Strengthening Little Cigar and Cigarillo Warnings to Prevent Adolescent Use: Randomized Controlled Trial among US Youth

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Registered at ClinicalTrials.gov, ID NCT06413797, https://clinicaltrials.gov/study/NCT06413797

Contents

Administrative Information

Trial Registration

Title: Strengthening Little Cigar and Cigarillo Warnings to Prevent Adolescent Use: Randomized Controlled Trial among US Youth

Short Title: Little Cigar and Cigarillo Warnings for Youth

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Registration Date: 5/9/2024

Roles and Responsibilities

The research team below is responsible for the study design, management, analysis and interpretation of data; writing any reports or publications; and decision to submit any reports or publications. Participant recruitment and data collection will be completed through Qualtrics and their panel provider, under the supervision of the study team.

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Abbreviations and Definitions of Terms

Abbreviation	**Definition**
LCC	Little cigars and cigarillos
NIH	National Institutes of Health
NCI	National Cancer Institute
FDA	Food and Drug Administration
CTP	Center for Tobacco Products
UNC	University of North Carolina at Chapel Hill
HWL	Health warning labels
OTP	Other tobacco product (products other than little cigars and cigarillos)

Introduction

Background and Rationale

Cigar use exposes youth to addictive effects of nicotine during a critical developmental period and increases the risk of multiple cancers and premature death (National Cancer Institute, 1998; Chang et al., 2015). Recent data indicate that cigars are the second most commonly used combustible tobacco product by youth and that past 30-day cigar use is 1.8%, which translates into 280,000 high school students (Birdsey et al., 2023). Of the three major types of cigars—large cigars, little cigars, and cigarillos—little cigars and cigarillos (LCCs) are the most commonly used in the US, particularly among younger people (Wang, 2019). LCC use also contributes to tobacco health disparities, as Black or African American youth use cigars more frequently than other youth (Wang, 2019). In 2016, the Food and Drug Administration (FDA) deemed LCCs subject to FDA regulation, requiring six rotating text-only warning statements to be on LCC packaging (Food and Drug Administration, 2016). Little research has examined the effectiveness of LCC warnings in reducing youth willingness to use LCCs.

Research from studies of *cigarette* warnings suggests that effective LCC warnings should employ images that illustrate negative health effects associated with use and a larger warning label prominently displayed on the pack (Noar et al., 2016; Hammond, 2011). Among youth, health warnings on *cigarette* packs that contain both text statements and images (i.e., pictorial warnings) are more effective (Noar et al., 2016; Hammond, 2011; Hammond et al., 2012; White et al., 2008; Vardavas et al., 2009; White et al., 2015; Peterson et al., 2010; Andrews et al., 2016) and engaging (Hammond, 2011; White et al., 2008; White et al., 2015; Peterson et al., 2010) than text-only warnings. However, evidence for cigarette warning labels cannot adequately inform implementation of improved LCC warnings for three reasons: 1) there is no evidence on the effectiveness of the FDA-mandated text-only LCC warnings on behavioral intentions or other outcomes among youth (Richardson et al., 2013; Sterling et al., 2013; Glasser et al., 2017), 2) courts have ruled that effective tobacco warnings on one type of tobacco product (i.e., for cigarettes) cannot be used to justify warnings on other types of tobacco (i.e., for LCCs) (R.J. Reynolds Tobacco Co. et Al. v. U.S. Food and Drug Administration, 2012), and 3) LCC users have different demographic and consumption profiles than cigarette users (i.e., LCC users are younger (Substance Abuse and Mental Health Services Administration, 2017), include more Black/African Americans (Substance Abuse and Mental Health Services Administration, 2017), and use LCCs on fewer days per month (Nyman et al., 2016; Jamal et al., 2018)). Furthermore, on July 7, 2020, the US Court of Appeals for the DC Circuit ruled that the FDA cannot require their new warning labels for cigars, claiming that the FDA did not provide evidence on the impact of cigar warnings on smoking rates, including initiation and cessation (*Cigar Association of America v. United States Food and Drug Administration, 2020)*.

Objectives

Our goal is to conduct research that advances the science on LCC warnings that are effective for youth who currently use, have ever used, or are susceptible to using LCCs. This study will inform FDA implementation of LCC warnings, which can reduce LCC use and lessen tobacco health disparities among youth.

