Cover Page

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Study Protocol:
Mindfulness-Based Intervention for Depression and Insulin Resistance in Adolescents

A multisite, randomized controlled pilot and feasibility trial

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Version 10.0

24 October 2023

Revision History

Version Number: 1.0
Version Date: 9 April 2021
Summary of Revisions Made: N/A, original protocol

Version Number: 2.0
Version Date: 29 June 2021
Summary of Revisions Made: Listed specific recruitment methods by site; adjusted language regarding provision of consent form copy; clarified use of immediate glucose analyzer for prompt determination of eligibility; clarified use of the independent monitoring committee (IMC) and provided more detail on IMC and the data safety and monitoring plan (DSMP); included food preferences and puberty questionnaires; provided more details on some assessments (e.g., eating in the absence of hunger paradigm) and data management; corrected clerical errors.

Version Number: 3.0
Version Date: 23 August 2021
Summary of Revisions Made: The Children's National site name has been changed to more accurately represent the official title of their institution. Additionally, Isabella Conte has been removed from the protocol, as her last day on the study is August 31, 2021.

Version Number: 4.0
Version Date: 28 September 2021
Summary of Revisions Made: Supplemented details of intervention training, delivery plans, and fidelity monitoring, including that expert raters will be non-blinded for mock session review and inclusion of non-participant/non-expert raters of adherence; added procedure for re-screening if baseline occurs >6 months from intervention initiation; protocol revision history log updated for version/date clarity and to comply with COMIRB and NCCIH document naming guidelines; clarified that lead coordinator will use the REDCap randomization module; supplemented details of inclusion/exclusion criteria for clarity and consistency across documents/tables; ensured consistency in referring to Children's National Medical Center site-specific consent/assent documents and added their planned use of recruitment business card; clarified inclusion of finger prick as backup to venipuncture for glucose measurement/eligibility; noted flexibility in timing of some assessments (e.g., pubertal exam, standard procedures regarding re-wear of home collection devices to maximize compliance); added stress test anticipated risks; updated study roster; corrected clerical errors.

Version Number: 5.0
Version Date: 1 December 2021
Summary of Revision Made: Clarified language regarding supervision by Drs. Lucas-Thompson and Gulley; corrected clerical error on height/weight measurement in first screening; added explicit note about study completion letter/referrals list at the end of participant's time in the study.

Version Number: 6.0
Version Date: 24 February 2022
Summary of Revisions Made: Made clarifying edits to the inclusion and exclusion criteria wording based on feedback from the IMC, such as specifying in the table the English-speaking eligibility inclusion criterion for adolescents, as groups will be led in English, clarifying that

exclusion criteria apply for current problems, and referencing an internal guide the IMC has reviewed and the study team will maintain throughout the trial for multisite consistency; added flexibility for some questionnaires to be completed at either screening visit 1 or screening visit 2; added clarifying language that the physical exam may occur at screening visit 1 or 2 to accommodate participant and medical provider availability; and added Michele Chen to the study roster.

Version Number: 6.1
Version Date: 3 April 2022
Summary of Revisions Made: In response to feedback from the Colorado Multiple IRB's review of protocol v6.0 approved by NCCIH, "English speaking" was removed as an inclusion criterion specified in Table 5 of the protocol. This modification is in line with the IRB's preference to instead specify within the Colorado Multiple IRB application document (IRB-specific form) the need to enroll adolescents who speak English, with the rationale that they will need to speak English in order to participate in group programs that will be facilitated in English. We had previously added "English speaking" in the table of the protocol v6.0 to respond to preferences of the study's IMC, yet with this version (6.1) we revert back to comply with COMIRB's preferences.

Version Number: 7.0
Version Date: 6 May 2022
Summary of Revisions Made: Supplemented recruitment methods for Colorado State University, Children's Hospital Colorado, and Children's National Hospital. Updated staff roles at UCD/CHCO.

Version Number: 8.0
Version Date: 25 October 2022
Summary of Revisions Made: In response to IMC guidance and NCCIH approval, modified the Schedule for Affective Disorders and Schizophrenia for School-Aged Youth (KSADS) interview to only administer the suicidality and self-harm module, with the presence of current active ideation or self-harm continuing to serve as an indicator of depression severity and need for exclusion/alternative treatment referrals at baseline. This modification alleviates participant burden, staff burden, and is in alignment with predominant views of depression symptoms as existing on a continuum. Added clarification that exclusionary diagnoses will continue to be assessed with medical/health history interview conducted by research staff with the parent and teen, with this interview already including assessment of adolescent mental health diagnostic history. While retaining the total enrollment target (N=120), omitted specific recruitment numbers by site to allow for more flexibility to recruit the target sample. Added recruitment strategies supported by IMC, NCCIH, and additional community stakeholder engagement efforts. Noted adjusted timeline and milestones established in conjunction with NCCIH. Made clerical and administrative updates, including updating the study roster and clarifying the physical examination protocol.

Version Number: 9.0
Version Date: 16 August 2023
Summary of Revisions Made: Added clarification to one-year physical exam section to accurately reflect procedures and to match sponsor approved case report forms.

Version Number: 10.0
Version Date: 24 October 2023
Summary of Revisions Made: Updated staff roster to reflect current key personnel for all study sites. Adjusted timeline to initiate staff focus groups once 1-year follow ups have been initiated, rather than waiting until this endpoint is complete, in order to maximize the viewpoints of staff members who have been working on the project since the recruitment phase. Revised the assessment of therapeutic alliance to include observational ratings on the Therapy Process Observational Coding System, rather than facilitator survey ratings which inadvertently were not collected. All of these proposed modifications have been approved by the study sponsor program official.

TABLE OF CONTENTS

Page

STUDY TEAM ROSTER / PARTICIPATING SITES

Table 1 displays the study team roster for key study team members and their roles by study site. Data enrollment will occur at all four sites.

Table omitted for privacy of coordinators/staff.

PRÉCIS

Study Title

Mindfulness-Based Intervention for Depression and Insulin Resistance in Adolescents

Objectives

Primary objectives:

a) Test multisite fidelity of training and implementation of 6-week group mindfulness-based intervention (MBI), 6-week group cognitive-behavioral therapy (CBT), and 6-week group health education (HealthEd), to adolescent girls and boys at risk for type 2 diabetes (T2D) with depression symptoms

b) Evaluate multisite feasibility/acceptability of recruitment, retention, and adherence for a protocol involving randomization to 6-week group MBI, CBT, or HealthEd with 6-week and 1-year follow-up

Secondary objectives:

a) Modify intervention training/implementation and protocol procedures for a future, fully powered multisite randomized controlled efficacy trial

Design and Outcomes

This is a multisite, pilot randomized controlled trial designed to test multisite fidelity, feasibility, and acceptability in preparation for a future multisite efficacy trial. The study will be carried out at four geographically diverse sites in order to recruit a total sample of N=120 adolescent girls and boys at risk for T2D. Adolescents, ages 12-17 years, who are at risk for T2D and who have elevated depression symptoms will be randomized to either 6-week group MBI, 6-week group CBT, or 6-week group HealthEd, and followed directly after the intervention (6-week follow-up) and 1-year later.

Interventions and Duration

Three behavioral group interventions are being compared in this trial:

1. Active/Experimental Treatment: MBI, using the Learning to BREATHE curriculum
2. Active/Standard-of-Care Treatment Comparator: CBT, using the Blues Program
3. Didactic Control: HealthEd, adapted from the Hey-Durham health knowledge program

All interventions involve ~6 total contact hours, spread over 1-hour weekly group-based interventions format. Each participant will be enrolled in the study for approximately 15 months (~1- to 3-month window for screening and baseline assessment; 6-week intervention phase; 6-week follow-up assessment; 1-year follow-up assessment).

Sample Size and Population

The target population includes adolescent girls and boys, 12-17 years old, who are at risk for T2D by virtue of having overweight/obesity (body mass index [BMI kg/m^2] ≥85th percentile for age and sex) and a family history of T2D. Adolescents will not have T2D or another major medical illness. Also, adolescents will report elevated depression symptoms, but will not have a psychiatric disorder that would impede compliance and necessitate more intensive treatment. A total of *N*=120 adolescents will be enrolled, with approximately one-third of the sample randomized to each arm (MBI: *n*=40, CBT: *n*=40, HealthEd: *n*=40).

1. STUDY OBJECTIVES

1.1 Primary Objective

a) We aim to test multisite fidelity of training/implementation of 6-week group mindfulness-based intervention (MBI), cognitive-behavioral therapy (CBT), and health education (HealthEd) to adolescent girls and boys at risk for type 2 diabetes (T2D) with depression symptoms.

We expect that facilitators can be trained consistently and competently across sites to achieve competence.

- The primary endpoint is that facilitators will score ≥80% on post-training knowledge/competency evaluations.
- Secondary endpoints are that adherence and competence ratings of mock group sessions of MBI, CBT, and HealthEd will be ≥8 (1=poor to 10=exceptional); and adherence and competence ratings of pilot trial group sessions of MBI, CBT, and HealthEd ratings will be ≥8 (1=poor to 10=exceptional).

b) We aim to evaluate multisite feasibility/acceptability of recruitment, retention, and adherence for a protocol involving randomization to 6-week group MBI, CBT, or HealthEd with 6-week follow-up and 1-year follow-up.

We anticipate that strategies used successfully in local trials will result in timely recruitment, adequate retention, and excellent adherence.

- The primary endpoint is that ≥80% of eligible adolescents will enroll in the study.
- The secondary endpoints are attainment of a target *N*=120 within a 12-month period; ≥80% of adolescents will attend 5 out of 6 (80% dose) of the MBI, CBT, and HealthEd group sessions; ≥80% of adolescents will endorse liking/credibility ratings ≥4 (1=not at all to 5=extremely); qualitative themes will be indicative of acceptability of interventions, as derived from grounded theory/qualitative analysis of adolescent focus-groups at 6-week follow-up; ≥80% retention at 6-week follow-up and ≥70% retention at 1-year follow-up; and ≥95% accuracy on standardized protocol checklists for all assessments.

1.2 Secondary Objectives

a) We aim to modify training/implementation and protocol procedures in preparation for a future multisite trial based upon the information gathered through the primary objectives, as well as focus groups conducted with study personnel toward the end of the data collection phase.

We will seek to optimize training, recruitment, intervention delivery, retention, and assessment in the following ways:

- Training optimization: Revise MBI, CBT, and HealthEd training protocols using expert feedback on videoed trainings and trainee survey feedback.
- Recruitment optimization: Select strategies most effective across multiple sites and tailor to local sites to maximize efficiency and increase rate of recruitment in a subsequent NCCIH/NIH UG3/UH3 grant application.
- Intervention optimization: Modify MBI, CBT, and HealthEd delivery based

upon focus group feedback from adolescents and intervention facilitators.

- Retention optimization: Solidify retention strategies based upon focus group feedback from research staff.
- Assessment optimization: Update assessment protocols with focus group feedback from research staff and compliance with standardized protocol checklists.

2. BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

Adolescent-onset type 2 diabetes (T2D) is a major healthcare problem. A serious chronic disease affecting 28 million Americans and 415 million individuals worldwide,[1,2] T2D costs over $245 billion annually in U.S. healthcare expenditures.[1] T2D is a leading cause of severe health complications including cardiovascular and peripheral vascular disease and stroke, retinopathy and blindness, renal failure, and amputations.[3-5] Individuals with T2D have a twofold higher risk of mortality than those without T2D, and mortality linked to T2D is the 7th leading cause of death in the U.S. and 9th leading cause of death worldwide.[1,2] Although T2D was previously limited to older adults, there has been an alarming rise in rates of adolescent-onset T2D that presents a serious healthcare challenge.[6,7] Adolescent-onset T2D has an exacerbated disease course with more rapid deterioration, greater comorbidities, and earlier mortality.[7-9] Adolescent-onset T2D disproportionately affects racial and ethnic minorities, including Hispanic/Latino, American Indian/Native American, and Black/African American youth.[6] Stressful life experiences, namely poverty, family psychopathology, domestic violence, and abuse/neglect, are commonly faced by teenagers who present with T2D and those at risk for T2D.[10-12] Unfortunately, effective treatment options remain elusive.[8,13] Given poor health outcomes and lack of effective treatment options, prevention of adolescent-onset T2D is a critical priority.

Decreasing insulin resistance is key to T2D prevention. T2D is preventable,[14,15] and prevention focuses on decreasing insulin resistance, the major physiological antecedent to T2D.[16] Insulin resistance refers to diminished sensitivity of the hormone insulin to uptake, utilize, and metabolize glucose by almost all of the body's tissues.[17] It is well-established that progression of worsening insulin resistance triggers the onset of T2D.[18] Therefore, development of effective interventions to decrease insulin resistance would significantly reduce T2D among at-risk youth.[16,19-21] Because obesity, or high body weight (BMI ≥95th percentile for age and sex), is a contributor to insulin resistance,[22] the standard-of-care for T2D prevention involves lifestyle intervention to decrease energy intake and increase physical activity, with the primary goal of weight loss.[14,15,23] Although this approach has demonstrated efficacy for diminishing T2D risk in adults,[14,15] lifestyle programs unfortunately show insufficient effectiveness in adolescents, particularly racial and ethnic minority and low-income youth.[24,25] Despite some promising short-term effects, lifestyle programs are costly and intensive (e.g., 2-3 sessions per week for 6 months), making adherence a challenge and weight regain common following the program's termination.[26-29]

Adolescence is a sensitive period to intervene to potentially alter the long-term course of insulin resistance and T2D.[18] Puberty is characterized by a natural rise in insulin resistance,[30,31] and continued exacerbation of insulin resistance in adolescents at risk for T2D plays a key role in the trajectory toward T2D.[18] Furthermore, adolescence is characterized by highly dynamic emotional, cognitive, and behavioral changes that affect insulin resistance,[30-32] offering a window of opportunity for psychological-physical integrative health interventions to decrease psychological distress, improve insulin resistance and, consequently, lessen T2D risk in at-risk

teenagers.

Depression in adolescence is common and a risk factor for insulin resistance/T2D. Depression is projected to be the 2nd leading cause of disability and premature mortality worldwide by 2020.[33,34] Depression is among the most common psychological problems, with the 12-month prevalence of major depressive disorder (MDD) estimated to be ~11% in girls and ~5% in boys in national cohorts of adolescents.[35] Individuals from racial and ethnic minority groups and low-income backgrounds have higher rates of early-life and chronic depression.[36-38] Depression markedly heightens early cardiovascular disease risk, partially through its impact on increasing the likelihood of developing T2D.[39] Although full-syndrome MDD often manifests in young adulthood (early to mid-20s),[34,40] adolescence (12-17 years) is a high-risk period for developing elevated depression symptoms: symptoms that do not fully meet MDD diagnostic frequency and/or duration criteria.[41] Youth's elevated depression symptoms, if untreated, are a strong predictor of developing MDD.[41-44] As much as 1 out of 3 adolescents report current, elevated depression symptoms,[45] and elevated depression symptoms are up to 3 times more likely in T2D as compared to community samples or individuals with type 1 diabetes (T1D).[46-48]

Data from our group and others have shown that depression symptoms relate to higher insulin resistance in adolescents, even after accounting for current BMI or body fat.[49-53] In a cohort of youth with overweight and obesity, we found that depression symptoms predicted the worsening of insulin resistance 5-6 years later, even after accounting for initial BMI and BMI change over time.[54] Other data show that adolescents' and young adults' depression symptoms are associated with a two-fold greater odds of developing T2D in young adulhood.[55] Thus, elevated depression symptoms appear to be a novel, potentially modifiable risk factor for worsening of insulin resistance and the onset of T2D. Intervening to decrease depression symptoms in adolescents at risk for T2D is, therefore, anticipated to prevent worsening insulin resistance and lessen T2D risk.

