b. Respiratory diseases: Emphysema, bronchitis, tuberculosis and chronic airway obstruction
    c. Cancers: Lung, bladder, liver, colon, cervical, esophageal, kidney, larynx, mouth, pancreatic, throat, stomach cancers and acute myeloid leukemia
    d. Diabetes
    e. Abnormal immune function, rheumatoid arthritis
    f. Other health risks including but not limited to infertility, ectopic pregnancy, lower bone density in postmenopausal women, hip fracture in women, male sexual dysfunction, age-related macular degeneration, blindness and cataracts.
4. Use of Vaping Devices: can exposure users to several chemicals including nicotine, carbonyl compounds, and volatile organic compounds, known to have adverse health effects. The health effects and potentially harmful doses of heated and aerosolized constituents of e-liquids, including solvents, flavorants, and toxicants, are not completely understood. Vaping device aerosol is not harmless "water vapor" although it generally contains fewer toxicants than combustible tobacco products. Specific potential known risks include
    a. Vaping devices contain nicotine which may contribute to some of the disease associated with smoking
    b. The most common side effects related to vaping devices are changes in taste, mucus in throat/sinus, dry mouth, dry cough, throat irritation, sore throat, mouth ulcers, dizziness, headache, and nausea.
    c. On rare occasions, batteries from vaping devices have exploded/ignited and injured users

d. Vaping devices can overheat and present minor burn risks if the button is turned on repeatedly. Participants are told to be careful if storing the device in a place where the button might accidentally be pressed often.
e. Ingestion of e-liquids containing nicotine can cause acute toxicity and possible death if the content of the cartridges containing nicotine are consumed.
f. Participants are told to keep study vaping devices and all e-liquids away from children and pets.

5. Use of Medicinal Nicotine: Most common adverse effects for medicinal nicotine include irregular heartbeat/palpitations, high blood pressure, mouth sores, mouth or throat irritation, heartburn, upset stomach, vomiting, diarrhea, dizzy or lightheadedness, and hiccups or belching. Additional adverse effects associated with nicotine gum include teeth or jaw problems. There may also be a risk of nicotine toxicity including symptoms such as nausea, dizziness, vomiting, diarrhea, and weakness.
6. Dual use of tobacco or nicotine products: There is also the chance of use of more than one product and/or continued use of the products; however, cessation of all tobacco products will be strongly recommended to the participants at the end of the study.
7. Smoking Withdrawal: Participants may experience smoking withdrawal symptoms during this study if they decide not to purchase tobacco products. The symptoms can be uncomfortable but are typically of minimal risk. Smoking withdrawal symptoms include:
    a. Anger, irritability, frustration
    b. Anxiousness, nervousness
    c. Depressed mood or sadness
    d. Desire or craving to smoke
    e. Difficulty concentrating
    f. Increased appetite, hunger or weight gain
    g. Insomnia, problems sleeping or waking at night
    h. Restlessness
    i. Impatience
    j. Constipation
    k. Dizziness
    l. Coughing
    m. Dreaming or nightmares
    n. Nausea
    o. Sore throat
8. Returning to Regular Smoking: It is possible that if participants return to smoking their usual brand of cigarette at the end of the study they may experience mild and transient nausea, dizziness, and lightheadedness.
9. Changes in Mood, Emotions and Psychiatric Symptoms: Smoking and nicotine can affect a person's mood and emotions and are associated with psychiatric disorders including major depressive disorder, general anxiety disorder, bipolar disorder and eating disorders. Any changes in nicotine use or cigarette consumption could adversely affect mood, emotions and the symptoms related to psychiatric conditions in some individuals.
10. Smoking and Oral Contraceptives in Women: Women who smoke and are over the age of 35 should not take oral contraceptives that contain estrogen without consulting their

physician. Smoking while using oral contraceptives can increase the risk of having a cardiovascular event such as a heart attack or stroke. Additionally, there is a potential risk of thrombosis associated with hormonal therapy (including contraceptives) and smoking.

Avoiding Risks during Pregnancy

Smoking during pregnancy can lead to miscarriage, preterm delivery, stillbirth, birth defects, and other problems. To avoid risks to the participant and fetus, female participants will be tested for pregnancy at the Screening Visit.

Expected benefits of participation

There are no immediate benefits from participating in the study. The information obtained from this study may ultimately help the Food and Drug Administration (FDA) decide how best to regulate tobacco products with the goal of improving public health.

Reporting Unanticipated Problems, Adverse Events or Deviations

Identifying Adverse Events

While participating in the study, adverse events will be assessed at Virtual Visit 6 and carbon monoxide levels from In-Person Lab Visit 3. Adverse events will typically be identified during the administration of the Health Changes Questionnaire. Other adverse events may be identified by spontaneous reports from the participant. Withdrawal symptoms are considered an adverse event if the symptom had a significant impact on the participant's daily life, caused a major disruption of functioning, or took any medication for it.

- Health Changes Questionnaire: If the participant answers "YES" to Questions 1, 2, or 3 the interviewer should assess for adverse events.
    1. Have you had any negative changes in your physical or mental health since your last virtual visit? If yes, briefly describe.
    2. Since your last virtual visit, have you received any form of medical care? If yes, briefly describe.
    3. Have you had any changes in medication since your last visit?

Physiological data that will be reviewed:

1. CO level: The 'Adverse Event Form' will be completed if the average of two (or three) consecutive measurements in the same visit is:
    - CO is greater than 50 ppm if CO at Screening/Baseline Visit is < 20 ppm.
    - CO is greater than 60 ppm if CO at Screening/Baseline Visit is 20 – 34 ppm.
    - CO is greater than 70 ppm if CO at Screening/Baseline Visit is 35 – 49 ppm.

For the participant's protection, participants will be withdrawn immediately from the study if any of the following occur:

1. Cardiovascular disease (CVD) event: Typically includes MI (heart attack), PTCA (angioplasty/stenting), bypass surgery, stroke, peripheral vascular disease (arterial

blockages in arms or legs leading to procedure or surgery). Less common CVD problems would be new cardiac arrhythmias (e.g., new atrial fibrillation) or new valvular disease (e.g., mitral or aortic regurgitation).

2. DVT/PE (deep vein thrombosis/pulmonary embolism, i.e., blood clots in the venous system).
3. Suicide Attempt: A participant will be withdrawn if they attempt suicide at any time during participation in the study
4. Psychiatric Hospitalization: A participant will be withdrawn if they are hospitalized for psychiatric reasons at any time during participation in the study.
5. Pregnancy: If a participant indicates they are pregnant at Virtual Visit 6 or In-Person Lab Visit 3, they will be withdrawn from the study, and this event will remain open until delivery. At that time the license medical monitor will contact the participant to ask a few questions about the baby's health and will update the open 'Adverse Event Form'.

The following will be monitored and can lead to the participant being withdrawn by the PI or Licensed Medical Monitor:

1. Expired breath CO >80 ppm
2. Any hospitalization or debilitation in which participation in the study could be detrimental to the recovery process. This will be self-reported by the participant and will be reviewed by the site PI and medical monitor to determine whether continued participation in the study is appropriate.
3. If a participant is behaving in an inappropriate or threatening manner, admits to lying about eligibility criteria, including omitting previous medical diagnoses and medications, is participating in other smoking research studies that could affect the primary outcome measures, does not follow study instructions, etc., then the PI can withdraw them from the study at the PI's discretion.
4. If a participant fails to attend her/his Virtual Visit 1 within the 21-day allowable visit window, they will not be eligible to reschedule the visit or continue participation in the study.