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Design of a Randomized Controlled Trial to Decrease Depression and Improve Insulin Sensitivity in Adolescents: Mood and INSulin Sensitivity to Prevent Diabetes (MIND)

Lauren B. Shomaker^{a,b,c,*}, Lauren Gulley^{a,b}, Allison M. Hilkin^b, Emma Clark^a, Shelly Annameier^a, Sangeeta Rao^d, Bonny Rockette-Wagner^e, Andrea Kriska^e, Kenneth P. Wright Jr.^f, Eric Stice^g, Kristen J. Nadeau^b, and Megan M. Kelsey^b

^aDepartment of Human Development and Family Studies, Colorado State University, Fort Collins, Colorado, United States

^bDepartment of Pediatrics, Section of Endocrinology, University of Colorado School of Medicine and Children's Hospital Colorado, Aurora, Colorado, United States

^cDepartment of Community and Behavioral Health, Colorado School of Public Health, Aurora, Colorado, United States

^dDepartment of Clinical Sciences, Colorado State University, Fort Collins, Colorado, United States

^eGraduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania, United States

^fDepartment of Integrative Physiology, University of Colorado Boulder, Boulder, Colorado, United States

^gOregon Research Institute, Eugene, Oregon, United States

Abstract

Background: Depressive symptoms often manifest in adolescence and predict worsening insulin sensitivity, a key precursor in the path to β -cell failure and type 2 diabetes (T2D).

Objective: To assess the efficacy of a six-week cognitive-behavioral group versus six-week health education group for improving insulin sensitivity and preserving β -cell function in adolescent girls at-risk for T2D with depressive symptoms and evaluate mechanisms underlying the association between depression and insulin dynamics.

Design: Randomized controlled trial of $N=150$ 12–17-year-old girls with overweight/obesity (body mass index [BMI; kg/m²] 85th percentile), elevated depressive symptoms (Center for Epidemiologic Studies-Depression Scale [CES-D] total score >20), and diabetes family history.

*Corresponding author. Correspondence to: L. Shomaker, 1570 Campus Delivery, Fort Collins, Colorado 80523. lauren.shomaker@colostate.edu. Phone: (970) 491-3217.

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Methods: Girls at-risk for T2D with elevated depressive symptoms are recruited from the Denver-metropolitan area and randomized to participate in one of two six-week interventions. The cognitive-behavioral group is a depression prevention program involving psycho-education, restructuring negative thoughts, and behavioral activation. The health education group is a didactic control that provides knowledge about healthy living. Participants are assessed at baseline, immediate post-intervention, and one-year follow-up. Primary outcomes are insulin sensitivity and β -cell function from oral glucose tolerance tests. Secondary outcomes are disinhibited eating, physical activity, sleep, and cortisol.

Summary: Results from this adequately powered randomized controlled trial will determine whether decreasing depressive symptoms with a behavioral health program preventatively alters insulin sensitivity and β -cell function trajectories in adolescents at-risk for T2D. Results from the MIND Project will add to knowledge of the contribution of depressive symptoms to T2D risk.

Keywords

Depression; Type 2 diabetes; Adolescent; Insulin sensitivity; Insulin resistance

1. Introduction

Forty-percent of U.S. adults will develop type 2 diabetes (T2D), with higher estimates for individuals from historically disadvantaged racial/ethnic groups [1]. T2D is a leading cause of severe health complications [2]. Mortality as a consequence of T2D is the seventh leading cause of death in the U.S. [3]. T2D incidence was formerly limited to older adults, but now is rising in adolescents and young adults [4]. Girls are twice as likely as boys to develop youth-onset T2D [4, 5], which appears to have a more aggressive clinical course than adult-onset [6, 7]. Preventing youth-onset T2D is critical [8].

Insulin resistance—poor action of insulin to regulate glucose—is a precursor to T2D. Insulin resistance increases demand on insulin-producing pancreatic β -cells, causing deterioration in insulin secretory capacity and ultimately β -cell failure/T2D [9]. Alteration of insulin dynamics during adolescence makes this period ideally suited for prevention. [10]. Puberty is characterized by physiologic insulin resistance that decreases upon maturation [11]; yet, in adolescents with obesity, pubertal insulin resistance may potentiate underlying β -cell stress and cause sustained β -cell dysfunction [11]. Youth-onset T2D is tightly linked with puberty, tending to present in the later pubertal stages, after the peak in pubertal insulin resistance [11].

