



Research paper

Reach versus effectiveness: The design and protocol of randomized clinical trial testing a smartphone application versus in-person mindfulness-based smoking cessation intervention among young cancer survivors

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ARTICLE INFO

Keywords:

Young cancer survivors
Smoking cessation intervention
Mindfulness
Smartphone application
Randomized clinical trial

ABSTRACT

Approximately 45% of young cancer survivors (18–40 years) are cigarette smokers. Continued smoking after cancer diagnosis leads to lower survival rates. A major logistical problem with smoking cessation efforts in this group is their geographic dispersion which makes them hard to reach. In addition, depression is a major predictor of smoking relapse and its rates are roughly twice as high in cancer survivors as the general population. Smartphone applications (apps) show promise in terms of efficacy, dissemination, and improving access to treatment. Mindfulness training (defined as maintaining attention on one's immediate experience and cultivating an attitude of acceptance toward this experience) is effective in improving smoking cessation outcomes by reducing psychological stress and controlling craving. Given that smartphone apps can address the issues of mobility and remote access, and mindfulness can address the high depression rate among cancer survivors, validating the feasibility and efficacy of a mindfulness-based smoking cessation intervention app in young cancer survivors is a high priority. Thus, the aims of the current study are: (1) test the feasibility, acceptability, and potential efficacy of the mindfulness-based smoking cessation app versus in-person mindfulness or usual care in a 3-arm pilot randomized clinical trial among young cancer survivors (n = 60; 18–40 years); and 2) conduct semi-structured exit interviews with participants in the two mindfulness groups to fine-tune the two active interventions based on feedback from participants. Findings will have implications for the development and dissemination of innovative and highly scalable tobacco cessation interventions designed for young cancer survivors.

1. Introduction

Approximately 45%–46% of young cancer survivors (18–40 years) are cigarette smokers [1–4]. Continued smoking after cancer diagnosis increases cancer treatment toxicity and lowers survival rate [5–7]. Tobacco cessation remains, however, a challenging issue in cancer survivors. Several reviews concluded that current evidence-based smoking cessation interventions are not successful among survivors [8]. One of the major logistical problems with smoking cessation efforts in young cancer survivors is their geographic dispersion, as the numbers of cancer

survivors in any given medical practice is likely to be low [2,9]. In addition, depression is a major predictor of smoking relapse and depression rates are roughly twice as high in cancer survivors as the general population [10]. To date, only one study has addressed the intersection between smoking and depression among cancer survivors by providing antidepressant medication [11]. Although it provided some evidence of benefit, it was methodologically limited by having a small sample size and not using standardized smoking abstinence outcomes. Therefore, developing innovative smoking cessation interventions that can improve survivors' access to treatment and decrease

Abbreviations: NRT, nicotine replacement treatment; RCT, randomized clinical trial.

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<https://doi.org/10.1016/j.conctc.2021.100784>

Received 8 August 2020; Received in revised form 10 February 2021; Accepted 5 May 2021

Available online 19 May 2021

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their stress and depression is important.

Smartphone applications (apps) have emerged as important tools for smoking cessation interventions [12,13]. In the US, 98% of young adults are smartphone users [14]. Smartphone apps provide a promising medium to deliver an intervention due to the propensity for widespread dissemination, their availability, relatively low cost, and ease of use. Compared to in-person interventions, this approach can be standardized, allow the use of multiple methods to deliver the intervention (e.g., video, audio), and facilitate the integration of the intervention into the user's daily life, all serving to boost the user's engagement, a strong predictor of smoking cessation [15–18]. In addition, mounting evidence suggests that mindfulness is effective in reducing negative affect and psychological stress [19,20]. Mindfulness approaches includes two components, maintaining attention on the individual's immediate experience and cultivating an attitude of acceptance toward this experience [21]. Mindfulness training typically involves the training of attention regulation, body awareness, and emotion regulation [22]. For smoking cessation, mindfulness training can help smokers learn to pay attention to craving as they arise and accept and ride out the cravings rather than to react by smoking [22]. Mindfulness also is effective in decreasing emotional reactivity and relapse related to avoidance of distressing symptoms [23]. However, no study has evaluated the efficacy of a targeted mindfulness-based smoking cessation intervention for cancer survivors. Given that smartphone apps can address the issues of mobility and remote access, and mindfulness can address the high depression rates among cancer survivors, validating the feasibility, acceptability, and efficacy of a mindfulness-based smoking cessation app in young cancer survivors is highly promising to improve their cessation outcomes.

Recently, an evidence-based mindfulness-based smoking cessation app, “*Craving to Quit*,” was developed based on an in-person mindfulness-based smoking cessation intervention that proved to be effective (quit rate 36% vs. 15% in the control group) [24–27]. Using a mixed methods sequential explanatory design approach of quantitative and qualitative research [28], the current study aims to: 1) test the feasibility, acceptability, and potential efficacy of the mindfulness app versus an in-person mindfulness intervention (the original in-person version of the of the *Craving to Quit* app intervention) [24] or usual care (brief advice to quit based on the 5A's Model: Assess, Advise, Agree, Assist and Arrange) [29] in a 3-arm pilot randomized clinical trial (RCT) among young cancer survivors (age 18–40 years) who smoke; and 2) fine-tune the two active interventions based on feedback from participants. We used a 3-arm study design for two reasons. First, to quantify the effect of the mindfulness app and group in-person mindfulness interventions compared to usual care as these two treatments are being tested for the first time among this population. Second, the usual care (our control group) represents the minimum intervention that our target population can receive based on the United States Treatment Clinical Practice Guidelines (USCPG) for tobacco use [29]. Nicotine Replacement Treatment (NRT) will be provided to all participants in the three treatment groups for compliance with the USCPG [29]. We targeted this age group based on previous evidence indicating that cancer survivors in this age reported the highest cigarette smoking (27.9%) compared to cancer survivors in older age groups (16.9%) [2,30]. Findings will inform a larger study of the effectiveness of cessation approaches with great potential for translation and broad dissemination to cancer survivors who smoke throughout the US.

2. Methods

2.1. Objectives

This RCT is designed to evaluate: (1) the feasibility and acceptability of the mindfulness app vs. group in-person mindfulness-based smoking cessation or usual care/control (UC) intervention; (2) the preliminary effect of mindfulness on perceived stress and depressive symptoms

among young cancer survivors seeking tobacco treatment, and (3) perceived distress as an underlying mechanism for the effects of mindfulness on cessation. We hypothesize that the mindfulness app will be more feasible and acceptable than the in-person mindfulness, the in-person mindfulness intervention will be more effective than the mindfulness app, and the two mindfulness interventions (app and in-person) will be more effective than the UC intervention in reducing perceived stress and depressive symptoms and increasing smoking cessation. We also hypothesize that reductions in perceived stress and depressive symptoms will mediate differences in smoking cessation. If the hypotheses are supported, this study will provide important insight on potential interventions targeted for young cancer survivors.

