Pilot Study of a Mobile and Virtual Reality-Based Digital Therapeutics for Smoking Cessation: A Randomized Controlled Trial

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Abstract

Background: Smoking cessation remains a global challenge with existing treatments showing limited long-term success. Digital therapeutics, such as app- and virtual reality (VR)-based interventions, have the potential to offer more personalized and accessible solutions. This study investigates the efficacy of combined digital therapeutic intervention for smoking cessation.

Objective: This study aims to evaluate the safety and efficacy of NICO-THERA, a digital therapeutic intervention combining VR and mobile applications, in supporting smoking cessation among individuals with nicotine dependence. Specifically, the study examines the impact of this intervention on smoking abstinence and nicotine dependence over a 12-week treatment period.

Methods: We conducted an open-label, randomized, controlled exploratory trial involving 30 participants who were randomly assigned to either the Digital Therapeutic Group (DTG) or the Basic Treatment Group (BTG). The DTG received the NICO-THERA program, which included VR-based relaxation, craving coping, and refusal training sessions along with additional therapy through a mobile application, all grounded in cognitive behavioral therapy (CBT) and motivational enhancement therapy (MET). The BTG received standard care including video education, printed materials. The primary outcomes measured were the 7-day point prevalence abstinence (PPA) and 30-day PPA at 8 and 12 weeks. Secondary outcomes included nicotine dependence and the motivation to change.

Results: The participants in the DTG demonstrated significantly higher smoking abstinence rates than those in the BTG. At 12 weeks, the 7-day PPA was 55.6% in the DTG and 41.7% in the BTG, whereas the 30-day PPA was 55.6% and 33.3%, respectively. Additionally, the DTG showed a reduction in nicotine dependence scores and an increase in the motivation to quit smoking. The VR intervention was well-tolerated, with no significant adverse events reported.

Conclusions: The NICO-THERA digital therapeutic program appears to be a safe and effective intervention for smoking cessation. The integration of VR and mobile applications into a structured therapeutic approach offers a promising complement to traditional smoking cessation treatments, potentially improving long-term abstinence rates and reducing nicotine dependence. Clinical Trial: Clinical Research Information Service, Republic of Korea (KCT0009801); https://cris.nih.go.kr/cris/search/detailSearch.do?seq=28285&status=5&seq_group=28285&search_page=M

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Original Paper

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Trial Registration: Clinical Research Information Service, Republic of Korea (KCT0009801); https://cris.nih.go.kr/cris/search/detailSearch.do?seq=28285&status=5&seq_group=28285&search_page=M

Keywords: Digital Therapeutics; Virtual Reality (VR); Mobile Health (mHealth); Smoking Cessation; Nicotine Dependence; Cognitive Behavioral Therapy (CBT); Motivational Enhancement Therapy (MET); Randomized Controlled Trial (RCT);

Introduction

The global tobacco crisis continues to be one of the most severe public health challenges, with over eight million fatalities annually worldwide [1], of which 6.2 million deaths are directly linked to tobacco consumption and approximately 1.3 million are owing to exposure to second-hand smoke among non-smokers [2]. According to the 2023 OECD Health Statistics, the average smoking rate across OECD countries is 15.9%, with South Korea showing a comparable rate of 15.4% [3]. Tobacco use is a leading contributor to a multitude of health issues, including lung cancer, heart disease, and chronic respiratory conditions, resulting in significant social and economic repercussions [4]. Despite the South Korean government's substantial investment in smoking cessation programs, amounting to approximately USD760 million annually [5]—the outcomes have not met expectations, with actual cessation rates remaining relatively low compared with the scale of investment. Although smoking cessation policies have been in place for over two decades, participation and completion rates of smoking cessation programs have declined significantly [6].

Additionally, the variety of tobacco products has expanded, and the willingness of smokers to quit smoking has waned. These trends indicate that smoking cessation policies must evolve to address the changing landscape of tobacco use and cessation efforts.

Despite the known harm of smoking, many smokers find quitting to be a challenging endeavor. Characterized as a chronic relapsing condition [7], smoking cessation frequently leads to a range of withdrawal symptoms such as cravings, irritability, depression, and restlessness [8]. Notably, the success rate of individuals attempting to quit smoking unaided without professional support remains low, with estimates ranging from 3% to 5% [9]. Medications are designed to mitigate the discomfort associated with nicotine withdrawal symptoms, thereby significantly enhancing the likelihood of smoking cessation [10, 11]. The most effective smoking cessation strategy appears to be a combination of behavioral therapy and pharmacotherapy [10-13], a method widely supported by national smoking cessation programs across various countries [14-16].

To overcome the limitations of accessibility identified in traditional smoking cessation treatments and provide cost-effective and time-efficient interventions, the development of digital therapeutics for smoking cessation has been extensively pursued. Mobile health (mHealth) technologies for smoking cessation began as basic text message-based interventions. Although effective [17-20], these early digital tools had limited functionality. [18, 21] Over time, these have evolved into complex smartphone applications and other forms of digital therapeutics that utilize technology to offer more accessible, flexible, and personalized support [22-25]. Following the development of wellness apps for smoking cessation, Digital Therapeutics (DTx) specifically designed for smoking cessation were developed [26, 27]. Digital therapeutics are characterized as interventions based on evidence provided by certified software programs to prevent, manage, or treat medical conditions, separating them from conventional wellness products [28].

In addition to smartphone-based interventions, encouraging advances have been made in the use of virtual reality (VR) in digital medicine. VR has been implemented in consultation and hospital settings under the supervision of health professionals [29]. Incorporating VR into treatments can alleviate patient symptoms in conditions such as obesity [30], claustrophobia [31, 32], PTSD [33], and smoking cessation [34-36]. Expanding the role of VR in smoking cessation, recent studies have explored its potential to not only assist in reducing cravings and withdrawal symptoms but also to modify behavioral patterns and increase long-term abstinence rates. For instance, the Cue Exposure Therapy (CET) approach, which uses VR to simulate real-life smoking triggers in a controlled environment, has demonstrated promising results in helping individuals resist cravings by practicing coping strategies in virtual scenarios [34]. Similarly, immersive VR environments have been used for mindfulness-based interventions to reduce stress and anxiety associated with quitting smoking, thereby supporting overall mental well-being during cessation efforts [36]. Future directions for VR in smoking cessation can involve more personalized VR experiences that adapt to the user's physiological and psychological states in real time, potentially by integrating biofeedback mechanisms. Moreover, as VR technology continues to evolve, its applications may expand beyond traditional therapeutic settings, offering at-home user-directed interventions that complement existing smoking cessation programs.

Building on these advances, this study aims to systematically integrate both app and VR interventions in smoking cessation treatment—an approach that, to our knowledge, has not been previously explored. Specifically, we examine the safety and efficacy of NICO-THERA—a digital therapeutic developed based on Cognitive Behavioral Therapy (CBT) and Motivational Enhancement Therapy (MET), which incorporates both an app and VR content for smoking cessation.