Hypotheses

- We hypothesize that LCC warnings at 30% size that include an image (i.e., pictorial warnings) will decrease willingness to use LCCs, compared with FDA-proposed text-only LCC warnings at 30% size and Surgeon General text-only warnings at 10% size.
- We hypothesize that LCC warnings at 30% size that include an image (i.e., pictorial warnings) will increase cognitive elaboration, knowledge of LCC harms, beliefs about LCC harms, and negative affect compared with FDA-proposed text-only LCC warnings at 30% size and Surgeon General text-only warnings at 10% size.
- We hypothesize that LCC warnings at 30% size that include an image (i.e., pictorial warnings) will decrease LCC susceptibility, past 7 day little cigar use, and past 7 day cigarillo use compared with FDA-proposed text-only LCC warnings at 30% size and Surgeon General text-only warnings at 10% size.

Trial Design

The study is designed to be a parallel group trial, with participants evenly allocated to each study condition, using a superiority framework.

Methods: Participants, Interventions, and Outcomes

Methods Overview

We will conduct a one-week web-based RCT among U.S. youth who are susceptible to, have ever used, or currently use LCCs. In this study, LCC warnings on packs will be electronically presented to participants daily to determine if pictorial LCC warnings at 30% size decrease willingness to use LCCs compared to FDA proposed text-only warnings at 30% size and a control condition (Surgeon General text-only warnings at 10% size). We will apply a daily diary methodology to present LCC warnings on packs to participants over time. Qualtrics will contact, screen, consent and administer the survey. To enroll participants, Qualtrics will screen participants using our inclusion criteria and measures and invite eligible participants to enroll in the study. To collect at least 700 quality completes, we anticipate enrolling up to 2,100 people.

At the beginning of the baseline survey (day 1), participants will first consent to participate in the study and then complete a questionnaire about their LCC use and susceptibility, exposure to cigar advertising and warnings, and demographic characteristics, in addition to other measures. At the end of the baseline questionnaire, survey software will randomly assign participants to one of the 3 study conditions. The three study conditions are 1) Pictorial (text + image) 30% size warnings , 2) FDA-proposed text-only LCC warnings at 30% size, and 3) Control condition (current status Surgeon General text-only warnings at 10% size). Participants will be contacted each day and invited to complete the survey for that day of the study protocol.

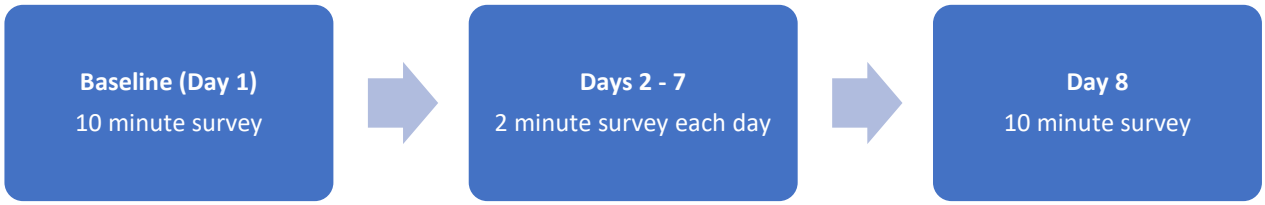
For six subsequent days (days 2-7), participants will be contacted and asked to complete a daily survey. During these daily surveys, participants will view an image of a cigarillo package with a warning according to the participant's condition. Participants will view a total of 6 different warnings over the course of 6 days. Before seeing the warning, participants will be asked about how often they have thought about the health risks of smoking cigars. After seeing the warning, participants will be asked about the appeal of the cigars in the package, how relevant they feel the warning is to their lives, and how worried the warning makes them feel. Participants will also be asked whether they saw any warnings outside the study about the harms of cigar use in the past day.

For the post-test on day 8, participants will be asked to complete a questionnaire about their willingness to use LCCs, LCC use, and susceptibility among other measures.

Participant timeline

Potential participants will be invited to complete the screener (Day 0) and those who are eligible will be invited to participate in the study. On Day 1, eligible participants will be asked to complete a baseline survey. The baseline survey will be open to enrollment for 2 days. After the baseline closes, participants will receive a survey every morning for Days 2-7 that includes an LCC warning and questions about their cognitive elaboration over the previous day, reactions to the warning, and warning exposure over the previous day. Participants will also be asked to complete a final post-test survey on Day 8.

Survey timing:



Study Setting

The study will be conducted with online surveys, so participants can complete the surveys from any location. Participants must reside in the United States (US) to meet eligibility criteria.