2.2. Study design

This study has been approved by the University of Miami Institutional Review Board. The study is a 3-arm pilot RCT: 1) mindfulness app, 2) in-person mindfulness, and 3) UC intervention (control group) using stratified random allocation by sex. Participants in the mindfulness app arm will receive one in-person orientation session, 6 months free access to the app, and two brief follow-up phone calls (1 day before quit date and 2 weeks after quit date). Participants in the group in-person mindfulness arm will receive twice weekly group sessions for 4 weeks (eight total) that are manualized and delivered by a certified mindfulness instructor with an extensive background in public health. Participants in the UC intervention arm will receive brief advice and self-help materials to quit smoking. Participants in all three study arms will receive a 6-week supply of Nicotine Replacement Treatment (NRT). The primary outcomes are biochemically confirmed 7-day point-prevalence abstinence using saliva cotinine ≤ 10 ng/ml [31], assessed over a 3- and 6-month follow-up period, and change in perceived distress and depression pre- and post-intervention. Testing the mediating role of perceived distress is considered an exploratory aim. Fig. 1 illustrates the flow of participants through the study.

2.3. Recruitment and study participants

Our target sample size is 60 young cancer survivors who smoke. Participants are recruited through three primary sources. First, direct recruitment is conducted using flyers and palm cards that are distributed in cancer medical clinics, cancer service organizations, survivorship support groups, and via social media. Second, we are utilizing the Consent-to-Contact Cancer Registry database at UHealth, the University of Miami's health system network. Access to this service allows us to contact cancer survivors who have consented to be contacted for studies for which they appear to meet inclusion criteria (e.g., 18–40 years old, diagnosed with any type of cancer). Lists of potential participants including their names, contact information, smoking status, and cancer history (diagnosis, age of diagnosis, type of cancer, cancer treatment) are provided. Participants are contacted by phone and invited to participate in the study. Third, an incentivized snowball sampling method is employed where enrolled participants receive \$5 for referring an individual who is subsequently judged to be eligible for the RCT.

Inclusion criteria are (1) 18–40 years old, (2) diagnosed with cancer (any histologic subtype of cancer is qualified for entry into this study), (3) have smoked ≥ 5 cigarettes/day in the past year, (4) interested in making a quit attempt in the next 30 days (indicating that participant is in the action stage based on The Transtheoretical Model) [32], (5) own a smartphone (Apple/Android), (6) read/speak English, (7) able to provide the consent form, (8) do not have plans to move in the next 6 months, and (9) are not pregnant or planning to be pregnant in the next 6 months (Table 1).

Exclusion criteria are (1) currently receiving active cancer treatment, (2) having contraindication to NRT (past month myocardial infarction, history of serious arrhythmias/or unstable angina pectoris, dermatological disorder) [29], (3) have cognitive or mental health impairment

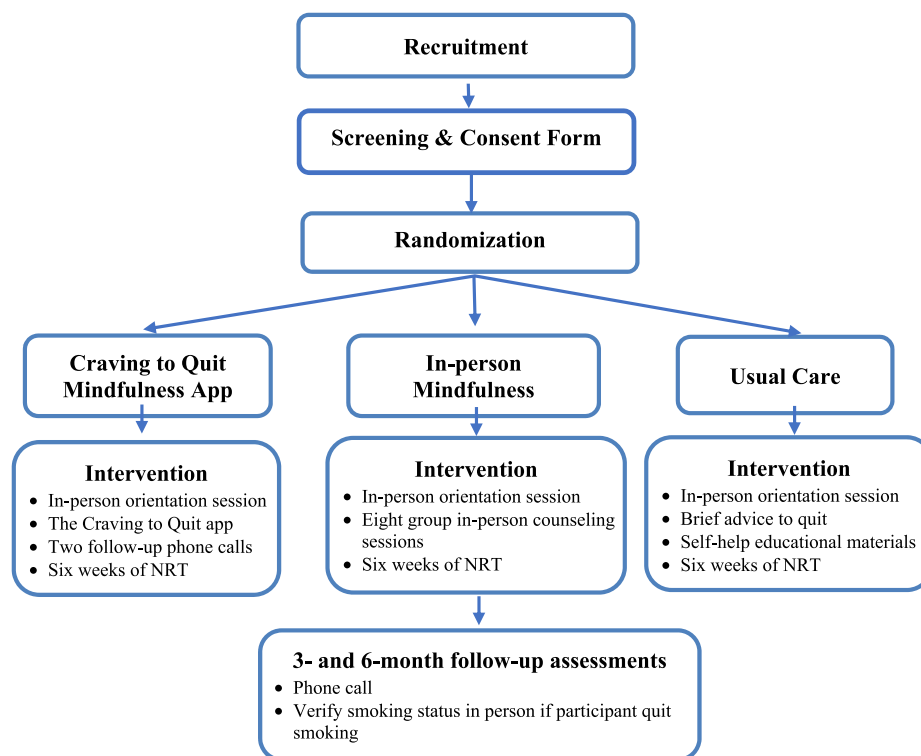


Fig. 1. The randomization clinical trial study schema.

Table 1
Inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> • 18–40 years old • Diagnosed with cancer (any histologic subtype of cancer is qualified for entry into this study) • Have smoked ≥ 5 cigarettes/day in the past year • Interested in making a quit attempt in the next 30 days • Own a smartphone (apple/android) • Read/speak English • Able to provide the consent form • Do not have plans to move in the next 6 months • Are not pregnant or planning to be pregnant in the next 6 months 	<ul style="list-style-type: none"> • Currently in active cancer treatment • Have cognitive/mental health impairment that inhibits mindfulness treatment • Having contraindication to NRT (past month myocardial infarction, history of serious arrhythmias/or unstable angina pectoris, dermatological disorder) • Use other tobacco/nicotine products regularly (which can interfere with biological verification of smoking cessation) • Currently receiving smoking cessation treatment • Inability to attend sessions • Active alcoholism or illicit drug use

that inhibits mindfulness treatment (4) currently using other tobacco products (e.g., smokeless tobacco, Hookah, electronic cigarette), regularly which can interfere with the assessment of cessation outcomes and contaminate the intervention effect (e.g., using electronic cigarette to quit smoking), (5) currently receiving smoking cessation treatment, (6) active alcoholism or illicit drug use, and (7) inability to attend sessions. Marijuana users will not be excluded from the study for generalizability. However, marijuana use will be monitor during the study (Table 1).

2.4. Randomization

Simple stratified randomization by sex is used to determine the assignment to mindfulness app, group in-person mindfulness, or UC.

Stratified random sampling by sex is used to generate randomization codes in blocks of 6. Eligible participants are randomly assigned in a 1:1:1 ratio, and those who provide informed consent are enrolled in the trial. The randomization sequence is computer-generated by the study biostatistician. Only the study biostatistician and the study coordinator will know the allocation. The research assistant who is recruiting participants and completing the study assessments and the interventionist who is providing the treatment will be in blinded for the intervention allocation to prevent selection and confounding biases. Due to the composition of the study arms, participants are aware of to which study arm they are allocated.

