Complete Title: Online Randomized Experiment Evaluating the Perceived Effectiveness of Alcohol Warning Labels

Short Title: Impacts of Alcohol Warning Labels: An Online Experiment

FDA IND/IDE (if applicable): N/A

Sponsor: National Institute on Alcohol Abuse and Alcoholism (NIAAA)

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PROTOCOL SYNOPSIS

Study Title	Online Randomized Experiment Evaluating the Perceived Effectiveness of Alcohol Warning Labels
Funder	NIAAA
Clinical Phase	N/A
Study Rationale	• Policymakers and public health organizations are increasingly interested in communicating alcohol's harms to the public, including through mandated warning labels as well as mass media campaigns. • Communicating alcohol's harms could increase consumer understanding of these harms and reduce alcohol consumption and alcohol-related health harms. • Alcohol contributes to more than 200 health harms, giving policymakers and public health organizations many options to choose from when selecting topics to include in messages about alcohol-related harms. • However, it remains unknown which of these topics should be prioritized in communication efforts.
Study Objective(s)	Primary • To evaluate whether alcohol warnings about different topics elicit higher perceived message effectiveness than control messages. Secondary • To evaluate whether alcohol warnings about different topics elicit higher reminding of alcohol's harms than control messages. • To evaluate whether people are more likely to learn something new from alcohol warnings about different topics compared to control messages.
Test Article(s) *(If Applicable)*	N/A
Study Design	Randomized experiment.
Subject Population key criteria for Inclusion and Exclusion:	Inclusion Criteria 1. Age 21 and older 2. Reside in the United States 3. Able to complete a survey in English 4. Consumed alcohol at least once per week during the past 4 weeks

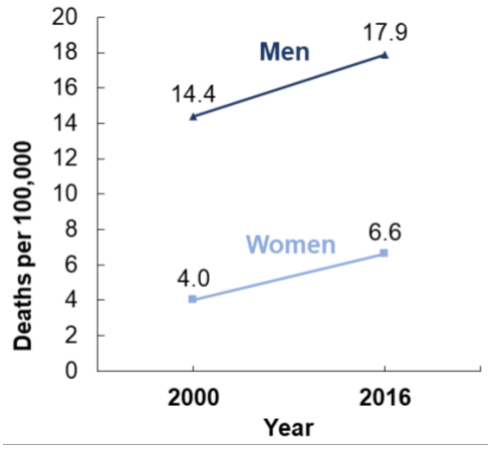
	Exclusion Criteria 1. Under the age of 21 2. Reside outside of the United States 3. Unable to complete a survey in English 4. Consumed alcohol less than once per week during the past 4 weeks
Number Of Subjects	1,000
Study Duration	Each subject's participation will last approximately 15 minutes. The enrollment period is expected to last ~2 weeks.
Study Phases **Screening** **Study Treatment** **Follow-Up**	There are two phases: (1) Screening: screening for eligibility and obtaining consent and (2) Intervention: study intervention/experimental treatment.
Efficacy Evaluations	The primary outcome is perceived message effectiveness for encouraging people to drink less alcohol. It is measured with 1 item adapted from prior studies. The secondary outcomes are reminding of alcohol's harms and learning something new.
Statistical And Analytic Plan	Primary outcome • We will use mixed effects linear regression to examine the effect of each alcohol warning topic on perceived message effectiveness compared to the control topic. Secondary outcomes • We will use mixed effects linear regression to examine the effect of each alcohol warning topic on reminding of alcohol's harms compared to the control topic. • We will use mixed effects logistic regression to examine the effect of each alcohol warning topic on learning something new compared to the control topic.
DATA AND SAFETY MONITORING PLAN	• The principal investigators are responsible for data quality management and ongoing assessment of safety.