Participants

Eligibility criteria for participation in this study:

1. Members of the recruitment panel (we are partnering with a panel provider for recruitment of all participants)
2. Agree to provide their honest answers
3. Susceptible to using LCCs, or have ever used little cigars and/or cigarillos, or currently use little cigar and/or cigarillos in the past 30 days
4. Age 15 – 20 years old
5. Currently living in US or a US territory
6. Inclusion criteria based on the design of the study:
    a. Able to complete 2 surveys that take approximately 10 minutes
    b. Able to complete a 2-minute survey each day for 6 days
7. Inclusion criteria based on verifying real participants:
    a. Able to verify they are not a bot using CAPTCHA
    b. Able to answer a simple, random math question

Interventions

Experimental Conditions

1) FDA-proposed warnings with added images at 30% size (pictorial warnings)
2) FDA-proposed text-only LCC warnings at 30% size
3) Control condition – Surgeon General text-only warnings at 10% size

Warning Stimuli

The stimuli will vary based on the day of the protocol. The packages that the study warning labels will be shown on will be standardized across the three conditions (see table below for warning text). Specifically, warning labels will be shown on cigarillo packages that are red and branded with the fictitious name “Grey Fox” to minimize the influence of brand loyalty and pre-existing brand perceptions.

Stimuli Order

Day	Condition 1	Condition 2	Condition 3
Day 2	WARNING: Tobacco use increases the risk of infertility, stillbirth and low birth weight.	WARNING: Tobacco use increases the risk of infertility, stillbirth and low birth weight.	SURGEON GENERAL WARNING: Tobacco Use Increases The Risk Of Infertility, Stillbirth And Low Birth Weight.
Day 3	WARNING: This product contains nicotine. Nicotine is an addictive chemical.	WARNING: This product contains nicotine. Nicotine is an addictive chemical.	SURGEON GENERAL WARNING: This Product Contains Nicotine. Nicotine Is An Addictive Chemical.
Day 4	WARNING: Cigar smoking can cause cancers of the mouth and throat, even if you do not inhale.	WARNING: Cigar smoking can cause cancers of the mouth and throat, even if you do not inhale.	SURGEON GENERAL WARNING: Cigar Smoking Can Cause Cancers Of The Mouth And Throat, Even If You Do Not Inhale.
Day 5	WARNING: Cigars are not a safe alternative to cigarettes.	WARNING: Cigars are not a safe alternative to cigarettes.	SURGEON GENERAL WARNING: Cigars Are Not A Safe Alternative To Cigarettes.
Day 6	WARNING: Cigar smoking can cause lung cancer and heart disease.	WARNING: Cigar smoking can cause lung cancer and heart disease.	SURGEON GENERAL WARNING: Cigar Smoking Can Cause Lung Cancer And Heart Disease.
Day 7	WARNING: Tobacco smoke increases the risk of lung cancer and heart disease, even in nonsmokers.	WARNING: Tobacco smoke increases the risk of lung cancer and heart disease, even in nonsmokers.	SURGEON GENERAL WARNING: Tobacco Smoke Increases The Risk Of Lung Cancer And Heart Disease, Even In Nonsmokers.

Additional intervention details

Participants can withdraw from the study at any time if they choose to do so by no longer responding to the survey links and may withdraw their data by contacting the UNC study team.

Multiple strategies have been implemented to maximize adherence to the trial protocol, including reaching out to participants with invitations and reminders each day.

There is no relevant concomitant care or interventions that are permitted or prohibited during the trial.

Outcomes

Primary

- Willingness to use LCCs (day 8)

- Average willingness to use score measured by survey, measured with 2 questions. The final willingness to use score is a mean of the response to the 2 questions, on a scale of 1 to 5, where 1 indicates low willingness to use LCCs and 5 indicates a high willingness to use LCCs.

