Complete Title: Optimization of a mHealth Behavioral Weight Loss Intervention for Young Adults

Sponsor: University of North Carolina at Chapel Hill

NCT number: NCT04922216

Final Protocol Date: 20 February 2023

University of North Carolina at Chapel Hill

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Protocol Version: 1.0

Version Date: 02/20/2023

I confirm that I have read this protocol and understand it.

Principal Investigator Signature: 

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ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACM	Adopt Core Measure
ADOPT	Accumulating Data to Optimally Predict obesity Treatment Core Measures
AGILE	Adaptive Goals and Interventions for Lifestyle Enhancement
API	Application Program Interface
BCT	Behavior Change Technique
BMI	Body Mass Index
CES-D	Center for Epidemiological Studies Depression Scale
DSMB	Data Safety Monitoring Board
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders
EARLY	Early Adult Reduction of weight through LifestYle intervention
ELM	Elaboration Likelihood Model
IMPACT	IMproving Physical Activity after Cancer Treatment
IRB	Institutional Review Board
JITAI	Just-in-Time Adaptive Intervention
JIT	Just-in-Time
MOST	Multiphase Optimization Strategy
MVPA	Moderate to Vigorous Physical Activity
NCI	National Cancer Institute
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIH	National Institutes of Health
OCT	Office of Clinical Trials
PAR-Q	Physical Activity Readiness Questionnaire
PAQ	Paffenbarger Physical Activity Questionnaire
REDCap	Research Electronic Data Capture
RCT	Randomized Clinical Trial
RF	Red Food
SDT	Self-Determination Theory
SNAP	Studies of Novel Approaches to Prevention
TraCS	North Carolina Translational and Clinical Sciences
YA	Young Adult

PROTOCOL SYNOPSIS

Study Title	Optimization of a mHealth Behavioral Weight Loss Intervention for Young Adults
Funder	National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
Clinical Phase	NA
Study Rationale	Young adults (YAs) are underrepresented in behavioral health and weight loss interventions and express interest in flexible, highly tailored programs. Mobile interventions are a lower-burden, scalable approach to providing behavioral support. Just-in-time-adaptive interventions (JITAI) promise to deliver the "right" support at the "right" time using real-time data from smartphones and sensors. JITAIs hold promise for promoting behavior changes needed for weight loss (eating, activity, and self-weighing); however, there is limited evidence for selecting treatment components and levels of adaptation that are needed for success. Results of this trial will be used to create an optimized JITAI for weight loss in young adults.
Study Objective(s)	Primary • To build an optimized JITAI consisting of the set of intervention components that yield the greatest improvement in weight change among young adults at 6 months Secondary • To conduct mediation analyses to test the relationships between the intervention components and hypothesized proximal mediators (self-regulation, competence, relatedness, relevance, autonomy) and more distal behavioral mediators (dietary intake, physical activity, and daily self-weighting) • To conduct exploratory analyses of program engagement
Test Article(s) *(If Applicable)*	All participants will receive a core 6-month weight loss intervention that includes evidence-based lessons, behavioral skills training, and daily weighing.
Study Design	The AGILE (Adaptive Goals and Interventions for Lifestyle Enhancement) trial utilizes the Multiphase Optimization Strategy (MOST) framework and a 2^5 full factorial experimental trial to test the efficacy of 5 intervention components, each with two levels, on weight loss among 608 YAs recruited from around the United States. All participants will receive a core 6-month weight loss intervention that includes evidence-based lessons, behavioral skills training, and daily weighing. With the goal of determining if greater adaptation leads to greater weight loss, we will test standard versus adaptive options of 5 additional intervention components: 1) diet monitoring approach (standard vs. simplified), 2) adaptive physical activity goals (weekly vs. daily), 3) decision points for message timing (fixed vs. adaptive), 4) decision rules for message content (standard vs. adaptive), and 5) message choice (no vs. yes). Assessments will occur at baseline, 3 months, and 6 months.
Subject Population	**Inclusion Criteria** 1. Age 18-39 2. Body mass index (BMI) of 25-45 kg/m^2 3. English speaking and writing

	4. Own a smartphone with a data and text messaging plan 5. Willing to be randomized to any levels of the factors **Exclusion Criteria** 1. Type 1 diabetes or currently receiving medical treatment for Type 2 diabetes. 2. Other health problems which may influence the ability to walk for physical activity or be associated with unintentional weight change, including cancer treatment within the past 5 years or tuberculosis. 3. Report a heart condition, chest pain during periods of activity or rest, or loss of consciousness on the Physical Activity Readiness Questionnaire (PAR-Q; items 1-4). 4. Lost 10 or more pounds (and kept it off) in the last 6 months. 5. Currently taking weight loss medications. 6. Report a past diagnosis of or receiving treatment for a DSM-IV-TR eating disorder (anorexia nervosa or bulimia nervosa). 7. Currently pregnant, pregnant within the past 6 months, or planning to become pregnant within the next 6 months. 8. Hospitalization for depression or other psychiatric disorder within the past 12 months. History of psychotic disorder or bipolar disorder. 9. Another member of the household is a participant or staff member on this trial. 10. Currently participating in a weight loss, nutrition or physical activity study or program or other study that would interfere with this study.
Number Of Subjects	608
Study Duration	Each subject's participation will last 6 months. The entire study is expected to last five years.
Study Phases **Screening** **Study Treatment** **Follow-Up**	(1) Screening: screening for eligibility and obtaining consent and (2) Baseline assessment (3) Intervention: study intervention/experimental treatment. (4) Follow-up assessment will occur at 3 and 6 months.
Efficacy Evaluations	Results of the optimization experiment will be used to determine which combination of components and component levels contribute most significantly to mean weight loss (primary) and achievement of 5% weight loss (secondary) at 6 months.
Pharmacokinetic Evaluations	NA
Safety Evaluations	All medical events and safety data will be assessed at assessment points or when interim events are reported by participants using a standard form used in our ongoing NIH funded trials.
Statistical And Analytic Plan	The primary outcome analysis will use mixed effects models to test for differences in weight by intervention components across time (baseline, 3, and 6 months).[24] Effects will be modeled as component x time interactions with the 6-month outcome as the primary endpoint. All higher-order interactions between components will be modeled. Additional models will evaluate the likelihood of reaching 5% weight loss at 6 months.
DATA AND SAFETY MONITORING PLAN	Data safety management in this trial is intended to achieve 4 objectives: 1) to minimize the occurrence of adverse effects, especially those related to intervention; 2) to effectively

manage adverse events as they relate to the study; 3) to identify when the interventions should be suspended because of concerns for participant safety; and 4) to determine when interventions may be resumed after having been suspended. The Principal Investigator (Tate) will have primary responsibility for the safety of participants as it relates to the study protocol, which must be approved by the UNC IRB prior to study initiation. In addition, the North Carolina Translational and Clinical Sciences (TraCS) Institute Data Safety Monitoring Board (DSMB) is responsible for reviewing data from clinical trials approved by the UNC Biomedical IRB. Because the risks to subjects participating in this phase of this study are expected to be low, we do not anticipate the need for a formal Data Safety Monitoring Board. The research team will provide continuous monitoring of participant safety and periodic reporting to the IRB as required, including any Unanticipated Problems/Severe Adverse Events that may have occurred during the study. If risk or complexity is significant, the UNC Office of Human Research Ethics may require additional reporting or alternative data and safety monitoring. Data safety and monitoring activities continue until all participants have completed treatment and until all participants have been followed to the point at which study related adverse events would likely no longer be encountered.

BACKGROUND AND RATIONALE

1.1 Introduction

Obesity has reached epidemic proportions in the United States and is recognized as a major cause of morbidity and mortality. There is an increased risk of weight gain during young adulthood, [1,2] and 40% of young adults (YAs) aged 20-39 years are living with obesity.[3] Obesity in this age group is associated with increased risk of hypertension, hyperlipidemia, diabetes, and cancer.[2,4] Despite these risks, YAs are underrepresented in behavioral weight loss programs [5–7] and few evidence-based programs have been designed specifically for YAs.[7–10]

1.2 Name and Description of Investigational Intervention

The AGILE (Adaptive Goals and Interventions for Lifestyle Enhancement) trial is a 2^5 full factorial experimental trial testing the efficacy of 5 intervention components (factors), each with two levels, to identify component levels that contribute to greater weight loss among YAs. To do so, we will randomize 608 YAs with overweight or obesity to receive one level of each of the 5 intervention components, in addition to a core mobile-delivered behavioral weight loss program.