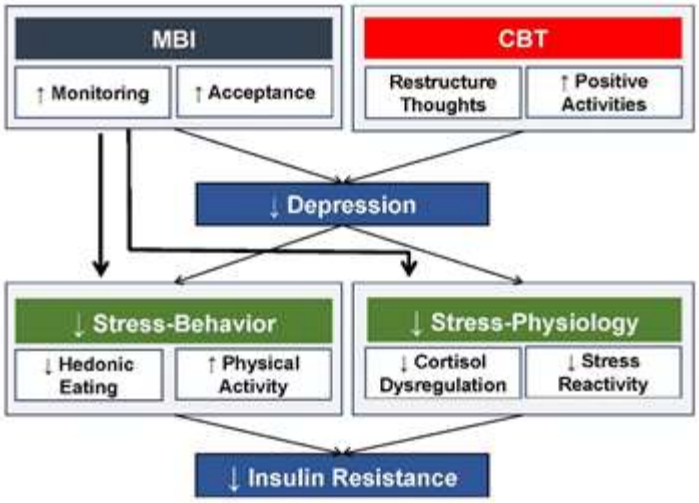
2.2 Study Rationale

Behavioral health interventions have promise to decrease depression and ameliorate insulin resistance. We conducted an initial single-site, randomized controlled efficacy trial (NIH/NICHD Grant# K99HD069516) to determine if intervening to decrease depression with the standard-of-care—cognitive-behavioral therapy (CBT)—would ameliorate insulin resistance in adolescents at-risk for T2D. Teens were randomized to a 6-week group CBT vs. 6-week health education (HealthEd) control group. In adolescents with elevated depression, CBT (vs. HealthEd) led to greater decreases in depression at post-treatment,[56] and lower 2-hour insulin after an oral glucose challenge at 1-year follow-up.[57] Also among those with elevated depression symptoms, CBT (vs. HealthEd) indirectly led to greater post-treatment to 1-year decreases in insulin resistance through decreasing depression during treatment.[58] All of the effects from this trial were independent of initial BMI, body fat, and body fat change.[56-58] These findings laid a foundation for the notion that brief, behavioral health interventions to decrease elevated depression symptoms may lessen T2D risk in adolescents, even in the absence of weight loss.

Mindfulness-based intervention (MBI) for psychological-physical integrative health. There has been rising scientific and clinical interest in MBI to decrease psychological distress[59,60] (e.g., depression) and improve physical health (e.g., cardiometabolic health).[61-63] A principal MBI goal is increasing dispositional mindfulness, the propensity to pay attention on purpose to one's present-moment experiences with an attitude of non-judgment and equanimity.[64] From the framework of Monitor and Acceptance Theory,[65,66] MBI is postulated to decrease depression and improve stress-related behavior and physiology through (i) increased attention to monitoring of present-moment experiences, combined with (ii) increased acceptance of experiences

regardless of their valence, mechanisms supported in recent MBI dismantling studies.[65,67-69] As show in **Figure 1** below, MBI is theorized to be particularly fitting for decreasing depression and improving insulin resistance in teen at-risk for T2D. MBI is postulated to: (a) alleviate ruminative, negative thoughts that perpetuate and exacerbate depression,[70-72] (b) ameliorate dysregulated stress physiology including cortisol dysregulation and stress reactivity, shown to promote insulin resistance and adverse metabolic outcomes,[73,74] and (c) lessen stress-related behavior such as hedonic eating, or eating for reward/pleasure as opposed to physiological hunger,[75] and physical inactivity.[76] Adolescent depression symptoms relate to increases in cortisol dysregulation,[77,78] stress reactivity,[79] hedonic eating,[80-82] and physical inactivity,[83] which, in turn, have each been related to increased insulin resistance independent of obesity.[84-97] Enhanced monitoring and acceptance of thoughts, emotions, and body sensations as they unfold moment-to-moment is theorized to improve stress-related behavior/physiology through its impact on decreasing depression; yet, one distinctive benefit of MBI may be its potential to offer direct, salutary effects for stress behavior/physiology. MBI may improve identification of cues (e.g., negative affectivity) that prompt behaviors triggered by stress, and to tolerate distress without acting habitually.[98] MBI also may improve executive function, including the ability to flexibly deploy attention away from cues that prompt stress-behavior and heighten stress physiology.[59,99]

Figure 1. Theoretical MBI, vs. CBT, effects on depression & insulin resistance by decreasing (a) depression, (b) stress physiology, and (c) stress-related behavior



In light of these theoretically informed, potentially distinctive benefits, we carried out a single-site, pilot randomized controlled trial of MBI vs. an active treatment, CBT, in adolescents at-risk for T2D with elevated depression symptoms (NIH/NICHD Grant# R00HD069516). The main aim was to test feasibility/acceptability of a 6-week/6-session MBI group, Learning to BREATHE, in teens at-risk for T2D. There was excellent attendance (median 6:6 MBI vs. 5:6 CBT sessions, p=.06), and acceptability ratings were positive. In exploratory analyses, we observed that both conditions decreased depression, but MBI led to greater decreases than CBT at post-treatment (Cohen's d=0.56)[100] and 1-year (d=0.68; 52% vs. 35% symptom reduction).[101] Whereas CBT was associated with stable insulin resistance, MBI decreased insulin resistance at post-treatment (Cohen's d=0.93)[100] and 1-year follow-up (Cohen's d=0.73).[100] These data must be considered preliminary,[102] but they support the notion that MBI could offer distinctive psychological and physical health benefits to adolescents at-risk for T2D with depression

symptoms.[103] If MBI leads to more clinically meaningful reductions in depression and insulin resistance in adolescents at-risk for T2D, this stands to inform our healthcare approach to T2D prevention.

Most existing research on MBI and diabetes has focused on MBI delivery in adults who already have T2D or samples combining adults with T2D and type 1 diabetes (T1D).[104-106] Randomized trials in adults with T2D/T1D show moderate MBI effects for decreasing depression, relative to waitlist, diabetes education, and treatment-as-usual controls, from post-treatment to 1-year follow-up.[104,106-112] Some of these trials show significant MBI effects on improved glycemic control (e.g., HbA1c, fasting glucose) and overall health.[104,107,110,112] Yet, not all studies have found physical health benefits, particularly trials combining T2D/T1D, which represent very different patient populations, and trials that included patients who already had good glycemic control.[106-109,111] From an alternative, prevention lens, MBI delivery to at-risk adolescents in order to decrease depression and ameliorate insulin resistance warrants testing and offers potential as a novel approach for targeted prevention of T2D. MBI may be especially valuable in adolescence, as marked developments in executive function, pubertal insulin resistance, high reward sensitivity, and openness to new experience render this period highly malleable.[113-117]

Few randomized controlled trials have compared MBI to active treatments. In the current research program, we will lay the groundwork for a multisite efficacy trial comparing MBI to CBT and to a didactic control group, HealthEd, for decreasing depression symptoms and insulin resistance in adolescents at-risk for T2D. Comparison of MBI to another active treatment is crucial to distinguish whether MBI is superior (or equivalent) to CBT, and to what extent there are distinctive benefits of monitoring and acceptance, above and beyond the time, attention, non-specific group/facilitator support, as well as training in thought restructuring, behavioral activation, and stress management, provided by CBT.

3. STUDY DESIGN

3.1 Design of Trial

This trial is a multisite, randomized controlled pilot and feasibility trial with three arms, including two active behavioral treatments, mindfulness-based intervention (MBI) vs. cognitive-behavioral therapy (CBT), and one didactic/attention control, health education (HealthEd). After a screening to determine eligibility and to collect baseline assessments, eligible adolescents will be randomized to participate in one of the arms. Each intervention is a 6-week group program. Follow-ups will be conducted at 6-weeks after the intervention and 1-year after the intervention.

3.2 Primary Outcomes

The primary outcomes for each study aim are described in **Table 2** below.

Table 2. Primary endpoints for each study aim of this multisite, randomized controlled pilot and feasibility trial

Aim 1: Test multisite fidelity of training/implementation of 6-week group MBI, CBT, and HealthEd to adolescent girls and boys at-risk for T2D with depression symptoms		
Objective	**Endpoint**	**Metric; Analysis**
Intervention Fidelity (Primary)	12-months	Facilitators score ≥8 on adherence and competence ratings of MBI, CBT, and HealthEd adolescent group sessions (*1*=poor to *10*=exceptional)

Aim 2: Evaluate multisite feasibility/acceptability of recruitment, retention, and adherence for a protocol involving randomization to 6-week group MBI, CBT, or HealthEd with 6-week and 1-year follow-up		
Objective	**Endpoint**	**Metric; Analysis**
Recruitment Feasibility (Primary)	12-months	≥80% eligible adolescents will enroll

3.3 Secondary Outcomes

The secondary endpoints for each aim are shown in **Table 3**.

Table 3. Secondary endpoints for each study aim of this multisite, randomized controlled pilot and feasibility trial

Aim 1: Test multisite fidelity of training/implementation of 6-week group MBI, CBT, and HealthEd to adolescent girls and boys at-risk for T2D with depression symptoms		
Objective	**Endpoint**	**Metric; Analysis**
Training Fidelity (Secondary)	6-months	Facilitators score ≥80% on post-training knowledge/ competency tests of MBI, CBT, and HealthEd
Training Fidelity (Secondary)	6-months	Facilitators score ≥8 on adherence and competence ratings of MBI, CBT, and HealthEd mock group sessions (*1*=poor to *10*=exceptional)
Aim 2: Evaluate multisite feasibility/acceptability of recruitment, retention, and adherence for a protocol involving randomization to 6-week group MBI, CBT, or HealthEd with 6-week and 1-year follow-up		
Objective	**Endpoint**	**Metric; Analysis**
Recruitment Feasibility (Secondary)	12-months	Attainment of target *N*=120 within a 12-month period; CONSORT flow/number of months to reach recruitment goal
Intervention Feasibility (Secondary)	6-weeks	≥80% adolescents attend 5:6 (80%) group MBI/CBT/HealthEd sessions
Intervention Acceptability (Secondary)	6-weeks	≥80% adolescent liking/credibility ratings ≥4 (*1*=not at all to *5*=extremely)
Intervention Acceptability (Secondary)	6-weeks	Themes indicative of acceptability of interventions, as derived from grounded theory/qualitative analysis of adolescent focus-groups at post-intervention
Retention Feasibility (Secondary)	12-months	≥80% at post-treatment follow-up and ≥70% at 1-year follow-up
Assessment Feasibility (Secondary)	18-months	≥95% accuracy on standardized protocol checklists for all assessments

3.4 Study Population

The sample will be *N*=120 adolescents at risk for T2D with elevated depression symptoms. We will exclude and provide referrals to adolescents with active suicidal ideation or current psychiatric disorder that would impede compliance and necessitate more intensive treatment. Likewise, adolescents who have T2D or another major medical illness will be excluded and

referred.

3.5 Study Location

This trial will take place at four sites, with two sites in Colorado (Colorado State University [**CSU**] and Children's Hospital Colorado/University of Colorado Anschutz Medical Campus [**CHCO**]) and two in Maryland/Washington, D.C. (Uniformed Services University of the Health Sciences [**USU**] and Children's National Medical Center [**CNMC**].

3.6 Study Timeline

An overview of the projected 4-year study timeline with key tasks is provided in **Table 4** below.

Table 4. Estimated study timeline**

<table>
<tr><th></th><th>Year 1 2020-2021</th><th>Year 2 2021-2022</th><th>Year 3 2022-2023</th><th>Year 4 2023-2024</th></tr>
<tr><td>Quarter 1
August-October</td><td rowspan="2">Multisite study start-up:
Hire personnel;
Assign roles & responsibilities for all personnel;
Obtain single IRB (sIRB), institution agreements & regulatory approvals;
Convene data safety and monitoring board (DSMB) and create Charter;
Establish data coordinating center, including randomization string, surveys, & data management systems in REDCap;
Finalize standard operating procedures</td><td>Multisite pilot randomized controlled trial and post-intervention follow-up:
Initiate recruitment; Track rate, sources, & all aspects of recruitment;
Conduct screenings/ baseline assessments for Cohort 1;
Monitor protocol compliance at all sites</td><td>Multisite feasibility/ acceptability of interventions:
Evaluate intervention attendance/homework completion/acceptability ratings (Aim 2);
Carry out qualitative data analysis of participant focus groups</td><td rowspan="2">Evaluate participant recruitment, retention, and protocol adherence through 1-year follow-up final endpoint (Aim 2);
Summarize, disseminate, discuss fidelity & feasibility/acceptability results to local sites & across sites;
Refine multisite study protocols based upon data (Aim 3)

Dissemination & future directions:
Submit key results to conference proceedings;
Draft NCCIH UG3/UH3 grant for multisite randomized controlled efficacy trial</td></tr>
<tr><td>Quarter 2
November-January</td><td>Deliver Cohort 1 MBI, CBT, & HealthEd;*
Conduct weekly intervention supervision;
Conduct Cohort 1 6-week follow-ups and focus groups;
Conduct screenings/ baseline assessments for Cohort 2;
Monitor protocol compliance at all sites</td><td>Summarize, disseminate, discuss fidelity & initial feasibility/acceptability results to local sites & across sites

1-year follow-up of multisite pilot randomized controlled trial:
Conduct Cohort 1 1-year follow-ups</td></tr>
</table>

	Year 1 2020-2021	Year 2 2021-2022	Year 3 2022-2023	Year 4 2023-2024
Quarter 3 February-April	**Multisite trainings for study protocols & interventions:** Conduct live/video trainings of standard operating procedures; Design recruitment materials & finalize recruitment methods; Conduct live, in-person trainings in MBI, CBT, & HealthEd in Colorado & Maryland/D.C.; Evaluate fidelity and feasibility/acceptability of study protocol and MBI, CBT, & HealthEd training (Aim 1)	Deliver Cohort 2 MBI, CBT, & HealthEd; Conduct weekly intervention supervision; Conduct Cohort 2 6-week follow-ups and focus groups; Monitor protocol compliance at all sites	Conduct Cohort 2 1-year follow-ups	Present key results at conference proceedings; Prepare manuscripts; Submit NCCIH UG3/UH3 grant for multisite randomized controlled efficacy trial
Quarter 4 May-July		**Multisite fidelity of intervention delivery:** Evaluate fidelity of MBI, CBT, & HealthEd delivery (Aim 1)	**Multisite feasibility/ acceptability of study protocols:** Conduct facilitator/ staff focus groups; Carry out qualitative data analysis of facilitator/staff focus groups	Publish results in peer-reviewed journals; Revise NCCIH UG3/UH3 grant for multisite randomized controlled efficacy trial

* *Note:* Planned enrollment is *n*=5 adolescents and n=5 parents/guardians per arm x 3 arms (i.e., MBI, CBT, HealthEd) x 4 sites x 2 cohorts, amounting to a total *N*=240. MBI: mindfulness-based intervention. CBT: cognitive-behavioral therapy. HealthEd: health education.
** Study timeline delayed. Updated GANNT chart and milestones created, and approved by NCCIH, in August 2022. Cohorts revised to ongoing enrollment across sites: n=15 per cohort x 8 cohorts: N=120.