Lifestyle approaches to address obesity as a risk factor for insulin resistance and T2D have demonstrated limited long-term success in adolescents [12]. Weight loss is difficult to achieve [13], and program adherence is especially problematic in teenagers [14, 15]. Alternative approaches that target modifiable risk factors for insulin resistance, independent of weight loss or adherence to an intensive program, are needed.

Depressive symptoms are common in adolescents and may play a role in worsening insulin sensitivity. Twenty-percent of adolescent girls experience elevated depression [16] with even higher rates in historically disadvantaged racial/ethnic groups [16, 17]. Adolescent girls with

T2D are up to three times more likely to have elevated depressive symptoms compared to boys with T2D or adolescents with type 1 diabetes [18]. As in adults [19], depressive symptoms are associated with lower insulin sensitivity in youth at-risk for T2D and healthy adolescents, after accounting for body fat [20–22]. Further, depression in youth with overweight/obesity predicts worsening of insulin sensitivity, independent of initial body mass index (BMI; kg/m²) and BMI change over time [23]. Similarly, elevated depressive symptoms in adolescence and young adulthood doubles the odds of developing T2D in young adulthood [24].

By expanding upon promising preliminary data supporting an effect of decreasing depression on improving insulin [25, 26], the Mood and INSulin Sensitivity to Prevent Diabetes (MIND) Project is a randomized, controlled trial to assess the efficacy of a behavioral intervention for depression on changes in insulin sensitivity and β -cell function in adolescent girls at-risk for T2D who have depressive symptoms. Additionally, because there is very limited understanding of how depression affects T2D risk, the study was planned to evaluate stress-related behaviors (disinhibited eating, physical activity, sleep) and cortisol physiology (awakening response, diurnal rhythm, daily output) that may underlie the associations of depression with insulin sensitivity and β -cell function.

2. Methods

This study is funded by the National Institute of Diabetes and Digestive and Kidney Diseases (R01DK111604, National Institutes of Health). Supplemental support is provided by a microgrant from the Colorado Clinical and Translational Sciences Institute (UL1TR002535, National Center for Advancing Translational Sciences, National Institutes of Health). All procedures have been approved by a single Institutional Review Board, the Colorado Multiple Institutional Review Board, which provides oversight for the University of Colorado School of Medicine and Children's Hospital Colorado, the site of participant enrollment. An Institutional Review Board authorization agreement was established between the Institutional Review Board of Colorado State University, an administrative site, and the Colorado Multiple Institutional Review Board. In addition to Institutional Review Board approval, the study protocol also was approved by the Research Institute of the Children's Hospital Colorado and the Scientific Advisory and Review Committee of the Colorado Clinical and Translational Sciences Institute. All study procedures adhere to the Consolidated Standards of Reporting Trials (CONSORT) guidelines in order to support scientific rigor and reproducibility.

2.1 Study aims

The MIND Project has three specific aims: (1) assess the effects of a six-week cognitive-behavioral therapeutic (CBT) group, compared to a six-week health education (Health Ed) control group, on insulin sensitivity and β -cell function in 150 overweight and obese adolescent girls with moderate depressive symptoms and a T2D family history; (2) evaluate stress-related behavioral mediators underlying the relationship between decreases in depressive symptoms and improvements in insulin sensitivity and β -cell function; and (3) determine stress-related physiological mechanisms underlying the relation between

decreases in depressive symptoms and improvements in insulin sensitivity and β -cell function.

2.2 Setting, inclusion criteria, and recruitment

The MIND Project is being conducted in the state of Colorado. Enrollment and study assessments take place at the outpatient Pediatric Clinical and Translational Research Center at Children's Hospital Colorado in Aurora, Colorado, and group interventions are facilitated in group rooms at the hospital.