1.3 Relevant Literature and Data

Almost all young adults in the United States own a smartphone (97%) and mobile phone ownership in this age group is widespread across all racial/ethnic, education, income, and residential groups.[11] Our formative work with YAs (n=137) with overweight or obesity indicates that at least 60% are interested in technology-delivered programs, and that YAs would like programs that are individualized, lower intensity, flexible, and minimize time burden.[12] Commonly cited barriers to weight management among YAs include not having enough motivation or time and not getting enough exercise.[12] Exclusively mobile treatments have produced weight losses of 1-6 kgs over 6 months,[9,13–15] demonstrating that mobile-delivered programs have the potential to increase the access, reach, and impact of weight management.

To date, the most effective digital obesity interventions have relied on predetermined, fixed schedules of treatment contact, typically providing email counselor feedback once per week and/or text messages delivered on a pre-specified schedule to all participants.[16] With the widespread use of smartphones and connected health devices that seamlessly collect daily participant health data, mobile programs are able to provide more tailored intervention messages, such as varying message content based on current or recent behavioral data (e.g., activity minutes so far that day at time of message; number of days a goal was met in the past week).[17–19] The availability of participants' real-time digital health data allows for highly individualized intervention and real-time support while minimizing burden to the participant. Rather than relying on largely pre-determined messaging schedules that evaluate a limited number of variables, emerging research has focused on improving the ability to send the "right message" at the "right time." These interventions, called "just-in-time adaptive interventions," (JITAIs) have the potential to improve upon outcomes by offering highly adaptive, personalized feedback on behavior when needed.[20] Examples of JITAIs have included providing just-in-time skills support for reducing alcohol intake,[21] in-the-moment messaging to disrupt sedentary behavior,[22] and using data to predict dietary lapses and provide supportive interventions before they occur.[23] Despite widespread availability of digital health devices and the emerging use of JITAIs, most JITAIs to date have been short in duration (12 weeks or less) and have targeted single behaviors versus multiple. In turn, there remains limited theoretical, empirical, and practical evidence to inform interventions.[20]

To improve weight, multiple daily behavioral targets are needed, including dietary intake, physical activity, and self-weighing. Thus, for weight loss, automated mobile interventions must be able to provide tailored, adaptive messaging that considers participants' behavioral contexts across all weight-related behaviors and sends the "right" message for the "right" behavior and at the "right" time. However, the level of tailoring provided in messaging exists along a continuum, and it is not yet known how much tailoring and adaptation is needed to be effective. Moreover, there are other components of automated interventions that could increase engagement or effectiveness, including adaptive goal setting and alternative methods of self-monitoring, but few studies have examined alternatives among YAs. We conducted a pilot 12-week remotely delivered JITAI that delivered up to 4 messages per day to young adults in a mobile behavioral weight loss program and found that participants viewed 68% of messages, and viewing messages was associated with increased likelihood of reaching daily behavioral goals.[18] While this was promising, many questions remain about how adaptive and personalized a JITAI needs to be to be effective for weight loss in YAs.

1. STUDY OBJECTIVES

To address evidence gaps regarding JITAIs, the objective of this trial is to simultaneously test innovative or adaptive intervention components, compared to their standard counterparts, that are expected to increase weight loss among YAs. This is an optimization trial, conducted as part of the Multiphase Optimization Strategy (MOST) framework.[24] Guided by Self-Determination Theory (SDT),[25] the trial will test 5 components that are designed to promote positive changes in SDT constructs: 1) diet self-monitoring approach (standard vs. simplified), 2) adaptive physical activity goals (weekly vs. daily adaptive), 3) decision points for message timing (fixed vs. adaptive), 4) decision rules for message content (standard vs. adaptive), and 5) message choice (no vs. yes).

Aim 1: Build an optimized JITAI consisting of the set of intervention components (and component levels) that yield the greatest improvement in weight change among young adults at 6 months. We will use a highly efficient experimental design, powered to detect both main effects and all two-way interactions between components. Results of the optimization experiment will be used to determine which combination of components and component levels contribute significantly to mean weight loss at 6 months. The proportion achieving 5% weight loss is our second-level decision-making criterion in cases of equal weight losses.

Aim 2: Conduct mediation analyses to test the relationships between the intervention components and hypothesized mediators. Mediators to be tested include the proximal theoretical mediators of component effects (self-regulation, competence, relatedness, relevance, autonomy) and the more distal behavioral mediators (dietary intake, physical activity, and daily self-weighing).

Aim 3: Conduct moderation analyses. The primary moderator to be tested is intervention engagement including self-monitoring engagement (weighing frequency, diet monitoring, tracker wear) and app engagement (app views, lessons, feedback, intervention message views). Exploratory moderators include gender, race/ethnicity, and initial BMI status.

The active component levels determined from this study will be used to create an optimized just-in-time adaptive intervention that will be tested in a separate RCT to examine weight losses at 6 months with follow-up at 12 months. If the proposed aims are achieved, we will expand our understanding of ways to improve public health with just-in-time support that accounts for individual variability in lifestyle and environmental contexts. Our work advances the science of JITAI development–answering key questions about adaptation and tailoring–and is guided by a conceptual model, which will further understanding of how JITAI components and mobile interventions may operate via key theoretical mediators. Our study will be one of the first to systematically

optimize a fully automated mobile JITAI. These aims are critical initial steps for overcoming the challenge of providing and evaluating broad-reach public health interventions that are more precisely tailored to the specific characteristics of individuals.

2. INVESTIGATIONAL PLAN

Study Design

Rationale for Component Selection

We selected components to evaluate for an optimized JITAI based on empirical and theory-based support (Figure 1). Factors 1 and 2 test two different methods of dietary tracking and two methods of physical activity goal adaptation, respectively. Factors 3-5 directly affect the just-in-time (JIT) messages being delivered to participants, specifically the "when" and "what" of the JITAI. Guided by the JITAI framework, in which the goal is to intervene at the right time and with the right type of treatment, this study evaluates different methods for choosing decision points, decision rules, and intervention options.[26] *Decision points* are the times at which a decision is made about whether and how to intervene and can occur one or several times per day or week. At these times, *decision rules* (a set of tailoring variables and their values) are evaluated to determine which *intervention option* (type of treatment or message) to deliver, if any.[20,26] In this study, all intervention options will be brief messages delivered via smartphone application; therefore, hereafter *intervention options* will be referred to as intervention messages.

Rationale of Factors/Intervention Components

Dietary Self-Monitoring Approach (Standard versus Simplified). Detailed calorie tracking is the standard form of dietary tracking in standard behavioral weight loss interventions,[27,28] but adherence to calorie tracking declines over time[29,30] and participants who stop tracking generally do not achieve clinically significant weight losses. Calorie tracking can be time intensive, and adherence may decline if the perceived cost of tracking does not outweigh its benefit.[31] Given that self-monitoring is a central feature of *self-regulation*,[32] there is a need to test other methods of dietary self-monitoring that might reduce burden and improve dietary self-regulation. We have conducted three pilot trials that have shown that a simplified Traffic Light approach,[33] in which participants track only their "red" (high-calorie) foods, is feasible among YAs and has similar adherence and weight losses at 6 months to detailed calorie tracking.[17,18,34] However, few, if any, fully powered trials have directly compared detailed calorie tracking ("Standard") with a simplified red food tracking approach ("Simplified").

Adaptive Activity Goals (Weekly Adaptive versus Daily Adaptive). Adaptive intervention components, such as adaptive physical activity goals, may support more precise shaping of an individual's behaviors, improve adherence, reduce treatment mismatch, and increase competence.[35] *Perceived competence*, or an individual's feelings about their capabilities with respect to a behavior, has been shown to be an important predictor of weight loss,[36] and adoption and maintenance of physical activity.[37] The current standard for physical activity goal progression, in the context of weight loss, is to gradually increase goals with a fixed progression over time, regardless of an individual's previous goal achievement, which may not be optimal for promoting behavior change[38] or supporting an individual's competence related to physical activity. Adaptive goal setting, in which the goals are set based on participants' personal activity levels, is emerging as an alternative to fixed progression goals,[38,39] with evidence that interventions with step goals that adapted on a daily basis improved steps/day compared to static step goals.[38–40] However, it is unclear whether this daily frequency of goal adaptation ("Daily Adaptive") is necessary for a daily activity goal and whether it is more effective than adapting goals on a weekly basis ("Weekly Adaptive").

