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Real-world exposure to graphic warning labels on cigarette packages in US smokers: The CASA randomized trial protocol

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ABSTRACT

Background: The US lags behind > 120 countries in implementing graphic warning labels (GWLs) on cigarette packs. US courts prevented implementation of FDA's 2012 rule requiring GWLs citing the need for more evidence on effectiveness. After more research, in 2020, the FDA proposed a revised rule mandating GWLs. This trial will test how the introduction of GWLs influence cognitions and behavior in US smokers.

Method: To investigate the "real-world" impact of GWLs in US smokers, we are conducting a randomized trial involving a 3-month intervention and 8-month follow-up. The study recruited California smokers between September 2016 through December 2019 and randomly assigned them into 3 groups (1) Blank Pack devoid of any cigarette branding; (2) GWL Pack featuring 1 of 3 rotating images added to blank pack; or (3) their usual Standard US Pack. Throughout the 3-month intervention, participants purchased study-packaged cigarettes and reported daily cognitions and behavior through ecological momentary assessments. We will validate self-reported tobacco use with saliva cotinine concentrations following the 3-month intervention and 8-month follow-up.

Results: The trial enrolled 359 participants (average age 39 years; average cigarette consumption half a pack/day). The 3 study groups were balanced on age, gender, race-ethnicity, education and income (17% low income) as well as on smoking related variables.

Conclusions: This 3-month real-world randomized trial will test the effect of repackaging cigarettes from standard US packs to GWL plain packs on smokers' perceptions of the risks of smoking, their perception of the appeal of their cigarettes, and on their smoking behavior.

1. Introduction

Cigarette brands use packaging as part of their overall marketing communication strategy [1] to influence consumers' perception of their products including taste, quality, satisfaction, and reduced harm compared to other brands [2–5]. To disrupt this communication channel, public health agencies have adopted 2 interconnected strategies, removing tobacco industry branding and applying graphic warning labels (GWLs). Removing tobacco industry branding can reduce brand appeal and the perceptions that the cigarettes are safer than other brands [6–10]. GWLs on cigarette packs are harder to ignore than text warnings and elicit strong cognitive and emotive reactions, which have been linked to increased intentions to quit [11].

Although the US was the first to introduce warning labels on cigarette packages in 1966, these did not evolve and were not effective [12]. Canada was the first nation to introduce GWL's in 2001. Over 120 other countries have upgraded to the minimum GWLs required by the 2003 World Health Organization's Framework Convention on Tobacco

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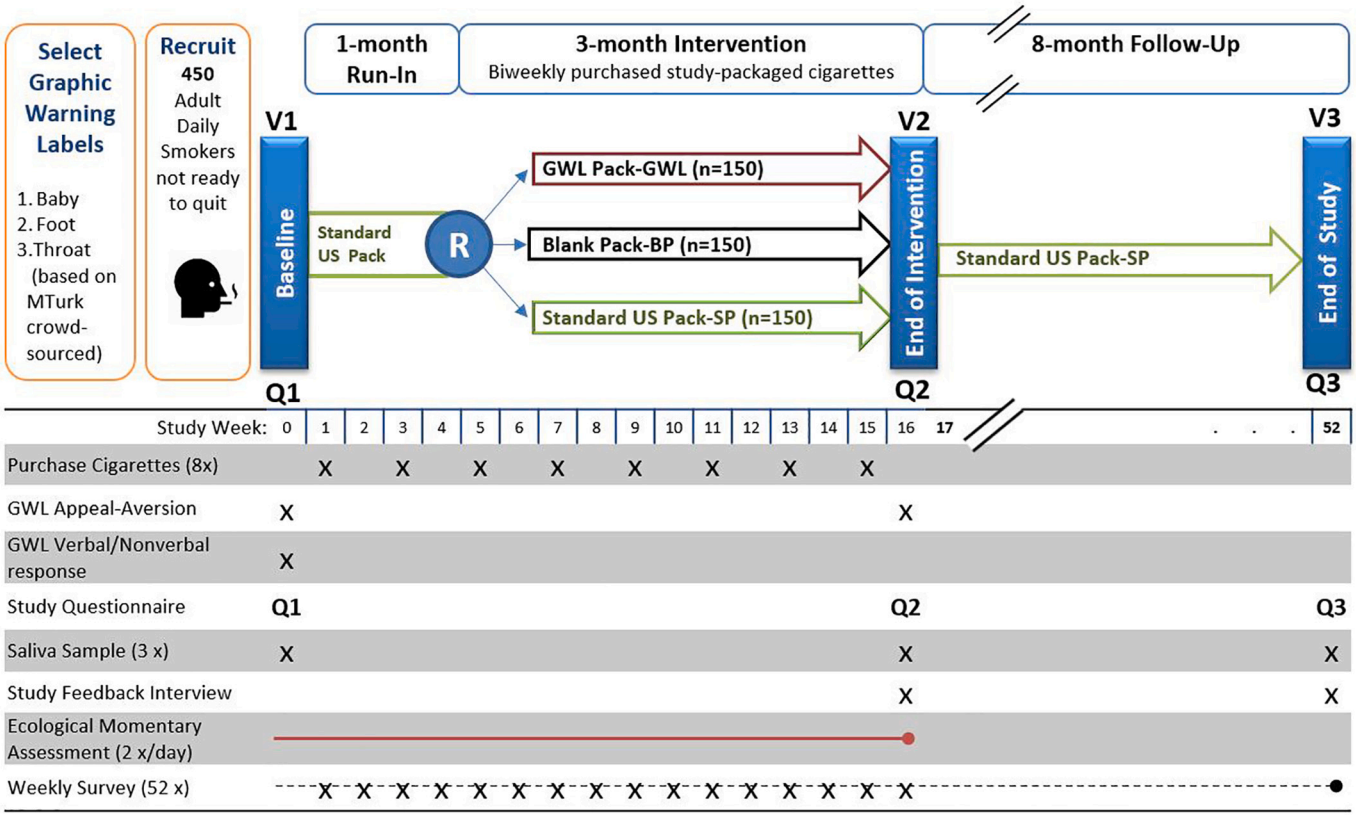

Fig. 1. .CASA Study Design.

Control (FCTC) treaty [13,14]. Seven countries have now gone further, following Australia's 2012 introduction of standardized packaging, which removes all branding and adds large GWLs. The US Tobacco Control Act of 2009 mandated GWLs on cigarette packs [15], but the FDA's 2012 implementation rule was struck down by the courts on First Amendment grounds citing a lack of evidence supporting smoking behavior change [16]. The FDA's revised rule in March 2020[17] was immediately challenged in another lawsuit [18].