BACKGROUND AND RATIONALE

Introduction

Alcohol consumption remains a pressing public health problem in the US. Alcohol consumption is a leading cause of death in the US, accounting for nearly 100,000 deaths each year.[1,2] Alcohol-related deaths have risen over the past 25 years in the US among both men and women[3] (**Figure 1**). Alcohol consumption contributes to both short- and long-term health harms. Acute alcohol intoxication can result in injuries, poisoning, and motor vehicle accidents.[4-9] Longer-term alcohol consumption contributes to chronic diseases such as hypertensive heart disease and liver cirrhosis.[10] Alcohol consumption is also the third leading modifiable cause of cancer in the US.[11] Even moderate drinking carries health harms, particularly for cancer risk.[9,12,13] For these reasons, federal guidelines indicate that "drinking less is better for health than drinking more."[14] However, many adults in the US consume unhealthy levels of alcohol. More than 30% of US adults consume more than the recommended daily limit for alcohol[15] and 1 in 4 report binge drinking in the past month.[16] One potential explanation for high rates of unhealthy alcohol consumption is that many American adults are unaware of the harms related to alcohol consumption.[12,17-20] *There is a critical need for research to design and evaluate interventions that inform consumers about alcohol's risks and reduce harmful alcohol consumption.*

Figure 1. Age-standardized alcohol-induced deaths in the US, 2000-2016



The current alcohol warnings in the US are out of date. The US has required the same warning label on alcohol containers for 33 years.[21] Studies of the current US warning suggest that it has had limited impact on overall alcohol consumption.[22,23] The limited effectiveness could be because the current US warning lacks the key elements of an evidence-based warning: it is shown in small text, typically appears on the back or side of product packaging, and does not include any pictorial elements. Moreover, the warning is static: its content never rotates. **In addition to being poorly designed, the current warning also does not reflect the latest alcohol epidemiology:** it discusses only 3 risks despite evidence that alcohol is associated with more than 200 health harms including cancer. Updating the current warning to discuss these health harms could better inform consumers and more effectively discourage alcohol consumption, but no research has examined which harms are most effective to include in alcohol warnings. *We will evaluate consumer reactions to evidenced-based alcohol warnings that communicate a range of health harms linked to alcohol.*

The goal of this current experiment is to examine responses to alcohol warning messages about 10 different topics among US adult alcohol consumers. The main questions this experiment aims to answer are:

Which warning topics make alcohol consumers in the US want to drink less alcohol? Which warning topics remind alcohol consumers in the US of alcohol's harms? Which warning topics help alcohol consumers in the US learn something new? We developed 2 warning messages about 8 warning topics (e.g., liver cancer, throat and mouth cancer). We also developed 2 control messages. Finally, the stimuli included the current US alcohol warning, for a total of 19 messages (16 new warning messages, 2 control messages, and the current US alcohol warning). Participants will view 10 messages shown in random order, each about a different topic: nine messages about warning topics and one about a control topic. For the control topic and all warning topics except the current US warning (for which there is only 1 message), participants will view 1 of the 2 messages developed for that topic, selected at random.

Participants will rate each message on how much it makes them want to drink less alcohol, reminds them that drinking can be harmful, and teaches them something new.

Name and Description of Investigational Product or Intervention

Participants will view and rate 10 messages shown on alcohol containers.

Arm	Assigned Interventions:
Experimental: Alcohol Messages	Behavioral: Liver Cancer Participants will view messages about the risk of liver cancer from alcohol consumption. Behavioral: Throat and Mouth Cancer Participants will view messages about the risk of throat and mouth cancer from alcohol consumption. Behavioral: Colorectal Cancer Participants will view messages about the risk of colorectal cancer from alcohol consumption. Behavioral: Multiple Cancers Participants will view messages about the risk of multiple cancers from alcohol consumption. Behavioral: Liver Disease Participants will view messages about the risk of liver disease from alcohol consumption. Behavioral: Hypertension Participants will view messages about the risk of hypertension from alcohol consumption. Behavioral: Dementia Participants will view messages about the risk of dementia from alcohol consumption. Behavioral: Drinking Guidelines Participants will view messages about guidelines for alcohol consumption. Behavioral: Current Warning Participants will view the current warning that is required on most alcoholic beverage containers sold in the US. Behavioral: Control Participants will view neutral messages unrelated to the harms of alcohol consumption.