2.5. Procedures

Screening occurs over the telephone. Those who are not eligible or decline to participate are still encouraged to quit smoking and given a list of available resources such as the Florida tobacco quitline (<http://tobaccofreeflorida.com/>). Eligible participants are re-contacted later by phone to confirm their participation and schedule their orientation session. In the orientation session (90–120 min), participants are screened to confirm their eligibility and provide an expired CO sample to verify their smoking status using a hand-held CO monitor (Bedfont piCO + Smokerlyzer; Bedfont Scientific Ltd, Maidstone) ($\text{CO} \geq 6$ ppm is the cut-off point for being active smoker) [33]. After confirming their eligibility, we obtain written informed consent, a detailed tracking form with at least one secondary contact, and Health Insurance Portability and Accountability Act (HIPAA) release to access their treatment records. Then, we randomize and enroll participants and provide an overview of the research study and treatment according to their group allocation, and participants complete the baseline assessment. All participants complete 3- and 6-month follow-up assessments (Fig. 1). Reminder calls, emails, and text-messages are used to encourage required attendance. Smoking status is verified using saliva cotinine ≤ 10 ng/ml [31,34]. Incentives for assessment completion include \$20 at baseline, \$30 at 3-month, and \$40 at 6-month. Data collection and management will be done using REDCap (<https://www.project-redcap>).

org/).

2.6. Intervention conditions

Both mindfulness interventions (app and in-person) are based on the theory of mindfulness-based cognitive therapy (MBCT) for relapse prevention [35]. The MBCT uses cognitive behavioral therapy methods in conjunction with mindfulness techniques. Cognitive methods focus on the development of personal coping strategies that target solving problems and changing unhelpful patterns in cognitions (e.g., thoughts, beliefs), behaviors, and emotional regulation [36], while mindfulness training focuses on becoming aware of all incoming thoughts and feelings and accepting them, but not attaching or reacting to them [37]. This latter process is known as "decentering" and aids in disengaging from self-criticism and rumination that can arise when reacting to negative thinking patterns [38].

2.6.1. Mindfulness app for smoking cessation intervention

Participants in this group receive one in-person orientation session, the mindfulness app, two brief follow-up phone calls, and a 6-week supply of NRT.

- a. Orientation session. This session is moderated by a certified instructor in mindfulness with a background in public health sciences and lasts 90–120 min. In addition, the study research assistant (s) will help in obtaining the consent forms and completing the baseline assessment. During the session, participants learn the purpose, format, and procedures of the study, provide written informed consent, and complete the baseline assessment. Then, participants are coached to download on their phone the “Craving to Quit” app (<https://www.cravingtoquit.com/>). After downloading the app, participants receive a 60-min tutorial explaining the app content and features to troubleshoot any issues, followed by training on how to use the app and to practice mindfulness techniques. Participants are asked to start using the app the next day and set a quit date on day 21 based on the app schedule. Participants also receive 6 weeks of nicotine patches and are instructed to start using the NRT at the quit date [29].
- b. The mindfulness app. The app is comprised of 22 modules for 22 days, 5–15 min each, designed to teach mindfulness using audio, video, and animation (Table 2; Fig. 2) [25]. Participants have access to only one new module per day, and subsequent days are locked to prevent skipping ahead. However, participants have full access to all previous modules and can always access them in case they missed some. They. The app teaches three basic formal mindfulness techniques including *Body Scan* (bringing awareness to different parts of the body to foster awareness of body sensations that constitute cravings and affective states), *Loving-Kindness* (repeating phrases such as “may X be happy” to foster acceptance of oneself and others), and *Breath Awareness* (paying attention to the breath wherever one feels it most strongly in the body to help retrain the mind away from habitually engaging in self-related thinking toward a more present-centered awareness). The app also teaches one informal mindfulness practice called “RAIN” (Recognize, Accept, Investigate, and Note what cravings feel like as they arise/pass away). In RAIN, participants are asked to identify their smoking trigger, rate their craving, and choose between using RAIN to ride out their craving, or completing an audio-guided exercise to “smoke mindfully” by paying attention to the moment-to-moment experience and bodily sensations of smoking. The app also includes other features such as social support (quit friend sign-ups, the tip of the week), activity feed (to track interaction with the app), and “my morning stats” (to track smoking). The research team receives a daily report from the app developers about participants’ activities.
- c. Two brief follow-up phone calls. The first phone call occurs one day before the quit date to remind participants about their quit date and

Table 2

The content of the Craving to Quit mindfulness app modules and the group in-person mindfulness-based smoking cessation intervention.

	Craving to Quit Mindfulness App	Group In-person Mindfulness
Week (1)	<ul style="list-style-type: none"> • Day 1: Introduces the Craving to Quit app, mindfulness, habit formation, and mindful smoking exercise. • Day 2: Asks to set personalized goals and provides a mindful smoking exercise. • Day 3: Teaches body scan meditation and provides a mindful smoking exercise. • Day 4: Teaches how to work with cues, affective states, and craving using RAIN, and provides a RAIN exercise. • Day 5: Introduces the concept of craving using an animation with the metaphor of craving as a tantrum toddler, i.e., let the toddler cry it out, and provides a RAIN exercise. • Day 6: Teaches how to recognize triggers and provides a RAIN exercise. • Day 7: Expands on the concept of craving using an animation with the metaphor of craving as a fire and provides a RAIN exercise. 	<p>Session 1:</p> <ul style="list-style-type: none"> • Discuss the role of automatic pilot in relation to cravings and urges to smoke. • Introduce the body scan. • Ask to set an aspiration for quitting. • Skills: mindfulness of smoking, body scan, setting aspiration, mindfulness of daily activity. <p>Session 2:</p> <ul style="list-style-type: none"> • Explore how thoughts, emotions, and body sensations become triggers for cravings. • Introduce RAIN. • Skills: RAIN.
Week (2)	<ul style="list-style-type: none"> • Day 8: Teaches how to use noting practice, i.e., the “N” of RAIN, in everyday life, and provides a noting practice exercise. • Day 9: Teaches strategies for staying on track and provides a noting exercise. • Day 10: Teaches resistance training and provides a noting exercise. • Day 11: Builds on noting practice by teaching curiosity, a core element of mindfulness, and provides a curiosity exercise. • Day 12: Expands on the concept of craving and curiosity using an animation with the metaphor of a hot coal, asks “What do you get from smoking mindfully today?” • Day 13: Teaches loving-kindness meditation, provides a loving-kindness exercise, and provides “Wild Geese” poem by Mary Oliver. • Day 14: Teaches evaluating the costs & benefits of smoking, provides a loving-kindness exercise. 	<p>Session 3:</p> <ul style="list-style-type: none"> • Introduce how emotions can arise and be perpetuated through expectations and attachment to concepts of self. • Discuss how these emotions can lead to cravings/wanting to smoke. • Introduce loving-kindness. • Skills: loving-kindness. <p>Session 4:</p> <ul style="list-style-type: none"> • Explain how habits keep us off-balance and aim us away from our aspirations/goals. • Understanding the differences between urges and aspirations • Discuss how resolve can help keep us moving along this path toward greater health and freedom from our habitual urges and drives. • Skills: reflecting on the benefits of not smoking, “AND THEN WHAT.”
Week (3)	<ul style="list-style-type: none"> • Day 15: Discusses misperceptions about quitting and how to get social support. • Day 16: Builds on noting and curiosity by teaching noting while walking meditation, provides a walking noting practice. • Day 17: Teaches open awareness of thoughts, to work mindfully with thoughts that trigger smoking, using animations such as “Thoughts like a Radio.” • Day 18: Builds on walking while noting with animations such as “Tripping on Thoughts,” “Autobiography in 5 short 	<p>Session 5:</p> <ul style="list-style-type: none"> • Discuss how mindfulness meditation can help us increase our awareness and make better choices in our everyday lives. • Introduce walking meditation. • Introduce a meditation that expands upon the noting of body sensations to include a focus on thoughts. • Skills: Mindfulness of breath meditation, 4 modes of walking. <p>Session 6:</p> <ul style="list-style-type: none"> • Explore how thoughts can trip us up, leading to autopilot and “runaway”/defeatist attitudes that can get us stuck back in our