With few exceptions, most GWL studies have either involved brief exposures (many limited to virtual exposures) in laboratory settings or observational reports in countries with GWL policies [19]. Evans et al. [20] randomized smokers to have text-only warnings or a GWL affixed to their cigarette packs (for 4 weeks - 244 completers). GWLs were more effective in encouraging smokers to consider quitting. Using a similar text vs GWL design, Brewer et al.[21] randomized 2149 smokers and showed that, over 4 weeks, affixing GWLs to participant packs was associated with more self-reported quit attempts than text-only warnings (40% vs 34%). Compared to the text-only warnings, GWLs were more likely to increase future intentions to quit, successful 7-day cigarette abstinence and forgoing a cigarette. GWLs increased quit attempts by increasing attention to the warning, eliciting negative emotional reactions, avoidance of the warning and thinking about the warning message [22].

Two large ecological studies reported conflicting findings on the effectiveness of GWLs in changing smoking behavior. Canada introduced GWLs in 2001; a pre-post policy period analysis found that GWLs were associated with lower smoking prevalence and increased quit attempts [23]. However, analysis of Euromonitor International Surveys with data from 60 countries did not replicate this finding [24].

This randomized trial seeks to advance the research on the influence of cigarette packaging on smoking cognitions and behavior. It includes a number of innovations that improve on previous studies. There is a real-world experience: for 3 months, participants purchase their US cigarettes repackaged into specially manufactured study packs. The study uses a blank pack (devoid of all advertising) as one control group for GWL packs to identify whether differences observed are from removing tobacco industry advertising or from using GWLs. We assess initial participant appeal-aversion responses to the study packaging to explore whether upfront reactivity modifies any downstream GWL effects. We use ecological momentary assessment (EMA) to obtain daily real-time measures of cognitions and behavior over the 3-month intervention. Finally, smoking behavior is validated biochemically after the intervention and after an additional 8 months.

2. Design and methods

2.1. Overview and study design

This randomized trial recruited US smokers who were not ready to quit from San Diego County, California. Following a 1-month run-in period, participants were randomized into 3 groups, and, for a period of 3 months, purchased discounted cigarettes through the study website packaged as follows: Group 1-Blank Pack devoid of any cigarette branding; Group 2-GWL Pack featuring 1 of 3 rotating images; and Group 3-Standard US Pack used by smoker.

The study will test whether 3 months of cumulative exposure to GWLs influences cognitions and behavior about smoking and whether such effects are maintained through a further 8 months when participants reverted to using their standard US packs. The GWL images (standardized packs) were obtained under license from Australia and we conducted a substudy to identify the 3 most effective images. For the GWL and Blank Pack groups, we manufactured cigarette packs labelled with the participant's cigarette brand. Fig. 1 outlines the study design and assessments.

During the 12-month study, assessments occurred at 3 clinic visits (V1, V2, V3) and through weekly electronic surveys. Additional

assessments during the 3-month intervention included frequent repeated measures of perceived sensory attributes of cigarettes and quitting cognitions collected twice daily through ecological momentary assessments (EMA). Clinic visit assessments included a detailed study questionnaire (Q1, Q2, Q3) a GWL appeal-aversion "willingness to pay" conjoint assessment, and a saliva sample to biochemically validate cigarette consumption. Clinic Visit 1 (V1) included a GWL Verbal/Nonverbal response task in which the participant's initial 'stream of consciousness' response to the study packs was recorded and coded. In addition, at V2 and V3, research staff recorded (audio) participant responses to a study feedback questionnaire (open-ended questions about their study experience).

During the 8-month follow-up, participants purchased their cigarettes through their regular sources and continued to receive the weekly e-mail survey. The trial was named "CASA – **CA**lifornia **S**mokers in **A**ustralia" to convey the "real-world" experience of purchasing and smoking cigarettes with Australian-style packaging.

2.2. Study objectives

To test the effect of 3 months of real-world exposure to different cigarette packaging (Blank Pack devoid of any cigarette branding and GWL Pack featuring 1 of 3 rotating images) on smokers' cognitions and behavior about smoking at the end of the intervention exposure as well as longer term after smokers have reverted to their industry-marketed US packs.

Aim 1: Assess changes in the perceptions (awareness, concern) of risks from cigarette smoking

Aim 2: Assess changes in perceptions of appeal of cigarette packs and their subjective reinforcing effects on smoking

Aim 3: Assess changes in cigarette smoking behavior including purchasing behavior, pack handling, quitting cognitions and cigarette consumption

Aim 4 (Exploratory): Test whether the participant's initial appeal-aversion response to the study pack designs as well as nicotine dependence modify responses to the 3-month intervention.

2.3. Manufacturing of study cigarette packs

We manufactured cigarette packs for the GWL and Blank Pack study groups using an olive-green pack background. The front and back of the GWL packs pictured an Australian GWL (neonatal baby, foot gangrene, or throat cancer) chosen based on our GWL pretest described below. Because the Australian packs included a quitline number for smokers to call, we replicated this on our manufactured packs, providing a study phone number. The packs featured a standard US Surgeon General warning label on the side and we designed 2 pack sizes to accommodate both regular and 100 mm cigarette sizes. Using information on brands purchased prior to randomization, the study purchased cigarette packs and repackaged cigarettes into study packs manufactured specifically for the GWL and Blank Pack study groups. The only component of the typical cigarette pack that we were unable to match was the tear-off cellophane cover. We cellophane wrapped each pack without an easy tear-off tab. (Fig. 2) For the GWL and Blank Pack study groups, the label of the participant's brand variant was printed in standard lettering and stuck to the front of the newly manufactured pack.

We established a University-approved commercial website to sell cigarettes to participant smokers (15% discount on usual store price) and contracted with a courier for rapid delivery (the following day, or same day for orders placed before 11 AM).

2.4. Choice of images: GWL pretest

We obtained a license from the Commonwealth of Australia to use up to 8 of the GWLs that were in use in Australia in 2014. To reduce pack manufacturing costs, we pretested the Australian images with US smokers to select 3 of these GWLs to rotate on our study packs [25]. For this pretest, we recruited a non-representative sample of 403 US-adult cigarette smokers (aged 21–50 years), via Amazon Mechanical Turk (www.mturk.com) [26]. The majority of this sample was younger than

Fig. 2. .Manufactured Study Packs: (A) Neonatal Baby*, (B) Foot Gangrene*, (C) Throat Cancer*, (D) Blank Pack. * © Commonwealth of Australia.