Recruitment and enrollment was anticipated to occur ~August 2021-March 2022, with enrollment anticipated to be completed no later than within a 12-month period from initiation of recruitment (i.e., August 2022). On account of delays, actual enrollment began in May 2022 and it is anticipated to finish in July 2023.

3.7 Description of Interventions and Administration

MBI: The group MBI active/experimental intervention program is Learning to BREATHE, a manualized curriculum[118] derived from mindfulness-based stress reduction[64] and adapted for adolescents by incorporating experiential activities and guided discussions to teach standard mindfulness skills. Adolescents meet for six group weekly sessions for 60-minutes each week. Each letter in the BREATHE acronym corresponds to a theme: **B**: Body, **R**: Reflections/ Thoughts, **E**: Emotions, **A**: Attention, **T**: Tenderness/Self-Compassion, **H**: Habits (of Healthy Living), for the overall goal of **E**: Empowerment. Example activities include breath awareness, body scanning, mindful eating, sitting meditation, loving-kindness practice, and gentle yoga. Brief homework (~10 minutes/day), including formal practices (e.g., meditation audio-recordings) and informal practices (e.g., personalizing mindfulness in daily living), is assigned weekly. Adolescents are given digital meditation audio-recordings, a yoga mat, a meditation cushion, a homework log, and worksheets. The original curriculum was designed to offer flexibility in delivery timing and selection of exercises.[118] We developed a manualized version of BREATHE for consistency in timing and content,[100,119] but minimally modified content from its original format. In session 1 (“B), we added a brief justification (~1 minute) of how program participation may help adolescents to lessen T2D risk through feeling happier, less stressed, and engaging in healthier ways of coping with stress. BREATHE is well-liked by at-risk, racially/ethnically diverse adolescents, including adolescents at-risk for obesity and T2D,[100,119]

increases dispositional mindfulness, and decreases depression symptoms and insulin resistance up to 1-year later in pilot randomized trials.[100,101,119-122]

CBT: The group CBT active/standard-of-care intervention comparator, the Blues Program, is a depression prevention program designed to prevent future major depressive disorder (MDD) among at-risk youth with current elevated depression symptoms.[123-125] Adolescents meet for six weekly group sessions for 60-minutes each week. Content includes psychoeducation on the cognitive-behavioral model of interrelated thoughts, emotion, and behavior; instruction in self-monitoring; tools for restructuring negative thoughts; behavioral activation by encouraging engagement in pleasant activities; use of self-rewards/reinforcement; and coping with stress. Sessions are interactive and activity-based to maximize engagement. Brief homework (~10 minutes/day) is assigned weekly, including a daily journal and scheduling activities. The Blues Program has demonstrated efficacy for decreasing depression symptoms and preventing MDD onset in diverse adolescents groups, compared to assessment-only and active control conditions, from 6 months to 2 years after treatment.[124,126] Further, we have shown that CBT decreases depression at post-treatment and stabilizes indices of insulin resistance 1-year later among adolescents at-risk for T2D with moderately elevated depression symptoms.[56,57]

HealthEd: The group HealthEd didactic/control program is derived from Hey-Durham, a didactic program for middle/high school age adolescents to increase health knowledge.[127] We created an abbreviated, manual used in multiple, previous studies.[56,119,128,129] Adolescents meet for six weekly group sessions for 60-minutes each week. This manualized curriculum covers 6 topics: i) domestic violence, ii) substance use, iii) nutrition/body image, iv) depression/signs of suicide, v) gang violence/conflict resolution, and vi) sun safety. The depression/suicide module focuses only on descriptive prevalence, relation to other health issues, and how to identify signs. Content does not overlap with MBI or CBT.[56,57] No direct advice is given unless in a psychiatric crisis, in which case a treatment referral is facilitated.

Administration: All three interventions will be delivered by a clinical or counseling psychologist. Programs will be co-facilitated by a graduate student in clinical or counseling psychology, social work, prevention science, or related field, or a research associate with a master's degree in clinical or counseling psychology, social work, prevention science, or related field. Psychologists and co-facilitators will participate in MBI, CBT, and HealthEd training. Sessions will be audio-recorded and reviewed weekly by Dr. Lucas-Thompson (MBI) and Dr. Gulley (CBT, HealthEd) for adherence and competence. Feedback will be provided in weekly supervision. Facilitators with drift or deficiencies will be re-trained via "booster sessions" as needed. To minimize facilitator effects, psychologist facilitators at each site will facilitate all three programs.

3.8 Randomization and Stratification

A separate randomization sequence will be created for each site. Within site, we will create four strata by crossing sex (male, female) and age (12-14 years, 15-17 years) and we will use permuted blocks within each stratum to ensure the three intervention conditions are balanced. A statistician in the Children's Hospital Colorado's Biostatistics Core, other than the study lead statistician Dr. Pyle, will create the computerized randomization sequence and enter the sequence into REDCap's randomization module. The randomization sequence will be created in randomly permuted blocks stratified by site, sex, and age. Permuted blocks will be restricted so that for each cohort of n=15, the conditions will be balanced. REDCap's randomization module conveniently conceals the randomization sequence. The lead research coordinator will be responsible for using the REDCap randomization module to carry out randomization of eligible participants.

3.9 Blinding

Trainers of the interventions will not be blinded in order to provide weekly supervision and feedback to the group facilitators. Independent reviewers will complete fidelity ratings of facilitators' delivery of the interventions with participants, and these reviewers will be blinded. Raters of quantitative group cohesion also will be blinded.

The research coordinators – and all study personnel – will remain blinded to allocation during the screening/baseline assessment phase, however during the intervention and follow-up phases, the research coordinators at each site, the group intervention facilitators, and trainers will be not be blinded to assignment. The unblinded coordinators will assist in preparation of any data reports to the IMC that necessitate unblinded data.

The PI (Dr. Shomaker) and the statistician (Dr. Pyle) will be blinded until the database is locked. Research staff conducting medical and physical health assessments, including insulin resistance, body composition, puberty and physical exams, will be blinded.

Research assistants (e.g. graduate research assistants) responsible for conducting depression and eating interviews and the laboratory stress and eating tasks will be blinded. Blinded research assistants also will be responsible for completing standardized protocol checklists at all sites.

Facilitators of adolescent focus groups at post-intervention and facilitators of personnel focus groups after initiation of 1-year follow-ups will not be blinded, because focus group guides will include open-ended and targeted questions to elicit information specific to intervention condition and site. Focus group facilitators will not be involved in any other aspects of data collection for this study.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

Participants must meet all of the following inclusion criteria in order to participate in this study: a) 12-17 years of age; b) overweight or obesity, as determined by a BMI ≥85th percentile for age and sex; c) elevated depression symptoms, as determined by a total score that exceeds 20 on the Center for Epidemiologic Studies-Depression Scale (CES-D); d) at least 1 first- or second-degree relative with T2D, prediabetes, or gestational diabetes; e) good general health, as determined by medical history and physical examination, and f) parent/guardian of qualifying participant. These criteria are outlined in **Table 5**.

Table 5. Inclusion criteria

Inclusion Criteria
a) Adolescent: Age 12-17 years
At-risk for T2D:
b) Overweight/obesity: BMI ≥85 percentile for age and sex
c) Family history of T2D: ≥1 relative with T2D, prediabetes, or gestational diabetes in first- or second- degree relative, referring to a biological parent, sibling, aunt, uncle, or grandparent
d) Elevated depression symptoms: Center for Epidemiological Studies – Depression Scale (CES-D) total score >20
e) Good general health: Medical history/physical examination
f) Parent/guardian: Parent/guardian of qualifying participant

4.2 Exclusion Criteria

All candidates for this trial meeting any of the following exclusion criteria at baseline will be excluded from study participation: a) current major renal, hepatic, endocrinologic (e.g., T2D or

T1D), rheumatologic, cardiac, or pulmonary medical problem that would be likely to affect mood, weight, and/or insulin sensitivity; b) current major depressive disorder (MDD) diagnosis with high acuity, as assessed by the Suicidality and Self-Harm Module of the Schedule for Affective Disorders and Schizophrenia for School-Aged Youth-Computerized Version (KSADS-COMP, semi-structured clinical interview), or other psychiatric diagnosis reported by parent and/or adolescent, that in the opinion of the study investigators would impede compliance and/or necessitate more intensive treatment, including anorexia nervosa, bipolar disorder, bulimia nervosa, conduct disorder, , obsessive compulsive disorder, panic disorder, posttraumatic stress disorder, psychosis, and substance/tobacco/alcohol use disorder; c) current regular medication use affecting mood, insulin, cortisol, insulin sensitivity, and/or weight (e.g. anti-anxiety medications, anti-depressants, anti-psychotics, insulin sensitizers, mood stabilizers, stimulants, and/or weight loss drugs); d) current active suicidal ideation or behavior; e) ongoing regular psychotherapy or structured weight loss treatment; and/or f) current pregnancy or breastfeeding in females. **Table 6** summarizes exclusion criteria for this trial. The study team will maintain an internal guide detailing exclusionary and non-exclusionary medical and psychological concerns, medications, alternative treatments, and more, in order to ensure consistency across sites.

Table 6. Exclusion criteria

Exclusion Criteria
a) Major medical problem: including T2D, assessed at baseline/screening as fasting glucose ≥126 mg/dL or 2-hour glucose ≥200 mg/dL, or any other significant current medical condition reported during the medical history/physical examination likely to affect mood, weight, and/or insulin sensitivity
b) Major psychiatric problem: current psychiatric diagnosis, that in the opinion of the study investigators would impede compliance and/or necessitate more intensive treatment, including but not limited to anorexia nervosa, bipolar disorder, bulimia nervosa, conduct disorder, major depressive disorder (MDD) with high acuity (suicidality/self-harm), obsessive compulsive disorder, panic disorder, posttraumatic stress disorder, psychosis, and substance/tobacco/alcohol use disorder
c) Regular medication use affecting mood, insulin, and/or weight: current anti-anxiety medications, anti-depressants, anti-psychotics, insulin sensitizers, mood stabilizers, stimulants, and weight loss drugs
d) Current active suicidal ideation or behavior
e) Regular ongoing psychotherapy or structured weight loss treatment
f) Current pregnancy or breastfeeding: as reported by adolescent participants (females)

4.3 Study Enrollment Procedures

Identifying and recruiting candidates: We will recruit youth and their parent/guardian to participate from four data enrollment sites, with two sites in Colorado (Colorado State University and Children's Hospital Colorado) and two in Maryland/Washington, D.C. (Uniformed Services University and Children's National Medical Center). Recruitment methods will be effective strategies from each site's prior and ongoing studies delivering interventions to adolescents with overweight/obesity (e.g., NCT#s 03085160, 02218138, 01425905, 03263351, 03527641, 03086161, 03869749, 00081328, 02310724, 01775813, 03120871, 02671292, 02334202, 00680979, 00263536). Recruitment methods for each site are as follows:

Colorado State University:

i) Flyers/letters/postcard mailings to area families with adolescents 12-17 years of age

ii) Flyers/letters/postcards to area physicians, including practice-based research networks

iii) Advertisements on school/parent listservs, other community-area listservs, radio, newspapers or newsletters, social media (e.g. Facebook), and institutional websites

iv) Flyers posted in hospitals, clinics, community health centers, fitness centers, and other area locations

v) Informational booths/presentations at health fairs and/or schools, walk/run events, and T2D dining clubs or similar programs for adults, who may have adolescent children or grandchildren at risk for T2D

vi) Phone, email, and/or letters/flyers to potentially eligible adolescents and their families through Health Data Compass and Research Match

vii) Notices to Colorado State University Extension rural health agents

viii) Phone, email, and/or letters/flyers/postcards to potentially eligible adolescents and their families who have been screened by the Colorado State University team for previous studies and have stated that they may be contacted for future research opportunities

ix) Outreach at healthcare visits or via phone calls, emails, and flyer/letter mailings to patients and families receiving care at Fort Collins/Northern Colorado-area healthcare practices of medical provider associate investigators at the CSU site (e.g. Sheena Crowe, MSN, ACNP-BC, FNP-C; Alexandra Paz-Cox, NP), who will refer eligible adolescents and/or notify families with diabetes

x) Outreach at healthcare visits or via phone calls, emails, and flyer/letter mailings to patients and families receiving care from study team investigators who are affiliated with Fort Collins/Northern Colorado-area healthcare practices (e.g., UC Health pediatrics and family medicine practices) that serve potentially eligible adolescents and/or families with diabetes

Children's Hospital Colorado:

i) Flyers/letters/postcard mailings to area families with adolescents 12-17 years of age

ii) Flyers/letters/postcards to area physicians, including practice-based research networks

iii) Advertisements on school/parent listservs, other community-area listservs, radio, newspapers or newsletters, social media (e.g. Facebook), and institutional websites

iv) Flyers posted in hospitals, clinics, community health centers, fitness centers, and other area locations

v) Informational booths/presentations at health fairs, walk/run events, and T2D dining clubs or similar programs for adults, who may have adolescent children or grandchildren at risk for T2D

vi) Phone, email, and/or letters/flyers to potentially eligible adolescents and their families through Health Data Compass and Research Match

vii) Direct outreach at clinical visits or via phone calls, emails, postcard mailings, and patient care portal messages to patients receiving care at the Children's Hospital Colorado Networks of Care: Drs. Kelsey, Gulley, Shomaker (PI) all see patients in obesity and specialty clinics and will refer eligible adolescents

viii) Recruiting from colleagues of Drs. Shomaker, Gulley, Kelsey in their clinics, such as endocrine, adolescent medicine, obesity clinics, pulmonary, and/or other affiliated clinics

xi) Notices to CCTSI community engagement practice-based research networks and other physician offices in surrounding areas

xii) Phone, email, and/or letters/flyers/postcards to potentially eligible adolescents and their families who have been screened by the Children's Colorado team for previous studies and have stated that they may be contacted for future research opportunities

Uniformed Services University:

i) Flyers/letters/postcard mailings to local families with adolescents 12-17 years of age

ii) Flyers/letters/postcards to area physicians who service both military and civilian youth, including practice-based research networks

iii) Flyers/letters/postcard mailings to military families with adolescents

iv) Advertisements on school/parent listservs, radio, newspapers, social media (e.g., Facebook), and institutional websites

v) Flyers posted in civilian and military hospitals, clinics, community health centers, fitness centers, and other area locations

vi) Informational booths/presentations at health fairs, walk/run events, and T2D dining clubs and other similar programs for adults, who may have adolescent children or grandchildren at risk for T2D

vii) Phone, email, and/or letters/flyers/postcards to potentially eligible adolescents and their families who have been screened by the Uniformed Services University team for previous studies and have stated that they may be contacted for future research opportunities

Children's National Medical Center:

i) Direct outreach at clinical visits or via phone calls, emails, and postcard mailing to patients receiving care at Children's National Medical Center: Drs. Mackey and Estrada all see patients in the IDEAL Obesity Clinic and Diabetes specialty clinics and will refer eligible adolescents

ii) Recruiting from colleagues of Drs. Mackey and Estrada in their clinics and/or other affiliated clinics (e.g., recruitment business card with link to flyer/REDCap survey)

iii) Flyers/letters/postcard mailings to area families with adolescents 12-17 years of age

iv) Flyers/letters/postcards/study business cards to area physicians, including practice-based research networks

v) Advertisements on school/parent listservs, radio, newspapers, social media (e.g. Facebook), and institutional websites

vi) Flyers posted in hospitals, clinics, community health centers, fitness centers, and other area locations

vii) Informational booths/presentations at health fairs, walk/run events, and T2D dining clubs or similar programs for adults, who may have adolescent children or grandchildren at risk for T2D

viii) Phone, email, patient care messages, and/or letters/flyers/postcards/business cards to potentially eligible adolescents and their families who have been screened by the Children's National investigative team for previous studies and have stated that they may be contacted for future research opportunities

We will record, by site, recruitment strategies used, percentage of phone pre-screen contacts from each strategy, percentage enrollment from each strategy, and percentage of eligible youth who enroll.