Decision Time Points (Fixed versus Adaptive). In a JITAI framework, *decision points* are the times at which a decision is made about whether and how to intervene and can occur one or several times per day or per week. To date, many mobile interventions have relied on pre-specified, fixed messaging times (e.g., sending a text message at 5 pre-determined times per week).[17,41,42] However, it is possible to collect and use behavioral and contextual data to determine the "right time" to deliver a message, such as JITAIs that have sent messages when participants are at risk of a behavioral lapse.[23] This requires evaluating participant data throughout a longer time interval instead of pre-determining the message times. This additional level of tailoring may increase program and message relevance. The Elaboration Likelihood Model (ELM)[43] of message processing posits that individuals show greater elaboration or thinking about a given circumstance when they are more motivated, find the content interesting and personally relevant, and when they can process it. [44] Prior intervention studies have shown that increased *perceptions of relevance* of the program and program messaging increased intervention effects.[45,46] However, it is not known if using participant behavioral data to determine decision points ("Adaptive") will increase the relevance of the messages, and in turn improve outcomes compared to predetermined decision points ("Fixed").

Decision Rules (Standard versus Adaptive). *Decision rules* are the sets of variables used to evaluate which intervention message a participant should receive and can include one or many tailoring variables. Delivering the "right message" should enhance feelings of *relatedness* or being respected and understood by the program, which is a critical aspect of autonomy support in self-determination theory (SDT).[47] Human-computer interaction research on mobile phone identity defines relatedness as the degree to which individuals feel connected when considering how they relate to their mobile phone and may also reflect the extent to which an app or mobile intervention provides support.[48] Within the context of a mobile program that delivers brief messages, the level of relatedness and personalization in message content is dependent upon the amount of behavioral and contextual data that is used to determine which message to deliver (i.e., the number of tailoring variables in a decision rule). It is currently not known whether increasing the complexity and adaptation of decision rules ("Adaptive") will enhance the effects of JIT support compared to simpler decision rules ("Standard").

Participant Message Choice (Choice versus No Choice). SDT posits that an individual will adopt and maintain more autonomous and self-determined motivation in an *autonomy* supportive context.[25,49] Autonomy supportive behavioral strategies include providing individuals multiple options for change, a lack of forced behavior, and allowing individuals to share their perspectives.[50] Formative work among YAs with overweight or obesity emphasizes the desire for autonomy, flexibility, and choice in behavioral weight loss programs[12] and indicate that an approach that offers choice has potential for promoting clinically meaningful weight loss.[7] While the option to have more frequent choices and control over the types of messages or intervention support received has been less studied in weight management, it has shown promise with other health behaviors.[51] It is currently not known whether providing choice in the types of messages received will enhance the effects of JIT support and improve weight outcomes.

Core Intervention Overview

All participants will receive a core intervention modified from concepts of the Diabetes Prevention Program[52] and adapted specifically for YAs.[53] The intervention is based on social cognitive and control theories focused on improving self-regulation via self-monitoring coupled with weekly tailored feedback. Participants will receive a Bluetooth-enabled scale (Fitbit Aria Air) and activity tracker (Fitbit) in the mail, followed by an introductory videochat session with an interventionist. In this session they will receive information relevant to their participation in the program, including an overview of how to use the AGILE app (for both iOS and Android) and other required apps (Fitbit; Traffic Light Log for participants assigned to it as described below), how to self-

monitor to achieve their daily goals (eating, activity, and self-weighing), and other information relevant to the conditions to which they have been randomized.

Activity, weight, and dietary data are synced to study servers and available in the AGILE app on pages that display participants' daily and overall progress towards their goals. The AGILE app also includes 24 behavioral lessons that are unlocked each week of the program. These include behavioral strategies with specific instruction on core cognitive and behavioral skills (i.e., goal setting, self-monitoring, problem solving, overcoming barriers, reaching out for social support, and cognitive restructuring). A Feedback page in the app displays weekly tailored feedback that summarizes participant progress based on weight change, self-monitoring frequency, and weekly goal achievement. Adaptive JIT intervention messages related to the components below are delivered 1-2 times per day.

Overview of Intervention Components and Messaging System

To equate frequency of message delivery across all conditions, all participants will receive 10 messages per week (1-2 messages per day), between 8:00AM and 9:00PM. Participants will receive a smartphone notification when a new message is displayed in the app. The messages are displayed on the Home page of the AGILE app and remain there until they expire at midnight. Participants can like or dislike messages with a thumbs up/thumbs down. Messages pertain to one of three behaviors (eating, activity, self-weighing) and are chosen based on decision rules that evaluate participant behavioral data at the time the rules are evaluated. A pre-determined schedule (which varies by some of the components as described below) assigns 1-2 behaviors that will be messaged on each program day, with unique decision rules or each behavior. Most intervention messages include one or two of the following message types: feedback on outcome, feedback with a data point, directive action, nondirective action, encouragement/motivation, and social comparison. Other intervention messages are short interactive action planning tools that guide the participant to develop a plan for one of their behavioral goals.

Description of Intervention Components (Factors)

Dietary Self-Monitoring Approach. Participants in this trial will be randomly assigned to a Standard or Simplified approach. Participants assigned to Standard tracking will receive a calorie goal ranging from 1425-2850 per day based on their sex and starting weight and will track their calories using the Fitbit app, which transmits to the study servers via the Fitbit API. The Simplified "red" food (RF) approach focuses on reducing overall caloric intake by tracking and reducing intake of RFs only; there are no specific goals for green and yellow foods. Participants assigned to Simplified tracking will receive a daily RF limit that ranges from 3-6 RFs per day and will track their RFs in a native Traffic Light Log app created for this study. They are not required to track their green and yellow foods but can do so if they choose. Participants will be able to see their current and historical dietary progress on the Eating page of the AGILE app, which will display RFs for the Simplified group and calories for the Standard group.

Adaptive Activity Goals. Participants will be randomized to receive weekly adaptive or daily adaptive daily physical activity goals. In the weekly adaptive group, participants will receive a new daily activity goal at the beginning of each program week and the daily goal remains constant throughout the week. In the daily adaptive group, participants will receive a new daily activity goal at the beginning of each day. Participants will use their Fitbit activity trackers to track their "active minutes" (AM), which are equivalent to moderate-to-vigorous physical activity minutes. At the beginning of the program, participants will receive a daily AM goal of 10- 20 AM per day based on their baseline level of activity during the run-in period. After the first program week or day (for weekly and daily adaptive, respectively), AM goal adaptations will be driven by an algorithm that sets the new goal as the 4th highest day of AM (55th percentile) in the prior 9 days.[39,54]

Decision Points. Participants in this trial will be randomly assigned to fixed timing or adaptive timing. Fixed timing runs from a schedule that specifies the exact time (1-2 times per day) that the decision rules are run, though the times vary each day. In adaptive timing, the decision rules run hourly and participant data determines when the message should be sent (limited to 1-2 per day, mirroring the fixed schedule). In adaptive timing, messages can be delivered in closer proximity to when a behavior is completed (< 1 hour; to immediately reinforce goal achievement), or, if their usual behavior patterns suggest that receiving the message at the current time would not be ideal, the decision rules can continue to run and send a more appropriate message later in the day (e.g., not sending an activity reminder message at 9am if the participant does not usually exercise until after 7pm). This is done with additional variables in the adaptive timing decision rules that take into account participants' usual behavioral patterns.

Decision Rules. Participants will be randomly assigned to standard decision rules or adaptive decision rules. In standard, the decision rules include a limited set of variables representing behavioral progress from the current and prior day. In addition, participants are eligible to receive an interactive action planning tool if they are in a 2-day lapse, meaning they have not met their goal the current or prior day. In adaptive decision rules, the rules mirror the fixed rules, with additional behavioral and contextual tailoring variables that allow for consideration of past progress on the given behavior, other behaviors, and recent weight change, such that a message about a different behavior can be sent if that might be more appropriate for the participant. Also, participants in adaptive decision rules are not eligible to receive an interactive action planning tool unless they are in a behavioral lapse of at least 4 days (compared to 2 in standard). These additional tailoring variables and adjustments are designed to provide flexibility in the messages that can be sent to participants. Rather than requiring that the system send a message about the behavior that was assigned for that day, the comprehensive rules allow the system to, when needed, send a message on another behavior that would be more appropriate. As an example, a fixed decision rule for eating may evaluate yesterday's dietary goal achievement, the current day's dietary tracking, and current dietary intake compared to their goal. If the participant has tracked nothing, they will receive a message prompting them to track their foods. In adaptive decision rules, the rules will also evaluate recent goal progress and weight change, such that a participant who regularly tracks their food intake and is losing weight would not receive this reminder message; instead the system would choose a message about a different behavior. However, these messages would be delivered if this pattern repeated, or if the weight trajectory was no longer favorable.