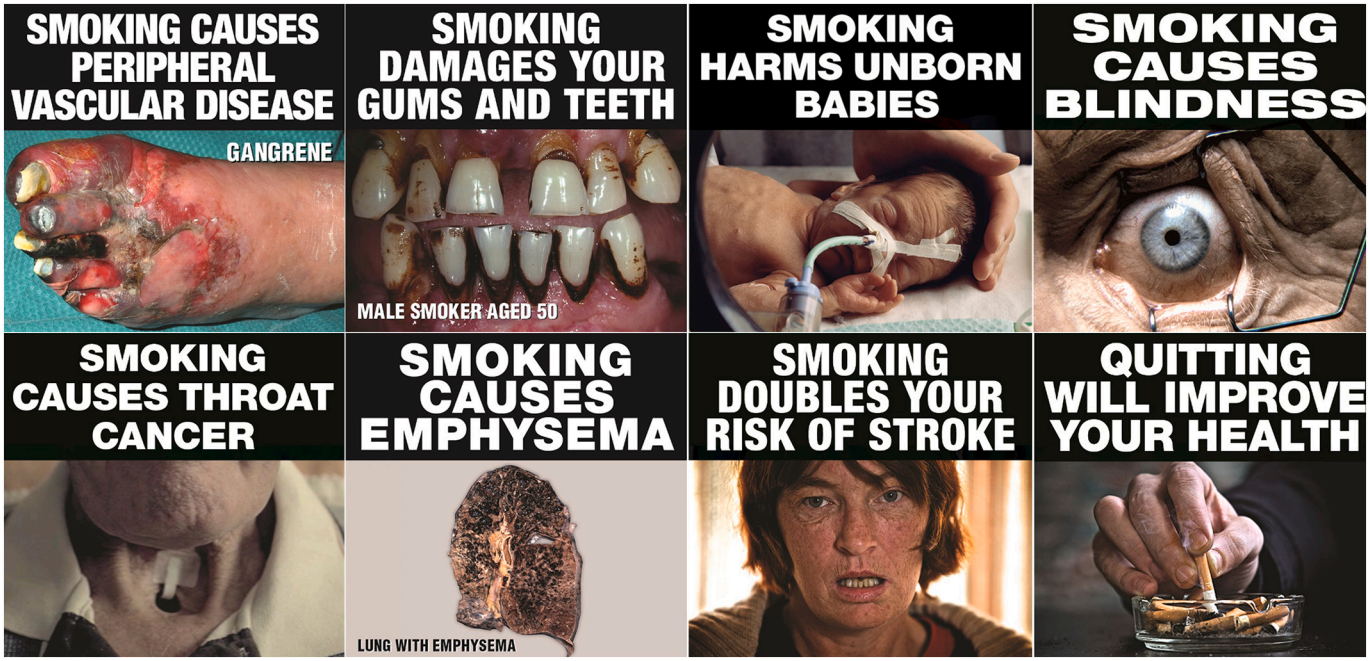

Fig. 3. GWL Pretest: 8 Graphic Warning Images in use on cigarette packs in Australia. From top left these are 1. Foot Gangrene, 2. Teeth, 3. Neonatal Baby, 4. Blindness, 5. Throat Cancer, 6. Emphysema, 7. Woman with Stroke, 8. Ashtray. © Commonwealth of Australia. "Smoking damages your gums and teeth": © Professor Laurence J Walsh, The University of Queensland, Australia.

40 years (82%), male (61%), white (77%), did not live with children < 5 years (83%), smoked on a daily basis (58%), had completed at least some college (85%). This sample took a brief survey that included 2 tasks related to the 8 Australian GWLs (Fig. 3).

The first component was a between-subjects design in which respondents were randomly exposed online to one of the 8 Australian images and asked to rate it on a number of constructs. One of these constructs was the Positive and Negative Affect Scale (PANAS) which includes ratings on 6 separate questions on emotion [27]. Participants rated each of these items on a 5-point scale from 1 = very slightly to not at all, 2 = a little, 3 = moderately, 4 = quite a bit, 5 = extremely. When comparing the psychometric properties of the PANAS in the entire sample of respondents across conditions, the internal consistency was high (Cronbach's $\alpha = 0.95$) and results from an exploratory factor analysis suggested that all items loaded highly on a single factor (factor loadings > 0.75). Accordingly, we averaged responses across items. Additional constructs were ratings on the following 4 single questions: "To what extent does the health warning in this image make you think about the health risks of smoking? How likely are smokers to experience this health consequence? To what extent does the health warning in this image make you concerned about the health risks of smoking? The image you have seen is already printed on cigarette packs in Australia; Do you think if this image was printed on US packages it would affect the amount of cigarettes you smoke?" Participants scored each question on a digital- analog scale where 1="downplays risk" and 10="exaggerates risk." The second component exposed respondents to all 8 images simultaneously and they were asked to rank them based on "how effectively each image communicates the health risks of smoking" and this was published separately [25]. The results of the first component of this pretest are shown in Fig. 4.

The *Foot Gangrene* image was associated with the greatest negative emotional response and was ranked the most effective at communicating health risks, although it was lowest on the likelihood that the respondent would suffer this health consequence. One subgroup response (those with a child < 5 years in the home) was very different on these rankings: this subgroup ranked the 'neonatal baby' as the most effective image (36% vs 24% for Foot Gangrene). The images *Throat Cancer*, *Teeth Damage*, and *Blindness* ranked equal second on the perceived effectiveness question, however, *Throat Cancer* ranked first on the question of how much the health warning in this image made you concerned about the health risks of smoking. Based on these data, we chose the following 3 images to rotate for our GWL pack: *Foot Gangrene, Neonatal Baby,* and *Throat Cancer* – 2 of these images are similar to the ones proposed by the FDA [28].

2.5. Participants and recruitment

The study enrolled smokers from San Diego County, California, where only tobacco industry branded packs (with a text Surgeon-Generals health warning) are sold. Participants experience purchasing GWL packs prior to contacting the study was coded from stream-of consciousness responses during the study's Pack Handling Task (see below). We did not enroll 2 participants from the same address to avoid contamination between the different pack conditions.

2.5.1. Eligibility criteria

Study *inclusion criteria* were as follows: 1) 21–65 years of age; 2) a current resident of San Diego County; 3) daily smoker of at least 5 cigarettes/day; 4) did not intend to quit smoking in the next 30 days; 5) smoke a popular US cigarette brand; 6) have a cell phone with an unlimited text messaging service plan, 7) have a debit or credit card. Study *exclusion criteria* included 1) non-daily cigarette smokers; 2) daily smokers of cigarette brands that were outside of regular or 100 mm cigarette size (e.g. Virginia Slims, Benson and Hedges); 3) unstable medical condition (such as a mild congestive heart disorder); 4) current pregnancy or intent to become pregnant during the next 12 weeks.