Methods

Study design

This study was conducted as a 2-arm, open-label, randomized controlled exploratory clinical trial (RCT; trial registration: Clinical Research Information Service KCT0009801) with a focus on evaluating the safety, feasibility, and preliminary efficacy trends of the NICO-THERA intervention. As this was a pilot trial, the outcomes were assessed directly by the researchers without the use of independent evaluators. While the absence of blinding could introduce potential biases, the primary objective of this study was to assess the feasibility and acceptability of the intervention along with the initial safety data rather than to establish definitive efficacy conclusions.

Participants were randomly assigned to either the Digital Therapeutic Group (DTG) or the Basic Treatment Group (BTG) using a pregenerated 1:1 random allocation sequence. Each participant was assigned to a group according to their screening number in the order of arrival. The allocation sequence was predetermined for screening numbers 1 to 30, ensuring that neither the participants nor the researchers knew in advance which group the participants would be allocated to, thereby maintaining the randomness of the allocation process. All participants provided written informed consent in accordance with the Declaration of Helsinki. The study protocol was approved by the Ministry of Food and Drug Safety (No.1271) and the Institutional Review Board of Seoul St. Mary’s Hospital (KC21DNSS0706). All experiments were performed in accordance with guidelines and regulations.

The study recommends a minimum sample size of 12 subjects per treatment arm in pilot trials according to established rules of thumb [37, 38]. In this exploratory study, participants were randomly allocated to two groups: DTG and BTG. To account for potential attrition, each group comprised 15 participants, culminating in a total enrollment of 30 individuals. No significant changes in the trial methodology were made after the trial commenced.

Recruitment and procedure

The study population consisted of patients visiting Seoul St. Mary's Hospital for smoking cessation and those who responded to a clinical study recruitment advertisement. Written informed consent was obtained from all participants before eligibility screening. Medical staff evaluated the participants based on the inclusion and exclusion criteria through individual interviews. Data were collected in a clinical setting at Seoul St. Mary’s Hospital, where the participants attended outpatient visits. Screening and follow-up assessments were performed in clinical settings. Subjects who met the eligibility criteria were randomly assigned to either the DTG or BTG. Regardless of the assigned group, participants received usual care during smoking cessation treatment, which included pharmacological therapy with varenicline or bupropion, as well as counseling from medical staff. The in-treatment period commenced with randomization and lasted until week 12, during which follow-up visits were conducted at 4-week intervals (weeks 4, 8, and 12). Participants received compensation of 40,000 KRW per visit, with a total of 160,000 KRW disbursed for four visits over the three-month study period.

The inclusion criteria were as follows: 1) adults aged between 19 and under 75 years, 2) individuals diagnosed with nicotine addiction according to the clinical criteria for mental and behavioral disorders owing to use of tobacco (F17) or toxic effect of tobacco and nicotine (T652) as per the Korean Classification of Diseases (KCD), and in accordance with the clinical criteria for nicotine use disorders specified in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (American Psychiatric Association, 2013), 3) individuals who smoked an average of five or

more cigarettes per day in the past six months, 4) participants who were able to communicate with the researcher and consented to the procedures required by the study protocol, understanding the objectives of the research and signing the consent form, 5) smartphone users who agreed to install and use an application for data collection and management, and 6) smartphone users who agreed to receive text messages and respond to survey items via their smartphones, consenting to data collection and management.

The exclusion criteria included: 1) individuals who did not meet the clinical criteria for mental and behavioral disorders owing to use of tobacco (F17) or toxic effect of tobacco and nicotine (T652) according to the KCD, based on individual interviews with a specialist or researcher, 2) individuals with cognitive impairments affecting decision-making capacity, 3) those unable to participate in the programs specified in the study protocol, 4) those who had started or were undergoing another CBT within the last three months, 5) (for the digital therapeutics group) individuals who either did not own a smartphone registered in their name or lacked significant ability to use smartphones including app utilization, 6) individuals without a smartphone or significantly limited ability to use smartphones including receiving text messages, 7) those at severe risk of depression, suicidal ideation, or suicide attempts, 8) other reasons deemed by the investigator as inappropriate for participation in the clinical trial. The participants completed eligibility screening and provided informed consent.

Intervention Condition

Digital Therapeutic Group; DTG

The NICO-THERA, the digital therapeutic device employed in this study, is a Software as a Medical Device (SaMD) designed to treat and manage nicotine dependence. NICO-THERA has been classified as a Class 2 (low-risk) medical device for cognitive therapy software by the Ministry of Food and Drug Safety (MFDS) in South Korea (E066060.02). Figure 1 illustrates the interface elements of the NICO-THERA, including screenshots of its main features. The app's content was reviewed by clinical experts in smoking cessation and CBT to ensure the accuracy and effectiveness of the therapeutic modules. The NICO-THERA app was developed through several iterations, including usability testing with target users, to refine the interface and content based on feedback. It delivers therapeutic interventions to patients through VR therapy content provided via a Head Mounted Display (HMD) and smartphone application. This nicotine digital therapeutic content is based on CBT and MET, which are prominent evidence-based therapies aimed at improving addictive disorders. The NICO-THERA app and VR content used for this study were Version 1.0, and the content was frozen for the duration of the trial to ensure consistency across all participants.

Virtual Reality (VR) Contents

The VR content used in this study includes image relaxation training, craving coping training, and refusal training, each taking approximately 10 minutes and provided during clinic visits at baseline, weeks 4 and 8. Image relaxation training, rooted in behavior modification theory, helps participants cope with stress-related triggers [39, 40]such as depression and anxiety by practicing deep breathing and relaxation techniques within a VR environment that replicates real-life settings. Participants can choose a preferred background setting among forest, campfire, or beach to conduct the imagery relaxation training (Multimedia Appendix 1). Craving coping training (Multimedia Appendix 2) uses role-playing in a realistic VR setting to apply learned relaxation and behavioral strategies to manage situations that trigger smoking cravings [41, 42]. Finally, refusal training (Multimedia Appendix 3) focuses on strengthening the participants' ability to clearly refuse smoking offers by practicing assertive communication and refusal skills [43] in VR scenarios that mirror real-life interactions,

thereby bolstering their smoking cessation efforts.

Smartphone Application

The participants accessed the NICO-THERA application on their smartphones. The application was provided free of charge, and the participants were given detailed instructions on how to download and install it. The app required an internet connection for certain features, and participants were encouraged to maintain access to the internet throughout the study.

The NICO-THERA application integrates CBT and MET to deliver structured therapeutic interventions tailored to nicotine addiction. This application is designed to facilitate users' engagement in their treatment processes by providing therapeutic sessions that help identify triggers, manage cravings, and develop effective coping strategies. This comprehensive approach encompasses operant conditioning to modify behaviors associated with smoking, cognitive restructuring to address dysfunctional thoughts related to nicotine use, and relaxation training to manage stress and emotional triggers. Each lesson took approximately 10 minutes per day to complete. Upon completion of the content each week, a quiz was provided to evaluate the effectiveness of the weekly program and reinforce the users' knowledge. The weekly topics and contents are detailed in Table 1.