(continued on next page)

Table 2 (continued)

	Craving to Quit Mindfulness App	Group In-person Mindfulness
	<p>chapters" reading by Portia Nelson, provides a noting exercise.</p> <ul style="list-style-type: none"> • Day 19: Asks to reflect on experience with treatment, noting practice with a particular eye out for doubt. • Day 20: Provides tips on staying motivated and maintaining mindfulness practice, writes a mantra to use and sets mantra reminder. • Day 21: Quit day ceremony, tell a friend/family that today is their quit day. 	<p>old habits, and that at each point in this chain there is an opportunity to bring in mindfulness such that we can step back out of these habits and make skillful responses.</p> <ul style="list-style-type: none"> • Skills: Tripping on thoughts.
Week (4)	<ul style="list-style-type: none"> • Day 22: Incorporates mindfulness practices as a new, healthy habit, and instructs the user on which modules to return to if they relapse. • Bonus "Big Mind Meditation" audio by Joseph Goldstein; Tree Analogy for reinforcing noting video; Attitude is Everything video; "Mountain Meditation" audio by Joseph Goldstein; Sitting Meditation audio. 	<p>Session 7:</p> <ul style="list-style-type: none"> • Discuss the difference between not accepting what is happening in this moment and accepting the situation as it is. • Skills: RAINing on high risk situations. <p>Session 8:</p> <ul style="list-style-type: none"> • Discuss new habits and how we can continue them. • Discuss high risk situations and how we can be mindful in these situations. • Skills: Reminder Cards.

provide support. The second occurs at the end of treatment (day 30 after enrollment) to review progress, provide support, and schedule the 3-month follow-up visit. These phone calls will be conducted by the study research assistant(s).

2.6.2. The in-person mindfulness-based smoking cessation intervention

Participants in this group receive twice weekly group sessions for 4 weeks (eight total) that are manualized and delivered by a certified mindfulness instructor with an extensive background in public health. The target group size is 10–15 participants. The overarching theme of momentary awareness and acceptance of cravings and affect (e.g., stress, anxiety, etc.) are introduced and reinforced in complementary ways throughout the training [39]. The intervention manual was developed by Dr. Judson Brewer at Brown University, also a collaborator on the development of the Craving-to-Quit app. The manual is based on an early version of Bowen, Chawla and Marlatt's Mindfulness-Based Relapse Prevention (the framework of which was drawn from Mindfulness-Based Stress Reduction and Mindfulness-Based Cognitive Therapy) [24].

- Session (1): We introduce participants to the concept of how smoking can become a habituated behavior triggered by an environmental, physical, or mental stimulus through associative learning. We also explore how cravings feel in the body and how mindfulness can help individuals become more aware of these processes.
- Session (2): We examine how thoughts, emotions and body sensations become triggers for craving and smoking and introduce a technique to 'mindfully' work with cravings (RAIN: Recognize, Accept, Investigate, and Note what cravings feel like as they arise).
- Session (3): We introduce how difficult emotions perpetuate smoking as well as a standard meditation technique called loving-kindness as a way to work with them [40]. Loving-kindness is practiced through directed well-wishing, typically by repetition of phrases such as "may X be happy," with X being oneself or named others in one's life.
- Session (4) (quit date): We teach participants how cravings thwart long-term goals and reinforce mindfulness techniques as a way to help individuals disengage from habitual responding and realign with their goals.

- Session (5): We introduce participants to mindfulness practice in everyday life, including awareness of breath, meditation, and mindful walking (four modes of walking, during which individuals practice systematically noting objects that they see, then objects that they hear, then objects that they smell, and then tactile objects such as the pressure of their feet on the ground).
- Session (6): We teach participants how to explore the automaticity of thought, and how thoughts can lead to habitual behaviors.
- Session (7): We reinforce the concept of acceptance and its role in changing habits. We also teach participants to explore how both mental and physical actions can "plant seeds" for future actions and habits.
- Session (8): We summarize the course tools and explore ways of maintaining these in the future.

Home practice is suggested after each session as a combination of formal meditations (e.g., body scan, loving-kindness, awareness of breath), and informal mindfulness practices (four modes of walking, mindfulness of daily activities, mindfulness of smoking, RAIN). Participants are encouraged to practice mindfulness at home.

2.6.3. Usual care (UC)/control

Participants in this group receive 10 min of brief advice to quit smoking based on the 5A's Model: Assess, Advise, Agree, Assist and Arrange. The intervention features 4 main keys including setting a quit date, preparing to quit, relapse prevention, and how to properly use NRT [29]. Participants also receive a 6-week supply of NRT and self-help materials to quit smoking. The control group intervention represents the minimum intervention that our target population can receive based on Tobacco Treatment Practice Guidelines and recommendations [29, 41].

2.6.4. Nicotine replacement therapy

Participants in all three study conditions receive 6 weeks of nicotine patch therapy. Transdermal nicotine patches are safe, effective, and available over the counter. Consistent with the tobacco clinical practice guidelines [29], participants receive 2 weeks at 21 mg, 2 weeks at 14 mg, and 2 weeks at 7 mg, with dosages adjusted by daily smoking intensity.

2.7. Follow-up and retention

All participants receive two in-person follow-up assessments administered by a research assistant at 3 and 6 months after enrollment to assess their smoking status and perceived distress and depression, as well as to get information about concomitant smoking and NRT use, use of additional NRT or cessation drugs (e.g., bupropion), and use of other tobacco methods. Those who report quitting smoking provide a saliva sample to validate their smoking cessation status using saliva cotinine ≤ 10 ng/ml [31,34], a widely used method to biochemically confirm smoking abstinence with 96–97% sensitivity and 99–100% specificity, with a well-tested cut-point of 10 ng/ml to distinguish between non-smokers (1–10 ng/ml) and active smokers (>10 ng/ml Saliva) [31,34]. Saliva samples are collected using Salimetrics kits [31], and analyzed at the University of Miami Diabetes Research Institute by automated gas liquid chromatography [42].

To maintain active participation for the entire length of the study, several retention strategies are used. These include collecting detailed contact information for relatives/friends, who would know the participant's whereabouts, contacting participants with personalized letters/cards, sending out study-relevant information at three months (e.g., changes in your body after quitting smoking, quitting rewards), and individual case management. In addition, we are providing incentives for participants at several occasions to improve adherence to the protocol (e.g., \$20 at baseline, \$30 at the 3-month follow-up, and \$40 at the 6-month follow-up).