2.5.2. Recruitment strategies

Community advertising to recruit participants started in September 2016 and continued until the study was closed to new participants on December 3, 2019. Over this period, 5890 smokers in San Diego County contacted the study and were telephone-screened by study staff. The following were the major recruitment sources for the study: Craigslist ($n = 3289$, 56%); newspaper ad ($n = 1076$, 18%); Facebook, Instagram

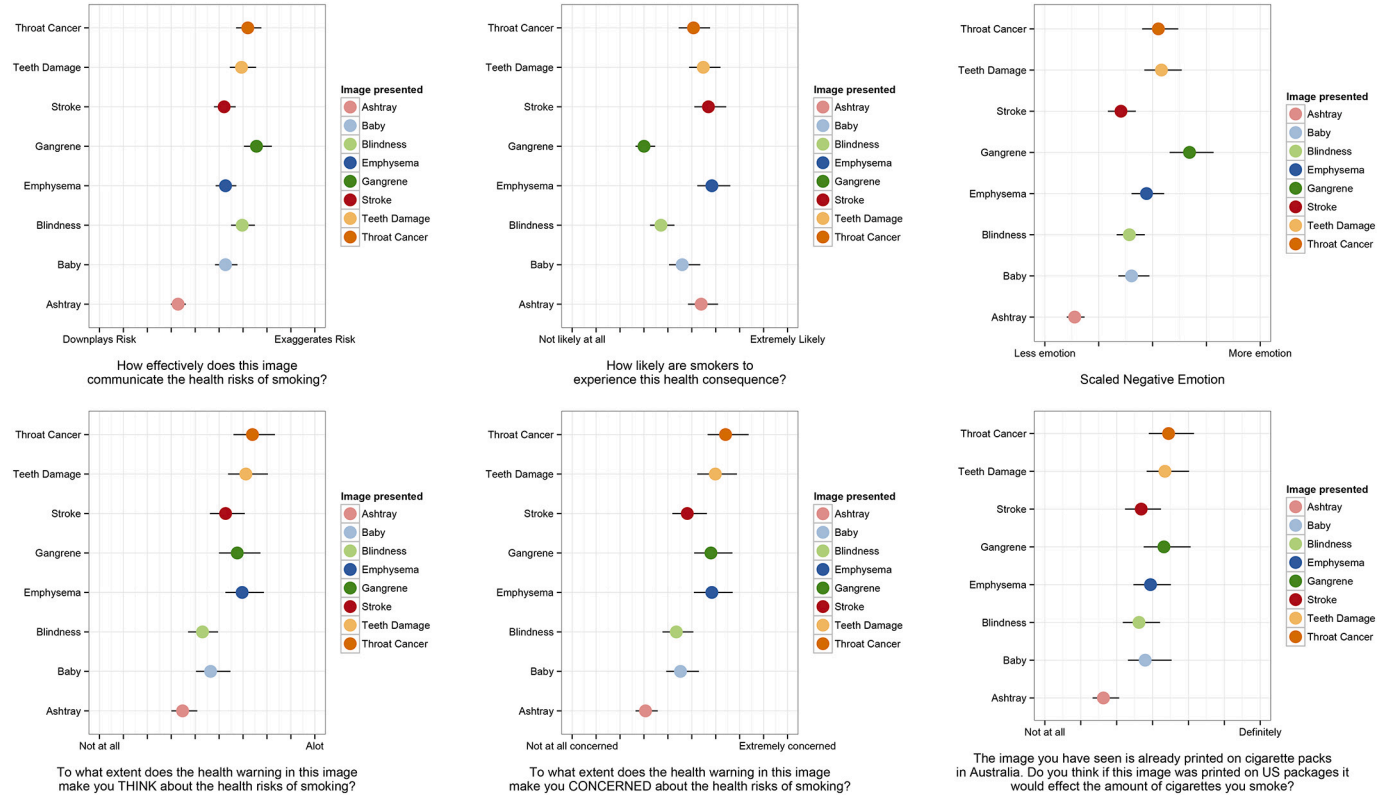

Fig. 4. Average responses to the survey questions asking about reactions to the Graphic Warning Labels. 6 separate linear regression models were run to obtain the output above. Respondents' reactions rated on the 6 scales above were set as dependent variables in the separate models. The predictor variable was the group randomization, which was an 8 level categorical variable. All regression models simultaneously adjusted for smoking status, age, level of education, race/ethnicity, the presence of children less than age 5 in the home and gender. The mean of each randomized group and 95% confidence intervals were calculated by using 1000 randomly drawn sets of estimates from the coefficient covariance matrix of each model and with all other variables held at their mean values.

or other online source (n = 449, 8%); referred by friend (n = 224, 4%).

2.5.3. *The telephone screener*

In this call, research staff described the study requirements to potential participants, verified eligibility criteria, and discussed the study's incentives for participation. During the call, 2414 (41%) were judged ineligible. A major reason for ineligibility was the smoker declaring that they intended to quit smoking in the next 30 days. The percent ineligible increased during the recruitment period when California imposed a $2 increase on cigarette taxes in 2016. During the initial contact, all potentially eligible participants were informed that they would be required to make a web-based credit/debit card purchase of 2 weeks supply of cigarettes (at 15% study discount) at the Baseline Clinic Visit. During the screening call, 1821 eligible participants withdrew. At the end of this call, 1655 eligible participants (48%) were scheduled for the Baseline Clinic Visit, although only 476 (14%) actually attended the Clinic Visit.