Procedures for documenting ineligibility and non-participation: At each site, we will maintain a parallel, participant tracking log that will contain all participants/families who the study team had contact with and/or who completed a phone or in-person screening for the study. This log will contain both eligible and ineligible participants. For those who are ineligible, or eligible but decided not to participate, we will document all reasons for exclusion, or non-participation, within this log. The multisite coordinator will be responsible for periodic monitoring of each site's log for thoroughness and completeness of study recruitment flow. Moreover, each screening visit has an accompanying progress note that will systematically record whether participants meet each eligibility criterion, and these data will be entered on the master tracker, in REDCap, and/or other approved, secure information-storing techniques as necessary.

Consent procedures: The purpose, all testing procedures, program components, and randomization will be reviewed, in detail, by a trained member of the study team at each respective site. Potential volunteers will be informed of possible risks, inconveniences, potential benefits, and right to withdrawal. Participants will be encouraged to ask questions and staff are trained to periodically pause to check for questions and for understanding. All participants and parents/guardians who choose to volunteer will sign a COMIRB-approved consent/assent form. In the event of remote visit consent, e-consent will be obtained using REDCap and explained via secure video software (e.g., Vidyo, Zoom) or by phone. Hard-copies and/or electronic copies of the consent and assent will be made available to participants for their records, depending upon family preference and mode of consent (i.e., in-person/remote).

Randomization procedure: Upon completion of all screening and baseline assessments, each eligible participant will be randomly assigned to either an MBI, CBT, or HealthEd group condition. A separate randomization sequence will be created for each site. Within site, we will create four strata by crossing sex and age group (12-14y, 15-17y) and we will use permuted blocks within each stratum to ensure the intervention group arms are balanced. A statistician in the Children's Hospital Colorado's Biostatistics Core, other than the study lead statistician (Dr. Pyle), will create the computerized randomization sequence and enter the sequence into REDCap's randomization module. REDCap's randomization module conceals the randomization sequence. The lead research coordinator will be responsible for using the REDCap randomization module to carry out randomization of eligible participants.

5. STUDY INTERVENTIONS

5.1 Interventions

Overview: In this three-arm multisite, randomized controlled pilot and feasibility trial, mindfulness-based intervention (MBI), cognitive-behavioral therapy (CBT), and health education (HealthEd) group programs are matched for time, attention, and facilitator training. All

interventions will be delivered for six weekly 1-hour group-based sessions. Group sessions will either take place via secure videoconferencing or in a conference room at each respective site. All interventions will be delivered by a clinical or counseling psychologist. Programs will be co-facilitated by a graduate student in clinical or counseling psychology, social work, prevention science, or related field, or a research associate with a master's degree in clinical or counseling psychology, social work, prevention science, or related field. To minimize facilitator effects, the lead psychologist facilitators at each site will facilitate all three programs. All facilitators and co-facilitators will receive training and weekly supervision as described below. Interventionists cannot be blinded to intervention assignment due to the nature of the intervention.

Intervention Training: All three interventions are manualized. Utilization of manuals for each of the three conditions supports fidelity, which will be closely monitored. Prior to delivery of the interventions as part of the multisite, pilot clinical trial, lead psychologist facilitators and co-facilitators will participate in MBI, CBT, and HealthEd training. The training will be 5-days (~3 days for MBI, ~1 day for CBT, ~1 day for HealthEd). We prefer to conduct the training in-person, but if circumstances (e.g., due to COVID-19) are more conducive to remote training, we will deliver some or all portions of the training remotely via videoconferencing. All trainings will video-recorded for future reference/training by the study team.

Training will include presentations of theoretical/empirical background, review of manuals, modeling of session elements, and role-play in mock-groups. Dr. Lucas-Thompson (Co-I), a psychologist completing BREATHE master training certification with Dr. Patricia Broderick (Consultant; BREATHE developer), will lead training in BREATHE, the MBI program. Dr. Lucas-Thompson has expertise delivering BREATHE with high fidelity/competence to at-risk teenagers. Dr. Gulley (Co-I), a psychologist trained in the Blues Program by Dr. Eric Stice (Consultant) and his team of Blues Program developers (Dr. Paul Rohde, Dr. Heather Shaw) and in HealthEd by Dr. Shomaker (PI), will facilitate training in the CBT Blues Program and the didactic control program, HealthEd. Gulley has demonstrated high fidelity/competence in CBT and HealthEd, as rated by the Blues Program development team and Dr. Shomaker.

To assess training fidelity: a) MBI, CBT, and HealthEd training sessions will be video-recorded and rated by Dr. Broderick, Dr. Rohde, and Dr. Shomaker, respectively, on training fidelity forms; b) Facilitators will complete post-training surveys assessing quantitative knowledge of MBI, CBT, and HealthEd, following the didactic portion of the training; and c) Facilitators' adherence and competence in conducting mock intervention sessions will be evaluated by experts (Drs. Broderick, Stice/Shaw/Rohde, and Shomaker) on standardized ratings scales to establish training fidelity prior to delivery to participants. Facilitators also will provide qualitative feedback on any recommended modifications to training procedures that they perceive would improve the training process, for use in a future NIH/NCCIH UG3/UH3 grant application/multisite efficacy trial. For descriptive purposes, facilitators will complete surveys of quantitative intervention knowledge prior to the didactic training, as well as feedback following the mock session training portion.

Intervention delivery: Supervision and fidelity monitoring: Sessions will be audio-recorded and reviewed weekly by Dr. Lucas-Thompson (MBI) and Dr. Gulley (CBT, HealthEd) for intervention fidelity/adherence and facilitator competence. Feedback will be provided in weekly supervision. Facilitators with drift or deficiencies will be re-trained via "booster sessions" as needed. These protocols have been successful, as evidenced by strong ratings of adherence, competence, and absence of cross-contamination.[56,57,128,130] Blinded experts will review audio-recorded sessions and complete standardized/structured rating scales of fidelity/competence in administration of MBI, CBT, and HealthEd. Non-participant/non-experts (e.g., trained undergraduate research assistants) also will complete ratings of intervention adherence.

Intervention acceptability: Attendance and home practice will be tracked at all sessions. Adolescents will report homework completion to facilitators, and also will record completion of home practices on journal logs for MBI and CBT. Adolescents will complete a weekly acceptability form.[131]

Group cohesion, therapeutic alliance, and expectancies: We will measure group cohesion and therapeutic alliance using two independent raters' review of audio-recorded sessions using the Therapy Process Observational Coding System, which shows good psychometric properties.[132] Raters will be blind to group assignment.

Adolescents will complete the reliable and valid 12-item Therapeutic Alliance Scale for Adolescents (TASA)[133] to assess their perceptions of their emotional bond and task collaboration both early (session 1) and at the end (session 6) of the interventions.[133-135] Finally, as a quantitative index of outcome expectancy, we will ask adolescents to report at the end of session 1, their perspective of the likelihood that their stress, mood, and risk for T2D can be improved.[136]

5.2 Prohibited Interventions

Adolescents will not be enrolled if they are currently engaged in regular psychotherapy, medication treatment that could affect mood, weight, insulin sensitivity, or cortisol secretion, or a structured weight loss program.

5.3 Allowed Interventions

Adolescents who are receiving counseling at school or through a non-professional counselor (e.g., church or religious affiliation), or adolescents who are not receiving regular weekly or biweekly psychotherapy (e.g., once per month) will not be excluded. Adolescents who are taking medications that do not affect mood, weight, cortisol, or insulin sensitivity will be allowed to participate. Likewise, adolescent females who are stabilized on birth control (~3 months) will not be excluded.

5.4 Adherence Assessment

Adolescents' adherence to the intervention will be measured by their attendance of MBI/CBT/HealthEd sessions. The benchmark for intervention adherence will be 5 out of 6 group sessions. An intervention session progress note will include an attendance log to track group session attendance, as well as make-up sessions. All adolescents who miss a group session in any of the three intervention arms will be invited to complete a make-up session to review the key material prior to the next group. If interventions overlap with holidays, an alternative day of the week will be offered (e.g., Tuesday instead of a Monday) or two consecutive group sessions may need to occur 2 weeks apart instead of 1 week (e.g., to avoid winter holiday break when many families are unavailable). Brief homework (10 minutes/day) in MBI and CBT will be tracked by participants on intervention participant workbooks, and also reported to facilitators at the start of session 2-6. Intervention adherence is calculated at the end of each cohort; attendance of at least 5 of the 6 group sessions is incentivized ($50). Total intervention adherence by arm, across sites, and homework completion will be described at the end of the study. Intervention adherence will be presented to the IMC and on the continuing review submitted to the IRB.

6. STUDY PROCEDURES

The overview of key study procedures for this multisite, pilot clinical trial is provided in **Table 7**.

6.1 Schedule of Evaluations

Table 7. Overview of key study procedures/assessments throughout the trial

Construct: Assessment	Screening/ Baseline Visit 1	Baseline At-Home Collection	Screening/ Baseline Visit 2	Randomization: MBI, CBT, or HealthEd 6-week Group	6-week Follow-up	6-week At-Home Collection	1-year Follow-up	1-year At-Home Collection
Informed consent/assent	X							
BMI indices: Height & weight	X		X		X		X	
Medical & family history	X				X		X	
Good general health: Physical & puberty exam	X*		X*				X	
Depression: CES-D survey	X (pre-screen)				X		X	
Psychopathology: Medical history & K-SADS interview	X				X		X	
Insulin sensitivity: OGTT			X		X		X	
Body composition: BodPod measurement			X		X		X	
Stress-related behavior								
Hedonic eating: Interview, survey, & laboratory test meal			X		X		X	
Physical activity: ActiGraph		X			X	X		X
Stress-related physiology								
Stress reactivity: Trier Social Stress Test			X				X	
Cortisol dysregulation: Saliva		X				X		X

***BMI**: body mass index indices derived from height and weight. **CBT**: cognitive-behavioral therapy; **CES-D** survey: Center for Epidemiologic Studies-Depression Scale, assessed at the phone pre-screen phase; **HealthEd**: health education; **K-SADS**: Schedule for Affective Disorders and Schizophrenia for School-Age Youth – Computerized Version semi-structured interview; **MBI**: mindfulness-based intervention; **OGTT**: oral glucose tolerance test; **T2D**: Type 2 diabetes. *Exam may be completed at either screening visit based upon medical provider availability.*

6.2 Description of Evaluations

6.2.1 Phone Screening Evaluation

We will conduct a phone screen to estimate eligibility. The phone screen will estimate the inclusion criteria of: age, height and weight to estimate BMI percentile, and family history of T2D; and the exclusion criteria of: major medical problem and exclusionary medication use. At this stage, we also will have adolescents complete a REDCap survey of the CES-D depression measure to determine the inclusion criterion for elevated depression symptoms (CES-D total score >20). Adolescents who cannot easily access REDCap may be screened by CES-D interview (i.e., asking the questions by phone). We have used the same approach in previous studies (e.g., COMIRB protocol #16-2571). Using this approach, approximately 74% of adolescents who meet eligibility criteria by phone screen also meet eligibility criteria when they proceed to the consent and screening/baseline assessment phase.

Adolescents who appear to be eligible following the phone screening phase will be scheduled for a series of two screening/baseline assessment appointments. The first screening/baseline assessment may take place either remotely via secure video software/phone or in-person. The second screening/baseline assessment will be conducted in-person in the laboratory. Laboratory assessments will be collected at one of the four sites: (i) the Pediatric Clinical and Translational Research Center (CTRC) at Children's Hospital Colorado, (ii) the Human Performance and Clinical Research Laboratory at Colorado State University, (iii) the Military Cardiovascular Research Outcomes Program at the Uniformed Services University, or (iv) the Children's Research Institute at Children's National Medical Center. Ambulatory measures of physical activity and cortisol will be assessed in between the first and second screening/baseline appointments.