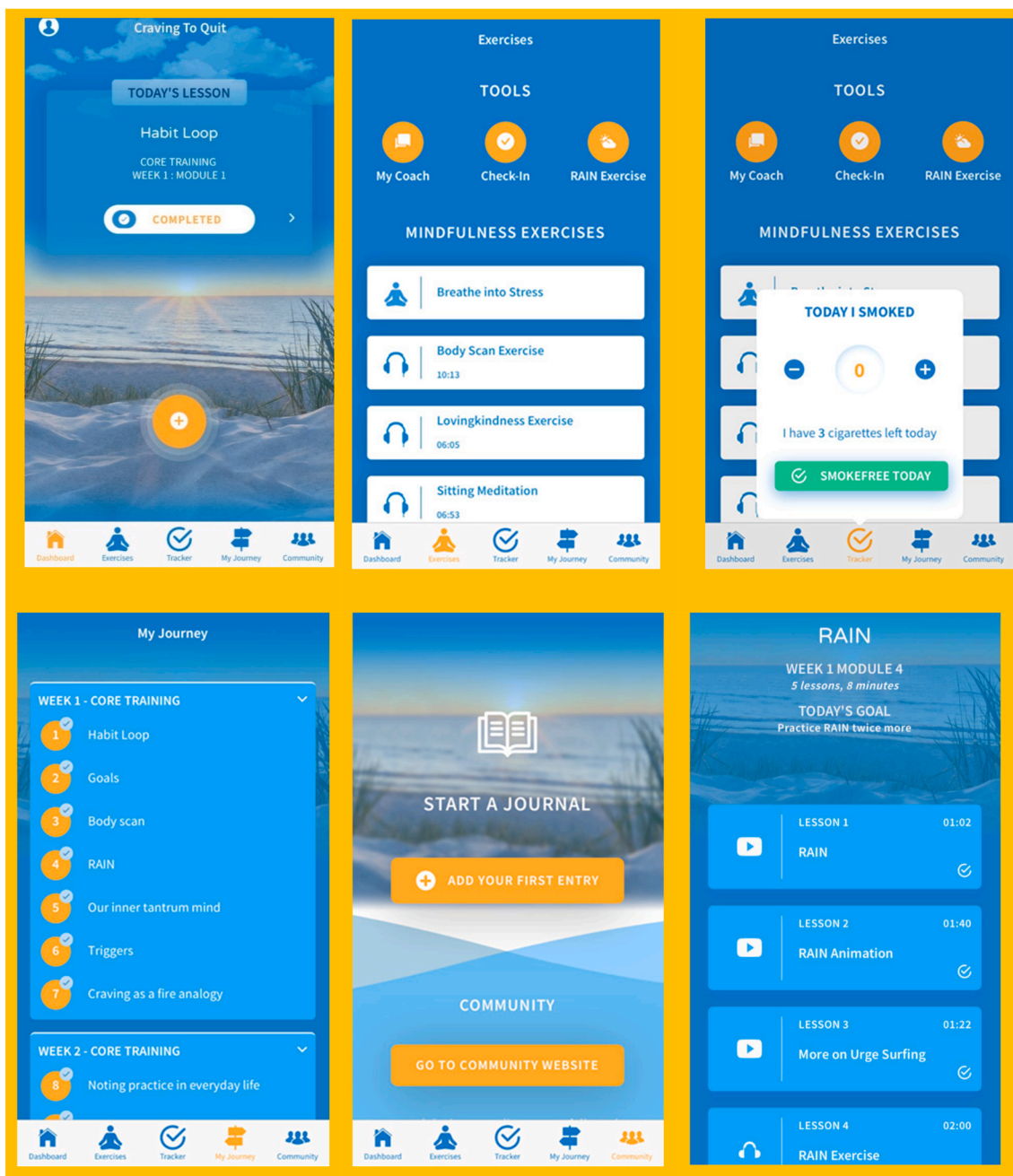


Fig. 2. Pictures of the Craving-to-Quit app.

2.8. Interventionist training and background

The interventionist is a certified mindfulness instructor with an extensive background in public health sciences. The interventionist has also completed an intensive 1-week training period specific to the intervention protocol. This involved training in human subjects protection, behavior change theories, pharmacotherapies used in smoking cessation and their adverse events, counseling protocol, quality control procedures, and role playing of project procedures. The interventionist's role will be to conduct the orientation sessions for both the app and in-person arms and deliver the 8 counseling sessions in the in-person intervention. The research assistant(s) will help in obtaining the consent forms and completing the baseline assessment and all follow-up phone calls assessment. The interventionist and research assistant(s) meet weekly throughout the project with an expert in tobacco treatment for quality control, supervision, and case review.

2.9. Quality assurance

To ensure the standardization of intervention content and delivery for quality assurance, we are using standardized treatment manuals, protocol, forms, and data management for each treatment group. Participants are responding to a brief questionnaire at baseline and the 3-month follow-up to assess whether key points were learned, including mindfulness techniques and information discussed in the intervention sessions. Standard procedures are used for instrument development, protocol and forms, and data management (e.g., entry, reconciliation, updating, and data security and confidentiality). Ongoing training and supervision are provided for quality assurance for the interventionists through weekly staff meetings, review of processes, and tracking reports. In addition, all sessions are audio recorded and discussed during weekly supervision meetings with the study investigator. Approximately 15% of sessions are randomly selected for fidelity assessments. Detailed

quality assurance checklists for each session have been developed to indicate topic coverage (Yes, adequate; Yes, but inadequate coverage; or No, not adequate). The Kappa statistic will evaluate inter-rater reliability.

2.10. Measures

2.10.1. Baseline assessment

Table 3 illustrates the study measures. The baseline measures is administered by a study research assistant and include (1) sociodemographic information (age, sex, race/ethnicity, relationship status, education, employment, income); (2) cancer history (time since cancer diagnosis, cancer type/stage, cancer treatment, time since ending cancer treatment); (3) smoking history (use of other tobacco products, past quit attempt, motivation to quit (On a scale from 1 to 10, how motivated are you to quit smoking?), confidence in quitting (On a scale from 1 to 10, how confident are you that you can quit smoking permanently), Fagerström test for nicotine dependence [43], 12-item smoking self-efficacy to resist urge to smoke [44], and 15-item Minnesota nicotine withdrawal scale) [45]; (4) the 24-item Five Facet Mindfulness Questionnaire (FFMQ) that measures mindfulness skills related to observing, describing, acting with awareness, non-judging of inner experience, and non-reactivity to inner experience [46]; (5) the Nottingham health profile (NHP) for evaluating quality of life (QoL) [47]; (6) alcohol and substance use (ASSIST) [48]; and (7) psychosocial assessments including PHQ-9 for depression [49], perceived stress scale (PSS-10) [50], the 20-item Centers for the Epidemiologic Study of Depression CES-D scale [51], and the positive and negative affect schedule (PANAS) [52]. All data, including baseline and follow-up assessment will be collected and managed in REDCap electronic data capture tools hosted at the University of Miami [53,54]. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources (see Table 3).