2.6. *Baseline clinic visit (V1)*

Study staff at UC San Diego (UCSD) in La Jolla and California State University San Marcos (CSUSM) scheduled and coordinated the Clinic Visits at their respective locations. The Baseline Clinic Visit (V1) took ~1 h and included a) written informed consent, b) completion of study questionnaires, c) a Verbal/Nonverbal recording of responses to first-time viewing of study packs, d) GWL appeal-aversion task, e) saliva collection, and f) introduction to the ecological momentary assessment, weekly survey, and g) cigarette purchasing.

a) Informed Consent. Participants provided their written informed consent to participate in the study. This study was reviewed and approved by the Institutional Review Boards of UCSD and CSUSM.

b) Study Questionnaire (Q1). Participants completed the first of 3 study questionnaires that collected details on the following variables/constructs, many of which are potential confounders to study results: Socio-demographics, Tobacco Use History, Nicotine Dependence Scale [29], Mental Health [30], Health Anxiety [31], Sensation Seeking [32], Cigarette Quality Scale [33], Package Design Appeal items [9,34], Pack Handling items, Support of GWLs scale, Brand Loyalty [35], Advertising Receptivity [36], Tobacco Related Health Concerns scale [37], Subjective Effects of Use (mCEQ) [33], Stage of Change [38], Quitting Cognitions scale [39], Recent Quitting History, Other Product Use/Attitudes, Exposure to Peer and Family Smoking [40], smoke-free home [41], and family interest in participant quitting [42].

c) Pack Handling Task/GWL Verbal/Nonverbal Response. In a randomized order, study staff presented a brand matched GWL Pack, Blank Pack, and Standard US Pack to the participant and asked them to rotate the pack and "think aloud" speaking their thoughts as they processed elements of each pack design, prompting for responses if the participant was silent. The GWL packs were randomized to 1st, 3rd or 5th presentation, and the Blank Pack and Standard US Pack were randomized to the 2nd or 4th presentation. As expected, participants took longer to explore the GWL Packs (median averaged across GWLs 1.1 min) than the standard US pack (median 0.9 min) with the Blank Pack having the shortest viewing time (median 0.6 min). We used the participant's own words (recorded) to score their reaction to each of the study packs. We used 3 levels (high, medium, low) for both appeal and aversion as well as a neutral score. Additionally, to further characterize participant responses we conducted natural language processing using a semantic analysis of their transcribed speech to quantify the polarity of word choice [43] and frequency of emotive words [44] that each pack elicited.

d) GWL Appeal-Aversion Task. We have developed a new tool to

Table 1
Sample characteristics by randomization group.

Characteristic	Standard US (n = 116)	GWL Pack (n = 118)	Blank Pack (n = 125)	P-Value
Age at study entry	39.32 (11.63)	39.26 (12.19)	39.62 (11.90)	.97[a]
Gender Female, *n (%)*	71 (61.2%)	55 (46.6%)	69 (55.2%)	.079[b]
Race/Ethnicity NH White, *n (%)*	81 (69.8%)	78 (66.1%)	86 (68.8%)	.82[b]
Education College degree, *n (%)*	53 (45.7%)	48 (40.7%)	48 (38.4%)	.51[b]
Income* < $50,000/year, *n (%)*	49 (42.2%)	46 (39.0%)	48 (38.4%)	.23[b]
Nicotine Dependence, *Mean (SD)*	3.86 (2.26)	3.69 (2.29)	3.90 (2.30)	.77[a]
Last 7 days Cigarettes/day, *Mean (SD)*	13.04 (10.19)	11.83 (8.69)	12.86 (8.89)	.55[a]
Serious Quit Attempt in past year, *n (%)*	53 (45.7%)	49 (41.5%)	55 (44.0%)	.81[b]
Smoke-Free Home, *n (%)*	32 (27.6%)	30 (25.4%)	27 (21.6%)	.55[b]
Family concern with smoking, None, *n (%)*	57 (49.1%)	63 (53.4%)	66 (52.8%)	.78[b]
Current Cigarette Brand				.90[b]
Marlboro/Camel/American Spirit, *n (%)*	99 (85.3%)	101 (85.6%)	109 (87.2%)	
Appeal of Current Pack, *Mean (SD)*	3.50 (1.31)	3.85 (1.06)	3.74 (1.19)	.069[a]
Feel loyal to current brand, *n (%)*	84 (72.4%)	89 (75.4%)	97 (77.6%)	.65[b]
Mental Health (K-6), *Mean (SD)*	0.95 (0.66)	1.00 (0.75)	0.99 (0.78)	.86[a]
Sensation Seeking, *Mean (SD)*	1.86 (0.64)	1.91 (0.62)	1.87 (0.74)	.81[a]

*Income question was not asked of first 99 people in study
Note. [a] Calculated using the ANOVA test. [b]Calculated using the χ^2 test.

identify the utility participants associate with pack marketing attributes using an adaptive choice-based conjoint (ACBC) task [45]. Using a web interface, first, participants indicated which components of pack design (pack marketing, tobacco origin, and presence of Quitline number) they preferred and the price of their current pack. Then, using an adaptive fractional factorial design [46], we presented a series of choice tasks, each comprising 3 alternative pack designs based on the participant's preferred pack design. This appeal-aversion task did not feature the same 3 GWLs used in the intensive intervention (*Foot Gangrene, Neonatal Baby,* and *Throat Cancer*). Based on our GWL substudy, we maintained *Foot Gangrene* (the image associated with the most aversion), and chose 2 other images to cover a range of emotional responses: *Teeth* (significantly lower negative emotion responses than *Foot Gangrene)*; and *Blindness* (significantly lower negative emotion than *Teeth.* Overall, there were 5 pack marketing options (current industry marketing, Blank Pack, and 3 GWL Packs), 2 tobacco origin options, and 2 Quitline number options. The 3 pack designs included in the repeated choice tasks was built on the participant's previous answers (adaptive design). The trade-offs made by participants across these repeated discrete choice tasks reveal the importance they place on cigarette pack attributes and their perceived level of utility (i.e., pay more) or disutility (i.e. pay less) associated with each level of an attribute.

e) Saliva Collection. Study staff assisted participants to rinse their mouth at the start of a clinic visit and then collected a saliva sample some 40 min later using a standard saliva collection kit that included a 2 mL cryovial and a straw for ease of getting the sample into the cryovial. Participants were instructed to fill the cryovial at least 1 mL of saliva (a minimum 75 ul is required). Saliva was stored in a -20° C freezer before being transferred to -80° C freezer for later analysis. Salivary cotinine will be biochemically analyzed in duplicate using Enzyme-Linked Immuno Sorbent Assay (ELISA) kit from Salimetrics, USA. We will use a cotinine value of 15 ng/mL as the cut-point for stated tobacco abstinence.

f) Introduction to EMA, Weekly Survey, and Cigarette Purchase. Study staff instructed participants on the daily EMA and weekly surveys and practiced these tasks with participants. Participants reported their normal waking hours (the 2 daily EMA's were scheduled at random times at least 4 h apart during the participant's waking hours and this data was collected via text message) and preferred day and time to receive the weekly survey via email or text message.

g) Cigarette Purchase. Based on their answers on the study questionnaire to their usual cigarette purchasing behavior, current smoking pattern, and cigarette brand of choice, study staff estimated a 2-week supply for each participant. The minimum purchase requirement was 4 packs (5 cigarettes/day eligibility criteria). Staff then helped participants with their first purchase, a 2-week pack supply, on the study portal.