In addition to these core therapeutic strategies, the application is equipped with several practical tools to support patients and healthcare providers. It includes a smoking cessation diary and medication adherence log, which are instrumental in tracking daily smoking behaviors and medication intake. Participants were instructed to record their smoking cessation diary and medication adherence log daily, and to complete the weekly lessons provided through the app. Each lesson took approximately 10 minutes per day to complete. These features allow healthcare providers to monitor patient's progress and compliance more effectively during clinical visits, providing crucial data that can be used to adjust treatment plans and interventions accordingly (Multimedia Appendix 4). The participants received weekly push notifications from the app reminding them to complete their therapy sessions and log their smoking behaviors

Table 1. CBT and MET techniques included in the NICO-THERA application

Weekly Program Topics	Detailed Content
Registration: Understanding Application Usage	Familiarize with the application's functionalities Complete registration and provide basic information.
Week 1: Treatment Plan and Functional Analysis	Structured approach for addiction treatment and identification of users' nicotine usage patterns
Week 2: Motivation Enhancement Training	Education on motivational theories, change motivations, and stages of change
Week 3: Creating an Environment for Success	Understanding conditioning and association, and eliminating factors related to smoking
Week 4: Identifying Triggers and Cravings	Pinpointing specific smoking triggers and understanding the underlying mechanisms of cravings
Week 5:	Education and implementation of relaxation

Relaxation Training	training with biofeedback signals
Week 6: Behavioral Craving Coping Strategies	Understanding cravings and learning strategies to cope with them
Week 7: Identifying Cognitive Distortions	Recognizing and categorizing thought patterns that contribute to smoking behavior
Week 8: Responding to Cognitive Distortions	Developing strategies to challenge and reframe distorted thoughts
Week 9: Refusal Training	Learning assertive communication skills useful in smoking cessation
Week 10: Coping with Depression and Anxiety	Learning about and dealing with depression and anxiety
Week 11: Coping with Anger	Learning about and dealing with anger
Week 12: Relapse Prevention and Review	Recognizing the possibility of relapse and responding to warning signs

Basic Treatment Group; BTG

In the control group, participants received both video and printed educational materials as part of their treatment for nicotine addiction. Specifically, video education comprised CBT-focused content tailored to manage nicotine addiction. Additionally, during their 12-week outpatient visits, they were provided with standardized educational booklets on CBT and MET prepared by the Ministry of Health and Welfare. Additionally, the participants were provided with a smoking cessation diary and medication log as part of their treatment plan to monitor their progress throughout the study. These resources were designed to improve the understanding and handling of nicotine-use disorders.

Measures

Prior to the commencement of the intervention, participants completed a comprehensive baseline questionnaire designed to collect demographic information and detailed smoking history. Demographic information included age, sex, education level, past and current medical histories, and information on concurrent medications. The questionnaire also inquired about participants' smoking history, including the type of tobacco products, number of cigarettes consumed per day, age at initiation, previous attempts at quitting, and methods previously employed in those attempts.

For the primary efficacy indicators of smoking cessation maintenance, assessments were conducted at two time points: during treatment at weeks 8 and 12. At each of these time points, both the 7-day point prevalence abstinence and 30-day point prevalence abstinence were assessed. Self-reported smoking abstinence was determined by asking patients whether they had smoked one or more cigarettes in the last 7 and 30 days, respectively. All assessments were conducted through clinical interviews with medical staff. Additionally, saliva cotinine tests and exhaled carbon monoxide measurements were performed to verify smoking abstinence. If the results of these biological tests

contradicted the self-reported abstinence, the participants were considered to have failed to maintain smoking cessation.

Secondary efficacy indicators (supplementary indicators) included the Fagerström Test for Nicotine Dependence (FTND) [44], a widely used instrument for evaluating the severity of nicotine addiction. The FTND consists of six questions that assess various aspects of nicotine dependence, including the time to the first cigarette after waking up, difficulty of refraining from smoking in non-smoking areas, and number of cigarettes smoked per day. Each question is scored on a scale, with higher total scores indicating greater nicotine dependence. Additionally, the Stages of Change Readiness and Treatment Eagerness Scale-Smoking (SOCRATES-S) was used to measure smokers' motivational readiness [45]. It assesses three key dimensions of motivation: recognition, ambivalence, and the steps taken. The recognition reflects a smoker’s acknowledgment of the problem and the understanding that smoking is detrimental to health. Ambivalence measures the smoker’s mixed feelings about quitting, capturing the internal conflict between the desire to quit and fear of change. Taking steps evaluates the proactive efforts that the smoker has already made toward cessation. The SOCRATES-S score provides insight into where smokers are on the continuum of change from pre-contemplation to maintenance.

Safety assessments for the VR intervention were conducted using the Simulator Sickness Questionnaire (SSQ) [46], which evaluates potential adverse effects such as nausea or disorientation, ensuring participant safety in the VR components of the study.

Data Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows version 28 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to examine the demographic characteristics and smoking/quit-related attributes of participants. Subsequently, at baseline and during treatment weeks 4, 8, and 12, the mean values of efficacy indicators, nicotine use assessments, and motivation to change indicators were compared between the DTG and the BTG to evaluate changes over time. This exploratory clinical study had a small sample size with only 15 participants assigned to each group. Normality tests indicated that the data did not follow a normal distribution ($P<0.05$), thereby invalidating the assumption of normality. Consequently, nonparametric tests that are appropriate for small sample sizes and do not require the assumption of normality were used. Specifically, statistical significance was assessed using the Wilcoxon Signed Rank Test and the Mann-Whitney U Test, which analyze rank-based data.

Results

Participant Engagement and safety outcomes

A CONSORT flow diagram is depicted in Figure 2. In this study, 30 participants were randomly assigned to either the DTG (15 participants) or the BTG (15 participants). Both groups completed the first week of the study (Visit 2). By the fourth week (Visit 3), 23 participants had completed the study—10 from the DTG and 13 from the BTG—with seven participants dropping out (five from the DTG and two from the BTG). By week 8 (Visit four), 22 participants remained, with one additional dropout from the DTG. By the 12th week (Visit 5), 21 participants had completed the study, with one additional dropout from the BTG. Overall, nine participants dropped out during the study, resulting in 21 participants adhering to and completing the trial. The adherence rates for maintaining a smoking cessation diary and medication log were 98.8% and 88.0% in the DTG and BTG, respectively, indicating higher treatment adherence in the DTG group.

In this exploratory clinical trial, the SSQ was used to assess the symptoms of motion sickness induced by a virtual environment before and after the use of a VR device. The results indicated that neither the pre- nor post-use scores exceeded the cut-off of 20, and no significant differences were observed between the two scores. Additionally, no adverse events related to the use of the VR or smartphone application were reported, confirming the safety of the digital therapeutic software NICO-THERA.

Participants' characteristics at baseline

The demographic characteristics of the participants are presented in Table 2. The mean age in the DTG was 43.07 years (*SD* 12.15) and in the BTG was 48.67 years (*SD* 14.53). In the DTG, there were 11 males (73.3%) and 4 females (26.7%), whereas in the BTG, there were 12 males (80.0%) and 3 females (20.0%). Regarding educational attainment, both the DTG and the BTG had the highest proportion of participants (60 %) who completed a bachelor's degree.