6.2.2 Consent and First Screening/Baseline Assessment

The following procedures will occur at the first screening/baseline assessment appointment to determine eligibility:

i. Informed consent/assent: The purpose, all testing procedures, program components and randomization will be reviewed by a trained member of the study team, in detail, at each respective site. Potential participants will be informed of the possible risks, inconveniences, benefits, and right to withdrawal. All participants and parents/guardians will sign COMIRB-approved consent/assent forms. In the event of a remote visit, e-consent will be obtained using REDCap and explained via secure video software or by phone. In the event that any changes are made to the consent/assent form(s) that require participants and parents/guardians to be re-consented, a member of the study team will explain the change in detail and have participants and parents/guardians sign a new copy of the updated consent/assent forms before further study procedures occur.

ii. BMI indices: BMI (kg/m^2) will be derived from height by stadiometer and weight by calibrated digital scale. BMI %ile[137] will be computed to estimate eligibility (≥85 percentile). If this initial screening/baseline visit is completed remotely, participants and parents/guardians will be provided with CDC instructions for obtaining an accurate height and weight, which will be used to estimate eligibility. These estimates will provide a reasonable estimate of whether youth will meet the BMI eligibility criterion. Using this approach in our other studies (e.g., COMIRB Protocol #16-2571), 100% of youth meet the BMI criterion at the second screening visit. The fasting measurement of weight and measured height collected at the second laboratory screening/baseline visit will be used to compute baseline BMI indices and

to determine final eligibility for this criterion.

iii. Medical and family history: A brief psychiatric and medical health history, including T2D, prediabetes, and gestational diabetes, of the participant and family will be conducted with a parent/guardian by a trained research staff member. Psychiatric history includes parent and teen report of any mental health diagnoses that could be exclusionary; if the family reports a current mental health diagnosis (e.g., anorexia nervosa, bipolar disorder, bulimia nervosa, conduct disorder, MDD with high acuity, obsessive compulsive disorder, panic disorder, posttraumatic stress disorder, psychosis, and substance/tobacco/alcohol use disorder), a psychologist will speak with the family for further assessment and follow-up/referrals (and exclusion), as indicated. Eligibility based upon at least one first- or second-degree relative will be determined, as well as medication status. As in our other studies,[119,138] females will report whether they are or suspect that they could be pregnant. Pregnant females will not be included.

iv. Psychopathology: The Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS) – Computerized Version[139] Suicidality and Self-Harm module will be administered to determine if adolescent girls and boys report depression acuity that, in the opinion of the study investigators, would warrant study exclusion and necessitate a referral for more intensive treatment. Any participant with current active suicidal ideation or self-harm, regardless of degree of mood concerns, will be referred for treatment (and excluded). If the screening visit is completed remotely, a parent or guardian will be asked to be in the home and accessible for the duration of the completion of the K-SADS to ensure access for communication of any safety concerns. Additionally, the interviewer will confirm the child's physical location prior to starting the interview. Written remote safety protocols have been developed in the event that suicidal ideation or other risks concerns arise.

v. Physical exam/puberty staging: Physical exam, including puberty staging as well as review of vitals, blood pressure, and waist circumference, will be conducted to evaluate adolescent health status. Exam may take place during either the first or second screening visit based on participant and provider availability.

6.2.3 Second Screening/Baseline Assessment

For the second screening/baseline assessment, participants will be asked to arrive for a morning appointment at the Pediatric CTRC at Children's Hospital Colorado, the Human Performance and Clinical Research Laboratory at Colorado State University, the Military Cardiovascular Research Outcomes Program at the Uniformed Services University, or the Children's Research Institute at Children's National Medical Center. They will be asked to observe a 10-hour overnight fast, meaning nothing to eating or drink other than water from ~10:00pm the night prior and the morning of their appointment. The following measurements to determine eligibility will be collected at this visit:

i. BMI indices: BMI (kg/m^2) will be derived from measured height in triplicate by stadiometer and fasting weight by calibrated digital scale. BMI z-score and BMI %ile[137] will be computed to determine eligibility (≥85 percentile).

ii. Physical exam/puberty staging: Physical exam including blood pressure in triplicate and waist circumference will be conducted to evaluate adolescent health status. Exam may take place during either screening visit 1 or 2 based on participant and provider availability.

iii. Insulin resistance: Oral glucose tolerance tests (OGTTs) are a well-validated, yet far

more practical and less invasive, costly, and labor-intensive method than clamps or intravenous glucose tolerance testing, while still permitting screening for T2D.[141] Following a 10-hour overnight fast, participants will receive 1.75 g/kg of glucola (max=75g). Blood will be sampled for insulin and glucose at fasting and 2-hours. Insulin resistance will be estimated from fasting insulin and glucose with the homeostasis model assessment of insulin resistance (HOMA-IR),[142] and we will calculate insulin sensitivity index (ISI) using fasting and 2-hour insulin and glucose.[143] Extant data suggest that ISI may yield more valid estimates of insulin sensitivity than HOMA-IR alone.[144-147] OGTT is well validated in youth, practical in large pediatric cohorts, and shows excellent convergence with estimates derived from more frequent sampling methods.[143-145,148,149] While for research purposes, blood will be processed and frozen until processing by the University of Colorado Core Laboratory for estimation of insulin/glucose to compute HOMA-IR and ISI metrics, fasting glucose and two-hour glucose will be checked at the visit, directly after each respective draw, for eligibility using an automated point-of-care device (e.g., StatStrip). If blood cannot be obtained with venipuncture, blood will be drawn using a finger prick by lancet to determine eligibility. Individuals with impaired fasting glucose (fasting glucose >=100 mg/dL), impaired glucose tolerance (2-hour OGTT glucose >=140 mg/dL), or with values potentially suggestive of T2D (fasting glucose >=126 mg/dL or 2-hour OGTT glucose >=200 mg/dL) will be notified and referred to their physician.

6.2.4 Enrollment, Baseline, and Randomization

Enrollment

This study uses a single informed consent form (for both parent/guardian and adolescent minor), that describe both the screening evaluations and the study procedures. Children's National Medical Center has a site-specific consent form and a separate site-specific assent form, reviewed and signed by the parent/guardian and adolescent, respectively. We will track the number of parents/participants who sign consent forms. "Enrollment" will be defined as the date of randomization. The enrollment date will be recorded on a case report form.

Baseline Assessments

As part of the screening process, adolescents will complete measures across both screening study visits. Measures may be completed at either visit or remotely, unless otherwise listed (e.g., Food Preferences Questionnaire).

i. Adolescents will report eating in response to negative affect on the Emotional Eating Scale-Adapted for Children (EES-C).[150] Youth rate the frequency of coping with negative affect in response to depression, as well as anxiety/anger/frustration and feeling unsettled. This measure shows good internal consistency, test-re-test reliability, discriminant and convergent validity,[150] including with our laboratory test meal studies.[86] Adolescents also will complete the Reward-Based Eating Drive Scale (REDS), a reliable/valid survey instrument of hedonic eating.[151,152] Participants will complete these surveys via REDCap.

ii. Theoretical therapeutic mechanisms: Adolescents in all conditions will complete four baseline surveys to measure theoretically informed therapeutic mechanisms underlying MBI and CBT. All adolescents will complete the Mindful Attention Awareness Scale (MAAS).[153] They also will complete the 20-item short form of the Five Factors of Mindfulness Questionnaire (FFMQ).[154] Parents will describe their adolescents on the Behavior Rating Inventory of Executive Functioning (BRIEF), assessing everyday

behavioral problems related to poor self-monitoring, emotional control, and related elements of executive dysfunction.[155] Adolescents will report frequency of negative and positive thoughts on the Children's Automatic Thoughts Scale-Negative/Positive.[156,157] They will describe frequency and perceived pleasantness of social and physical activities on the Pleasant Events Schedule (PES).[158]

iii. Socioeconomic status: Parents will report on a number of standard demographic and socioeconomic factors that are indicators of the multifaceted construct of socioeconomic status (SES), including items from the Hollingshead Index,[159] the MacArthur Scale of Subjective Social Status,[160] and the Household Food Insecurity Access Scale.[161]

In addition to the screening evaluations described in **section 6.2.1**, the following baseline assessments will be collected:

Screening Visit 1

At the first screening visit, which will take place either remotely or in-person, the following additional survey will be given:

i. Food Preferences Questionnaire: Participants will be asked to rate how much they like or dislike the foods that will be served during the laboratory eating paradigm (see below). We will assess average liking of lunch meal foods and average liking of snack foods, as well as the percentage of foods that were rated as "liked" (>5 on a Likert Scale from 1=I hate the food to 10=I love the food) for the lunch meal foods and for the snacks.

Baseline ambulatory home assessments

Adolescents will complete the following assessments in between the first screening visit and the second screening visit; adolescents will be offered an opportunity to re-wear/recollect home measures after the second screening visit, if they are non-compliant, in order to minimize missing data:

i. Stress-related behavior: Physical activity: Habitual activity will be measured with the ActiGraph GT3X accelerometer (ActiGraph, Pensacola, FL), a lightweight monitor with well-established validity, reliability, and low reactivity in diverse child and adolescent samples for over 10 years.[3] Adolescents will wear the monitor on their right hip during waking hours for 7 days. Consistent with recommended protocols, devices will be set to record with a 30 Hz sampling frequency and analyzed with 15-second epochs throughout the wear period. Adolescents will be given a log to record wear. Data will be reduced manually with data output and logs to delete non-wear periods. Following expert recommendations, data recorded on the first/last day will be discarded for incompleteness and possible reactivity on day 1. Adolescents with ≥4 complete days of data, including 1 weekend day will be retained in analyses.[192,193] Mean ActiGraph counts/minute will be classified as moderate-to-vigorous or sedentary time according to validated count thresholds determined by Evenson et al.[194] and validated in youth.[195,196] ActiGraph offers the advantage of characterizing the entire picture of habitual physical activity, including MVPA and sedentary time.

ii. Stress-related physiology: Cortisol diurnal rhythm: Cortisol awakening and diurnal rhythm will be assessed with saliva collected in the home on 1 weekday and 1 weekend day.[200] Samples will be obtained with an oral swab under the tongue for 120 sec at awakening, 2, 15, 30, and 45 minutes after awakening, 4:00 pm, and bedtime.[201,202] Adolescents will be instructed to refrain from eating/drinking (other than water) until after the 45-minute sample and for 15 minute prior to afternoon/bedtime samples. As in our

past studies, the use of a participant log, phone/text reminders, and alarms will be used to support adherence. We will use color-coded screw-top bottles that record opening times to improve accuracy of collection timing, given its high importance.[201] Salivary cortisol is a well-accepted non-invasive indicator of circulating physiologically active free plasma cortisol.[203] Latent growth models will model non-linear change in cortisol across 2 days as awakening response and diurnal rhythm.[202]

Screening Visit 2

At the second screening visit in the laboratory, the following additional baseline assessments will be evaluated:

i. Pubertal staging: As puberty is related to insulin resistance,[18] Tanner staging for breast and pubic hair (females) and testicular volume and public hair (males) will be performed by a trained medical provider. To accommodate medical provider schedules and participant/family schedules, pubertal staging may be carried out at screening visit 1 instead. Additionally, Tanner stage will be collected through adolescents' self-report on a validated questionnaire.[162] Participants will be asked to define their physical development based on illustrations of their external characteristics, which corresponded to Tanner stages 1-5 of breast and pubic hair development for girls and Tanner stages 1-5 of testicular volume and pubic hair development for boys.

ii. Body composition: During a fasted state, fat/fat-free mass will be assessed via air displacement plethysmography (BodPod), which shows good test-retest reliability and convergence with dual energy x-ray absorptiometry,[163] but is far more cost-effective.

iii. Stress-related behavior: Several measures of hedonic eating, referring to eating for reward/pleasure as opposed to physiological hunger,[75] will be collected. The overeating section of the Eating Disorder Examination (EDE), a semi-structured interview, will be administered by a trained research assistant to identify frequency of 3 types of eating episodes: objective binge (overeating with loss of control), subjective binge (loss of control without objective overeating as assessed by the interviewer, but viewed as excessive by the interviewee), and objective overeating (overeating without loss of control). Tests of the EDE's discriminant validity, internal consistency, concurrent validity and test-retest reliability support its use in adolescents.[164-166] The EDE may be conducted in-person during the screening visit, or alternatively, may be conducted remotely using secure video software or by phone.

A laboratory paradigm[138] will be used to observe eating in the absence of hunger, which we have shown is related to dispositional mindfulness in adolescents at risk for T2D.[168] After eating a lunch-type meal until no longer hungry, youth will eat *ad libitum* for 15 minutes from a large, palatable snack food array. Youth are instructed to taste and rate their preferences for the snack foods and then to consume as much as they would like. Activities (e.g., magazines, coloring sheets, handheld video game like a Nintendo Switch) are provided during the snack period. Snacks consumed are assessed as changes in weight (g) before-after eating, and total energy intake (kcal) in the absence of hunger is calculated using USDA National Nutrient Database for Standard Reference and nutrient manufacturer information.

iv. Stress-related physiology: Adolescents will complete the Trier Social Stress Test,[169] involving a 10-minute speech and 4-minute mental arithmetic task in front of an

evaluator, which is known to induce a physiological stress response.[170] Blood pressure and heart rate will be monitored approximately every 3 minutes throughout the test and summarized as area under the curve. We have shown that dispositional mindfulness relates to adolescents' reactivity in this task.[171]

Randomization

Upon completion of all screening and baseline assessments, a research staff will notify the adolescent and their parent/guardian that they completed all screening and baseline assessments and are eligible. The ideal window is that screening/baseline assessments will occur within 12 weeks/3 months of the start of the intervention phase (first group session); we will allow for up to 6 months between screening/baseline and group initiation. In the event that more than 6 months transpires since the screening/baseline interval, all interested adolescents who appeared to be eligible or who had been determined to be eligible, will be invited to complete a re-screening, referring to a repeat of all screening/baseline assessments. Re-screening will only be offered if there is sufficient opportunity for the participant to take part in a subsequent intervention cohort (e.g., originally screened for cohort 1, but after >6 months, could be re-screened to be considered for participation in cohort 2). After all screening/baseline assessments are complete and prior to randomization, adolescents and parent/guardians will be asked to confirm their desire to continue to participate in the study. Adolescents and parents will each, independently report their preference for group condition (MBI, CBT, HealthEd, or no preference). Adolescents then will be randomly assigned to either a MBI, CBT, or HealthEd group using the RedCAP randomization module by the lead study coordinator. Date of randomization will be considered date of enrollment.

6.2.5 Blinding

The RedCAP randomization module conceals the randomization sequence. Thus, prior to randomization, all study personnel will be blind to allocation. Upon randomization, follow-up research staff assessors will remain blinded to allocation. These staff include those performing follow-up interviews, test meals, body measurements, and insulin resistance. Additionally, raters of intervention administration fidelity/competence (Drs. Patricia Broderick and Eric Stice research groups, experts in MBI and CBT programs, respectively) will remain blinded to rating of the adolescent group intervention sessions, as well as raters of group cohesion. Dr. Shomaker and Dr. Pyle will remain blind until the database is locked.

To protect the blind, the intervention arm allocation will be limited to the minimum number of study documents necessary to pragmatically operate the study. Research staff running follow-up assessments, as well as the expert raters and Drs. Shomaker and Pyle, will not have access to any study document that reveals the blind.

6.2.6 Follow-up Visits

There are two follow-ups for this study: a 6-week/post-treatment follow-up and a 1-year follow-up. The 6-week follow-up visit ideal window will be within 4 weeks of the last group session; the 6-week follow-up will be completed no longer than 8 weeks after the last session of the group intervention. The 1-year follow-up visit ideal window will be 12 months (-/+ 4 weeks) after the first group session; the 1-year follow-up will be completed no longer than 18 months after the first day of the group intervention.