Secondary

- Past 7 day little cigar use (day 8)
  - Measured by survey with 1 item
- Past 7 day cigarillo use (day 8)
  - Measured by survey with 1 item
- LCC susceptibility (day 8)
  - Measured by survey with 3 items
- Cognitive elaboration about risk of LCC use (day 8)
  - Measured by survey with 1 item
- Warning negative affect/worry (each day)
  - Measured by survey with 1 item
- Knowledge of LCC harms (day 8)
  - Measured by survey with 13 items
- Beliefs about LCC harms (day 8)
  - Measured by survey with 10 items

Other

- LCC quit intentions (day 8)
  - Measured by survey with 3 items
- Past 7 day use of other tobacco products (day 8)
  - Measured by survey with 1 item
- Past 7 day butting out of LCCs (day 8)
  - Measured by survey with 1 item
- Past 7 day forgoing LCCs (day 8)
  - Measured by survey with 1 item
- LCC self efficacy to quit (day 8)
  - Measured by survey with 1 item
- Past 7 day use of blunts (day 8)
  - Measured by survey with 1 item
- Reactance to warnings (day 8)
  - Measured by survey with 3 items
- Conversations about cigar health risks (day 8)
  - Measured by survey with 1 item
- Cigar appeal (each day)
  - Measured by survey with 1 item
- Warning relevance (each day)
  - Measured by survey with 1 item
- Unaided recall of cigar warnings (day 8)
  - Measured by survey with 1 item
- Confirmed recall of cigar warnings (day 8)
  - Measured by survey
- Recognition of cigar warnings (day 8)
  - Measured by survey with 6 items
- Self-reported learning (day 8)
  - Measured by survey with 1 item

Sample Size

The sample size is based on a meta-analysis that compared text-only cigarette warnings to warnings with text and images and reported a standardized mean difference in willingness of d=0.26 (Noar, 2016). Based on the standardized effect size observed in that study and enrolling 700 people in the study (233 per group), we would have 80% power at α=0.05 to detect the same standardized effect size change between the FDA pictorial warning and FDA text only warning group. Secondary outcomes that are measured daily will have higher power to detect differences between groups.

Recruitment

We are working with Qualtrics research services to conduct this study and enroll participants from one of the panel providers that they work with. Qualtrics has access to high quality research panels across the US. Qualtrics is able to leverage its panels to provide timely and reliable data collection to UNC and other research universities. We have high confidence that Qualtrics will be able to meet our recruitment goals.

Compensation Plan

Qualtrics will manage participant incentives. Participants in studies conducted by Qualtrics receive an incentive based on the length of the survey and their specific profile. The types of rewards vary and may include cash, airline miles, gift cards, redeemable points, sweepstakes entrance and vouchers. For this study, participants who complete the baseline, 3 of the daily message surveys, and the post survey on day 8 will receive an incentive. Participants who complete only a few of the surveys but do not satisfy the criteria above will not receive an incentive.

Methods: Assignment of interventions

Allocation and Blinding

Participants will not be informed specifically about the possible interventions that they may be assigned to. Researchers will not be blinded to the condition that participants have been assigned to. All outcome measures will be assessed via online survey. At the end of the baseline survey, survey software will randomly assign participants to one of the three study arms. Participants will have an equal chance of being randomized to each study arm.

Methods: Data collection management, and analysis

Data collection methods

Data collection will be conducted using Qualtrics web survey platform. Where possible, the measures used are previously developed and validated measures. Multiple strategies have been implemented to maximize adherence to the trial protocol, including reaching out to participants with invitations and reminders each day, and compensating them based on completion of the most important questionnaires (i.e., baseline, at least 3 daily surveys, and the post survey).

Screener

Qualtrics will invite potential participants to complete the screening survey and people who are eligible will be invited to complete the baseline survey. The screener is used to assess participant eligibility and collect demographic data.

Baseline Survey: Day 1

- Eligible participants will be invited to participate in the study and complete the baseline survey to enroll. The baseline survey will be open to enrollment for 2 days.
- The first part of the baseline survey will be an assent/consent form with an agreement to participate in the study.

- The baseline survey contains baseline tobacco use and susceptibility questions and additional demographic questions.
- At the end of the baseline questionnaire, survey software will randomly assign participants to one of the 3 study conditions.

Daily Surveys: Days 2-7

- There are 6 daily surveys, which align with each participant's condition. Participants will stay in their condition throughout the study. Depending on the day, participants will see a different message and be asked questions about their perceptions of the warning and the previous day.

Post Survey: Day 8

- For the post-test on day 8, participants will be asked to complete a questionnaire that is approximately 15 minutes in length about their willingness to use LCCs, susceptibility to LCCs, cigar knowledge, and other relevant survey questions.
- Participants will also be asked about their study experience.

Data Management

Data management will be conducted by the study team. Multiple processes will be implemented to ensure high data quality, including internal pilots to test the protocol and ensure that data collection instruments are working properly, and ongoing data monitoring will be conducted during data collection to ensure that any issues with data quality are caught early and fixed. A pilot of the protocol with actual participants will be conducted before the full study is launched and participants will be asked about their experience in the study at the end of the pilot to further ensure that the protocol is working as intended and ensure high quality data collection.