Table 2. Demographics and baseline characteristics for participants

Characteristics	DTG	BTG
Participants, n	15	15
Age, mean (*SD*)	43.1 (12.2)	48.7 (14.5)
Sex, n (%)		
Male	11 (73.3)	12 (80.0)
Female	4 (26.7)	3 (20.0)
Education level, n (%)		
Elementary school graduate	0 (0)	1 (6.7)
High school graduate	4 (26.7)	2 (13.3)
Two-year college degree graduate	0 (0)	1 (6.7)
Bachelor's degree	9 (60)	9 (60)
Graduate degree	2 (13.3)	2 (13.3)
Number of years smoking, mean (*SD*)	23.3 (11.22)	29.2 (12.90)
Number of cigarettes per day, mean (*SD*)	9.5 (8.2)	9.2 (7.4)
Medication for smoking cessation, n (%)		
Bupropion	10 (66.7)	8 (53.3)
None	5 (33.3)	7 (46.7)
Type of tobacco used, n (%)		
Manufactured cigarettes	8 (53.3)	13 (86.7)
Heat-not-burn tobacco	2 (13.3)	0 (0)
Liquid e-cigarettes	1 (6.7)	1 (6.7)
Multiple tobacco product use	4 (26.7)	1 (6.7)
FTND, mean (*SD*)	2.8 (2.5)	4.9 (2.6)
Exhaled carbon monoxide levels, mean (*SD*)	6.1 (6.2)	6.6 (4.6)
Salivary cotinine qualitative test results, n (%)		
Positive	11 (73.3)	14 (93.3)

Negative	4 (26.7)	1 (6.7)

The average number of years participants had been smoking was 23.3 years (*SD* 11.22) in the DTG and 29.2 years (*SD* 12.90) in the BTG. Daily cigarette consumption was similar, with DTG participants smoking an average of 9.5 cigarettes (*SD* 8.2) and BTG participants with 9.2 cigarettes (*SD* 7.4) per day. Regarding smoking cessation medication, 66.7% of the DTG participants and 53.3% of the BTG participants used bupropion. Regarding the type of tobacco used, in the DTG, 53.3% used manufactured cigarettes, 13.3% used heat-not-burn tobacco, 6.7% used liquid e-cigarettes, and 26.7% used multiple tobacco products. The BTG had a higher proportion of manufactured cigarettes (86.7%); no participants used heat-not-burn tobacco, 6.7% used liquid e-cigarettes, and 6.7% used multiple tobacco products. The Fagerström Test for Nicotine Dependence (FTND) mean score was 2.8 (*SD* 2.7) in the DTG and 1.6 *SD* 2.6) in the BTG. Exhaled carbon monoxide levels averaged 6.1 (*SD* 6.2) in the DTG and 6.6 (*SD* 4.6) in the BTG. Salivary cotinine test results were positive in 73.3% of the DTG participants and negative in 26.7%, whereas 93.3% of the BTG participants tested positive and 6.7% tested negative.

The primary efficacy indicators

Figure 3 presents the variations in the 7-day point smoking prevalence abstinence rates alongside the recorded smoking quantity across the different evaluation time points. The 7-day point abstinence rates at 8 weeks showed 66.7% and 50.0% for DTG and BTG respectively. At the end of the 12-week study period, 55.6% of the DTG and 41.7% of the BTG reported achieving 7-day point abstinence, reflecting a 13.9% difference between the groups. The average number of cigarettes smoked over the course of 7 days at the 12-week mark was 2.2 for the DTG and 14.4 for the BTG, showing 12.2 fewer cigarettes smoked in the DTG.

To statistically evaluate the effects of the basic treatment and digital therapeutic program, the Wilcoxon Signed Rank Test was conducted to analyze the differences between the baseline and each time point after the intervention for each group (Table 3). Analyzing the difference in 7-day point abstinence between baseline and each time point after the digital therapeutic program in the DTG, there was a statistically significant difference at the 8-week point (z=-2.000, N_a=0, N_b=4, P<.05). This implies that there were more positive ranks than negative ranks, indicating that the digital therapeutic program was effective in increasing smoking abstinence at the 8-week point compared to baseline. Conversely, in the BTG, none of the differences between the baseline and each time point after basic treatment were statistically significant.

Table 3. Analysis of the difference in 7-day point prevalence abstinence before and after treatment by assigned group

	Group	The time of evaluation	Negative Ranks[a]	Positive Ranks[b]	Ties	*z*	*p*
			N (Mean Ranks)				
7-day point prevalence abstinence	BTG (n=12)	week4-week0	0 (0.00)	3 (2.00)	9	-1.732	0.083
		week8-week0	1 (2.50)	3 (2.50)	8	-1.000	0.317
		week12-week0	1 (2.00)	2 (2.00)	9	-0.577	0.564
	DTG (n=9)	week4-week0	0 (0.00)	2 (1.50)	7	-1.414	0.157
		week8-week0	0 (0.00)	4 (2.50)	5	-2.000	0.046
		week12-week0	0 (0.00)	3 (2.00)	6	-1.732	0.083

a. Smoking (0) > Smoking abstinence (1)

b. Smoking (0) < Smoking abstinence (1)

At the 12-week mark, the 30-day point prevalence abstinence rate was 55.6% for the DTG and 33.3% for the BTG, indicating that the abstinence rate for the DTG was 22.3% higher than that for the BTG (Figure 4). Additionally, the average number of cigarettes smoked over the course of 30 days at the 12-week mark was 3.9 for the DTG and 72.7 for the BTG, with the BTG reporting 68.8 more cigarettes smoked (Figure 4).

Similar to the 7-day point prevalence abstinence, the 30-day point prevalence abstinence in the DTG also showed statistically significant differences at evaluation points after 8 weeks of the digital therapeutic program compared with baseline (Table 4; z=-2.000, N_a=0, N_b=4, P<.05). This indicates that the digital therapeutic program was effective not only in achieving 7-day smoking abstinence but also in achieving 30-day smoking abstinence. Conversely, in the BTG, none of the differences between the baseline and each time point after basic treatment were statistically significant.

Table 4. Analysis of the difference in 30-day point prevalence abstinence before and after treatment by assigned group

	Group	The time of evaluation	Negative Ranks[a]	Positive Ranks[b]	Ties	z	p
			N (Mean Ranks)				
30-day point prevalence abstinence	BTG (n=12)	week4-week0	1 (1.50)	1 (1.50)	10	0.000	1.000
		week8-week0	1 (2.50)	3 (2.50)	8	-1.000	0.317
		week12-week0	1 (1.50)	1 (1.50)	10	0.000	1.000
	DTG (n=9)	week4-week0	0 (0.00)	1 (1.00)	8	-1.000	0.317
		week8-week0	0 (0.00)	4 (2.50)	5	-2.000	0.046
		week12-week0	0 (0.00)	3 (2.00)	6	-1.732	0.083

a. Smoking (0) > Smoking abstinence (1)

b. Smoking (0) < Smoking abstinence (1)

Note. The baseline (week 0) was replaced with the 7-day point prevalence abstinence.