The following assessments will take place at each follow-up:

6-week Follow-up Visit

The following assessments that were collected at baseline will be repeated:

- BMI: height/weight body measurements
- Physical: blood pressure/waist circumference (no Tanner/pubertal staging)
- Body composition: BodPod
- Depression symptoms: CES-D survey
- Suicidality/self-harm: K-SADS-COMP interview to assess suicidality and self-harm only since the group program started
- Insulin resistance: OGTT
- Hedonic eating: EDE interview, EES-C, REDS, and laboratory test meal and food preference questionnaire
- Stress reactivity: Trier Social Stress Test
- Therapeutic mechanisms: MAAS, FFMQ, BRIEF-Parent Version, Children's Automatic Thoughts Scale, and PES
- Medical health history: Medical health, including treatment history (e.g., new medications, initiation of counseling, etc.), will be updated
- At-home collection: Adolescents will re-wear ActiGraph assessment of physical activity and repeat home saliva collection

In addition to the repeat assessments, we also will conduct the following evaluations at the post-treatment/6-week follow-up interval:

- Adolescent focus groups: We will conduct adolescent focus groups with each MBI, CBT, and HealthEd group. This qualitative strand adds patient voice to this multisite intervention refinement and optimization phase, ensuring outcomes of a future, larger efficacy trial are meaningful, valuable, and helpful for adolescents.[172] Trained moderators will facilitate small group discussions, using a mix of open-ended and targeted questions designed to engage adolescents and elicit emergent themes that may not have been captured through the quantitative strand.[173] Focus groups will cover adolescents' subjective experiences of: 1) enabling mechanisms, 2) stress/mood management, 3) negative aspects of interventions, 4) facilitators/barriers to home practice, and 5) perceptions of group cohesion/facilitator alliance.
- Parent acceptability: Parents will complete an adapted program acceptability questionnaire[131] to assess parents' knowledge and monitoring of their adolescents' home practice assignments, as well as parents' perceptions of likeability, credibility, and perceived benefits to their teenagers' stress, mood, health behaviors, and physical health and T2D risk. In addition to structured questions, we also will include open-ended prompts to provide feedback on enablers/barriers to group participation and home practice.

1-year Follow-up Visit

The following assessments that were collected at baseline will be repeated:

- BMI: height/weight body measurements
- Physical/puberty: blood pressure/waist circumference/Tanner staging and self-reported puberty questionnaire
- Body composition: BodPod

- Depression symptoms: CES-D survey
- Suicidality/self-harm: K-SADS-COMP interview to assess suicidality and self-harm only since the last assessment
- Insulin resistance: OGTT
- Hedonic eating: EDE interview, EES-C, REDS, and laboratory test meal and food preferences questionnaire
- Stress reactivity: Trier Social Stress Test
- Therapeutic mechanisms: MAAS, FFMQ, BRIEF-Parent Version, Children's Automatic Thoughts Scale, and PES
- Medical health history: Medical health, including treatment history (e.g., new medications, initiation of counseling, etc.), will be updated
- At-home collection: Adolescents will re-wear ActiGraph assessment of physical activity and repeat home saliva collection

In addition, adolescents will report their degree of maintenance of techniques or application of knowledge learned during the intervention:

- Maintenance: Adolescents will report the degree to which they are using MBI, CBT techniques and/or application of HealthEd knowledge.

6.2.7 Completion/Final Evaluation

The 1-year follow-up visit, including at-home collection evaluations, represents the participant's completion of the study and final evaluation. In line with the intent-to-treat principle, we will follow all participants who are enrolled/randomized regardless of their participation in the intervention phase. Adolescents who are eligible at baseline but who develop conditions that would have been exclusionary will continue to be studied unless there is a concern about safety and/or a significant concern about validity (e.g., female who becomes pregnant and is pregnant or nursing at the time of the 6-week or 1-year follow-up evaluation). In samples of adolescents with overweight/obesity, family history of T2D, and elevated depression symptoms, it is anticipated that some adolescents will develop T2D and MDD. Safety assessments are in place, as in our other trials, and are addressed in this protocol, **section 7**. At completion of the 1-year follow-up/study endpoint, we will give study participants a letter of appreciation for their participation. Because we are working with at-risk adolescents in this study, we will provide a site-specific study mental health referral list to all participants at the conclusion of the study.

Upon initiation of the 1-year follow-ups for the study, we will conduct personnel focus groups (e.g., research coordinators, research assistants, intervention facilitators) to qualitatively evaluate the protocol. These focus groups will cover personnel's subjective experiences of: 1) enabling mechanisms, 2) negative aspects, and 3) protocol barriers. Information gleaned from these focus groups will inform modifications to optimize all aspects of the protocol for a future larger scale multisite efficacy trial.

7. RISK ASSESSMENTS

7.1 Risks

The risks associated with participation in the proposed study are consistent with IRB definitions of minimal risk. Participants and their parents/guardians will be informed in detail of all potential risks during the informed consent and assent process. We anticipate the follow risks:

i. Physical examination: Physical examination by a licensed medical provider, including a physician or advanced practice provider, will be performed in a private examination room. Although appropriate measures will be taken to protect privacy, some adolescents may find this embarrassing.

ii. Phlebotomy: We will draw a blood sample in a fasted state and two-hours after glucola administration. We will minimize the pain of blood drawing by offering the participant numbing cream prior to the blood draw. Blood will be drawn by venipuncture, but finger prick for point-of-care glucose assessment will be offered if blood cannot be obtained by venipuncture. Discomforts are common, but minor. In about one in 10 cases a small amount of bleeding under the skin will produce a bruise (uncommon risk). The risk of a blood clot forming in the vein is about one in 100, while the risk of infection or significant blood loss is one in 1000 (rare, but serious). Amount of blood withdrawal (no more than 3 tablespoons at the screening, and 3 tablespoons at each of the 2 follow-up appointments: 6-week and 1-year) is well below the NIH and pediatric IRB guidelines for a safe amount of blood withdrawal.

iii. ActiGraph: This small device to measure moderate-to-vigorous physical activity and sedentary time will be worn on the hip for 7 consecutive days at the baseline period and again at the 6-week and 1-year follow-up intervals. Aside from the inconvenience of wearing the device and removing it during water-based activities (e.g., swimming), as well as the time required to complete the accompanying log to record activity, there is no risk involved with these devices.

iv. Air displacement plethysmography (BodPod): Body fat and fat-free mass measurements by BodPod involve no risk and are not painful. It is possible that some participants may feel slightly claustrophobic because the BodPod requires the occupation of a small space for a short period of time. Participants also must wear tight-fitting clothing, such as a bathing suit, for the test. Participants can always communicate with the experimenter during the test. Any individual who is uncomfortable may stop the test at any time.

v. Salivary samples: Saliva samples entail no risk but may be inconvenient.

vi. Psychological questionnaires, interviews, and focus group: Psychological testing involves no risk but may cause inconvenience because of the time required for testing. It also may cause slight discomfort if the wording of some questions makes the subject uncomfortable. The scales and interviews used are well-validated instruments designed to seek information without undue embarrassment to the participants. Qualitative focus group queries will be prepared with the guidance of Dr. Thompson (Co-I), a psychologist and qualitative expert, and administrators will be thoroughly trained in their proper, standard administration. For all quantitative and qualitative measures, participants are not required to answer a question if it makes them uncomfortable. Psychological questionnaires will be administered by trained research staff. Psychological interviews will be conducted by a psychologist or trained post-doctoral fellow, graduate student, or research coordinator.

vii. Laboratory test meals: Food ingestion under controlled conditions involves no risk and is not expected to cause any participant discomfort. Participants who report food allergies to items on the laboratory test meal will not participate in this assessment for safety; based upon our prior implementation of this meal paradigm with 1,000s of youth, the vast majority (>99%) are not allergic and report high liking of the foods served. Research staff who will be preparing and measuring food for the laboratory

test meals will have completed food safety training that focuses upon safe food handling, proper temperatures, hand washing, and using gloves for handling foods. Staff also will be trained on the weighing/processing of foods for controlled feeding studies to ensure consistency in the method and presentation within and across the study sites.

viii. Trier Social Stress Test (TSST): The TSST has been used in multiple vulnerable populations, including children and adolescents, the elderly, and pregnant women. While it may make participants temporarily nervous or uncomfortable, the TSST is designed to specifically elicit the physiological response system. Performing this task may cause some temporary emotional distress. Typically, this distress does not last long. The amount of physiological arousal that the TSST generally elicits is roughly comparable to mild physical exertion. Participants are told ahead of the task that they have the right to stop the task at any point should they wish. If there is evidence of severe distress, researchers are trained to stop the task. All participants are debriefed after each visit in which the TSST is administered.

ix. Group participation: In the course of MBI, CBT, and HealthEd, issues arise that may be uncomfortable or stressful for some participants. Based upon the participant's level of comfort and relevance of the concern to the group process, such issues may be discussed in the group. In querying adolescents about their psychological functioning, serious psychiatric disturbances may be uncovered. In addition, topics that may be personally sensitive will be discussed in group. Emotional distress is typically expected and often an important component necessary to make the changes required for improvements in mood or stress. There also may be times of conflict between group members. While stress and interpersonal conflict are emotionally difficult experiences and may cause distress for participants, they are often part of the process of making changes. The goal of the group facilitators and the group as a unit is to support each participant through stressful periods in order to reduce depressive symptoms and improve mood. Groups will be led by a psychologist, who will be fully trained in the programs, and they will receive weekly supervision from Dr. Lucas-Thompson (MBI) and Dr. Gulley (CBT, HealthEd).

7.2 Adequacy of Protection Against Risks

Subjects will be encouraged to report any discomforts during testing and any illness or change in wellbeing immediately to the local site PI or study coordinator at any time during the study. The following protection against risks are in place:

i. Phlebotomy: Sterile technique followed by brief compression and utilization of trained phlebotomists will minimize risk of infection or bleeding. ELA-Max cream or an over-the-counter numbing cream (e.g., Anusol) can be applied to minimize pain. Participants will rest in bed or chair while phlebotomy is performed to ensure safety. Phlebotomy will be collected at Colorado State University (CSU; Site 1) in the Human Performance/Clinical Research Laboratory, at Children's Hospital Colorado (CHCO; Site 2) in the Pediatric Clinical and Translational Research Center (CTRC), at the Uniformed Services University (USU; Site 3) in the Military Cardiovascular Outcomes Research (MiCOR) program, and at Children's National Medical Center (CNMC; Site 4) in the Clinical Research Unit. All units are familiar with blood drawing and equipped to perform far more complex procedures (e.g., intravenous glucose testing, clamps, biopsies, etc.) than the fasting and two-hour blood draws proposed in the current protocol. In addition, a physician or advanced practice provider will always be on call.

ii. Emotional assessments, monitoring, and referrals: It is anticipated that within samples comprised of adolescents with overweight/obesity and elevated depression symptoms, there will be participants who develop more severe depressive symptoms or suicidal ideation or behavior. Should a participant demonstrate signs of active suicidal ideation or suicidal behavior or worsening depression or mental health, referrals to mental health providers will be provided. All participants are carefully debriefed and written procedures for managing risk and safety circumstances (e.g., suicidality) are in place. During the baseline screening, if the KSADS-COMP interview assessment reveals current suicidal ideation or self-harm or if parents/teens reports a current exclusionary mental health diagnosis, the participant will be referred for treatment and excluded from the study. During the active intervention phase, participants' mood will be monitored weekly on a mood monitoring form that includes an assessment of suicidal ideation. During the 6-week and 1-year follow-ups, the KSADS-COMP is re-administered to assess for suicidality/self-harm. All research KSADS-COMP interviewers and MBI, CBT, and HealthEd interventionists will be trained to assess suicidal intent, plan and possible method, and they will discuss this assessment with a clinical psychologist supervisor at each site. A specific, detailed protocol is in place for addressing concerns about worsening mood or reports of suicidality. If indicated, a treatment referral will be facilitated with the participant and the family. If the participant is in need of an urgent evaluation (e.g., is actively suicidal with a plan and intent to carry out such actions), she or he will be immediately referred to the nearest emergency department until the participant can be safely referred for outside treatment as recommended.

Based upon our prior studies,[56,57,100,119] we anticipate that depression symptoms will improve in both MBI and CBT, with potentially greater improvements in MBI. We also anticipate that depression symptoms will improve in adolescents assigned to HealthEd, but to a lesser extent than adolescents in MBI and CBT. CBT is a treatment of choice for prevention and treatment of depression,[174] and the particular CBT manualized program used in this study has demonstrated efficacy and effectiveness in reducing depression symptoms and preventing future MDD occurrence in adolescents over a 1-2 year follow-up.[123-125] MBI has less research evidence, particularly for long-term follow-up/duration of effects, but our preliminary data support the possibility that the particular manualized intervention proposed in this trial, Learning to BREATHE, may be superior to CBT, for decreasing depression symptoms at post-treatment and up to 1 year later.[100,101] Adolescents recruited for participation in the current, proposed study will have elevated depression symptoms, but will not report a psychiatric diagnosis that, in the opinion of the study investigators, necessitates treatment. Likewise, adolescents will not be enrolled who report current active suicidality or self-harm. Most adolescents with subthreshold depression symptoms, as well as the majority of adolescents with depression disorders like MDD, do not seek or obtain treatment. Thus, participation in the study holds the prospect, regardless of condition, of increased monitoring than would be likely if adolescents did not participate.

iii. Physical assessments, monitoring, and referrals: During the baseline screening, if assessments reveal a physical health problem (e.g., T2D), the participant will be referred for treatment and excluded from the study. Eligible adolescents who proceed to enrollment/randomization will be identified as being at risk for developing T2D, but they will not have current T2D. The vast majority of adolescents at-risk for T2D do not receive interventions to reduce their risk of developing T2D. Intensive, structured lifestyle interventions in clinical trials have demonstrated some short-term

success in adolescents, but typically have limited sustainability and poor adherence.[24] Thus, adolescents who are randomly assigned to the attention- and time-matched didactic control condition, HealthEd, will receive more support and psychoeducation than they would very likely receive if they did not participate in the study. Our preliminary data also are suggestive of the possibility that CBT and MBI (Learning to BREATHE) may improve or prevent the worsening of insulin resistance.[56,57,100]

iv. Vulnerable subjects: Adolescent minors (ages 12-17 years) are included as vulnerable subjects in the proposed study. In the absence of sufficient evidence-based programs to address the major public health problems of obesity and cardiometabolic disease in adolescents, there is a strong need for the scientific advancement of targeted therapies that jointly address depression and insulin resistance as the main precursor to T2D. The PI, Co-investigators, and the expert Consultants are experienced in working with minors. The research of key members on the investigative team, to date, has primarily focused on this vulnerable population in an effort to intervene prior to adulthood, at a time when the course of depression and insulin resistance is more malleable. Study staff will be thoroughly trained in identifying any emotional or physical distress or discomfort and will be instructed to terminate the protocol if a participant demonstrates distress. Study staff will emphasize to participants that they are able to withdraw from the study at any time, without penalty.