A variety of recruitment methods are utilized to identify volunteers who may meet eligibility criteria. Inclusion criteria are: (1) female; (2) 12–17 years of age; at-risk for T2D based upon (3) a BMI $\geq 85^{\text{th}}$ percentile for age and sex and (4) a family history in at least one first- or second-degree biological relative (i.e., parent, sibling, aunt, uncle, grandparent) with T2D, prediabetes, or gestational diabetes; (5) English speaking; and (6) elevated depressive symptoms determined as a Center for Epidemiologic Studies-Depression (CES-D) scale total score > 20 . The designated criterion in this trial for elevated depressive symptoms (CES-D total score > 20) has been used in previous selective depression prevention interventions to identify youth at-risk for, but who have not yet developed, major depressive disorder (MDD) [27]. Further, our preliminary data suggest that this particular cut-point—indicative of moderate depressive symptoms as opposed to mildly elevated symptoms (e.g., CES-D score = 16–20)—identifies adolescents most likely to benefit from a highly targeted, depression intervention approach to ameliorating insulin resistance and T2D risk [25, 26]. We chose to focus on adolescent girls because they are twice as likely as boys to be at-risk for youth-onset T2D [4] and because girls are disproportionately more likely than boys to have elevated depressive symptoms and to develop MDD [28]. In terms of T2D risk, similar criteria for adolescent BMI and diabetes family history have been used in prior studies to effectively identify adolescents who have decreased insulin sensitivity, a primary early risk marker in the progression to T2D [25]. Adolescents must be English-speaking to participate in the CBT or Health Ed intervention sessions, which are conducted in a group format and facilitated in English. However, given a high prevalence of Latino/Hispanic families at-risk for T2D nationally and in the Denver-metropolitan area specifically, the consent form and questionnaire surveys were translated to Spanish to facilitate inclusion of participants with Spanish-speaking parents/guardians.

Exclusion criteria include: (1) pregnancy or breastfeeding, (2) T2D determined as fasting glucose ≥ 126 mg/dL, two-hour glucose > 200 mg/dL, or HbA1c ≥ 6.5 , (3) regular medication use likely to affect mood, weight, insulin sensitivity, or cortisol, including medications such as antidepressants, stimulants, insulin sensitizers, or steroids, (4) current DSM-5 psychiatric disorder that would impede study compliance and/or necessitate more intensive treatment, including MDD, substance abuse, psychosis, bipolar disorder, conduct disorder, panic disorder, and obsessive-compulsive disorder, (5) current psychotherapy or structured weight loss program, and (6) active suicidal ideation, suicidal behavior, or self-injurious behavior. Adolescents who are determined to have T2D are referred to their primary care physician for follow-up. Not studying adolescents on psychotropic medication and/or insulin sensitizers may result in excluding some adolescents who could potentially

benefit from intervention participation; we selected this approach for two main reasons. First, for an efficacy trial, we wanted to enroll participants who were not on a drug treatment that could inadvertently confound the effect of intervention on key outcomes. Second, youth who have already progressed to drug treatment for depression and/or T2D risk may require more intensive treatment than the interventions offered in this study, particularly the control condition of Health Ed. Adolescents with a psychiatric disorder or active suicidal ideation, behavior, or self-injurious behavior, as determined by clinical interview, are provided therapy and psychiatry referrals and research staff facilitate referrals in the event of acute safety issues and/or if the family would like assistance.

The main recruitment methods are direct mailings and phone calls to parents/guardians of adolescents who are current patients in obesity and adolescent medicine clinics at Children's Hospital Colorado and direct mailings to Denver-metropolitan area families identified as being likely to have a teenage daughter living in the home. In addition to direct mailings and phone calls to Children's Hospital Colorado patients, research staff also present the study in person at medical appointments, when scheduling permits, to interested patients who appear to be eligible based upon the electronic medical record and/or a provider referral. For existing patients at Children's Hospital Colorado, research staff use electronic medical records to identify girls who may be eligible. Additional means of recruitment include: notices to area physicians and practices other than Children's Hospital Colorado that serve overweight/obese adolescents and/or adults with T2D who may have a teenage daughter or granddaughter; social media advertisements; flyers in community areas and local health fairs; and advertisements to community email Listservs. Using these recruitment strategies, we have been highly successful in enrolling adolescents with similar eligibility criteria (NCT01425905, NCT02218138, NCT01779375, NCT00081328). A preliminary evaluation of Children's Hospital Colorado electronic medical records suggests that >550 existing hospital patients would be eligible within a one-year period, suggesting that 150 eligible volunteers can be feasibly enrolled in the study within a 3-year planned enrollment period.

Contacts with any individual whom research staff approach or any individual who reaches out to the study team are carefully tracked. Interested volunteers complete a brief phone screening to evaluate preliminary eligibility; this phone screen includes an assessment of parent-reported adolescent BMI, family history of diabetes, adolescent medication use, and perceived adolescent health status. In addition, a trained research staff member administers a CES-D by phone with the adolescent to estimate depressive symptoms. Adolescents who are interested and appear to be eligible based upon the phone screen are scheduled for a series of two screening visits at Children's Hospital Colorado's Pediatric Clinical and Translational Research Center. Based upon prior data [25], we anticipate that approximately 20% of individuals screened by phone will be eligible for and interested in a laboratory screening. The first laboratory visit is a screening and baseline assessment appointment, offered during non-school hours, involving: BMI estimation from objective measurements; the CES-D survey; a medical history and physical exam by a pediatric endocrinologist to determine health status and pubertal stage, medication use, and family history of diabetes; and a semi-structured clinical interview to rule out the presence of a psychiatric disorder or suicidal ideation or behavior necessitating more intensive treatment, and consequently, study exclusion and referrals. Adolescents receive \$50 for attending the first screening visit. Those