Statistical Methods

We will analyze the data using intention-to-treat analyses. Our primary outcome is willingness to use LCCs at post-test. We will model willingness to use LCCs with randomly assigned experimental condition as the between-participant predictor.

Analysis methods will depend on the time point that the outcome was measured. Post-test measures will be analyzed differently than repeated measures from the daily surveys, as outlined below.

Analysis methods for post-test measures will use linear models for continuous outcomes, including the primary outcome of willingness to use, and logistic models for dichotomous outcomes. Participants who were randomized to an intervention will be included in the analysis. Missingness will be accounted for by including covariates in regression models where the covariates are assumed to satisfy a missing at random (MAR) assumption for the outcomes. Estimation will proceed using maximum likelihood.

Mixed models will examine differences between treatment groups for items measured multiple times in the daily surveys (e.g., negative affect). For these models, we will use linear mixed modeling to account for the repeated measure design.

Methods: Monitoring

To ensure maximum protection of human subjects, we submitted our research project information to the School of Medicine Data Safety and Monitoring Board at the University of North Carolina at Chapel Hill and asked them to make the final decision regarding risk to participants and whether our study should receive their supervision. A representative of the board agreed that given that the study involves a low risk behavioral intervention in a healthy population, oversight by the board was not necessary.

Adverse events are not expected in this trial due to the minimal risks to participants, and no threat to participant health. Accordingly, plans for collecting, assessing and reporting adverse events are not necessary.

We have no plans for auditing trial conduct.

Ethics and dissemination

This trial was approved by UNC's IRB under IRB # 23-2455.

All protocol changes will be communicated to the study team, and any change in participant interaction will be approved by UNC's IRB. Protocol changes will be tracked in an appendix table with new versions after initial approval including the date, version number, and a summary of changes.

Consent

Consent will be collected electronically as part of the baseline survey at the beginning of the study. At the beginning of the baseline survey, potential participants who are 18 years old or older will view the consent form with an agreement to participate in the study. For participants who are younger than 18, we will collect consent from their parent or guardian and then collect assent from the potential participants themselves. Participants will only be able to proceed with the study with appropriate consent/assent agreements.

Confidentiality

We will take the following steps to minimize the risk to a breach of confidentiality via unauthorized access, use, disclosure, modification, loss or theft of participants' information:

- We will use and enforce appropriate security measures including physical, technical and administrative safeguards.
- Data will be stored on a university secure server that is password accessed and is only accessible to key research personnel.
- All study personnel are required to have valid training on ethics of research on human subjects and to complete confidentiality certification procedures upon employment.
- The research team will not collect nor have access to personal identifying information.

This study proposes research that has been determined to include Security Level 2 data security requirements. The MPIs have agreed to accept responsibility for managing these risks appropriately in consultation with departmental and/or campus security personnel. The Data Security Requirements addendum can be reviewed here: https://guides.lib.unc.edu/datasecurity/irbis

Declaration of Interests

The study team declares that they have no competing interests.

Access to data

On reasonable request, we will make deidentified data sets available, stripped of individual identifiers, following publication of the relevant study's main findings. We may submit deidentified data collected in this study to a data repository, such as UNC Odum Institute's Dataverse (https://dataverse.unc.edu/dataverse/unc) to make our deidentified data publicly available. As part of submitting the data to a repository, we will provide basic information about how the data was collected and upload a deidentified dataset to the repository.

Ancillary and post-trial care

This trial presents no more than minimal risk to participants, does not collect data on harms to participants or assess interim data during the trial. There is no need for ancillary or post-trial care.

Dissemination Plan

The study team plans to disseminate study findings via conference presentation and peer reviewed manuscripts in scientific journals. The study team will also share findings via ClinicalTrials.gov registration. We will follow authorship guidelines depending on the journal to which manuscripts are submitted.

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Protocol structure and contents based on SPIRIT 2013 Statement: Defining standard protocol items for clinical trials, https://www.spirit-statement.org/wp-content/uploads/2013/01/SPIRIT-Checklist-download-8Jan13.pdf

Protocol Amendment History

Version	Date	Description of Change	Brief Rationale
1	6/26/2024	Original protocol finalized	
2	8/28/2024	Protocol updated to reflect that baseline may be open for 2 days	Allows eligible potential participants more time to enroll in the study