7.3 Specification of Safety Parameters

The following key measures and corresponding parameters will guide risk/safety handling:

i. Oral glucose tolerance testing (OGTT): OGTT is conducted at three time points during the course of the study, including screening/baseline, 6-week follow-up, and 1-year follow-up. If an adolescent has impaired fasting glucose (fasting glucose >=100 mg/dL), impaired glucose tolerance (2-hour OGTT glucose >=140 mg/dL), or with values potentially suggestive of T2D (fasting glucose >=126 mg/dL or 2-hour OGTT glucose >=200 mg/dL) based upon immediate glucose analysis (e.g., StatStrip), they and their parent/guardian will be notified and referred to the primary care physician for follow-up. Those adolescents with T2D at baseline will be excluded. Adolescents with impaired fasting glucose or impaired glucose tolerance will not be excluded, but they and their families will be notified at baseline as well as any follow-up assessment.

ii. Medical history/physical exam: A medical history is conducted at baseline/screening and updated at the 6-week and 1-year follow-up. A review of physical health is conducted at all three of these intervals, with pubertal staging only at baseline/screening and repeated at 1-year if a physician/provider reported adolescent to be below tanner staging 5 at baseline . Any adolescent with a major medical problem or taking medications that could interfere with safety or validity, at baseline, will not be included. Any adolescent with a current exclusionary mental health diagnosis reported by parents and/or adolescents will not be included. Physicians/medical providers at each site will review medical histories during the follow-up interval and if any medical condition develops that was not present at baseline, will refer families for medical treatment, as indicated. Likewise, psychologists will refer families for psychological treatment, as indicated.

iii. Schedule for Affective Disorders and Schizophrenia for School-Aged Youth – Computerized Version (KSADS-COMP) – Suicidality/self-harm module and mood monitoring: The KSADS-COMP semi-structured clinical interview – Suicidality and Self-harm Module is conducted at three time points during the course of the study, including screening/baseline, 6-week follow-up, and 1-year follow-up. Mood monitoring is carried

out during the 6-week intervention phase, with adolescents completing a mood monitoring form at each intervention session, in all conditions (MBI, CBT, and HealthEd). As determined on the KSADS-COMP, adolescents who have, at baseline, active suicidal ideation or self-harm—a discreet marker of depression severity—will not be studied. The KSADS-COMP administered at the two follow-ups re-assesses suicidality/self-harm and in the event that an adolescent develops a suicidality or self-harm at either follow-up, the adolescent and parent/guardian will be notified and treatment referrals will be provided as indicated.

7.4 Adverse Events and Serious Adverse Events

7.4.1 Adverse Events

An **adverse event** is defined as any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during the study, having been absent at baseline, or if present at baseline, appears to worsen. All adverse events will be recoded regardless of their relationship to the study intervention (i.e., study and non-study related adverse events, as well as expected and unexpected adverse events).

7.4.2 Serious Adverse Events

A **serious adverse event** is defined as any untoward medical occurrence that results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly.

7.4.3 Adverse Events Reporting

All adverse events, including serious and non-serious, expected and unexpected, will be reported to the IRB at the annual continuing reviews in the form of electronic data sheets or summary language. Serious adverse events will be reported by the PI verbally and in writing as soon as possible to the IRB, IMC, and NCCIH, with a maximum of 7 calendar days for death or life-threatening adverse events, and within 15 calendar days for all other serious adverse events. All site PIs will be responsible for monitoring adverse events at their respective sites and if serious events arise, reporting this immediately to the study PI Dr. Shomaker.

Adverse event forms will be completed by study coordinators on a form which is saved on REDCap or a secure server, which can only be accessed by site personnel using a username and password.

7.5 Follow-up for Adverse Events

All adverse events will be reviewed at a weekly coordinators meeting, run by the lead study coordinator and attended by all four local site coordinators (CSU, CHCO, USU, and CNMC), as well as at a monthly all hands investigator/staff team meeting. For expected adverse events (e.g., development of MDD, suicidal ideation, or T2D), we will follow protocol and risk/safety management plans, as outlined in **section 7.3 of this protocol**. For any unexpected, study-related events, we will use a team-based approach to problem solve a resolution that minimizes the likelihood of the event recurring.

7.6 Safety Monitoring

We have formed an independent monitoring committee (IMC) comprised of three individuals who are not part of the proposed research and who have experience in the conduct and analysis of clinical trials. Dr. Olga Gupta is a physician with expertise in adolescent obesity and type 2 diabetes; Dr. Angelica Eddington is a clinical psychologist with expertise in adolescent

depression and diabetes; and Dr. John Brinton is a biostatistician who has experience in randomization, monitoring, and analysis of clinical trials.

In the start-up phase of the study (Year 1, Quarters 1-2), we will convene an initial meeting with the IMC, including the PI Dr. Shomaker (CSU) and the study statistician, Dr. Pyle, to discuss and establish the complete and detailed data safety and monitoring plan (DSMP). The investigative leads at each side (i.e., Drs. Kelsey, Tanofsky-Kraff, and Mackey) will review the DSMP and be available for consultation and questions. Specifically, we will review the protocol methods, steps that will be taken to monitor and maintain confidentiality of data, consent documents, all risks and protections to participants, and qualitative and quantitative data analytic plans. We will review expected adverse events and planned steps to minimize risks, and we will discuss the timeline for reporting of serious adverse events and non-serious adverse events to the IMC and IRB. Additionally, we will specify stopping rules.

Following the initiation of recruitment, a report will be prepared every 6 months by Dr. Shomaker and Dr. Pyle, with administrative support from the multisite coordinator, which will include information regarding timeline/milestones, participant recruitment, accrual, and attrition by condition and site, potential adverse events by condition and site, summary statistics for key variables by site, including reports of any missing data, preliminary analyses of fidelity, feasibility, and acceptability, as they become available, and any other issues or unanticipated problems or challenges that may have arisen during the course of the study.

The IMC will convene every 6 months to provide feedback on the progress of the study as well as assistance in approaching any potential difficulties that may arise. More frequent meetings will be scheduled as needed. Dr. Shomaker, as well as the statistician and investigative leads at each site, will be available to attend IMC meetings to answer questions during an open session, prior to the IMC's private deliberation. The role and responsibilities of the IMC will include: reviewing the protocol and the DSMP; considering any possible major changes to the protocol; evaluating the progress of the study, including assessments of data quality, timeliness, recruitment, retention, and participant risk vs. benefit; reviewing serious adverse events; and considering modifications to the study protocol based upon progress. The IMC will issue a formal memo, signed by all members of the IMC, at the conclusion of their deliberations. All reports prepared by the study team for the IMC and all memos issued by the IMC on the progress of the study will be provided to NCCIH.

8. STATISTICAL CONSIDERATIONS

8.1 General Design Issues

The current project is a pilot randomized controlled trial implemented at four sites with three arms. In line with the NCCIH U01/R01 grant mechanism, the purpose of the project is to gather information for use in designing a subsequent trial to compare the efficacy of the three arms.

8.2 Sample Size and Randomization

Aim 1: Assuming that the true proportion of sessions within an intervention arm during which fidelity criteria are met is 85%, ρ=0.06,[175] 4 clusters (one facilitator per treatment arm per site), 16 sessions per cluster, and coefficient of variation of the number of sessions equal to 0.01, then the width of the 95% CI is 24%. This estimate indicates that we will have reasonable precision in our estimates of fidelity after accounting for the intraclass correlation coefficient (ICC).

Aim 2: Assuming that the true proportion of loss to follow up within an intervention arm is 15%, ρ=0.06, 4 clusters, an average of 8 participants per cluster, and coefficient of variation of the

number of participants equal to 0.11, then the width of the 95% CI is 28%. In the original power calculations, the width of the 95% CI was 26%, so we will still have reasonable precision in our estimates of loss to follow up after accounting for the ICC.

8.3 Definition of Populations

The intent-to-treat sample will be all adolescents who are randomized (N=120).

8.4 Interim Analyses and Stopping Rules

Given the pilot nature of this study, no interim analyses or stopping rules are planned outside of the outcomes listed subsequently in **sections 3 and 8.5**. Analyses of primary and secondary outcomes will be conducted when all data for the respective outcomes have been collected. In line with NCCIH's recommendations, no analyses of outcomes will be carried out prior to study completion.

8.5 Outcomes

Dr. Pyle is the study biostatistician and she will be responsible for conducting the analyses of this pilot trial and discussing those results at the all hands investigator/staff monthly meeting. Dr. Thompson is the study qualitative expert and she will be responsible for overseeing the analyses of the focus groups with adolescents and focus groups with study personnel. Dr. Thompson will present these results for discussion, as they become available, at the all hands investigator/staff monthly meeting.

8.5.1 Primary Outcome

The primary outcomes for each study aim are:

Aim 1: Test multisite fidelity of training/implementation of 6-week group MBI, CBT, and HealthEd to adolescent girls and boys at-risk for T2D with depression symptoms		
Objective	**Endpoint**	**Metric; Analysis**
Intervention Fidelity (Primary)	12-months	Facilitators score ≥8 on adherence and competence ratings of MBI, CBT, and HealthEd adolescent group sessions (*1*=poor to *10*=exceptional)

Aim 2: Evaluate multisite feasibility/acceptability of recruitment, retention, and adherence for a protocol involving randomization to 6-week group MBI, CBT, or HealthEd with 6-week and 1-year follow-up		
Objective	**Endpoint**	**Metric; Analysis**
Recruitment Feasibility (Primary)	12-months	≥80% eligible adolescents will enroll

8.5.2 Secondary Outcomes

The secondary endpoints for each aim are:

Aim 1: Test multisite fidelity of training/implementation of 6-week group MBI, CBT, and HealthEd to adolescent girls and boys at-risk for T2D with depression symptoms		
Objective	**Endpoint**	**Metric; Analysis**
Training Fidelity (Secondary)	6-months	Facilitators score ≥80% on post-training knowledge/ competency tests of MBI, CBT, and HealthEd

Training Fidelity (Secondary)	6-months	Facilitators score ≥8 on adherence and competence ratings of MBI, CBT, and HealthEd mock group sessions (*1*=poor to *10*=exceptional)
Aim 2: Evaluate multisite feasibility/acceptability of recruitment, retention, and adherence for a protocol involving randomization to 6-week group MBI, CBT, or HealthEd with 6-week and 1-year follow-up		
Objective	**Endpoint**	**Metric; Analysis**
Recruitment Feasibility (Secondary)	12-months	Attainment of target *N*=120 within a 12-month period; CONSORT flow/number of months to reach recruitment goal
Intervention Feasibility (Secondary)	6-weeks	≥80% adolescents attend 5:6 (80%) group MBI/CBT/HealthEd sessions
Intervention Acceptability (Secondary)	6-weeks	≥80% adolescent liking/credibility ratings ≥4 (*1*=not at all to *5*=extremely)
Intervention Acceptability (Secondary)	6-weeks	Themes indicative of acceptability of interventions, as derived from grounded theory/qualitative analysis of adolescent focus-groups at post-intervention
Retention Feasibility (Secondary)	12-months	≥80% at post-treatment follow-up and ≥70% at 1-year follow-up
Assessment Feasibility (Secondary)	18-months	≥95% accuracy on standardized protocol checklists for all assessments

8.6 Data Analyses

8.6.1 Primary Analyses

In Aim 1, descriptive analyses will be conducted to: (i) describe post-training knowledge/competency of MBI, CBT, and HealthEd to determine if facilitators score ≥80%; (ii) describe adherence and competence ratings of mock group sessions of MBI, CBT, and HealthEd to determine if ratings ≥8 (1-10 scale with 10 being the most positive valence); and (iii) describe adherence and competence ratings of pilot group sessions of MBI, CBT, and HealthEd by blinded, expert reviewers to determine if ratings ≥8. Chi-square analyses will be used to explore whether the percentages meeting these criteria vary across conditions (MBI vs. CBT vs. HealthEd) and site. In Aim 2, study flow will be described according to CONSORT guidelines for the reporting of clinical trials.[176,177] Descriptive analyses will be generated to determine: (i) the percentage of adolescents who enroll after being determined to be eligible, (ii) number of months to reach recruitment goal, (iii) percentage of adolescents who attended 5 of 6 (≥80% sessions), (iv) percentage of adolescents whose likability/credibility ratings were ≥4 (1-5 scale, with 5 being the most positive valence), (v) percentage of adolescents who complete post-treatment and 1-year follow-up assessments, and (vi) percentage compliance with standardized operating procedure checklists for all assessments. Analyses of variance (ANOVA) and chi-square will be used to describe any potential differences across the 4 sites and the 3 intervention arms. A Tukey adjustment will be used to control for multiple comparisons. For the primary analyses in Aims 1 and 2, we do not plan to adjust for covariates as our interest is in estimating measures of success independent of participant characteristics.

8.6.2 Secondary Analyses

One goal of the secondary analyses is to assess for a signal of a clinically significant effect of the interventions on depression and insulin sensitivity, which would be important outcomes in a larger efficacy trial. For these analyses, we will follow the approach of Cocks and Torgesen,[178] in which one-sided 80% CI's are calculated for the treatment effect. If the appropriately powered pilot study does not show evidence of an effect, this does not necessarily preclude the main trial going forward. Careful consideration for the possible reasons for the lack of effect and regarding how the intervention can be strengthened are needed. However, powering a pilot study in this way ensures that it provides as much information as possible. Given our final sample size after accounting for attrition, the pilot study is powered to detect a standardized effect size of 0.3, which is considered a small to medium effect size.

Another purpose of secondary analyses is to supplement the mixed-methods analyses in Aim 3 used to refine study procedures and interventions in preparation for a future efficacy trial by understanding predictors associated with study outcomes, as well as mediators and moderators of intervention effects. This study is not designed as an efficacy study, and we will not necessarily have sufficient statistical power for the secondary analyses. However, results of these analyses may help inform changes to the interventions. We will examine predictors of participant attrition, attendance, and likability/credibility ratings. We will use multilevel mixed-effects models to examine change over time in measures of depression, insulin resistance, stress-related behavior, and stress physiology. These models will allow us to account for and estimate the correlation within study site and intervention cohort, as well as the correlation between repeated measures within a participant. ICC will be estimated using the method of Donner[179] for continuous variables and Ridout[180] for binary variables. The models will contain terms for group, time, and a group by time interaction. We will adjust for the baseline value of the outcome, and will also consider adjustment for baseline age, sex, race/ethnicity, particularly if these variables are not balanced across study groups. Models will be adjusted for baseline adiposity and change in adiposity to examine whether decreases in depressive symptoms improves insulin sensitivity independent of adiposity. If we find significant between-group differences in the insulin resistance, stress-related behavior, and stress physiology outcomes, we will test whether those effects are moderated by baseline depressive symptom severity (CES-D score) by including an interaction term in the model. We will also examine participant characteristics associated with these outcomes in order to better understand factors that moderate the response to intervention. Mediation analyses, using the product-of-coefficients method and bootstrapped standard errors, will be used to explore whether improvements in insulin sensitivity (if present) are mediated by changes in stress-related behaviors and stress physiology. Quantitative measures of group cohesion, therapeutic alliance, and perceived credibility/expectancy, summarized by intervention arm, will inform modifications to facilitator training, optimization of interventions, and study design in the larger trial. Finally, we will examine theoretical therapeutic mechanisms to explore the hypotheses that in MBI, mindfulness, monitoring/acceptance, and executive function will improve and in CBT, thoughts and pleasant activities will improve, compared to each other and to HealthEd.