Consistency between self-report results and biological test results

Data on smoking abstinence and status were collected through verbal self-reports. To enhance the validity of these self-reports, a qualitative saliva cotinine test and an exhaled carbon monoxide test (eCO Test), a recognized biological marker of nicotine exposure, were concurrently administered. The concordance rate between the qualitative saliva cotinine test results and the patients' verbal self-reports was 80.9% (n=17)) at week 4, 95.2% (n=20) at week 8, and 95.2% (n=20) at week 12. Conversely, the discordance rates were 19.0% (n=4), 4.7% (n=1) and 4.8% (n=1) at weeks 4, 8, and 12, respectively. At the 4-week assessment, false negatives included participants who reported smoking over the past 30 days but reported abstinence in the past 7 days. Specifically, their exhaled carbon monoxide levels were all found to be 0 ppm or 1 ppm, indicating a non-smoker level (≤ 7 ppm). On average, these false-negative participants had smoked for 6 days [range: 1-12 days] in the past 30 days, with an average daily consumption of five cigarettes [range: 1.5-15 cigarettes]. This suggests that the false positives were likely owing to a small amount of smoking at least 7 days prior, with most of the cotinine having been eliminated from the body by the time of assessment. In cases of false negatives, participants reported exposure to secondhand smoke and their exhaled carbon monoxide levels were 5 and 7 ppm, respectively, corresponding to non-smoker levels. This suggests that cotinine remained in their bodies owing to exposure to secondhand smoke rather than direct

smoking. Overall, the concordance rate between self-reports and the saliva cotinine qualitative test was approximately 80–95%, indicating a high level of reliability for the self-reported data. Detailed concordance rates at each assessment time point are presented in Table 5.

Table 5. Concordance rate between self-reported and saliva cotinine qualitative test results

%(n)

Classification of diagnosis for smoking abstinence/smoking			Biological Test Results : Saliva cotinine qualitative test		
			S	SA	All
Self-Reported Results: Verbal Reports from Participants (30-day point prevalence abstinence)	week 4	S	true positive 47.6 (10)	false negative 19.1 (4)	66.7 (14)
		SA	false positive 0 (0)	true negative 33.3 (7)	33.3 (7)
		All	47.6 (10)	52.4 (11)	100 (21)
	week 8	S	true positive 42.9 (9)	false negative 0 (0)	45.0 (9)
		SA	false positive 4.8 (1)	true negative 52.3 (11)	57.1 (12)
		All	47.7% (10)	52.3 (11)	100 (21)
	week 12	S	true positive 52.3 (11)	false negative 0 (0)	52.3 (11)
		SA	false positive 4.8 (1)	true negative 42.9 (9)	47.7 (10)
		All	57.1 (12)	42.9 (9)	100 (21)

Note. S: Smoking, SA: Smoking Abstinence

The secondary efficacy indicators (Supplementary indicators)

Additionally, to compare and verify the levels of nicotine dependence and sub-factors of motivation to change between the DTG and BTG, the Mann-Whitney U test was conducted (Figure 5, Table 6). First, the examination of FTND revealed no statistically significant differences between the control and experimental groups before treatment, as both groups exhibited similar levels. As the treatment progressed, FTND in the DTG decreased slightly from baseline, whereas it increased slightly in the BTG. From week 4, a trend of difference between in FTND the groups was observed (U=26.000, DTG=9, BTG=12, P=.052), and by week 8, the difference in FTND between the DTG and BTG groups was statistically significant (U=26.000, DTG=9, BTG=12, P<.05). At the 12th week, the trend in the FTND scores between the groups was maintained (U=31.000, DTG=9, BTG=12, P=.051).

The results of comparing the sub-factor scores of the K-SOCRATES-S to examine the motivation to change smoking cessation were as follows. There was no significant difference in motivation recognition between the DTG and BTG owing to the random assignment. This likely reflects that most participants were aware of the need to quit smoking, as they voluntarily chose to participate in this clinical trial.

Next, the motivation-ambivalence showed an increasing difference between the BTG and DTG starting from week 4, with a statistically significant difference observed at week 8. Specifically,

ambivalence in the BTG gradually increased, whereas that in the DTG gradually decreased. The initial 1–4 weeks of the digital therapeutic program included a series of content focused on MET approaches, such as addiction education, addressing ambivalent emotions, creating supportive environments, and understanding confidence in quitting smoking. This suggests that digital therapeutic programs are more effective than basic treatment for altering ambivalent thoughts and attitudes toward smoking cessation.

Table 6. Comparative analysis results of supplementary indicators between DTG and BTG

		Week	Random	*N*	Mean Rank	Sum of Ranks	*U*	*p*
	FTND	0	BTG	12	12.96	155.50	30.500	0.092
			DTG	9	8.39	75.50		
		4	BTG	12	13.08	157.00	29.000	0.052
			DTG	9	8.22	74.00		
		8	BTG	12	13.33	160.00	26.000	0.029
			DTG	9	7.89	71.00		
		12	BTG	12	12.92	155.00	31.000	0.051
			DTG	9	8.44	76.00		
K-SOCRATES-S	recognition	0	BTG	12	9.92	119.00	41.000	0.354
			DTG	9	12.44	112.00		
		4	BTG	12	10.67	128.00	50.000	0.774
			DTG	9	11.44	103.00		
		8	BTG	12	11.38	136.50	49.500	0.748
			DTG	9	10.50	94.50		
		12	BTG	12	12.38	148.50	37.500	0.238
			DTG	9	9.17	82.50		
	ambivalence	0	BTG	12	11.75	141.00	45.000	0.513
			DTG	9	10.00	90.00		
		4	BTG	12	13.13	157.50	28.500	0.068
			DTG	9	8.17	73.50		
		8	BTG	12	13.54	162.50	23.500	0.029
			DTG	9	7.61	68.50		
		12	BTG	12	13.13	157.50	28.500	0.068
			DTG	9	8.17	73.50		
	taking -steps	0	BTG	12	10.54	126.50	48.500	0.695
			DTG	9	11.61	104.50		
		4	BTG	12	9.67	116.00	38.000	0.253
			DTG	9	12.78	115.00		
		8	BTG	12	9.46	113.50	35.500	0.187
			DTG	9	13.06	117.50		
		12	BTG	12	8.08	97.00	19.000	0.012
			DTG	9	14.89	134.00		

Finally, the motivation-taking steps sub-factor showed an increasing difference between the BTG and DTG starting from after week 4, with a statistically significant difference observed at 12 weeks. Both

groups exhibited an upward trend; however, the increase was more pronounced in DTG than in BTG. While the DTG demonstrated an increase in the action score, the recognition scores gradually decreased, indicating a transition to the behavioral dimension, where participants were already engaging in smoking cessation activities.