who are eligible following the initial screening attend a subsequent screening at the Pediatric Clinical and Translational Research Center. The second screening and baseline assessment visit involves a morning appointment following an overnight fast, at which: oral glucose tolerance testing occurs; BMI is assessed in a fasted state; measures of body composition are completed; and survey/interview measures are administered. Adolescents receive \$100 for completing the second screening visit. Between the first and second outpatient hospital screening visits, adolescents complete ambulatory measures of physical activity and sleep using accelerometers and cortisol via serial saliva samples. To incentivize adherence, participants can receive up to \$55 for the completing these at-home measurements.

We expect, based upon previous data [25], that 65–70% of adolescents who attend an initial screening visit will meet eligibility criteria. This estimate means that our study team plans to conduct in-person screenings with approximately 230 youth in order to identify a total of 150 eligible participants.

2.3 Randomization

Adolescents who are determined to be eligible upon completion of the screening and baseline assessment phase are randomized to one of two behavioral group interventions, a six-session CBT intervention or a six-session Health Ed intervention. Computerized randomization is performed by the study statistician in randomly permuted blocks. Randomization is stratified by age (12–14 years versus 15–17 years), BMI status (overweight, BMI 85–94th percentile versus obese, BMI ≥ 95th percentile), race/ethnicity (Latino/Hispanic versus Other non-Latino/Hispanic race/ethnicity), and baseline depression level (CES-D total score 21–27 versus CES-D total score ≥ 28) in order to ensure equivalence between conditions on these characteristics that could potentially affect outcomes. A minimum of 3 and a maximum of 10 adolescents will be included in each intervention group. Interventions are delivered only to adolescents, with no caregiver component in either condition.

In both conditions, participants earn \$50 for completing at least 80% of the intervention, meaning coming to at least five out of six total group sessions. If adolescents miss a session, our staff makes every effort to schedule a make-up appointment, typically in the 30–60 minutes prior to the subsequent week's session.

2.3.1 Cognitive-behavioral therapeutic (CBT) intervention—CBT approaches have the largest evidence base for intervening with depression in adolescents [29]. The Blues Program is a selective depression prevention program, meaning that it was designed to reduce depressive symptoms and future MDD among youth who are at heightened risk for MDD because of current elevated symptoms of depression. The Blues Program is comprised of six weekly one-hour group sessions that involve core CBT modules for addressing depressive symptoms, including: psycho-education on the interconnectedness of thoughts, feelings, and behaviors; mood monitoring; identifying and restructuring negative thoughts; behavioral activation by scheduling pleasant activities; rewarding oneself; and identifying strategies for coping with stressful life events [30]. An overview of the core content areas covered in each session is presented in Table 1.

The goal of this efficacy trial is to isolate the effects, and underlying mechanisms, of directly intervening to decrease depressive symptoms in adolescent girls at-risk for T2D on changes in insulin sensitivity and β -cell function over time. Consequently, the Blues Program CBT depression prevention program was minimally modified from its six-session standard version. The Blues Program already emphasizes the use and benefits of physical activities for behavioral activation. The only modifications that we made to the intervention manual were: (1) in session one, we added a brief justification (~1 minute) of how program participation may lessen T2D risk; (2) in session two, when adolescents generate a list of fun activities, we added brief psycho-education (~2 minutes) on emotional eating and encouraged the use of alternative and healthier pleasant activities. We made the latter modification because emotional eating and relying on food as a reward may occur as part of depression and may be promoting of excess weight gain and insulin resistance, particularly in this specific population of youth at-risk for T2D with depressive symptoms.

The Blues Program has demonstrated efficacy for decreasing depressive symptoms and preventing MDD in diverse adolescents groups [31], compared to assessment-only and active control conditions, from six months to two years after treatment [32]. There also is initial evidence for the program's effectiveness in real-world settings for lowering adolescents' MDD risk up to two years later [33]. Stronger effects have consistently been observed in adolescents with more elevated baseline depressive symptoms as compared to those with milder symptoms [27].