2.10.2. During the treatment

In the group in-person mindfulness intervention, the assessment at each session includes breath carbon monoxide (CO), measured using a portable CO monitor (Micro CO™ by Micro Direct, Inc.) connected to a smartphone, the Minnesota Withdrawal Scale, and the Questionnaire of Smoking Urges-Brief Scale [55]. Participants also record number of cigarettes per day and nicotine patch use since the previous session using timeline follow-back calendars [56]. Same assessment is being conducted in the mindfulness app intervention during the two follow-up phone calls (Table 3).

2.10.3. Follow-up assessment at 3- and 6-month

Table 4 illustrates the main study outcomes. At 3- and 6-month follow-ups, measures include perceived stress, depressive symptoms, and nicotine withdrawal. To assess the intervention feasibility, we are monitoring rates of recruitment and effort required (e.g., number of staff hours) as well as the number of screenings conducted, proportion eligible, and proportion who agree to be enrolled. Although a priori cut-offs for determining study feasibility based on accrual and retention rates are not established, we will consider the study feasible if at least 70% of the eligible participants enrolled in the study, and at least 80% of enrolled participants remained in the study through to the final follow-up evaluation at 6-month [42,57]. We are also recording the number of rescheduled, cancelled, and missed assessment visits as well as received visits/calls in each treatment arm to inform estimation of staffing needs and retention protocols for a planned efficacy RCT. Other outcomes are rate of attrition (not having a final visit at the end of treatment), rates of

Table 3
Measures.

	Baseline assessment	During treatment	3- and 6-month assessments
Contact information	X		
Demographics	X		
Cancer history	X		
Smoking history	X		
Social support	X		
The Nottingham health profile for evaluating quality of life (QoL)	X		
Alcohol and substance use (ASSIST)	X		
Questionnaire of Smoking Urges-Brief Scale	X	X	X
Use of other tobacco products	X	X	X
Fagerström test for nicotine dependence (FTND)	X	X	X
Smoking self-efficacy/temptation	X	X	X
Hatsukami withdrawal scale	X	X	X
The 24-item Five Facet Mindfulness Questionnaire (FFMQ)	X	X	X
PHQ-9 for depression	X	X	X
Perceived stress scale (PSS-10)	X	X	X
Centers for the Epidemiologic Study of Depression CES-D scale	X	X	X
Positive and Negative Affect Schedule (PANAS)	X	X	X
Smoking Status Assessment/smoking reduction	X	X	X
NRT use	X	X	X
Number of cigarettes per day	X	X	X
Self-reported use of other products or programs to quit smoking	X	X	X

several categories of attrition (mortality, withdrawal from the study, transfer to non-study clinics, loss to follow-up without identifiable cause), and response rates to questionnaires (operationalized as 70% or higher), adherence/compliance rates (operationalized as completing at least 70% of the module in the mindfulness app, or attending at least 6 sessions in the group in-person mindfulness), and time needed to collect and analyze data. In the mindfulness app group, we are assessing the app usability by self-reported number of completed days, calculating the mean number of times logged into the app, and level of comfort with the app: "I am comfortable using the app" (on a 10-point rating scale). In the in-person group, usability is operationalized as the total number of sessions that were attended. The treatment acceptability is assessed by 3 items: "How satisfied were you with the intervention?", "How likely are you to recommend this intervention to a friend?", and "How useful was the intervention?"

The main smoking cessation outcome is 7-day point-prevalence abstinence (defined as self-report of not smoking in the past 7 days; not even a puff) confirmed by saliva cotinine ≤ 10 ng/ml at 3- and 6-month follow ups [31,34]. The secondary outcome is the reduction in number of cigarettes smoked per day [58,59]. Relapse is defined as smoking at least once per week over two consecutive weeks [55] (see Table 4).

2.11. Sample size plan and statistical power

The primary focus of the proposed formative clinical research is to examine the feasibility and acceptability of the mindfulness app and group in-person mindfulness for smoking cessation to inform a larger-scale planned efficacy RCT. Although we will conduct intent-to-treat analyses of our combined intervention on primary and secondary outcomes using data from the proposed pilot RCT, this is only to explore the

Table 4
Study outcomes.

Outcomes	Measures
Feasibility outcomes	
Reach/Recruitment ^a	<ul style="list-style-type: none"> • Number screened per month • Number enrolled per month • Average time delay from screening to enrollment • Average time to enroll enough participants to form classes (group-based interventions)
Randomization	<ul style="list-style-type: none"> • Proportion of eligible screens who enroll • Proportion of enrolled who attend at least the orientation session
Adherence to treatment	<ul style="list-style-type: none"> • Treatment-specific adherence rates to study protocol (in-person session attendance, homework, home sessions, etc.); treatment-specific competence measures
Fidelity	<ul style="list-style-type: none"> • Treatment-specific fidelity rates
3- and 6-month assessments	<ul style="list-style-type: none"> • Proportion of planned assessments that are completed • Duration of assessment visits; reasons for dropouts
Credibility	<ul style="list-style-type: none"> • Treatment-specific expectation of benefit ratings
Retention ^b	<ul style="list-style-type: none"> • Treatment-specific retention rates for study measures • Reasons for dropouts
Adherence to treatment	<ul style="list-style-type: none"> • Treatment-specific adherence rates to study protocol (in-person session attendance) • Treatment-specific competence measures • App's usability (self-reported number of completed days, the mean number of times logged into the apps; level of comfort with the app, "I am comfortable using the app")
Treatment acceptability	
Acceptability	<ul style="list-style-type: none"> • Acceptability ratings • Reasons for dropouts (e.g., mortality, withdrawal from the study, transfer to non-study clinics, loss to follow-up without identifiable cause) • Treatment-specific preference ratings (pre- and post-intervention)
Satisfaction	<ul style="list-style-type: none"> • How satisfied were you with the intervention? • How likely are you to recommend this intervention to a friend? <p>How useful was the intervention?</p>
Qualitative assessments	<ul style="list-style-type: none"> • Pros and cons of practicing mindfulness exercise • Treatment-specific feedback on program/App schedule, design, and content • Recommendation for improvement
Potential efficacy outcomes	
Smoking abstinence	<ul style="list-style-type: none"> • 7 days point-prevalent abstinence (defined as self-report of not smoking in the past 7-days; not even a puff)
Smoking reduction	<ul style="list-style-type: none"> • Reduction in number of cigarettes smoked per day

^a Operationalized as an enrollment rate of 70% or higher.