Message Choice. Participants will be randomly assigned to choice or no choice, which differ in two ways. First, all messages have a like/dislike rating. In the choice group, participant like/dislike ratings change the probability that they will receive similar message types in the future based on their ratings. As described above, all messages were designed and coded based on the message type (feedback on outcome, feedback with a data point, directive action, nondirective action, encouragement/motivation, or social comparison). When a participant likes or dislikes a message, those data are used to increase or decrease, respectively, the probability that they will receive a similar message type for that given behavior in the future. In the no choice group all message types are equally likely to be chosen. Secondly, participants in the choice group are given more options and autonomy when completing the interactive action planning tools. In the no choice group, when an action planning tool is displayed on the Home page, the participant can select the 'Take Action' button, at which point they can view one available action planning activity. In the choice group, participants have two actions available, 'Take Action' or 'No Thanks.' If they select 'No Thanks,' the app does not provide them with any activity or messaging. If they select 'Take Action,' they are given two action planning activity options and can choose between them.

Study Population

Individuals will be eligible if they meet the following criteria: age 18-39; body mass index (BMI) of 25-45 kg/m^2; English-speaking and writing; own a smartphone (iOS or Android) with a data and texting plan; and willing to be randomized to any levels of the factors. Exclusion criteria include being currently pregnant, pregnant within the past 6 months, or planning to become pregnant within the next 6 months; type 1 diabetes or receiving medical treatment for type 2 diabetes; a heart condition, chest pain, or other health problems that influence the ability to follow physical activity recommendations; lost 10 pounds or more in the past 6 months, history of weight loss surgery, or currently taking weight loss medications; report a past diagnosis of or receiving treatment for an eating disorder; hospitalization for depression or another psychiatric disorder in the past 12 months or history of bipolar or other psychotic disorder; another member of the household is a participant or staff member on this trial; currently participating in another weight loss, nutrition, or physical activity study or program. Individuals that reported joint problems, some prescription medications, or current treatment for hypertension or hyperlipidemia will be required to obtain written physician consent to participate (Appendix).

The trial is registered on clinicaltrials.gov (NCT04922216) and was approved by the Institutional Review Board at the University of North Carolina at Chapel Hill on July 26, 2022.

3. STUDY PROCEDURES

Data Collection

All study participants will complete objective weight measurements, two dietary recalls, and self-administered online surveys at baseline and 6 months (post-intervention). At 3 months, only psychosocial measures and medical events will be collected via online survey and telephone. Participants will receive $50, $25, and $75 for completing baseline, 3, and 6-month assessments, respectively. Online surveys will include measures of theoretical mediators, other psychosocial constructs, and process measures. We will send emails and texts prompting participants to complete assessments, with follow-up emails and phone calls to non-respondents, as necessary. Measures and timing are described below.

Measures

Where possible, we are measuring constructs using validated and recommended scales from the ADOPT Core Measures Project [58-60] (indicated below with ACM), an NIH-supported initiative to permit collaboration, pooling across obesity interventions, and to search for predictors of heterogeneity in response to treatment.

Primary outcome (Weight)*:* Weight will be objectively measured at the participant's home at all time points. We will instruct participants to weigh themselves in light clothing, without shoes, on the wireless scales at each assessment time point. The participant will weigh themselves 3 times in succession to indicate the assessment weight on the date requested. A subset of participants local to our facilities (up to n=40) will be invited at baseline to complete in-person weight measurements to further validate smart scale weights with clinic weight.

Other Anthropometric and Key Behavioral Mediators (collected at baseline, 3 months, and 6 months)

- *Height* (Baseline only). Participants will self-report height using an item from the Behavioral Risk Factor Surveillance System (BRFSS), [61] adapted for the Health Information and National Trends Survey. [62]
- *Dietary Intake* (Baseline, 6 months). Changes in dietary intake will be assessed using the NCIs Automated Self-Administered 24-hour Recall (ASA-24). Participants will complete two self-reported recalls; one weekday and one weekend day. The 24 recall is a validated method of measuring diet. [63] Using two recalls permits adjustment of estimates for intraindividual variation and is superior to administering one recall.

- *Self-reported Physical Activity* (ACM). Physical activity will be assessed with the Paffenbarger Physical Activity Questionnaire (PAQ) [56] which assesses leisure-time activity. The PAQ provides an estimate of minutes per week of moderate-to-vigorous intensity, and calories/week of light (5 kcal/min), medium (7.5 kcal/min), and high (10 kcal/min) intensity activities. PAQ changes have been predictive of weight change.
- *Sedentary Activity* (ACM). Given the increasing recognition of the effects of sedentary activity independent of physical activity, we will use the Sedentary Behavior Questionnaire from CARDIA/EARLY trials. [64]

Proposed Theoretical Mediators (collected at baseline, 3, and 6 months)

- *Autonomy Support (3 and 6 months only)*. We will adapt items from the Health Care Climate Questionnaire, which is a measure of how the participant perceives support from a healthcare provider, to measure autonomy support from the program.[65] The scale includes 15 items rated on a scale of 1 (*strongly disagree*) to 7 (*strongly agree*) (e.g., "I feel that [the program] has provided me choices and options.")
- *Competence for Diet and Physical Activity* (ACM). The Perceived Competence for Scale includes 4 items that measure perceived competence for diet and 4 items for physical activity.[66] Items are rated on a 7-point of 1 (*not at all true*) to 7 (*very true*) (e.g., "I feel confident in my ability to maintain a healthy diet.")
- *Relatedness (3 and 6 months only)*. Relatedness will be measured with 3 items adapted from the 8-item Relatedness subscale of the Basic Need Satisfaction at Work Scale.[49,67] Examples include "The messages demonstrate caring about me as a person" and are scored on a Likert scale from 1 (*strongly disagree*) to 7 (*strongly agree*).
- *Message Relevance (3 and 6 months only)*. Perceived message relevance will be measured with two items used in our previous work [68] and adapted from previous studies of tailored messages. [45,69] Participants were asked to rate how strongly they disagree or agree with the statements about messages being "written personally for me" and "applied to my life." Responses are on a 5-point scale from 1 (*strongly disagree*) to 5 (*strongly agree*).
- *Treatment Self-Regulation* (ACM). The Treatment Self-Regulation Questionnaire (TSRQ) will be used to assess autonomous and controlled motivation for making changes in diet (15 items) and physical activity (15 items). [70] Examples item: "Because I feel that I want to take responsibility for my own health" answered on a scale of 1 (*not at all true*) to 7 (*very true*).

Other Psychosocial and Behavioral Measures (collected at baseline, 3, and 6 months)

- *Quality of Life.* All participants will complete the CDC Health-Related Quality of Life measure (referred to as "Healthy Days Measures"). [136] This 4-item questionnaire reliable, valid, and responsive to change.
- *Depression* (ACM). *D*epressive symptoms have been associated with changes in weight, diet, and physical activity and will be assessed with the Center for Epidemiological Studies Depression Scale (CES-D). [137]
- *Weight Control Strategies* (ACM). Participants will be asked about frequency of use of 20 weight control strategies such as "ate only when I was hungry" with a scale used in the EARLY trials. [138]
- *Hunger, Restraint, Disinhibition.* The Three Factor Eating Questionnaire (TFEQ) is a 51-item self-report instrument assessing three factors of dietary restraint, disinhibition and hunger. [139]
- *Perceived Stress* (ACM). The Perceived Stress Scale is a 10-item measure that assesses stressful situations in the last month.[140]
- *Binge Eating* (ACM). Participants will complete the revised Questionnaire on Eating and Weight Patterns (QEWP-5) to assess frequency of binge eating, loss of control, and compensatory behaviors. [141]

Process and Adherence Measures (collected over 6 months)

- *Dietary Monitoring.* Objective self-monitoring of dietary intake will be assessed using data from the smartphone application food log (for simplified conditions) and Fitbit food log (for calorie conditions).
- *PA monitoring.* Objective self-monitoring of PA will be assessed via the Fitbit tracker data. Using the Fitbit API, the study will collect data on the number of days the Fitbit was worn (steps $\geq$ 500/day). [95]
- *Self-weighing.* Self-weighing habits will be objectively measured via the smart scales to calculate percent of days weighed, and average self-weighing days per week.