In the digital therapeutic program, participants engaged in VR content for relaxation training, craving coping training, and refusal to training in clinical settings. Additionally, in everyday settings, the program included application content covering relaxation training, cognitive restructuring, refusal skills, coping with negative emotions, and relapse prevention from weeks 5 to 8. By acquiring and repeatedly practicing cognitive, behavioral, and emotional coping strategies conducive to smoking cessation, participants were able to establish and consolidate resources to effectively apply coping skills. By contrast, the BTG maintained a similar level of recognition, whereas the scores for ambivalence and taking steps gradually increased. This pattern suggests that the BTG remained at the motivational and cognitive levels without fully transitioning to the action stage, likely owing to unresolved ambivalence and ongoing conflict between the cognitive and behavioral dimensions.

In summary, the results demonstrated that adults who participated in a digital therapeutic program had a significantly higher success rate in smoking abstinence. Additionally, compared to those who received basic treatment, participants in the digital therapeutic program exhibited lower nicotine dependence and higher motivation to quit smoking. Participants in the digital therapeutic program exhibited adaptive changes conducive to smoking cessation consistent with the weekly intervention strategies of the MET and CBT. Thus, the efficacy of the digital therapeutic program was validated, suggesting its greater potential to facilitate successful smoking cessation than basic treatment.

Discussion

Principal Results

This exploratory clinical trial aimed to evaluate the safety and efficacy of NICO-THERA, a digital therapeutic software program developed to alleviate nicotine dependence symptoms in patients diagnosed with nicotine use disorder. The discussion will focus on the primary findings observed when comparing DTG with BTG as well as the broader implications of these findings.

First, the study found that DTG participants experienced a more significant reduction in nicotine dependence and a higher rate of smoking abstinence than those in the BTG following the program intervention. This suggests that NICO-THERA, as a digital therapy, has the potential to enhance the effectiveness of smoking cessation treatments by supplementing pharmacotherapy and counseling.

Nicotine dependence is a chronic condition with a high relapse rate necessitating long-term and consistent therapeutic management. Traditional treatments for nicotine addiction typically involve medication and face-to-face CBT sessions. However, adherence to prescribed medications is often suboptimal, which reduces the efficacy of pharmacotherapy. Additionally, CBT sessions require considerable time and financial investment from the patients, which can be a significant barrier. In practice, the national smoking cessation support services in South Korea are typically available only during working hours, which limits physical and temporal accessibility. Although available, online services are typically limited to one-time consultations via telephone or messaging. Consequently, many smokers struggle to maintain their motivation and commitment to quit outside the clinical settings, in their daily lives. The number of smokers utilizing national smoking cessation services in South Korea is steadily declining, with only approximately 30% completing the program [47]. These challenges highlight the need for alternative strategies to address the limitations of traditional smoking cessation treatments in the digital age.

In this context, digital therapeutics, such as NICO-THERA, could play a pivotal role as an adjunct to existing smoking cessation treatments. Specifically, these interventions can be integrated into daily life by providing continuous support, along with national smoking cessation programs as a complementary method. As digital therapy based on MET and CBT, NICO-THERA has the potential to enhance treatment accessibility for nicotine addiction and advance patient-centered participatory medicine. It can also assist healthcare providers in monitoring the patients' daily conditions and incorporating this information into treatment plans.

Furthermore, the study observed that the DTG participants exhibited a progressive change in their motivation to quit smoking, which aligned with the structured approach of the digital therapeutic program. According to the Stages of Change model, intentional behavior change, such as quitting smoking, typically progresses through five stages: Precontemplation, Contemplation, Preparation, Action, and Maintenance [48]. NICO-THERA is a 12-week program that aligns with the five stages of change. It is also designed to support smoking cessation and maintenance by integrating evidence-based educational, cognitive, behavioral, and emotional techniques derived from the MET and CBT. Specifically, the initial 1–4 weeks of the program emphasized MET approaches, which are effective in promoting behavioral changes for smoking cessation. Consequently, by week 8, individuals were better able to resolve ambivalence and strengthen their commitment to change, thereby enhancing motivation. From the week 5 onward, the program gradually introduced cognitive, behavioral, and emotional techniques focused on CBT, helping individuals acquire strategies that are practically useful for maintaining smoking cessation. By the week 12, participants had solidified their resolve to sustain smoking cessation, demonstrating the effectiveness of the program's approach. Consistent with the theoretical framework, DTG participants exhibited significant behavioral changes that supported their efforts to quit smoking. Starting from week 4, difference in nicotine dependence between DTG and BTG participants began to emerge, followed by the statistically significant difference between two groups by week 9 and by the continuation of this trend through week 12. In addition, a consistent difference in amount of cigarette smoking between the DTG and BTG participants was observed from week 4 to week 12. Even in week 9, a time period when the abstinence of smoking was examined, a statistically significant difference in the prevalence of abstinence was noted. This suggests that the NICO-THERA can enhance treatment outcomes by guiding individuals through adaptive behavioral changes for smoking cessation.

Smoking cessation is not merely a matter of short-term efforts; it requires ongoing management to ensure long-term success. NICO-THERA, as a software that combines application and VR components, provides cognitive, behavioral, and emotional strategies designed to support smoking cessation across various stages of behavioral change. Notably, VR allows participants to engage in motivational, cognitive, and behavioral training in clinical settings, helping them develop strategies to cope with smoking triggers. The smartphone application supports self-directed therapy and habit formation in daily life through its content and daily functions. As a digital therapy based on MET and CBT, NICO-THERA has the potential to enhance the effectiveness of smoking cessation treatments by expanding therapeutic interventions and improving accessibility.

Limitations

This study has some limitations. As a pilot study, the sample size was intentionally kept small, limiting the statistical power to detect significant differences in some analyses.
The small sample size (30 participants) necessitated the use of non-parametric tests, which affected the generalizability of the results. Future studies with larger sample sizes are required to confirm the observed trends and to establish statistical significance through parametric tests.

Additionally, the open-label nature of the study, in which both participants and researchers were aware of group assignments, may have introduced bias in outcome reporting. However, the primary focus of this study was to assess its feasibility and safety rather than to establish definitive efficacy conclusions.

Conclusion

This exploratory clinical trial demonstrated that NICO-THERA, a digital therapeutic combining MET and CBT, has the potential to improve smoking cessation outcomes by providing an accessible, structured intervention for nicotine dependence. Participants in the DTG experienced significant reductions in nicotine dependence and higher smoking abstinence rates than those in the control group, suggesting that the NICO-THERA may serve as a valuable complement to traditional pharmacotherapy and counseling in smoking cessation programs.

The ability of NICO-THERA to integrate therapeutic interventions into daily life, supported by both a smartphone application and VR sessions, highlights its potential as a patient-centered tool that can enhance engagement and long-term adherence to smoking cessation efforts. The digital nature of this therapeutic intervention allows for more flexible and continuous support, which is crucial for managing chronic relapsing conditions, such as nicotine dependence.

Currently, a confirmatory clinical trial with an adequate sample size is underway to establish the statistical significance using parametric testing methods. Additionally, it may be beneficial to explore the efficacy of digital therapeutics by distinguishing groups based on the use of pharmacotherapy, allowing for a discussion on the role of digital therapeutics as either an alternative or a complement to traditional treatments.

Future research should focus on confirming these findings in larger clinical trials to establish definitive efficacy and further explore how digital therapeutics, such as NICO-THERA, can be optimized to complement or substitute traditional treatment approaches in smoking cessation.