2.7. 1-Month run-in period

Participants who successfully completed the Baseline Clinic Visit (including the cigarette purchase) then completed a 1-month run-in period to assess compliance to intervention data collection and tasks. To be eligible for randomization, participants were required to: (1) respond to ≥80% of the EMAs (≥48 of 60 tasks) and weekly surveys (≥3 of 4 surveys); and (2) purchase another 2-week supply of cigarettes from the study website.

2.8. Randomization

Participants were allocated to the 3 study groups using an urn randomization scheme [47]. We stratified on 3 variables each with 2 levels: age (< 45 or ≥ 45 years old), sex (male / or female), and nicotine dependence (low to moderate FTND /or high FTND) [29].

Of the 476 participants who signed informed consent at the Baseline Clinic Visit, 26 did not complete the visit (almost all of whom did not complete an online cigarette purchase with a credit card). Of the 450 who started the run-in period, 359 (80%) met the adherence performance requirements and were randomized to one of the 3 study groups resulting in 125 participants to the Blank Pack group, 118 participants to the GWL Pack group; and 116 participants to the Standard US Pack group.

The comparability of study groups on baseline characteristics is presented in Table 1. The average age for each group was 39 years. There was no difference between study groups in representativeness of gender, race-ethnicity, education, or income levels. Participants were mainly white with over one third with a college degree. Over 40% earned < $50,000/year with 17% earning < $25,000/year, indicating that the study had a good representation of smokers earning lower incomes. There was no between-group difference in any of the smoking variables (cigarettes/day, recent quit attempts, nicotine dependence, current cigarette brand, loyalty to current brand, appeal of current pack).

The most common brand variants smoked were Marlboro Gold (9%), Marlboro Red (7%), Camel Crush (6%), Camel Crush Menthol (5%) and Natural American Spirit Yellow (Mellow) (5%), with 69 different brand variants reported. The vast majority of participants (86%) smoked 1 of the 3 most common brands: Marlboro (42%), Camel (26%) and Natural American Spirit (18%). Participants smoked a little over a half pack/day and a little under half had made a serious quit attempt in

the past year. About half had a family member concerned about smoking and one quarter had a smoke-free home, with no difference between study groups. There was no between-group difference on mental health symptoms or sensation seeking.

2.9. The 3-month intensive intervention

Following randomization, participants began a 3-month intensive intervention that involved (1) purchasing cigarettes packaged for their study group from the study website (6 pack purchasing opportunities for participants in each study group); (2) completing the daily EMA (180 opportunities) and (3) completing the weekly survey (12 opportunities). The daily EMA and weekly survey tasks are described below.

2.9.1. EMA task

Twice daily texts included the following questions: 1) "In the last 4 hours how many cigarettes did you smoke?"; "Of those, how many did you smoke from the study pack?"; 2) "In the last 4 hours did you hold the pack so others would not see it?"; 3) "Please rate the following 3 statements from 1-5 (strongly disagree, disagree, agree, strongly agree, no cigarettes today): a) "My last cigarette was satisfying;" b)"I enjoyed the taste of my last cigarette;" c) "My last cigarette relieved my craving;" and 4) "Did your last cigarette come from the study pack?" (Yes/No).

2.9.2. Weekly survey

This survey was texted to participants and the questions pertained to the past week and response options included "never," "some of the time," "most of the time," "always," and "not applicable" for the following questions: 1) "How often did you think about the effect of smoking on your health"; 2) "How often did you think about wanting to quit?"; 3) "How often did you think about the effects of smoking on others?"; 4) "How often did you keep the pack out of view?"; 5) "How often did you offer a cigarette from the pack to others?"; 6) "How often did you purchase non-study cigarettes?". Part 2 of the survey had response options of "strongly disagree," "disagree," "agree," "strongly agree," and "not applicable" for the following questions: 7) "The cigarettes I purchased from the study vendor are high quality"; 8) "The cigarettes I purchased from the study vendor are better than others"; 9) "The cigarettes I purchased from the study vendor are appealing"; and 10) "Have you used any of the following products in the past 7 days (including today)?: a. Electronic cigarette; b. Cigars; c. Smokeless tobacco; d. Pipe tobacco; e. Hookah; f. Nicotine replacement products (example: gum, lozenges, patches); g. Other tobacco products."

2.10. Clinic visit 2 (V2)

At the end of the 3-month intensive intervention participants attended Clinic Visit 2. Clinic visit assessments are displayed in Fig. 1 and described in detail under Clinic Visit 1. Participants completed the Study Questionnaire (Q2), GWL Appeal-Aversion task, provided a saliva sample, and completed Study Feedback Interview 1.

2.10.1. Study feedback interview 1

Participants responded to a recorded study feedback interview that asked about any benefits and challenges faced throughout the intensive intervention period. Open-ended verbal responses were sought from all participants: a) any benefits the participant felt from taking part in the study, b) any challenges they encountered during the 3-month intervention. Blank Pack and GWL study groups were asked the following additional questions: c) if they ever experienced any unusual circumstances while carrying the "graphic" packs of cigarettes, d) if they ever encountered any difficult reactions from family members and/or friends when they opened the pack of cigarettes, e) where they kept the packs that they were not smoking: out in the open or hidden. If participants did not answer the question in some detail, they were prompted to provide more information.

2.11. Follow-up

In the 8 months between Clinic Visit 2 and Clinic Visit 3, participants reverted to purchasing their cigarettes from a vendor in the community and were scheduled to complete another 32 Weekly Surveys via text (described above).

2.12. Clinic visit 3 (V3)

After 8 months participants attended Study Visit 3 where they completed Study Questionnaire (Q3), provided a saliva sample, and completed Study Feedback Interview 2.

2.12.1. Study feedback interview 2

This study feedback Interview focused on likes and dislikes of the study. Participants in the Blank Pack and GWL study groups were asked additional questions about: a) family and friends' reactions to their participation, b) how they thought individuals in their communities would react to having GWL packs in stores, c) whether they believed that having GWL packs and BP in stores would be effective in changing their smoking behavior and the smoking behavior of teens/young adults.