^b Treatment retention will be defined as completing 70% of App mindfulness training modules.

potential for a treatment effect. There is increasing recognition that the effect size estimates from pilot RCTs should be interpreted with caution because they lack sufficient precision for establishing efficacy or informing subsequent power analyses [60]. Therefore, our power estimates are based on detecting a difference between the (a) app-based mindfulness, (2) in-person mindfulness, and (3) UC on biomarker-confirmed prolonged abstinence at 6-month follow-up assessment using unadjusted proportions, which is a conservative approach to powering cessation trials. Given the paucity of data on our approach in cancer survivors, we chose a conservative approach to ensure adequate statistical power to examine both our primary and secondary outcomes. We assumed nominal values for the Type I and II error rates (i.e., 5% and 20%, respectively; two-tailed) and based power on 6-month cessation rates. In a study by Brewer et al., in-person mindfulness yielded a 31% quit rate at end-of-treatment assessment [24]. In Garrison et al., the mindfulness app yielded a 10% quit rate at end-of-treatment assessment [27]. We used the cessation rates (3.8%) found by Li et al. to estimate cessation rates in the UC condition [61]. If we assume a 3.8% quit rate in the UC, a 10% quit rate in the app-based mindfulness, and a 31% quit rate in the in-person mindfulness, we would

need 60 participants (20/arm) to detect a 21% difference in quit rates between the app and in-person when the interclass cluster correlation is high (ICC = .05); this sample size is more than adequate under lower ICC conditions. Expecting an overall 20% attrition rate, this requires us to recruit a sample of 72 participants [62]. However, we are planning to recruit more participants to substitute those who withdraw from the trial until we reach our target sample (n = 60).

2.12. Statistical analyses

The analysis of the feasibility and acceptability outcomes are mainly descriptive. We will use Chi-square tests and one-way ANOVA to compare between-group differences in baseline characteristics, indices of treatment implementation, adherence, retention, and treatment perceptions. Attrition analyses will compare respondents who complete all measurements to those who do not based on baseline characteristics. For potential treatment effects, we hypothesize that: 1) in-person mindfulness will achieve better smoking abstinence rates and a significant reduction in depression than either the mindfulness app or UC interventions; and 2) the mindfulness app will achieve better abstinence and reduction in depression than the UC. Chi-square tests will be used to compare main outcomes (cessation) between the three arms at 3- and 6-month follow ups. Univariate and multivariable logistic regression models will be used to explore baseline predictors of 3- and 6-month smoking cessation and the app usability and acceptability, as well as the feasibility of the intervention. Crude and adjusted odds ratios, 95% confidence intervals, and corresponding p-values will be calculated. Reported counts of formal (meditation) and informal (RAIN) mindfulness practice will be included in the model as independent predictor variables to test whether meditation practice during treatment moderates the change in the prediction of smoking by craving across study time points [23]. Cross-tabulations for ordinal variables and mean and corresponding 95% confidence intervals for continuous variables will be used to explore secondary outcomes including reduction in perceived distress and depression and in cravings, and improvement in smoking self-efficacy, quality of life, and the FFMQ [49]. Although we are underpowered to detect differences by sex, we will consider exploring the sex effect on our main outcomes in our analysis. Data management and statistical analysis will be performed with SAS Software v9.4 (SAS Institute Inc., Cary, NC).

2.13. Post-intervention evaluation

Semi-structured post-intervention evaluation interviews will be conducted with participants in the mindfulness app and in-person mindfulness groups (n = 40; 20/group) to identify emergent themes related to acceptability and specific targets for refinement of content and delivery [63]. The rationale for mixing quantitative and qualitative data within one study is grounded in the fact that neither quantitative nor qualitative methods are sufficient, by themselves, to capture the details of a situation. However, when used in combination, quantitative and qualitative methods complement each other and allow for a more robust analysis, taking advantage of the strengths of each [28,64]. In particular, the mixed-methods sequential explanatory design is highly popular among researchers and implies collecting and analyzing first quantitative and then qualitative data in two consecutive phases within one study to help explain, or elaborate on, the quantitative results [65]. Participants will receive a \$25 incentive for completing the interview. Interviews will be audio-recorded and transcribed verbatim. We will employ inductive thematic analysis using the Grounded Theory approach aimed at generating, confirming, and modifying the theory, and data collection continued until saturation is reached, indicating that no new themes were emerging [66]. We will use NVivo version 12 for qualitative data analysis (QSR International software product) [67]. NVivo software facilitates hierarchical linkage of codes for clear visualization of the structure of the findings [67]. This program is designed

for the storage, coding, retrieval, and analysis of qualitative data. Two complementary coding schemes will be used to evaluate the interview data: 1) manual description using words or short phrases to summarize passages of data, and 2) NVivo analysis, in which actual language from participants is used to name concepts and themes. Two investigators independently will review transcripts and develop a consensus plan to identify recurring themes and variants. Through an iterative, line-by-line reading of the entire transcription, and using a two-step open coding process, the team identified and reached consensus on a list of codes that corresponded to emerging themes [68]. First, analytic codes will be based on primary thematic areas of interest (e.g., barriers to adherence, recommendation for improvement, etc.). This first step of coding organized the text into primary themes. In the second step, the coding team further identified sub-themes within each of the primary areas of interest, and a codebook will be created in which each primary and sub-theme is listed and defined. Themes and definitions will be compared across interviews to ensure consistency and reliability. Reliability in qualitative research refers to the stability of responses to multiple coders of data sets. To be accepted as trustworthy, qualitative researchers must demonstrate that data analysis has been conducted in a precise, consistent, and exhaustive manner through recording, systematizing, and disclosing the methods of analysis with enough detail to enable the reader to determine whether the process is credible [69].

3. Discussion

In 2016, it was estimated that there were 15.5 million cancer survivors [70]. Compared to cancer survivors aged older than 40 years, young survivors (18–40 years old) had significantly higher rates of continuing smoking after diagnosis (45% vs. 17%) [1,2]. Continued smoking in cancer patients is associated with increased treatment toxicity, higher risk of treatment failure, higher incidence of second primary tumors, poorer quality of life, and shorter survival [71]. Several systematic reviews have concluded that current evidence-based tobacco cessation interventions did not demonstrate the same efficacy among cancer survivors compared to the general adult population [72,73]. In the most recent meta-analysis review on smoking cessation interventions in cancer survivors, the effect size across 21 RCTs involving 4155 survivors was approximately zero [8]. In addition, none of these trials was focused on young survivors. This has recently contributed to the National Comprehensive Cancer Network's (NCCN's) recommendation that every cancer patient who smokes must be offered evidence-based cessation intervention [74]. However, despite this recommendation, tobacco treatment targeting cancer patients is still inadequate due to several system-level barriers (e.g., lack of insurance coverage, lack of clinical staff training and time, lack of integration of cessation service into routine cancer care) [75]. These challenges demonstrate the need for broader methods to reach cancer patients who smoke. This study will be the first to evaluate novel strategies that have the potential to tackle two major barriers to smoking cessation in young cancer survivors: their limited access to tobacco treatment given their geographic dispersion, and their elevated rates of depression and anxiety that could negatively impact their smoking cessation efforts. The proposed intervention has the potential to both increase their access to smoking cessation resources through the use of a technology-based smartphone app intervention and reduce their stress and depression by integrating mindfulness practice techniques in the smoking cessation intervention. This combination of efforts has promise to improve their smoking cessation outcomes. In addition, this study will be the first to investigate the relationship between mindfulness, stress, and cessation among young cancer survivors. Data resulting from this project will inform larger studies of the effectiveness of cessation approaches that have great potential for translation and dissemination in young cancer survivors throughout the US.