STUDY OBJECTIVES

Primary Objective

The purpose of this study is to evaluate whether alcohol warnings about different topics elicit higher perceived message effectiveness than control messages.

Secondary Objectives

Additionally, this study will evaluate whether alcohol warnings about different topics elicit higher reminding of alcohol's harms than control messages. This study will also evaluate whether people are more likely to learn something new from alcohol warnings about different topics compared to control messages.

INVESTIGATIONAL PLAN (brief overview)

Study Design

This study is a within subjects online randomized experiment with single group assignment.

This study will consist of 2 phases—Screening and Intervention. During the Screening phase, potential participants will be screened for eligibility and complete informed consent procedures. During the Intervention phase, participants will take part in the experimental treatment.

There will not be a follow-up phase, nor a plan to deal with unscheduled visits since this study will be taking place during a one-time online experiment.

Allocation to Treatment Groups and Blinding

All participants will be in a single arm experiment. Within this arm, participants will view and rate messages shown on alcohol containers. Participants will view 10 messages shown in random order, each about a different topic: nine messages about warning topics and one about a control topic. For the control topic and all warning topics except the current US warning (for which there is only 1 message), participants will view 1 of the 2 messages developed for that topic, selected at random. Participants will rate each message on how much it makes them want to drink less alcohol, reminds them that drinking can be harmful, and teaches them something new. There is no blinding.

Study Duration, Enrollment and Number of Subjects

This study will take place entirely online via an online survey programmed in Qualtrics over the course of about 2 months. NORC will recruit roughly 1,000 US adults to participate in this study.

Study Population

The survey research company NORC at the University of Chicago will recruit a sample of 1,000 people. Additionally, in order to be eligible for this study, participants must meet all of the following criteria:

- Age 21 or older
- Reside in the United States
- Able to complete a survey in English
- Consumed alcohol at least once per week during the past 4 weeks.

If any of the following are true, a participant is ineligible for participation:

- Under the age of 21
- Reside outside of the United States
- Unable to complete a survey in English
- Consumed alcohol less than once per week during the past 4 weeks

STUDY PROCEDURES

Screening/Baseline Visit procedures

Participants will reside in the US, speak English, be 21 years of age or older, and have consumed at least 1 alcoholic drink per week over the past 4 weeks. The screener questions at the start on the online study will assess these eligibility criteria via self-report.

Intervention/Treatment procedures (by visits)

Participants will rate each message on its perceived effectiveness using 1 item from the UNC Perceived Message Effectiveness Scale, a measure that has been used extensively in similar experiments to identify the potential impact of warning labels on consumers. Perceived effectiveness is a measure that is sensitive enough to detect small differences between warnings yet is also predictive of messages' ability to change actual behaviors. Participants will also rate messages on secondary outcomes (e.g., reminding of harms, learning something new). All outcomes will be measured with Likert-type response scales ranging from 1 to 5, except learning something new which is binary (yes/no). Participants will respond to survey questions programmed in Qualtrics and will receive incentives in the form of cash, points, or other prizes in accordance with the NORC's standard protocols.

Follow- up procedures (by visits)

N/A—there will not be follow up.

Unscheduled visits

N/A

Subject Completion/Withdrawal procedures

A participant will be considered complete when they complete the online survey. At the end of the survey, participants will be rerouted back to the AmeriSpeak homepage, where NORC is responsible to providing compensation in the form of cash, points, or other prizes in accordance with the panel company's standard protocols, equivalent to $2 USD.

We currently do not have any criteria that would involve withdrawing an individual subject. Although unlikely, any potential withdrawals will be considered by the PI on a case-by-case basis, considering risk to the participant.

Screen failure procedures

If a potential participant fails to meet eligibility criteria and/or fails to give consent for participation, the online experiment is programmed to redirect respondents to the AmeriSpeak website with a message informing the respondent that they are not eligible for this particular study.