8.6.3 Qualitative Analysis Plan

At post-intervention, we will conduct adolescent focus groups with each MBI, CBT, and HealthEd, group. This qualitative strand adds patient voice to this U01 multisite intervention refinement and optimization phase, ensuring outcomes of a larger efficacy trial are meaningful, valuable, and helpful for adolescents.[172] Trained moderators will facilitate 24 semi-structured small group discussions (*n*=5), using a mix of open-ended and targeted questions designed to engage adolescents and elicit emergent themes that may not have been captured through the quantitative strand.[173] Focus groups will cover adolescents' subjective experiences of: 1) enabling mechanisms, 2) stress/mood management, 3) negative aspects of interventions, 4)

facilitators/barriers to home practice, and 5) perceptions of group cohesion/facilitator alliance. Upon initiation of 1-year follow up visits, we will conduct personnel focus groups (e.g., coordinators, assistants, facilitators) to qualitatively evaluate the protocol. These focus groups will cover personnel's subjective experiences of: 1) enabling mechanisms, 2) negative aspects, and 3) protocol barriers.

Regarding the analytic plan, for all focus group discussions, an observer will take detailed notes and audiotape all dialog. Following the discussion, the facilitator and observer will complete a content summary form, briefly describing the context of the group and "memoing" any evolving themes.[181] Audiotapes will then be transcribed verbatim and uploaded along with observer notes and summary forms to a qualitative analytic software program (ATLAS.ti or NVivo). Two researchers with training and experience in qualitative methods will jointly analyze the data using a constant comparative analytic approach, including open and axial coding within and between transcripts.[182] Dr. Thompson has expertise in qualitative analyses and grounded theory and will lead the creation of focus group moderator guides in collaboration with the study team. Dr. Thompson will lead all qualitative data analysis tasks with assistance from a research staff member trained in qualitative analysis, and regular consultation and feedback from Dr. Pyle, Dr. Shomaker (PI), and additional input from the entire investigative team. Analysis will progress iteratively until codes have reached saturation, when data will be triangulated to integrate key findings into several broad descriptive themes. Subsequently, these data will be merged with the quantitative strand of the study in a convergent parallel design mixed-methods analysis to compare and contrast qualitative themes with statistical results.[183] A thorough assessment of areas of congruence and discordance between the qualitative/quantitative data sets will provide a more robust understanding of enabling mechanisms, negative aspects, and any barriers, generated from the social experience sustained from participation in each arm (adolescents) and from implementation of the protocol (personnel) to inform further refinement and optimization.

9. DATA COLLECTION AND QUALITY ASSURANCE

9.1 Data Collection Forms

All participant encounters, from initial phone screening through 1-year follow-up, will be carefully and thoroughly documented. A data collection checklist and progress note will accompany each assessment interval. These forms will be completed by the study staff members who run the respective visits. Staff will be responsible for active completion of these forms during the visit and for any necessary follow-up regarding documenting – or remedying – missing data, protocol deviations, and/or adverse events associated with the evaluation, as well as communicating with the lead coordinator and site PI, as indicated. Any issues that arise will be discussed at a weekly multisite coordinators meeting. All staff conducting evaluations will be thoroughly trained on completion of forms and standard operating procedures for all evaluations prior to running visits. The lead coordinator will periodically check/audit forms for thoroughness and provide additional trainings as indicated (at minimum, 10% of data every 3 months).

Surveys will be filled out directly by participants and parents/guardians and housed in REDCap. Blood samples collected during each study visit will be tracked with a document that is completed by the phlebotomist performing each oral glucose tolerance test (OGTT). Each sheet will indicate the exact timing of each draw (i.e., fasting and 2-hour) and ingestion of the glucola, and also will provide the phlebotomist an opportunity to document any abnormal occurrence during the blood draw. The research staff at the study visit will be responsible for verifying that the blood draw form has been thoroughly completed. Timing of saliva samples collection will be filled out by adolescent participants using a paper tracking log, and ActiGraph wear will also be

tracked using a paper document filled out by participants. The activity data on each ActiGraph device will be immediately downloaded upon return from participants and stored on a password protected device. The data will then be deleted from the device upon download. The activity data will only be linked to participants' three digit subject ID.

Participants will be audio-recorded during each Schedule for Affective Disorders and Schizophrenia for School-Aged Youth-Computerized Version (KSADS) and Eating Disorder Examination (EDE) interview, along with each group session for quality assurance and training purposes.

At all sites, any participant record that includes identifying information will be housed in a locked cabinet (hard copies) or password-protected file (electronic) and separated from the remaining hard copy/electronic data collection forms. We have used a similar system for other trials and it is effective in maintaining the blind for research staff who will be blinded for follow-up data collection.

9.2 Data Management

Data will be collected specifically for the research purposes of this study only. Research staff administering assessments will be fully trained in their administration. All data will be kept confidential, and no individually identifiable information that can be linked to participants will be retained in public areas. Data with identifying information will be stored on password-protected computers, in the HIPAA-compliant REDcap web-based survey and data management system (in a separate database from the primary data entry/survey databases) or other secure electronic information-storing techniques as necessary, or in locked filing cabinets in the laboratories of each site PI. Only people directly involved with the study, including the PI, site PIs, Co-investigators, and study coordinator(s), and who have been certified for human subjects by the Colorado Multiple IRB and/or have human subjects protection training, as documented by the study team, will have access to identifiable private information. Standard security procedures will be used to assure patient confidentiality. Specimens stored and/or sent to the laboratory will be labeled with a study ID code only, and this study code is only known by the non-blinded study staff.

Data collection for the current project will take place at four enrollment sites, with two in Colorado: (1) Colorado State University **(CSU)** in Fort Collins, Colorado/Northern Colorado (Site 1) and (2) University of Colorado School of Medicine/Children's Hospital Colorado **(UCD/CHCO)** in the Aurora/Denver, Colorado metropolitan area (Site 2), and two in the Maryland/Washington, DC area: (3) Uniformed Services University **(USU)** (Site 3) in Bethesda, Maryland, and (4) Children's National Medical Center (CNMC) in Washington, DC (Site 4).

i. Site 1: Colorado State University: Phlebotomy will be conducted in the Human Performance/Clinical Research Laboratory (HPCRL) in the College of Health and Human Sciences on the Colorado State University main campus. The HPCRL is fully equipped to perform phlebotomy, handle blood specimens, and store samples (e.g., -80^{i} C freezers) prior to shipping, all of which will be overseen by Dr. Shomaker (PI). In order to establish eligibility and rule out T2D, fasting and two-hour glucose will be determined immediately using an automated device (e.g., StatStrip). Also, the HPCRL has designated space for laboratory test meal studies, which will be available for the current project. Dr. Shomaker has the equipment to perform air displacement plethysmography body composition testing (BodPod; COSMED), which is currently housed in the HPCRL. Dr. Shomaker also has access to two additional -80 degrees Celsius freezers for storage of blood and cortisol samples, a refrigerator for the

storage of test meal foods, and access to several fully equipped kitchens with scales for food preparation and weighing food items.

ii. Site 2: University of Colorado School of Medicine/Children's Hospital Colorado: Phlebotomy will be collected in the University of Colorado School of Medicine/Children's Hospital Colorado's (CHCO) Pediatric Clinical and Translational Research Center (CTRC). The Pediatric CTRC is fully equipped to perform phlebotomy, process blood specimens, and analyze glucose, which will be overseen by Dr. Kelsey (Co-I) and Dr. Shomaker (PI). Samples will be transferred directly to the Core Laboratory at the University of Colorado School of Medicine or stored in a -80 degrees Celsius freezer, designated for Dr. Shomaker's collaborative studies with Pediatric Endocrinology and located on the University of Colorado School of Medicine's campus. The CTRC also houses a BodPod (COSMED) to perform air displacement plethysmography body composition testing. The CTRC Nutrition Core is well-prepared to carry out standardized laboratory test meal studies with the necessary equipment (refrigerator, food scale) and space for food preparation and weighing of food items.

    After the appropriate regulatory approvals are obtained and material/data transfer agreements are established, samples from Sites 1, 3, and 4 will be shipped by authorized personnel at Colorado State University, the Uniformed Services University, and Children's National Medical Center, respectively, to Site 2/University of Colorado School of Medicine's Core Laboratory. The Core Laboratory will be the central processing site for research analysis of insulin and glucose blood samples collected from oral glucose tolerance testing throughout the proposed multisite pilot trial. Salivary cortisol samples will be processed by the Pediatric CHCO Core Laboratory. With support from Dr. Kelsey and the multisite coordinator, Dr. Shomaker (PI) will oversee all samples that are processed in the Core Laboratory.

iii. Site 3: Uniformed Services University: Phlebotomy and body composition will be collected in the Military Cardiovascular Outcomes Research (MiCOR) program, for which Dr. Tanofsky-Kraff (Co-I) serves as Research Director. MiCOR houses a BodPod (COSMED) that is dedicated to the research visits at the laboratory and will be available for air displacement plethysmography body composition testing. MiCOR also has two private exam rooms for blood draws and equipment for processing blood samples and immediate glucose analysis, as well as a -80 degrees Celsius freezer to store blood samples prior to shipping. MiCOR is equipped with a room to conduct laboratory test meal studies as well as a fully furnished kitchen with the necessary equipment (i.e., refrigerator, food scale) and storage space to carry out laboratory meal assessments.

iv. Site 4: Children's National Medical Center: Phlebotomy will be collected in the Clinical Research Unit= located at the main hospital at Children's National that will provide the expertise and infrastructure for the clinical services proposed for the current study. The nursing support, overseen by Dr. Estrada (Co-I), will administer phlebotomy and collection and storage of blood samples. The Children's National Clinical Research Unit is also able to provide biorepository support to store and safely ship all samples to Colorado. Dr. Mackey has access to a BodPod (COSMED), which will be utilized for body composition assessments and is currently housed in the Clinical Research Unit.

Data will be collected at all sites and managed at Site 2/University of Colorado School of Medicine/Children's Hospital Colorado through the web-based REDCap system, a data collection and data management system compliance with the Health Insurance Portability and Accountability Act of 1996. REDCap is highly conducive to facilitating multisite data coordination. FreezerPro, a software application used for tracking biological samples, will be

used to manage all saliva and blood samples collected at each site. FreezerPro allows study teams to conveniently record where biological specimens are stored (i.e., which boxes, which freezers); study identification numbers and intervals that are de-identified will be utilized for biological specimens and corresponding tracking within FreezerPro. Participants in the proposed study will complete electronic survey measures at all sites on REDCap, and all psychological, behavioral, and physiological/biological data will be managed via these systems.

9.3 Quality Assurance

9.3.1 Training

All research staff administering evaluations will be thoroughly trained in their administration prior to collecting data. All research clinicians will receive additional, thorough training by experts in MBI, CBT, and HealthEd and will participate in weekly ongoing supervision from experts throughout the course of the intervention delivery.

The multisite coordinator for this project will be responsible for providing or arranging all of the trainings to the local site coordinators for evaluations, case reporting documents, and so forth in order to ensure protocol fidelity across sites. The multisite coordinator also will monitor fidelity regularly throughout the trial.

9.3.2 Metrics

Our metrics for quality assurance of data collection will be as follows: For retention to group interventions, our threshold is receiving 80% of either mindfulness-based intervention (MBI), cognitive behavioral therapy (CBT) or health education (HealthEd). For retention to follow-up visits, our threshold is at least 70% of randomized adolescents completing a 1-year follow-up, the planned endpoint for the current study.

9.3.3 Protocol Deviations

Study coordinators from each site will log protocol deviations as they occur, and they will be documented on a form specifically for protocol deviations. Deviations will be discussed at the weekly coordinators meeting and also summarized at the all hands monthly investigator/staff meeting. Further, the deviations documented will be reviewed by the IMC in the report prepared every 6 months, along with the IRB at the time of each continuing review.

9.3.4 Monitoring

We will have scheduled site visits from the NCCIH prior to initiating the trial and for supporting and assuring protocol compliance. Also, as outlined in **section 7.6**, monitoring will be performed by an IMC, with reports prepared every 6 months.

10. PARTICIPANT RIGHTS AND CONFIDENTIALITY

10.1 Institutional Review Board (IRB) Review

The Colorado Multiple IRB has agreed to serve as the single IRB (sIRB) for this multisite study. Upon Colorado Multiple IRB approval, we will arrange for institutional IRB reliance agreements with each of the other sites (Colorado State University [CSU], Uniformed Services University (USU), and Children's National Medical Center [CNMC]) who have agreed to this arrangement of allowing the Colorado Multiple IRB to serve as the primary sIRB. The study protocol and the informed consent/assent form, along with all key protocol documents, will be reviewed and approved by the Colorado Multiple IRB prior to initiating the pilot randomized controlled trial. Additionally, all subsequent modifications to these documents will be reviewed and approved by the Colorado Multiple IRB.

10.2 Informed Consent Forms

A single signed informed consent/assent form will be obtained from each participant's parent/guardian and the participants, who will be 12-17 years of age. Children's National Medical Center has a site-specific informed consent and separate site-specific assent form. In the instance that the consent/assent forms are obtained electronically, the process will be obtained via secure videoconferencing software or via phone and REDCap to facilitate explanation of the consent and provide an opportunity for participants and their parents/guardians to ask questions. The purpose, all testing procedures, program components, and randomization will be reviewed in detail. Potential participants and their parents/guardians will be informed of the possible risks, inconveniences, potential benefits, and right to alternatives and withdrawal.

10.3 Participant Confidentiality

This study has been issued a Certificate of Confidentiality from the federal government to help protect participant privacy. The Certificate prohibits researchers from disclosing participants' name, or any identifiable information, document, or biospecimen from the research. Consent forms include waivers of confidentiality for suicide, child abuse, and homicide, for which we are mandated reporters. All sessions begin with a discussion of confidentiality and its limitations, and throughout the consent process, confidentiality and its limitations are discussed. Specific written procedures have been developed and tested for handling cases that necessitate a breach of confidentiality. For cases that involve a breach of confidentiality (i.e., suicide, child abuse, and homicide), depending on the individual circumstances, the appropriate authorities, such as a parent, are contacted. All distressed adolescents are given a list of referrals that include hotlines and crisis centers. We also facilitate referrals to counseling services if the situation calls for this. Suspected child abuse is reported to Social Services.

All data from the protocol will either be stored in REDCap or on a secure server that is username and password protected. Any data or records that leave the sites will be identified only by a participant identification number to maintain confidentiality. All paper records will be kept in a locked file cabinet. Information will not be released without written permission of the participant, except as necessary for monitoring by the IRB, IMC, and/or the NCCIH.

10.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the IMC, NCCIH, or other government agencies as part of their duties to ensure that research participants are protected. Investigators also may terminate a participant's participation in the study with or without the consent of the participant. For example, if a participant develops a medical or psychiatric condition that requires treatment, they will be referred for treatment and might not continue in the study.

11. PUBLICATION OF RESEARCH FINDINGS

All publications resulting from this work will be discussed by the all hands investigators/staff at the monthly meeting. The order of authorship and plan for the publication will be determined before any work begins. Any presentation, abstract, or manuscript will be made available for review by the sponsor and the NCCIH prior to submission.

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