There are two major public health methods that are advocated in promoting smoking cessation. The first are population-based methods

that employ less intensive interventions that can reach large populations (e.g., routine advice from healthcare providers). These approaches have the potential for considerable impact through a combination of effectiveness and reach [76]. Even though absolute quit rates may be low, the population impact can be substantial with widespread implementation [77]. A second, but equally valid, public health approach is to target very high-risk participants (e.g., cancer survivors) with more aggressive interventions [76]. Both methods seem to be applicable and vital to improving smoking cessation among young cancer survivors. While the population-based smoking cessation interventions have great potential for reach and dissemination, the in-person intensive interventions have greater potential for effectiveness. This notion aligns with current recommendations that all health promotion programs should employ a reinforcing combination of both population-wide strategies and in-person more intensive interventions to reach high-risk populations [78]. The current study will be the first to directly compare the feasibility and potential efficacy of these two methods, "Reach vs. Effectiveness," in a high-risk population for tobacco use. While a technology-based mindfulness app intervention promises to have a greater potential for "reach," the group in-person mindfulness intervention is very intensive and is expected to produce greater "effectiveness." As such, the current study will provide insight into two highly promising interventions to reach and improve smoking cessation in young cancer survivors.

A meta-analysis review concludes that depression in cancer survivors is roughly twice as common as in healthy controls [10]. In particular, younger and middle-aged long-term survivors had the highest rate of depression [79]. Evidence also indicated that continued smoking among survivors was significantly associated with having feelings of anxiety, moderate to severe stress, and symptoms of depression [4,80,81]. Smoking cessation attempts are considered to be a major life stressor strongly linked with psychological stress, depression, and negative and positive affect, which in turn can lead to relapse [82,83]. To date, only one study tried to address the intersection between smoking and depression in cancer. In Duffy et al., a multifaceted intervention concurrently targeting smoking, alcohol, and depression was developed and tested among head and neck cancer patients diagnosed as adults [11]. Although it provided some evidence of benefit, the study was methodologically limited by the small sample size, the recruitment of both new and post-treatment patients, and the lack of biomedical verification of smoking status after abstinence [11].

One promising strategy to address depression among cancer survivors seeking tobacco treatment is mindfulness training. Mindfulness has been operationalized into two components: maintaining attention on immediate experience, and maintaining an attitude of acceptance toward that experience [37]. Through these complementary components, mindfulness has been hypothesized to not only bring habituated behaviors into consciousness, but also target the associative learning process with an emphasis on affect and craving as critical components of positive and negative reinforcement loops [26,37,84]. Mindfulness practice can improve individuals' ability to avoid absorption in maladaptive mental patterns, behaviors, and emotional reactions that lead to depression [37,84]. Mindfulness training is proved to be effective in reducing both self-report and objective indices of negative affect and psychological stress [19,20]. It is also effective in controlling cravings among smokers attempting to quit by teaching them to be less emotionally reactive and less prone to relapse related to avoidance of distressing symptoms [23]. Mindfulness training in cancer survivors has also been shown to be effective at improving psychological symptoms of anxiety and stress, quality of life, emotional well-being, and immunological status [23]. Survivors also might be more interested in tobacco treatment that addresses their stress and depression compared to only tobacco-focused treatment. Mindfulness-based interventions show promise for promoting smoking cessation in diverse populations [85]. However, mindfulness for smoking cessation in young cancer survivors has not been investigated. We believe that mindfulness-specific

techniques may increase survivors' willingness to be involved in tobacco treatment, thus facilitating smoking cessation in this population.

There are a few challenges and potential limitations with this study. The external validity of the results is limited by the small sample size. However, this is a small pilot and needs to be tested in a larger trial. Second, the in-person mindfulness intervention is intensive and may not attract some smokers. As such, findings may be less generalizable to smokers who would prefer to quit without extensive professional assistance or in the context of a formal cessation. However, we are testing a comparable intervention that requires minimum involvement. Third, the results of this trial may not be generalizable to cancer survivors who do not own a smartphone. However, the use of smartphones has increased dramatically in recent years, and will continue to increase, particularly in this younger age group. Therefore, over time the availability of this method of smoking cessation intervention will become more widespread, if not universal. Finally, adherence to treatment in the app group might be low as was observed historically. However, we have added two phone call follow-ups around quit date to improve participants' adherence to treatment.

Notwithstanding the potential limitations, the originality of this study stems from: 1) a focus on an understudied population that is hard to reach and at high risk of tobacco use; 2) using a technology-based smartphone app intervention, a novel, low-cost, and highly scalable delivery method; 3) using mindfulness techniques that emerge as a new treatment method for smoking cessation in cancer survivors; 4) the consideration of distress and depression as underlying mechanisms for cessation outcomes; and 5) improving survivors' willingness to participate in a smoking cessation study by incorporating strategies that address their stress and depression. Findings will have implications for the development and dissemination of innovative and highly scalable tobacco interventions designed for young cancer survivors. There are several options to pursue based on the results of this pilot study. For example, if the app intervention proved to be more feasible, acceptable, and effective than the in-person intervention, we are planning to test the Craving-to-Quit app intervention versus the National Cancer Institute's QuitGuid app (control group; <https://smokefree.gov/tools-tips/apps/quitguide>) in a national large-scale double-blind randomized controlled trial. We chose the QuitGuide as a control group because its content: 1) follows USCPG [29], 2) is directly based on [Smoke-free.gov](https://smokefree.gov), the most accessed cessation website in the world, and 3) is non-proprietary and free to the public, thereby providing maximal transparency, accessibility, and replicability. If the in-person intervention was superior to the app, we are planning to develop multilevel implementation strategies to integrate this intervention in the cancer care and test it compared to the standard care using hybrid type 1 effectiveness-implementation trial. multilevel implementation strategies have the potential to influence more than one contextual level (e.g., individual, organization) with the goal to improve health outcomes mainly by creating a more efficient, effective, and coordinated delivery system that achieves the desired outcomes at a reduced cost to all involved [86,87]. The hybrid type 1 effectiveness-implementation trial design will allow us to simultaneously evaluate the clinical effectiveness and implementation potential of the program [88]. This approach is recommended to speed up the process of evidence development and translation to real-world settings.

In summary, smoking is a major public health problem among young cancer survivors in the US. The current study is the first to pilot test innovative smoking cessation interventions that specifically address poor access to cessation resources and high prevalence of depressive symptoms among young cancer survivors. If interventions are found to be effective, this RCT will provide a formative foundation for large-scale clinical trials comparing mobile mindfulness with a more intensive in-person mindfulness intervention for smoking cessation nationally to reduce smoking among young cancer survivors who are at significant risk of tobacco use-related complications and co-morbidities.

Funding

Research reported in this publication is supported by the National Cancer Institute of the National Institutes of Health under Award Number P30CA240139. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The study is registered at the Clinical Trials Registry (#NCT04038255).

Trial registration

Clinicaltrials.gov #NCT04038255. Registered on July 26, 2019.

Declaration of competing interest

The authors declare they have no conflicts of interest.

Acknowledgment

We thank our research staff Ms. Eliana Maritza Reyes and Ms. Parisa Varanloo for their assistance in implementing the study.

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