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Conflicts of interest

none declared.

Abbreviations

DTG: Digital Therapeutic Group
BTG: Basic Treatment Group
CBT: Cognitive Behavioral Therapy
MET: Motivational Enhancement Therapy
VR: Virtual Reality
FTND: Fagerström Test for Nicotine Dependence
K-SOCRATES-S: Korean Stages of Change Readiness and Treatment Eagerness Scale-Smoking

Multimedia Appendix 1

Background settings for image relaxation training through VR.

Multimedia Appendix 2

VR-based training session for craving coping.

Multimedia Appendix 3

VR-based training session for refusal training.

Multimedia Appendix 4

App screenshot of the NICO-THERA.

Multimedia Appendix 5

CONSORT-eHEALTH checklist (V 1.6.1).

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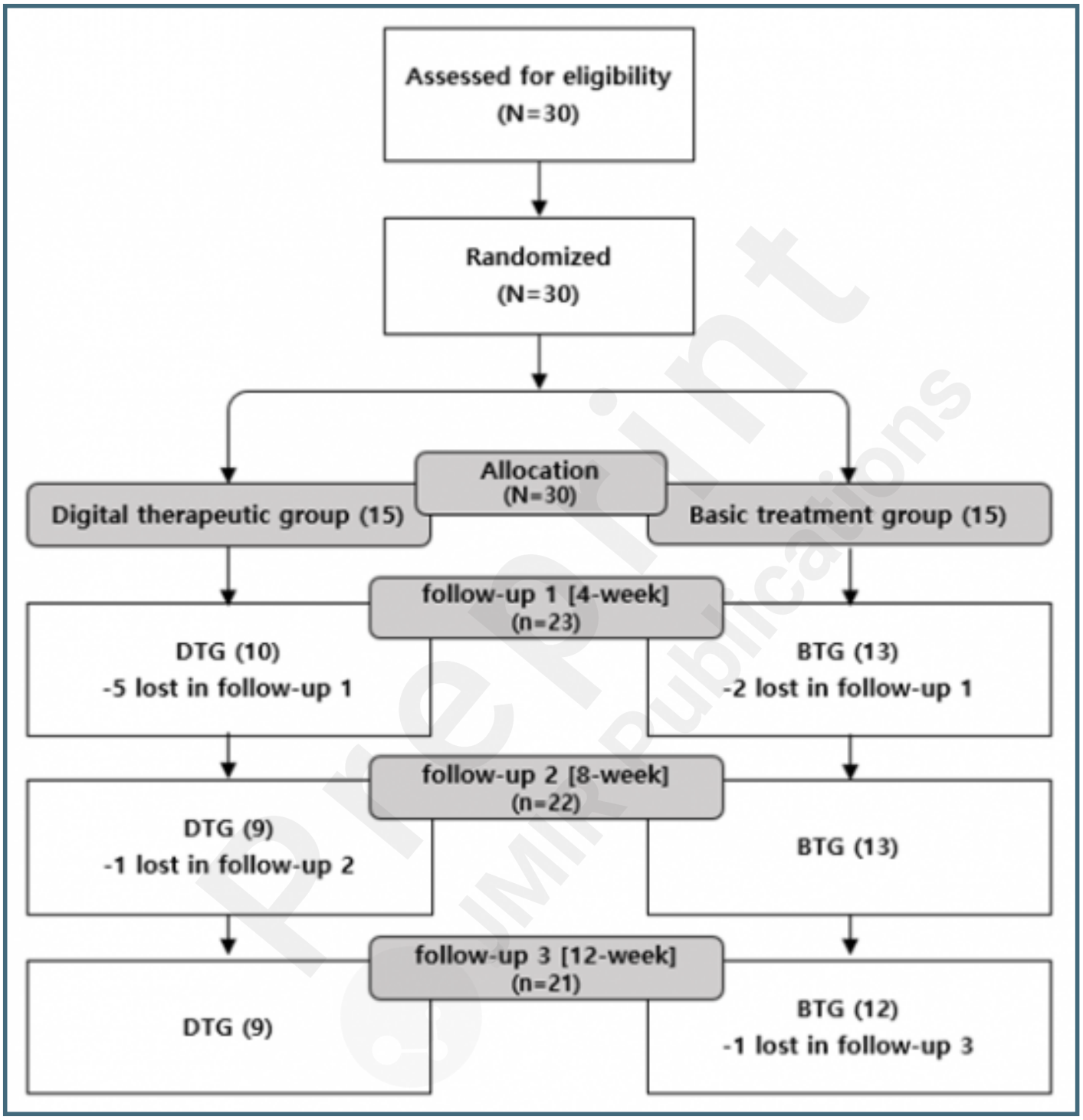
Supplementary Files

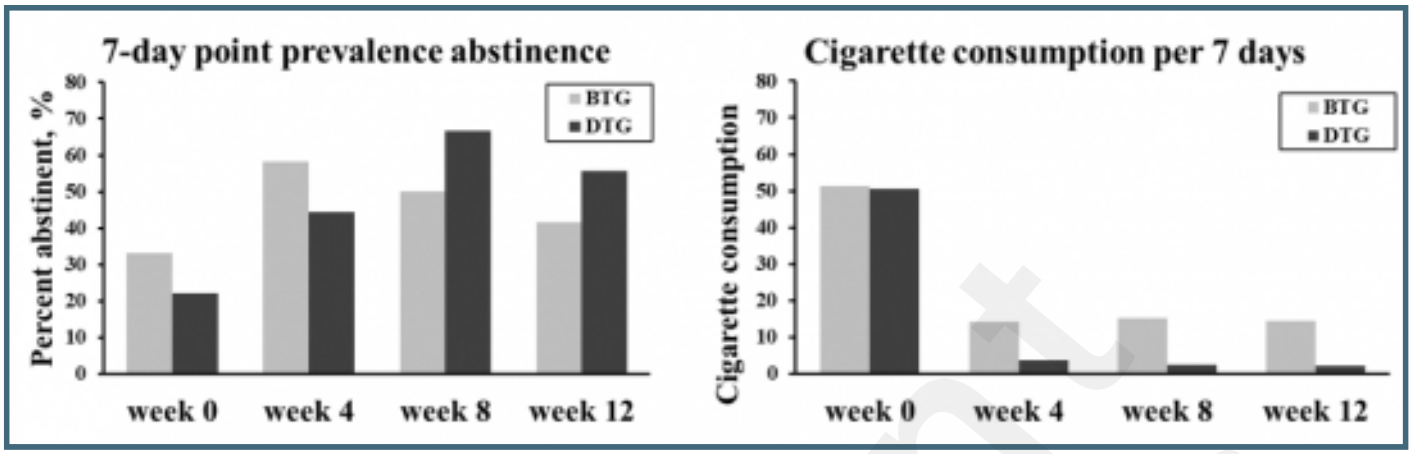
Figures

Overview of the NICO-THERA digital therapeutic program: The top section shows app screenshots, including the main dashboard and CBT-based contents, while the bottom section illustrates VR-based sessions for relaxation training, craving coping, and refusal training.