- *Other Engagement Measures.* We will examine app views as mean, median, and monthly percentage, to account for the skewing of app data. App views are similar to website logins, which have been associated with weight loss.[48,50,82,83] We will examine number of lessons accessed and feedback messages viewed.
- *Program Acceptability and Satisfaction.* Participants will complete a post-treatment program evaluation about intervention perceptions and experiences, using questions from our previous studies.

Other Measures (collected at baseline, 3, and 6 months, unless otherwise indicated)

- *Medical events* and symptoms will be collected at 3 and 6 months in a scheduled telephone call. Responses will be reviewed to determine if a Serious Adverse Events form is required.
- *Demographics.* At baseline, standard demographic information will be collected
- *Medical history, Medication use.* Self-report of both prescription and non-prescription medications.
- *Smoking, alcohol use*. Smoking and alcohol use will be assessed at each time point.

4. STATISTICAL CONSIDERATIONS

Sample Size and Power

We defined a 1-kg weight change as more than a minimal effect of any given component on overall weight loss. We estimated standard deviation based on a prior cell phone-delivered intervention for YAs that found a standard deviation of 6.9 kg for a weight change difference of 2.2 kg between groups;[9] therefore, we conservatively estimated a standard deviation of 4 times our 1-kg weight change estimate. Assuming a type 1 error rate of 5% and a standard deviation of 4 kg, reaching 80% power would require 505 total participants. Assuming a 17% attrition rate at 6 months based on our previous studies with YAs and rounding up to a whole number per condition results in a total of 608 participants needed. Thus, each of the two levels of each component will have 304 randomly assigned participants, with 19 participants in each of the 32 conditions.

Statistical Analysis

Aim 1 Analysis. To test for differences in weight change across time by the five intervention components, we will use mixed effects models on an intention-to-treat data set, with effects modeled as component × time interactions and the 6-month outcome as the primary endpoint. We will run separate models for (a) mean weight change and (b) the proportion of participants achieving 5% weight loss, the latter constituting a second-level decision-making criterion in cases where effects for mean weight change are equal. All higher-order interactions between components will also be modeled (e.g., adaptive physical activity goals × message choice × time interaction). The ability to test all higher-order interactions between intervention components, without reducing power, is a key advantage of the factorial experiment, as this is not possible in a traditional multi-component RCT. We will be using effect (-1,1) coding rather than dummy (0,1) coding, which keeps any covariances among main effects and interactions to a minimum. Once we have identified important effects in the initial set of models, we will establish parsimonious prediction models in which coefficients that do not contribute significantly to mean weight loss (or proportion achieving 5% weight loss) will be set to zero.

Aim 2 Analysis. In Aim 2 we will conduct mediation analyses to test the relationships between the intervention components and hypothesized mediators, thus refining the underlying conceptual model. In contrast to mediation analyses conducted on data from an RCT, we will be able to fit models specifying which intervention component is mediated by each hypothesized mediator. For example, while we hypothesize that autonomy will mediate the relationship between the intervention component, message choice, and weight, it is possible that other mediators—e.g., relatedness—will explain this relationship. It is also possible that autonomy will mediate the relationship between other intervention components (e.g., decision points for message timing) and weight. This step will provide important information for improving our understanding of how the intervention components work and for revising our conceptual model. Mediators to be tested include the proximal theoretical

mediators of component effects (self-regulation, competence, relatedness, relevance, and autonomy) and the more distal behavioral mediators (daily self-weighing, dietary intake, and physical activity). We will test the mediation effects for significance using the general approach described in MacKinnon.

Aim 3 Exploratory Analyses. In Aim 3 we will conduct moderation analyses to test differential response to intervention components. The primary moderator to be tested is intervention engagement, which will include percentage of messages viewed, number of days of diet self-monitoring, number of days of physical activity tracking, number of days of self-weighing, and lessons viewed. Exploratory moderators will include gender, race and ethnicity, and initial BMI status. Results will provide important information for future research aimed at developing mobile interventions tailored and optimized for differing levels of engagement and subgroup membership.

Handling Missing Data

While every effort will be made to avoid missing data with proper tracking efforts, we do expect some missing data due to attrition and nonresponse. Under the MAR assumption, we will use the suite of multiple imputation tools in Stata (v.15 or greater) to (1) conduct a detailed analysis of the missing data, beginning with an examination of the number and proportion of missing values among the variables of interest; (2) identify potential auxiliary variables that are either correlated with a missing variable/(s) or are believed to be associated with missingness; (3) use MI IMPUTE, with at least 20 imputations, to derive the imputed data set; (4) rerun analyses on the imputed data set; and (5) verify the stability of MAR inference by conducting sensitivity analyses which modify the imputation step to accommodate potentially nonignorable missing-data mechanisms. This process will be followed separately for each estimation model (i.e., mean weight change from baseline to 6 months, proportion achieving 5% weight loss).

Strengths and Limitations.

One limitation is the potential for contamination, as YAs may be connected to others via social media and learn about the study from common sources. This is mitigated by the fact that the intervention components of interest are uniquely tailored to individuals and the intervention is delivered via individual smartphones. Although participants will be limited to those with smartphone and internet access, prevalence of smartphone use is highest among young adults (96% of 18-29-year-olds, 92% of 30-49-year-olds), and the app will be available to iPhone and Android users, thereby extending generalizability. While our study requires extensive programming, our preliminary work, in which we have created complex algorithms and decision rules for multiple libraries of intervention messages (400+ for Nudge pilot, 1000+ for IMPACT study tailored feedback), demonstrates our ability to create infrastructure and content for this project. Our proposal has several strengths that outweigh its limitations. It targets an understudied population of YAs at risk for weight gain. Our work advances the science of JITAI development–answering key questions about adaptation and tailoring–and is guided by a conceptual model, which will further our understanding of how JITAI components and mobile interventions may operate via key theoretical mediators. We use ADOPT Core Measures to enable collaboration, data pooling, and identification of predictors of heterogeneity in treatment response. Moreover, our delivery via a smartphone app increases potential for widespread reach and adoption around the country. Our study builds upon our prior work focused on YAs and will be one of the first to systematically optimize a fully automated remotely delivered JITAI. Our work will elucidate appropriate and feasible mobile intervention strategies among YAs and holds promise for promoting weight loss among YAs that may decrease their risks for morbidity and mortality.

5. SAFETY MANAGEMENT

Data safety management in this trial is intended to achieve 4 objectives: 1) to minimize the occurrence of adverse effects, especially those related to the intervention; 2) to effectively manage adverse events as they relate to the study; 3) to identify when the interventions should be suspended because of concerns for

participant safety; and 4) to determine when interventions may be resumed after having been suspended. The Principal Investigator (Tate) will have primary responsibility for the safety of participants as it relates to the study protocol, which must be approved by the UNC IRB prior to study initiation. In addition, the North Carolina Translational and Clinical Sciences (TraCS) Institute Data Safety Monitoring Board (DSMB) is responsible for reviewing data from clinical trials approved by the UNC Biomedical IRB. Because the risks to subjects participating in this phase of this study are expected to be low, we do not anticipate the need for a formal Data Safety Monitoring Board. The research team will provide continuous monitoring of participant safety and periodic reporting to the IRB as required, including any Unanticipated Problems/Severe Adverse Events that may have occurred during the study. If risk or complexity is significant, the UNC Office of Human Research Ethics may require additional reporting or alternative data and safety monitoring. Data safety and monitoring activities continue until all participants have completed treatment and until all participants have been followed to the point at which study related adverse events would likely no longer be encountered.

Participant Safety

The risks to human subjects in this study, including psychological and physical risks, are judged to be minimal. The anticipated benefits are great, insofar as the results will be used to determine if mobile-delivered behavior change strategies are effective for obesity risk reduction in a sample of young adults.