2.13. Cohort maintenance incentives

In addition to the 15% discount on all cigarette purchases, the study provided gift cards to major retailers to show appreciation for participants completing study assessments. Initially, these incentives totaled $160 throughout the study ($20 after completing Visit 1, $20 for completing the run-in month, $10 for being randomized, $30 after Visit 2, $20 for completing text messages consistently for 4 months and $60 for completing Visit 3). Working with the UCSD Institutional Review Board, we increased the incentives 2 more times throughout the study to boost recruitment. The first time we increased compensation in September of 2016 to $300 throughout the study ($40 after Visit 1, $80 at randomization, $80 at Visit 2, and $100 at Visit 3). In June 2017, the IRB approved increasing these incentives again to $80 at Visit 1, $100 at randomization, $100 at Visit 2, and $120 at Visit 3 for a total of $400.

3. Statistical considerations

3.1. Handling missing data

Our study has 2 main sources of missing data. The Baseline Study Questionnaire (Q1) contained an error that omitted the income question for the first 99 of those randomized, and Clinic Visit data collection (V2, V3) was affected by the COVID-19 pandemic affected in March and April 2020. We treat both of these sources of missing data as missing at random. For covariates or confounders that are missing at 10% prevalence or less we will use multiple imputation or related EM likelihood-based procedures [48]. For participants who are missing follow-up assessments of primary outcomes, we will use inverse probability weighting approaches [49].

3.2. Assessment sources for study primary outcomes

Aim 1: Perceptions (awareness, concern) of risks from cigarette smoking are measured on both the Weekly Survey and on the Study Questionnaires (Q1, Q2, and Q3).

Aim 2: Perceptions of appeal of cigarette packs and their subjective reinforcing effects on smoking: These constructs are measured on the Daily EMA, the Weekly Survey and the Study Questionnaires (Q1, Q2, and Q3).

Aim 3: Cigarette smoking behavior including purchasing behavior, pack handling, quitting cognitions and cigarette consumption: Purchasing behavior is measured on the study purchasing website, on the EMA and on the Weekly Survey. Quitting cognitions are measured on the Weekly Survey and smoking behavior including consumption was measured on the Study Questionnaires (Q1, Q2, and Q3) and validated with cotinine analysis of saliva samples collected during Clinic Visits (V1, V2, and V3).

Aim 4 (exploratory): To test whether the participants initial appeal-aversion response to the study pack designs as well as their nicotine dependence level modify their response to the 3-month real-world experience. The appeal-aversion response is measured in 2 ways: 1) in the quantification of the verbalized reactions to pack designs during the V1 pack-handling task, and 2) in a measure of price aversion and appeal derived from the ABCB purchasing task designed to probe willingness to pay valuations for differing pack designs collected at V1 and V2.

3.3. Assessment sources for study covariates

The majority of study covariates, including nicotine dependence levels, are measured on the Study Questionnaire. The exception was the recorded Pack Handling Task/GWL Verbal/Nonverbal Response at the first Clinic Visit.

3.4. Analytic plan

3.4.1. EMA data

The daily texting data includes measures of a) perceived quality of sensory effects from their cigarettes (Aim 2), b) willingness to display their study packs in social settings (Aim 3), and c) smoking behavior including avoidance of cigarettes from study packs (Aim 3). As these questions were asked twice daily over 4 months, we will aggregate the daily data to provide an average daily score, that we will normalize using min-max scaling based on the 1-month run-in period observations. When comparing patterns of EMA measures for Aim 2 and Aim 3 between study groups, we will use either a generalized linear model or a generalized quadratic model with a compound symmetry covariance structure for each outcome of interest, based on the trends of the raw data. We will allow a linear spline or a quadratic term for the generalized linear mean structure as needed. The study will be divided into the 1-month run-in period and the 3-month intervention period, to allow inferences comparing the difference among the 3 pack groups adjusted for differences during the run-in period data. We will use a Wald test for statistical inference comparing the model-fitted mean difference between any 2 study groups over any specific time period during the 3-month intervention. In all analyses, Type I error for multiple comparisons will be controlled at familywise 5% level using a Holm step-down approach.

3.4.2. Weekly survey data

The Weekly Survey data includes 12 months of measures on the following constructs: for Aim 1, a participant's positive cognitions about their cigarettes; for Aim 2, perceptions of risks from smoking and the perceived quality of their cigarettes; and for Aim 3, willingness to display their study packs in social settings; and quitting cognitions. We will normalize these data using min-max scaling based on the 1-month run-in period observations. We will use the same procedure as above to model each of the outcomes and we will use a similar approach to make statistical inferences regarding model-fitted mean differences.

3.4.3. Study questionnaire data

The 3 study questionnaires (Q1, Q2, and Q3) administered at each clinic visit included measures for each study aim including perceptions (awareness, concern) of risks from cigarette smoking (Aim 1); appeal of cigarette packs (Aim 2); and pack handling, quitting cognitions, average daily cigarette consumption, and use of other tobacco products (Aim 3). For analyses of questionnaire measures for each aim, we will use linear or generalized linear models to make statistical inference about differences between the 3 study groups at the end of the 3-month intensive intervention and again at the end of the 8-month follow-up. The difference of each outcome between each of the last 2 time-points and the baseline will be assessed.

3.4.4. The purchasing data set

Participants had 6 opportunities to purchase cigarettes during the 3-month intervention., Their expected purchase amount was established with 2 purchasing opportunities prior to randomization. To address Aim 3, we will aggregate these data and calculate the proportion of expected purchases made throughout the intensive intervention for each study group. Data will be presented as box-plots and mean differences compared using one-way ANOVA.

3.4.5. Cotinine concentrations

Cotinine values (ng/mL) will be collected at each study visit. Changes in levels will be evaluated using linear models to make statistical inference about hypothesized (Aim 3) differences in the 3 study groups at the end of the 3-month intensive intervention and again at the end of the 8-month follow-up. Information about past 7-day tobacco product use including cigarettes, e-cigarettes, cigars, pipe, hookah, smokeless or other tobacco will be collected. Cotinine values below 15 will biochemically verify Q2 or Q3 self-reports of 7-day point prevalence abstinence for tobacco.

3.5. Appeal-aversion willingness to pay assessments

Willingness to pay will be calculated at baseline (V1) and after the 3-month intervention (V2). A multinomial logit hierarchical Bayes analysis of the conjoint task will be used to deconstruct cigarette packaging into its various parts (i.e., attributes) and varying options across products (i.e., levels) by estimating the importance of each part (i.e., attribute importance), the preference for each level of an attribute (i.e., part-worth utility), and the corresponding price thereof (i.e., willingness to pay) [50]. Part-worth utility estimates are relative to the set of examined levels and sum to zero with positive scores indicating greater preference. Attribute importance scores that sum to 100 are calculated by dividing the range the utility scores by the sum of the ranges and reflect the preference for that attribute in comparison to all other examined attributes. To examine the relative effect of GWLs on willingness to pay, part-worth utility estimates for the design attribute will be re-centered with the blank pack design as the referent level. Utilities will be converted to dollar values by multiplying each individual utility by the median value of the dividend between the difference in the spread of the reported pack prices (i.e., $3.00–$15.00) and the difference in the utility of the pack prices [51]. The resulting estimations reflect the appeal-aversion valuations (i.e., willingness to pay) attributed to each pack design. Differences in willingness to pay for GWLs will be estimated using one way ANOVAs run on the posterior distributions of attribute importance, price utilities, and price utility differences for each study arm. The Benjamini– Hochberg *p*-value adjustment will be used to account for false discovery [45].