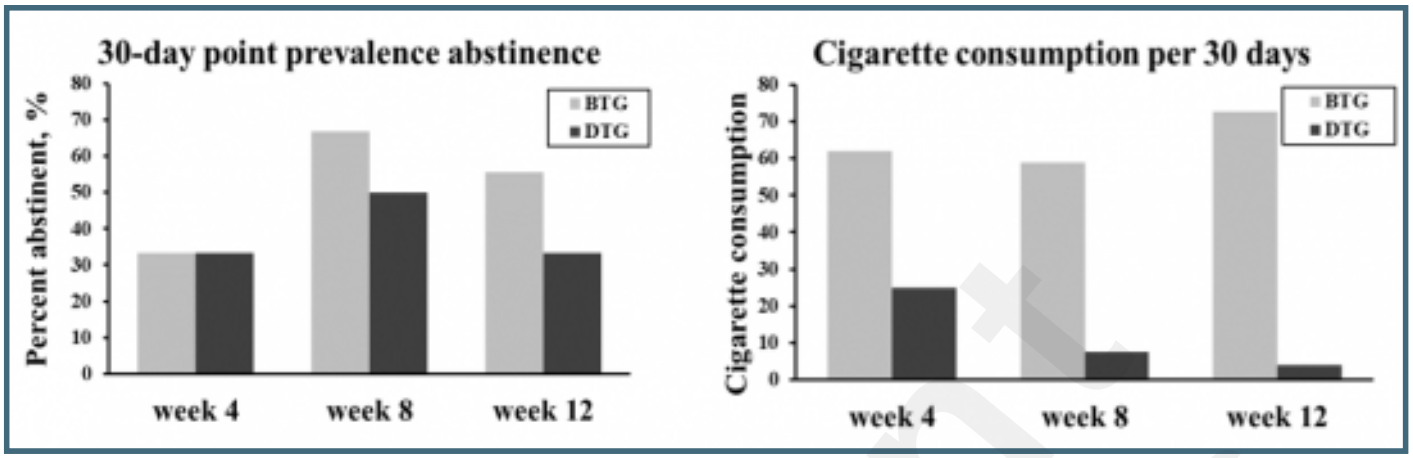
Study participant CONSORT (Consolidated Standards of Reporting Trials) flow diagram.



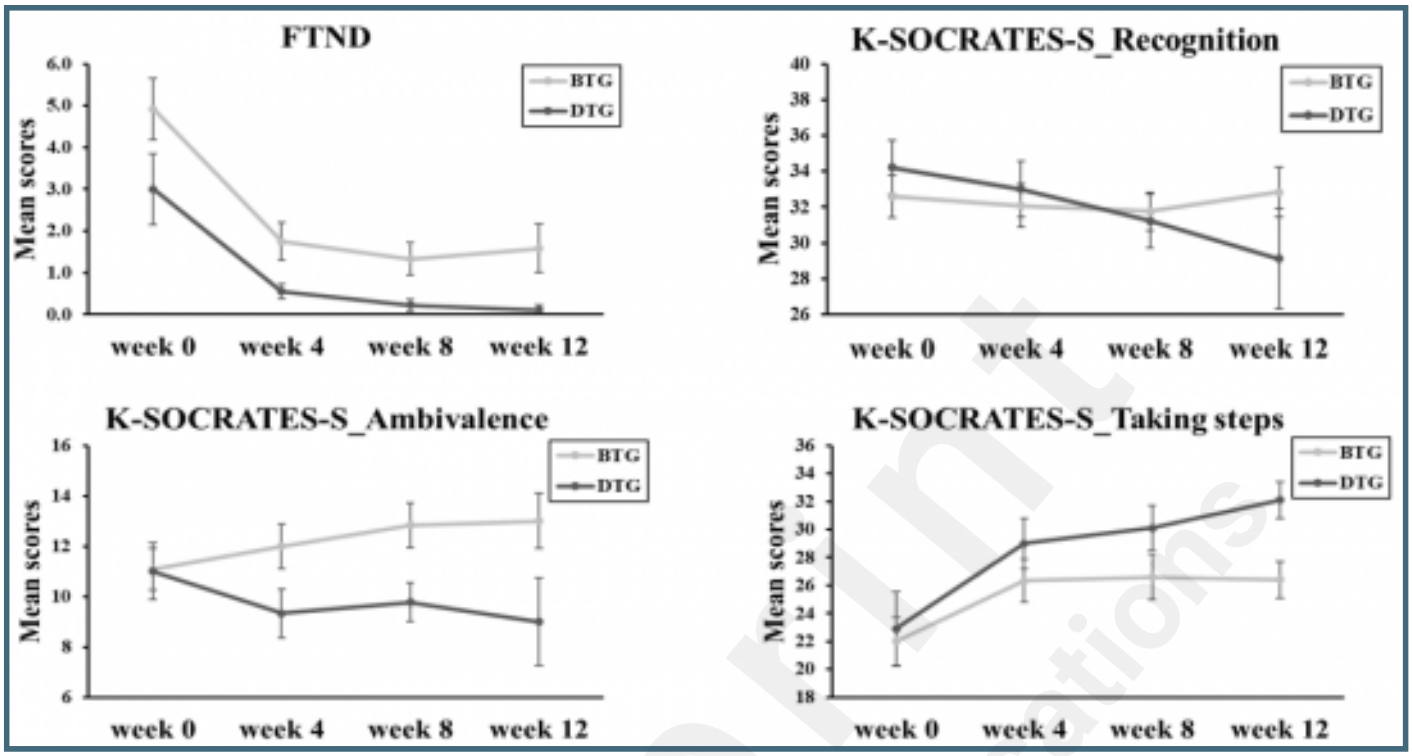
Untitled.Changes in 7-day point smoking prevalence abstinence rates and smoking quantity at each evaluation time point.



Changes in 30-day point prevalence abstinence rates and smoking quantity at each evaluation time point.



Changes in nicotine dependence and motivation for change at each evaluation time point.



Multimedia Appendixes

Background settings for image relaxation training through VR, presented sequentially: Forest, Campfire, Beach.
URL: http://asset.jmir.pub/assets/16ec69de94d413f7a4af2b450a32365d.png

VR-based training session for craving coping: A screenshot depicting a situation at a social gathering where friends are stepping out to smoke.
URL: http://asset.jmir.pub/assets/c58fc812f95f3d473ea4d0654f992fdb.png

VR-based training session for refusal training: A situation where a friend offers a cigarette to someone who is in the process of quitting smoking.
URL: http://asset.jmir.pub/assets/7f44a70e30e90cbbdb201f307b781f87.png

App screenshot of the digital therapeutic intervention NICO-THERA, presented sequentially from left to right: Smoking cessation therapy contents, Smoking cessation diary and medication log, and a graph displaying the number of cigarettes smoked and changes in motivation levels.
URL: http://asset.jmir.pub/assets/b5ac552bb31441f9c5187da26093d65e.png

CONSORT (or other) checklists

CONSORT checklist.
URL: http://asset.jmir.pub/assets/5449d7bd652cd39d2ce594865110a383.pdf