Psychological Risks: We expect risk of harm, including psychosocial and emotional distress or breach of confidentiality, as a result of this study to be rare or infrequent. Most communication during the intervention period will take place via telephone, the smartphone app, direct emails, or text messages—to deliver intervention components, conduct assessments, or remind participants to complete questionnaires. We do not anticipate any risks of harm as a result of these communications. As part of the intervention, participants may be asked about personal factors related to their diet, physical activity, and weight. Participants are not required to share this information and can elect not to share sensitive and confidential information with the study. Participants will be encouraged to contact the Principal Investigator if they feel they have incurred any emotional distress as a result of study participation. As this is a voluntary study, a participant is free to exit at any point if discomfort should occur. Individuals scoring >16 on the Center for Epidemiological Studies Depression Scale (CES-D) at baseline, 3-, or 6-month assessments (indicating levels of depressive symptoms that might benefit from follow up with a health care provider) will be given a letter explaining the survey and providing information and referral to resources (Appendix).

Physical Risks: There are no major physical risks associated with the weight loss intervention or data collection. There may be some risk to increasing physical activity, including, but not limited to, injuries to the muscles, ligaments, tendons and joints of the body. Other risks include abnormal blood pressure, fainting, dizziness, disorders of heart rhythm, exacerbation of exercise-induced asthma symptoms, and very rare instances of heart attack, stroke, or even death. Although increasing physical activity can have great benefits, participants may also experience some general fatigue, sore muscles or joints from exercising. Because several studies indicate that walking is the preferred exercise type for most adult populations, the study focuses on encouraging moderate-intensity walking. To help ensure safety, the study will follow guidelines and safety recommendations for physical activity set forth by the American College of Sports Medicine. Educational materials during the course of the intervention will educate participants on exercise safety and inform them of precautions in starting an exercise program and how to manage increasing amounts of exercise. Messages will encourage participants to start at a reasonable frequency and intensity of exercise based on their current level and to increase their exercise gradually. The informed consent will also clearly communicate the potential physical risks related to starting an exercise program and increasing physical activity. Participation is fully voluntary, and we will ask participants to report any problems to the study researchers. There is a rare, but possible, risk of extreme dieting in this intervention. However, the intervention recommendations are geared toward simplified dietary changes and should be of very low risk. The greatest concerns are that participants may engage in unsafe dietary practices, lose weight more quickly or to lower levels than recommended, or develop untoward psychological

reactions. However, prior weight loss studies indicate that participants in these programs increase their use of healthy weight control practices and decrease their use of unhealthy practices.

Risk to privacy and/or confidentiality. We expect a breach of confidentiality to be rare or infrequent. Most communication during the study period will take place via telephone, direct emails, text messages, or through the smartphone app—either to deliver questions, conduct assessments, or remind participants to complete questionnaires. We do not anticipate any risks of harm as a result of these communications; however, there is always a possibility that their scale data, tracker data, or activity in the app will be intercepted.

Adequacy of Protection Against Risks

a. Informed Consent and Assent

Recruitment and Informed Consent: Several different efforts will be used to recruit potential participants and obtain informed consent from those eligible participants. The research team is responsible for assuring that the UNC IRB has approved the study protocol and has reviewed and approved the informed consent document. Written approval must be obtained from the IRB before the study can begin. Once an individual has been deemed potentially eligible to participate through online and telephone screening, study staff will provide more study details and describe the concept of random assignment, the 32 study conditions, and assessment procedures over the telephone. Individuals who remain interested will receive an email directing them to a unique and secure REDCap link to an online informed consent. After clicking on the link, they will be directed through a series of screens that present the informed consent document. The online informed consent records will be retained, and recruitment of participants will be done by adhering to HIPAA regulations. Accrual reports will list enrolled participants and excluded participants throughout the stages of the research. This routine monitoring allows for early identification and resolution of potential problems during the recruitment phase. The anticipated recruitment duration is 30 months. All key personnel have attended the required courses on human subject protection and HIPAA regulations, and certificates of IRB training completion are on file with the University of North Carolina.

b. Protections Against Risk

Protections against Psychological Risks: As noted above, participants are not required to share this information and can elect not to share sensitive and confidential information with the study. Participants will be encouraged to contact the Principal Investigator if they feel they have incurred any emotional distress as a result of study participation. As this is a voluntary study, a participant is free to exit at any point if discomfort should occur. Individuals scoring >16 on the Center for Epidemiological Studies Depression Scale (CES-D) at baseline, 3- or 6-month assessments (indicating levels of depressive symptoms that might benefit from follow up with a health care provider) will be given a letter explaining the survey and providing information and referral to resources (Appendix).

Protections against Physical Risks: To ensure medical readiness to begin physical activity, participants will complete a physical activity readiness questionnaire (PAR-Q). The PAR-Q assesses for the following medical conditions: heart problems, chest pains, faintness or dizzy spells, high blood pressure, bone or joint problems such as arthritis that has been or could be aggravated by exercise, prescription medication use, and other medical reasons why exercise would not be advisable. Participants endorsing yes to any items 1-4 on the PAR-Q (experience of heart problems, frequent chest pains, faintness or dizziness, bone or joint problems) will be excluded from the study. We also will monitor any major musculoskeletal problems that develop during the intervention (e.g. broken bones) using a medical events questionnaire at 3 and 6 months and will determine whether these appear related to our study. Participants who develop musculoskeletal problems or other health problems that may affect safe participation will be instructed to stop exercising until the problem resolves and their physician approves resumption of physical activity.

All participants will be advised about safe weight loss practices including dietary change and increasing physical activity at their initial study visit. Participants will be advised to gradually increase their physical activity and to

use walking as a primary form of activity and will be taught that the appropriate rate of weight loss is 1 to 2 pounds per week. In addition, we will carefully monitor changes in weight during our trial. We will collect information at each assessment timepoint on hospitalizations for any psychiatric problem, including depression and eating disorders. We will track weight changes using smart scale weights and will identify any individual who loses more than 20% of their body weight, has a BMI ≤ 18.5 kg/m2 at any point during the program, or loses more than 15 pounds in any month during the trial. We will have a telephone call with these participants within 2 weeks, discuss our concerns with them, and make referrals if appropriate. If there is no improvement in weight status, the participant will be unable to continue to participate in the intervention.

Protections to Ensure Confidentiality of Participants: All data records related to a participant's involvement in this research study will be stored in a locked file cabinet and/or in encrypted files on servers that adhere to the University policy on storage and transmission of sensitive data. Participant identity on these records will be indicated by an ID number, and the information linking these numbers with participant identity will be kept separate from the research records. In addition, all research databases will have password-controlled access, and this will be controlled by critical staff. Participants will be encouraged to contact the Principal Investigators if they feel they have incurred any emotional distress as a result of study participation. As this is a voluntary study, a participant is free to exit at any point if discomfort should occur.

The Fitbit API will be used to access data from the participant's scale, activity tracker, and Fitbit app. During the consent process, participants will consent for the data from their specific device IDs to be accessed by our study. They will need to enter their Fitbit username and password during the app setup process to allow Fitbit data to be sent to our study server. The study smartphone app uses a Standard OAuth 2.0 security model for logging in to Fitbit. The study uses temporary access tokens that are stored only on the user's device and is not stored on our servers. Therefore, Fitbit usernames and passwords will not be stored in any way with this study. Instead, the weight and tracker data will be connected to participants by their unique study ID that they will also enter during the app setup process. Data are transmitted on secure servers that adhere to University policy on Sensitive Data. The risk of breach of confidentiality over the Fitbit websites will be partly subject to each individual's comfort in sharing information in their individual profile. To further minimize the risk of breach of confidentiality, all participant activities on the Fitbit websites will be voluntary. Consent forms will also clearly communicate the risk of this type of disclosure to participants.

Removal of Patients from Protocol**.** Participants will be removed from the protocol should they experience greater than minimal risk as detailed above. Participants will be reminded that their participation is voluntary and that they may withdraw from the study at any time without consequence by contacting the Principal Investigator. In addition, we expect that pregnancies will occur. We will stop all intervention activities for anyone who becomes pregnant.

Potential Benefits of the Proposed Research to Research Participants and Others

Intervention participants are expected to improve dietary behaviors, physical activity, and may lose modest to clinically significant amounts of weight, ultimately reducing their risk of developing type 2 diabetes, cardiovascular disease, and other chronic diseases. In addition, the results of this study could be used to develop an optimized weight loss intervention to be tested in a similar population and, if effective, could be generalizable to a larger population of young adults. If successful, an automated program that uses a smartphone and other relatively low-cost digital technologies that is optimized for effective treatment components could be disseminated in a larger-scale program, thus benefiting a greater number of young adults.