STUDY EVALUATIONS AND MEASUREMENTS

All evaluations will be collected via an online survey programmed in Qualtrics lasting roughly 15 minutes. All data collected is self-reported.

Primary Outcome: Perceived Message Effectiveness
The study will assess perceived message effectiveness using 1 item: "How much does this message make you want to drink less alcohol?" Response options will range from "not at all" (coded as 1) to "a great deal" (coded as 5). Higher scores indicate more perceived message effectiveness.

Secondary Outcome: Reminding of Alcohol's Harms
The study will assess reminding of alcohol's harms using 1 item: "How much does this message remind you that drinking alcohol can be harmful?" Response options will range from not at all (1) to a great deal (5). Higher scores indicate greater reminding of alcohol's harms.

Secondary Outcome: Learning Something New
The study will assess learning something new with 1 item: "Did you learn something new from this message?" Response options will be yes (1) and no (0). Proportion of participants who endorsed learning something new (i.e., answered 1).

STATISTICAL CONSIDERATIONS

General Principles
We will use a two-sided critical alpha of 0.05 to conduct all statistical tests. All confidence intervals presented will be 95% and two-sided. We will use complete case analysis to handle any missing data in analyses of the primary and secondary outcomes. In all analyses, we will use survey weights to account for NORC AmeriSpeak's sampling design and enable results to be representative of the US population of drinkers ages 21+.

Primary Endpoint
The primary outcome is perceived message effectiveness for encouraging people to drink less alcohol. We will measure perceived message effectiveness with 1 item adapted from prior studies: "How much does this message make you want to drink less alcohol?" Response options will range from not at all (1) to a great deal (5).

Hypothesis 1. We hypothesize that all warning topics elicit higher perceived message effectiveness ratings than the control topic.

Secondary Endpoints
The secondary outcomes are reminding of alcohol's harms and learning something new. We will measure reminding of alcohol's harms with 1 item: "How much does this message remind you that drinking alcohol can be harmful?" Response options will range from not at all (1) to a great deal (5). We

will measure learning something new with 1 item: "Did you learn something new from this message?" Response options will be yes (1) and no (0).

Hypothesis 2. We hypothesize that that all warning topics elicit higher reminding of alcohol's harms than the control topic.

Hypothesis 3. We hypothesize that all warning topics elicit higher likelihood of learning something new than the control topic.

Statistical Methods

Analyses of the primary outcome:

a. We will use mixed effects linear regression to **evaluate the effect of each warning topic compared to the control topic on the primary outcome of perceived message effectiveness.** We will regress perceived message effectiveness on a set of indicator variables representing each alcohol warning topic (e.g., mouth cancer, liver cancer, etc.), excluding the control topic as the referent. We will treat the intercept as random to account for repeated measures within participants. The coefficients on the warning topics give the average difference in mean perceived message effectiveness between each warning topic and the control topic. Hypothesis 1 will be supported if all coefficients on the warning topics are positive and statistically significant. Given the exploratory nature of the study, we do not plan to adjust p-values for multiple comparisons.
b. In addition to testing Hypothesis 1, we will also **descriptively rank the warning *topics*** on the primary outcome of perceived message effectiveness. We will estimate mean perceived message effectiveness for each alcohol warning topic (averaging across messages for each topic) and rank those means.
c. Finally, we will **descriptively rank the alcohol warning *messages*** on the primary outcome of perceived message effectiveness. We will estimate means for each alcohol warning message and rank those means.