3.5.1. Effect modification

In order to explore effect modification of nicotine dependence and appeal-aversion response to pack designs on study outcomes (Aim 4), for all planned analyses we will include a cross product interaction term between study arm by each modifier of interest (e.g. nicotine dependence, appeal-aversion valuations and reactions). Wald's method will be used for statistical inference of the interaction on the multiplicative scale. Models with significant interactions will be stratified to facilitate the interpretation of the effects.

4. Discussion

In this real-world randomized trial of US smokers, we investigate how cigarette pack design influences smoking behavior and cognitions. Our trial investigates 3 cigarette pack conditions: a standard US cigarette pack and 2 study-designed packs: the first involved a blank olive-colored pack without any tobacco industry marketing (Blank Pack); the second condition was a standardized pack with rotated 3 GWL images currently sold in Australia (GWL Pack). This standardized GWL Pack involves a higher level of GWLs than those proposed by the US FDA for implementation in 2021 (GWLs cover 75% vs 50% of the pack) and the FDA will allow reduced Industry marketing to remain on the pack. We used standardized packs for 2 reasons: first, this enabled a cleaner test of the study hypotheses as the Blank Pack condition removed all tobacco marketing images and the standardized GWL Pack *added* GWLs to the Blank Pack condition. We did not use the FDA-proposed hybrid condition (smaller GWL + Industry marketing). To have such a condition would have meant that we needed to modify current tobacco imagery on packs, and University Counsel strongly advised us against manipulating copyrighted images. Rather, they suggested that we use a pack that was already available for retail somewhere in the world. As cigarette brand varieties are quite different in other English language countries with hybrid GWLs, it proved quite difficult to identify available hybrid pack options that would be close to the FDA's proposed GWL + Industry marketing pack design.

This trial includes several important innovations to current research on cigarette pack design that has been reported in the peer review literature. First, we assessed the appeal-aversion responses when participants had their first opportunity to handle and explore the study packs (the US smokers recruited for this trial had limited previous experience purchasing GWL packs). The negative emotional response to GWL packs is a major component in the Tobacco Industry lawsuit to prevent the implementation of the FDA rule in 2021 [18]. Not only did we undertake a detailed assessment of negative emotional response of the GWLs, but we also conducted a baseline “willingness-to-pay” assessment to see the discount that the smoker would want before they would voluntarily purchase their cigarettes in a GWL pack. There is a literature from countries that have implemented GWL packaging [50,51]. that smokers become desensitized to GWLs [5,49]. By repeating the willingness-to-pay assessment at the end of the 3-month intensive intervention, we will be able to test if smokers became desensitized to the GWL associated with the highest emotional response during this period as well as whether any such desensitization extended to other GWLs that were not included in the study intervention.

Our trial is a real-world study in which we provide incentives to smokers to purchase their cigarettes from the study. Of course, at any time, the participant can revert to purchasing their cigarettes from local community sources. One might expect that those smokers who had a major aversive reaction to the study GWL packs at the start of the study would be less than adherent to purchasing their cigarettes from the study if they were randomized to the GWL group. To properly test the effect of GWLs on smoking cognitions and behavior, it is very important that all participants obtain an extensive exposure to their study pack. Our measures of exposure include data on the number of cigarettes purchased from the study for all 3 pack groups and the twice daily EMA responses during the 3-month intervention; these data included a question asking the smoker twice daily whether their last cigarette was from a study pack. The EMA data also allows us to identify the timing of study effects on participant cognitions and behavior.

However, the twice daily EMA data and the weekly surveys add up to a significant participant burden in this study. While study incentives can be sufficient to ensure that participants complete study assessments, participants may be inclined to change their smoking behavior and cognitions in response the frequent measurements [52,53]. As this was a randomized trial, the Standard Pack group controls for this measurement effect. We tried to minimize this effect by only enrolling smokers who had no immediate intention to quit smoking. Nevertheless, the price of getting daily data on cognitions and smoking behavior may well be that the study encouraged quitting in all study groups. The other effect of the considerable participant burden was the difficulty in recruiting otherwise eligible smokers once they understood fully what would be required of them throughout the study. Only 14% of eligible participants who contacted the study attended the initial Clinic Visit where they were first exposed to the study packs. This level of recruitment limits the generalizability of study results.

The challenges of conducting a real-world experiment were evident in this study. In response to tobacco control concerns about young people purchasing cigarettes over the internet, the US postal service changed its policies and would no longer deliver cigarettes through the mail. This occurred between the time of our grant proposal and study initiation and forced us to seek a funding supplement to deliver cigarettes through an expensive courier service. Further, in 2020, the COVID-19 pandemic led to significant restrictions on clinic visits, which resulted in higher than expected rates of missing data toward the end of the study period. Nevertheless, the 3-month real-world exposure to the different cigarette pack designs is a significant strength of the study, especially because of the many repeated measures used. These data will allow us to analyze important daily reactions to the packs over 3 months (perceived quality of their cigarettes, willingness to display their study packs in social settings, and smoking behavior including avoidance of cigarettes from study packs).

5. Conclusion

This randomized trial of the effect of implementing GWLs on US cigarette packs is timely given that the Tobacco Industry has filed a recent lawsuit to prevent the implementation of the FDA proposed rule on GWLs on the grounds that they are associated with unacceptable negative emotions and violate the first amendment. In addition to having detailed measures of appeal-aversion of different cigarette packaging before the start of the trial, US smokers have an in-depth 3-month real-world experience of smoking cigarettes from the different study packs, during which they respond to daily EMA measures of their cognitions and behavior. The results of this trial will significantly add to the literature on the role of GWLs as an influence on a) increasing smokers' perception of risks, b) decreasing perceptions of appeal of tobacco industry marketing on US packs and their subjective reinforcing effects on smoking. It will also provide validated evidence of GWL packs on both short- and long-term effects on smoking behavior.

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Declaration of Competing Interest

None.

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