Importance of the Knowledge to be Gained

There are currently few trials that have used a strictly mobile weight loss intervention that have resulted in clinically significant weight loss in young adults. Should this trial prove effective, it will have great public health relevance, as young adulthood is a critical period for excessive weight gain that is associated with future

comorbidities, including type 2 diabetes, hypertension, and cardiovascular disease. Results from this trial have the potential to lead a new generation of scalable, low-cost technology-based intervention strategies that could significantly enhance the adoption of healthy behaviors and prevent or treat overweight and obesity. The risks to study participants are minimal, whereas the potential benefits for improved health are significant.

6. DATA COLLECTION AND MANAGEMENT

The rigorous system used for participant tracking, data collection, management, and quality control procedures for our previous projects (SNAP: U01HL090864; IMPACT: R01CA204965) will be modified for this study. All data will be entered using the REDCap computer-assisted program that has built-in validation checks for range, data type, and completeness. All measurements will undergo consistency and outlier checks, compared with raw data, and edited as required. REDCap includes detailed audit logs that document any database changes, and we will document protocols for cleaning data.

Participants will provide physical data (objective weight and self-reported height), self-reported questionnaire data online, and self-reported physical activity data over the telephone specifically for research purposes. All self-report online data will be collected using secure REDCap surveys. A subset of participants local to the UNC clinic will have objective height and weight data taken in the clinic in order to validate home scale weights. Food log data from the study smartphone application will be transmitted to study servers, and weight and activity data from Fitbit be will transmitted to study servers. Identifiable information collected in online surveys will include the participant's name, address, phone numbers, and date of birth.

Risk to privacy and/or confidentiality

We expect a breach of confidentiality to be rare or infrequent. Most communication during the study period will take place via telephone, direct emails, text messages, or through the smartphone app—either to deliver questions, conduct assessments, or remind participants to complete questionnaires. We do not anticipate any risks of harm as a result of these communications; however, there is always a possibility that their scale data, tracker data, or activity in the app will be intercepted.

7. RECRUITMENT, CONSENT, AND RETENTION STRATEGY

Recruitment

Young adults will be recruited using a multi-pronged approach including: 1) postings on social media including Facebook, Instagram, and Twitter; 2) emails through listservs comprised of the target audience; 3) advertisements on select media accessed by young adults, including television, radio, Spotify.

Using Facebook, Instagram, and other social media to recruit has been shown to be an efficient and cost-effective manner of recruiting diverse participant samples, both in the literature and in our prior research, including our pilot study. We will purchase advertisements and "Boosted Posts" with recruitment information about the study that will link to the recruitment website and online screening survey. The ads and posts will be targeted specifically to reach adults between the ages of 18 and 39 that live in the United States and can also be targeted specifically to reach only men and minorities, if needed. We have used similar strategies to recruit 599 young adults in the Chapel Hill, NC and Providence, RI area for a weight gain prevention study (NIH R01HL090864) as well as recruitment of participants across a larger geographic area (U.S.) for a mobile-delivered physical activity promotion trial among 280 young adult cancer survivors (NIH R01CA204965).

All recruitment efforts will direct participants to a study website with a more detailed description of the research study and FAQs about participating in research. Interested individuals will click through to a REDCap web screening survey to determine initial eligibility. Those who are preliminarily eligible will be contacted by trained study staff and will undergo additional phone screening. Following an approach we have used in the past, eligible and interested individuals will receive an email directing them to a unique REDCap link to an online informed consent. After providing consent, participants will be instructed on procedures for 1) completing one weekday and one weekend self-reported 24-hour dietary recall, 2) completing baseline online questionnaires, and 3) completing their baseline weight measurement using a Bluetooth-connected scale. The Fitbit scale and activity tracker will be mailed to the participant. After completion of baseline assessments, the participant will be randomized to one level of each of the 5 factors, or one of the 32 conditions (Table 1). The participant will be scheduled for a one-on-one telephone/videochat session during which they will be informed of condition assignments, assisted with downloading of the study smartphone app, and questions about getting started will be answered.

Inclusion of Women and Minorities

All individuals will be eligible for enrollment independent of sex/gender and race/ethnicity. As women are generally over-represented in weight control studies, we do not anticipate having inadequate representation by women. To be able to test for differences in the treatment effect by sex/gender, we may need to specifically target recruitment of men. Our research group has had success in recruiting higher percentages of men by using pictures of men in Facebook/social media advertisements, and by using terms such as “wellness” and “health” instead of “weight loss.” Therefore, we will use these strategies to increase our recruitment of men if we are under our targets.

We will specifically aim to recruit participants representing a wide variety of racial/ethnic backgrounds. In past studies, we have successfully recruited minority populations through direct mailings to targeted heads of households, identification of minority groups through social media platforms and community groups, and tailored recruitment materials. In the pilot Nudge study (N = 52), we recruited a sample, almost entirely through Facebook, that was 34.6% minority (17.3% Black or African American, 7.7% multiple races, 5.8% Asian, 3.8% other; 5.8% Hispanic or Latino). For the current trial we will aim to recruit at least 30% non-white participants, with specific emphasis on black and Hispanic populations, given the burden of overweight in these groups. Because we will be opening recruitment to eligible individuals across the United States, we anticipate that with a targeted recruitment plan we will be able to meet goals for inclusion of minorities.

Initially, no groups will be excluded or limited based on sex/gender, race, and or/ethnicity. However, if the enrollment targets for minority participants are proceeding slower than expected compared to white participants, we may limit enrollment of white participants in order to raise the percentage of minority participants closer to our targets.

Retention

Participant retention strategies have been used effectively in our other studies. A systematic protocol will be followed to minimize dropouts. Top priority will be for assessment visits. At baseline, names and addresses of several friends and family members who can be contacted are obtained for use if we lose touch with the participant. The study provides incentives for completing the follow-up assessments to offset any time costs and to promote retention ($50 for completing the baseline assessment, $25 for the abbreviated 3-month assessment, and $75 for completing the 6-month assessment). For each assessment visit, we will send participants an email that will include a link to online questionnaires with an expected completion date as well as a scheduled date and time to step on their scale. Missed weights and/or questionnaires will be immediately followed up by phone and rescheduled.

In addition to our assessment retention protocol, participants who complete all three assessments will be able to keep their Fitbit and scale at the end of the study, which we will believe will also encourage retention to assessment measures. In addition, regardless of condition assignments, the study smartphone application is designed to enhance engagement by sending notifications one or several times per day, including reminders to use the app or self-monitor, among other behavior change techniques. This method of prompting engagement will also serve to remind participants of their participation in the study, and thus will serve as cues for completing study assessments. We will review participant engagement weekly and will use structured protocols for promoting engagement with the intention of also promoting retention.

8. PLANS FOR PUBLICATION

As Principal Investigator of this grant application and clinical trial, Dr. Tate will comply with the clinical trial information dissemination expectations of the NIH policy to register and submit summary results at ClinicalTrials.gov. Karen Hatley, Project Manager, will be responsible for handling ClinicalTrials.gov requirements for this project under the Dr. Tate's oversight. Consistent with the terms and conditions of NIH funding, we will ensure the submission and updating of registration and results information for this clinical trial in the timeframes established by the Final Rule. Registration and results reporting in ClinicalTrials.gov will be completed within the following timeframes:

- Registration of the trial at ClinicalTrials.gov no later than 21 days after enrolling the first participant
- All submitted information will be updated at least once a year.
- Any apparent errors, deficiencies, and/or inconsistencies identified by NIH as part of the quality control review process and any other errors identified will be addressed by the responsible party.
- Corrections to submitted information will be made within 15 days for registration information and 25 days for results information.
- Trial results will be submitted no later than one year after the primary completion date.

Informed Consent Documents for the clinical trial will include a specific statement relating to posting of clinical trial information at ClinicalTrials.gov. The UNC IRB has template language explaining that the study will be posted on ClinicalTrials.gov that investigators are required to include in the consent document for the trial.