Analyses of the secondary outcomes:

a. We will use mixed effects linear regression to **evaluate the effect of each alcohol warning topic compared to the control topic on the secondary outcome of reminding of alcohol's harms.** We will use the same approach as for the primary outcome (see no. 1 above). We will use mixed effects logistic regression to **evaluate the effect of each alcohol warning topic compared to the control topic on the secondary outcome of learning something new.** We will use the same approach as for the primary outcome, but with a logistic model to account for the binary outcome variable. Hypotheses 2 and 3 will be supported if all marginal effects of the warning topics (vs. control) on the secondary outcomes are positive and statistically significant.
b. We will **descriptively rank the alcohol warning *topics*** on the secondary outcomes of reminding of alcohol's harms and learning something new. We will estimate mean reminding of alcohol's harms for each alcohol warning topic (averaging across messages for each topic) and

rank those means. We will also estimate the proportion of participants who indicated they learned something new from each alcohol warning topic and rank those proportions.

c. We will **descriptively rank the alcohol warning *messages*** on the secondary outcome of reminding of alcohol's harms and learning something new. We will estimate mean reminding of alcohol's harms for each alcohol warning message and rank those means. We will also estimate the proportion of participants who indicated they learned something new from each alcohol warning message and rank those proportions.

We do not plan to conduct moderation analyses.

Sample Size and Power

We plan to collect data from 1,000 participants. We used G*Power to estimate sample size needs.[1] We estimated sample size needs to detect an effect of each warning topic vs. the control topic assuming an alpha=0.05 and correlation among repeated measures of 0.5 (similar to our prior studies of product warnings[2,3]). We estimated power assuming 2 repeated measures, reflecting that our contrast of interest has two within-subjects levels (warning topic vs. control). Under these assumptions, our sample size will yield >85% power to detect a small standardized effect of Cohen's f=.05 (or Cohen's d=.10) or larger of each warning topic vs. the control topic. A prior study of alcohol warning topics found effects of this size or larger when comparing perceived message effectiveness of alcohol warning topics vs. control topics.[2]

Exclusions and Outliers

We will exclude participants who complete <90% of the survey or who complete the survey implausibly quickly (defined as <1/3 of the median completion time).

Interim Analysis

N/A

STUDY INTERVENTION (DEVICE, DRUG, OR OTHER INTERVENTION)

Participants will view warnings about 10 topics: 9 warnings topics and 1 control topic, shown in random order. For each warning topic, participants will view 1 message (selected at random from a pool of 2 messages about that topic) and respond to survey items about that message.

STUDY INTERVENTION ADMINISTRATION (IF APPLICABLE)

Participants will view warnings about 10 topics: 9 warnings topics and 1 control topic, shown in random order. For the control topic and all warning topics except the current US warning (for which there is only 1 message), participants will view 1 of the 2 messages developed for that topic, selected at random. This randomization is accomplished via Qualtrics Randomizer.

SAFETY MANAGEMENT

Since this study is taking place entirely online during a single session, we will not be monitoring for Adverse Events or Serious Adverse Events. We do not have a plan in place for Medical Emergency procedures due to the online nature of this study. No study staff will have direct contact with any participants.

The principal investigators are responsible for data quality management and ongoing assessment of safety. All data will be stored in Qualtrics, accessible only to select IRB-approved study staff who need access to participant data.

DATA COLLECTION AND MANAGEMENT

Participants will be able to take the online experiment survey at the location of their choosing to allow for privacy. We will avoid collecting sensitive data that is not required (e.g., IP addresses). Required identifying participant information (names, city of birth, phone numbers, and/or email addresses) will be stored on a secure virtual platform that only IRB-approved study members will be able to access. They will also be required to access this from a password-protected computer. Only one virtual linking document will have identifying participant information and id numbers. Whenever possible, data will be linked to participants only by the participant id number.

RECRUITMENT STRATEGY

All participants will be recruited by NORC at the University of Chicago through their AmeriSpeak panel. Research staff at UNC and Stanford will have no direct contact with any participants. We will not be sharing any recruitment materials. Participants will receive incentives in the form of cash, points, or other prizes in accordance with the panel company's standard protocols.

CONSENT PROCESS

Participants will read an electronic version of the informed consent form before beginning the survey and will be asked to select a checkbox to confirm their consent. The consent forms for these surveys will include information about the study's purpose, potential risks, expected benefits, protection of confidentiality, and time expectations. The form will also include contact information for the IRB and the PI in case participants have concerns or questions about the study.

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