As PI, Dr. Tate will work closely with the UNC-CH Office of Clinical Trials (OCT), which serves as the university's internal PRS. The OCT has responsibility for ensuring that clinical trial registration and reporting occurs in compliance with NIH policies. The OCT has support staff to facilitate the process of registration and results reporting to ClinicalTrials.gov, and our team will work closely with them to register this trial and to submit summary results to the website in a timely manner, in keeping within the required timeframes. Once data collection is complete, our research team will work to prepare and submit trial results no later than one year after the primary completion date.

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APPENDIX

Table 1. Experimental conditions in the 2^5 factorial trial

Condition	Core	Diet Self-Monitoring Approach	Adaptive Activity Goals	Decision Points for Message Timing	Decision Rules for Message Content	Message Choice
1	Yes	Standard	Daily	Fixed	Standard	No
2	Yes	Standard	Daily	Fixed	Standard	Yes
3	Yes	Standard	Daily	Fixed	Adaptive	No
4	Yes	Standard	Daily	Fixed	Adaptive	Yes
5	Yes	Standard	Daily	Adaptive	Standard	No
6	Yes	Standard	Daily	Adaptive	Standard	Yes
7	Yes	Standard	Daily	Adaptive	Adaptive	No
8	Yes	Standard	Daily	Adaptive	Adaptive	Yes
9	Yes	Standard	Weekly	Fixed	Standard	No
10	Yes	Standard	Weekly	Fixed	Standard	Yes
11	Yes	Standard	Weekly	Fixed	Adaptive	No
12	Yes	Standard	Weekly	Fixed	Adaptive	Yes
13	Yes	Standard	Weekly	Adaptive	Standard	No
14	Yes	Standard	Weekly	Adaptive	Standard	Yes
15	Yes	Standard	Weekly	Adaptive	Adaptive	No
16	Yes	Standard	Weekly	Adaptive	Adaptive	Yes
17	Yes	Simplified	Daily	Fixed	Standard	No
18	Yes	Simplified	Daily	Fixed	Standard	Yes
19	Yes	Simplified	Daily	Fixed	Adaptive	No
20	Yes	Simplified	Daily	Fixed	Adaptive	Yes
21	Yes	Simplified	Daily	Adaptive	Standard	No
22	Yes	Simplified	Daily	Adaptive	Standard	Yes
23	Yes	Simplified	Daily	Adaptive	Adaptive	No
24	Yes	Simplified	Daily	Adaptive	Adaptive	Yes
25	Yes	Simplified	Weekly	Fixed	Standard	No
26	Yes	Simplified	Weekly	Fixed	Standard	Yes
27	Yes	Simplified	Weekly	Fixed	Adaptive	No
28	Yes	Simplified	Weekly	Fixed	Adaptive	Yes
29	Yes	Simplified	Weekly	Adaptive	Standard	No
30	Yes	Simplified	Weekly	Adaptive	Standard	Yes
31	Yes	Simplified	Weekly	Adaptive	Adaptive	No
32	Yes	Simplified	Weekly	Adaptive	Adaptive	Yes

THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

Weight Research

1700 Martin Luther King Jr. Blvd, Room 136 T 919.966.5852
Chapel Hill, NC 27599-7294 F 919.966.7827

Date:_____

Dear ,

Thank you for being a participant in the AGILE study! We take seriously our obligation to protect the health and confidentiality of all participants in our research study. You are receiving this letter because the responses you gave to questions on the Moods Questionnaire indicate that you may be feeling down and if this feeling lasts for any length of time it may indicate symptoms of depression. These survey results provide important information about symptoms, but only your physician can diagnose actual depression. Consider talking with your doctor about your symptoms, or use the resources below to get more information or identify a qualified provider. These results do not prevent you from participating in AGILE, but we want to make you aware of these results so that you can make an informed decision about seeing a physician or other provider to get checked.

If you are interested in learning more about the symptoms, causes and/or treatment of depression, you may find it helpful to take a look at the following online resources:

- The National Institute of Mental Health has a page dedicated to the topic of depression (http://www.nimh.nih.gov/health/topics/depression/index.shtml). On this page, you can find more information about depression, signs and symptoms of depression, information about treatment, and how to locate service providers near you.
- NC Health Info (https://www.nchealthinfo.org/) is a joint project of UNC-Chapel Hill and the National Library of Medicine that allows users to find local health resources in North Carolina. In the upper right box labeled Quick Start, you will find pull-down menus for both "Topic" and "Location." If you choose "Depression" from the Topic menu and either your home county or city, you will be shown a list of websites that specifically address mental health providers that work in your area.
- The North Carolina Psychologists Association's website (http://www.ncpsychology.org/) has information available under the "General Public" tab. In this area, you will find a list of Frequently Asked Questions along with a tool that can help you find a licensed psychologist near you.
- Mental Health America offers a screening tool (https://screening.mhanational.org/screening-tools/depression/) whose results you can share with a health care provider. On this site, you can find information about depression and locate some local resources that can provide referrals to professionals, services or support groups in your area.
- Contact your Human Resources Director or Benefits Coordinator at your workplace to inquire about a depression-related Employee Assistance Program.

If you have any questions, please email the AGILE research team at agilestudy@unc.edu or call us at (919) 966-5852, and we will return your call within 24 hours during regular business days.

Sincerely,

Deborah Tate, PhD
Principal Investigator

PHYSICIAN CONSENT TO PARTICIPATE IN A DIET AND EXERCISE PROGRAM AT UNC-CHAPEL HILL

TO:

Physician's Name

Address

City **State** **Zip**

( )
Telephone Number

RETURN TO:

Karen Hatley, MPH, RD
UNC Weight Research Program
Lineberger Comprehensive Cancer Center
1700 Martin Luther King Jr. Blvd., CB 7294
Chapel Hill, NC 27514

Telephone: (919) 966-5853
FAX: (919) 843-6663
Email: agilestudy@unc.edu

Your patient _____ has asked to participate in a weight loss program conducted by the University of North Carolina at Chapel Hill that is specifically designed for young adults to help them adopt healthier eating and activity habits and learn effective ways to manage their weight.

The 6-month program is delivered using a study smartphone app and digital health tools. All participants will receive a standard program using the study smartphone app, which will have weekly lessons and feedback on progress. Each participant will receive a combination of tools to help them keep track of their diet and meet diet and physical activity goals. The combination of tools will vary the method of dietary monitoring, physical activity goals, and personalization of study messages in the app for each study participant.

All participants will receive the following intervention:

1. A diet program that will reduce calories and involves dietary monitoring on a smartphone app.
2. A physical activity program that will be primarily home-based. The exercise will gradually be progressed to 150 – 300 minutes per week (depending on starting activity levels) with activities akin to brisk walking.
3. Behavioral modification techniques for changing eating and exercise behaviors.
4. Digital tools including a smartphone app, Bluetooth-connected digital scale, and Fitbit activity tracker.

Please indicate below if this program seems appropriate for your patient or if you see any contraindications for his/her participation (*please check the appropriate box below)*.

☐ I know of no contraindications to this patient participating in any of the above components of the program.

☐ I feel that this program would not be appropriate for this patient for the following reason(s):

_____

_____

_____
Signature of Physician

Inclusion Criteria:

1. Age 18-39.
2. Body Mass Index (BMI) of 25-45 kg/m^2.
3. English-speaking, reading, and writing.
4. Own a smartphone with a data and texting plan.
5. Willing to wear a Fitbit activity tracker and to be randomized to any levels of the factors.

Exclusion Criteria:

1. Type 1 diabetes or currently receiving medical treatment for Type 2 diabetes.
2. Other health problems which may influence the ability to walk for physical activity or be associated with unintentional weight change, including cancer treatment within the past 5 years or tuberculosis.
3. Report a heart condition, chest pain during periods of activity or rest, or loss of consciousness on the Physical Activity Readiness Questionnaire (PAR-Q; items 1-4).
4. Lost 10 or more pounds (and kept it off) in the last 6 months.
5. Currently taking weight loss medications.
6. Report a past diagnosis of or receiving treatment for a DSM-IV-TR eating disorder (anorexia nervosa or bulimia nervosa).
7. Currently pregnant, pregnant within the past 6 months, or planning to become pregnant within the next 6 months.
8. Hospitalization for depression or other psychiatric disorder within the past 12 months. History of psychotic disorder or bipolar disorder.
9. Another member of the household is a participant or staff member on this trial.
10. Currently participating in a weight loss, nutrition or physical activity study or program or other study that would interfere with this study.

No exclusion criteria shall be based on race, ethnicity, or gender.