The CBT program is facilitated by a clinical psychologist who received training in the Blues Program from a developer (E. Stice, P. Rohde, and/or H. Shaw). The Blues Program is co-facilitated by a graduate student in marriage and family therapy, psychology, or a related discipline with experience working with adolescent girls. Facilitators receive feedback on audio-recorded sessions of program delivery by a developer (H. Shaw) until adherence and leader competence are acceptable, as determined by ratings on scales established by the Blues Program developers. At least 20% of all sessions throughout the trial are reviewed by an expert in the Blues Program to ensure adherence and competence throughout the trial. In addition, all facilitators participate in a one-hour weekly clinical supervision meeting to review and receive feedback on audio-recorded sessions with the PI (L. Shomaker), who is a licensed child clinical psychologist with expertise in the administration of this intervention with adolescents at-risk for T2D [25].

2.3.2 Health education (Health Ed) intervention—The Health Ed control group intervention is derived from Hey-Durham, a didactic health education curriculum designed for middle and high school students [34]. An abbreviated, manualized curriculum that we adapted and used in previous studies [25] includes six topics covered in six weekly one-hour sessions: (1) domestic violence, (2) alcohol, drug, tobacco use, (3) nutrition, body image, (4) identifying depression and signs of suicide, (5) gang violence, nonviolent conflict resolution, and (6) sun safety. The depression and suicide module focuses only upon prevalence of these problems, their relation to other health issues, and how to identify signs of MDD and suicide. Health Ed content does not overlap with CBT [25]. No direct, individualized advice is given other than in the event of a psychiatric crisis or worsening of mood, in which case a

treatment referral is promptly facilitated. Health Ed offers an ideal attention and time-matched control condition to most directly test the aims of this efficacy trial.

To match the CBT condition, the Health Ed group program is facilitated by a clinical psychologist and co-facilitated by a graduate student in marriage and family therapy, psychology, or a related discipline. The facilitators received feedback on audio-recorded sessions from the PI (L. Shomaker) to promote program adherence and to ensure no overlap with CBT. At least 20% of Health Ed randomly selected sessions throughout the trial will be rated by an expert in CBT to document the lack of overlap with CBT. All facilitators alternate between CBT and Health Ed program administration in order to control for any potential facilitator effects. The use of a credible alternative intervention, rather than a minimal control condition, should permit the isolation of the effects of the Blues Program and to rule out the possibility that reductions in outcomes are due to expectancies, demand characteristics, or non-specific effects.

2.4 Outcome evaluation

Following the completion of the intervention phase, participants return for two follow-up visits to repeat measures collected initially during the baseline phase. Participants return for an immediate post-intervention follow-up within two-to-four weeks following the end of the intervention program, and they return again for a final, one-year follow-up, scheduled approximately one-year from the initiation of the intervention. No intervention content is delivered following the last intervention session, except in the event of worsening psychiatric or medical symptoms, in which case an appropriate referral to independent treatment will be facilitated by the study team. For an overview of assessments, please refer to Table 2.

Adolescents receive \$150 for the time and effort of completing each follow-up. In addition, at each of these follow-up intervals, adolescents are asked to repeat at-home measures of physical activity, sleep, and cortisol and may earn up to \$55 for each of the two follow-up weeks of at-home data collection. In addition to the payment incentives at follow-up, retention of adolescents will be supported through a range of strategies, including monthly study newsletters, requests for updated contact information, and birthday cards.

2.4.1 Primary outcomes—The primary outcomes are insulin sensitivity and β -cell function, as derived from a two-hour oral glucose tolerance test (OGTT). We opted for an OGTT because it is a well validated, practical in large cohorts, and has shown excellent convergence with estimates derived from more frequent sampling [35, 43], yet is a less invasive, costly, and labor-intensive, approach than estimates derived from clamps or intravenous glucose tolerance testing. The OGTT also permits screening for T2D from fasting and two-hour glucose values, yields more valid estimates of insulin sensitivity than fasting values alone, and permits estimation of β -cell function [35, 43]. Following a 10-hour overnight fast, participants ingest 1.75 g/kg of glucola (max = 75g). Using an intravenous line, blood is sampled for insulin, glucose, and C-peptide at -5 (fasting), 0 (fasting), and 10, 20, 30, 60, 90, and 120 minutes after glucola. This two-hour protocol is administered by a

pediatric research nurse in the Pediatric Clinical and Translational Research Center of Children's Hospital Colorado.

Insulin sensitivity will be estimated by the whole body insulin sensitivity index (WBISI), which has good convergent validity with clamp-derived measures of insulin sensitivity in nondiabetic youth with obesity [35]. β -cell function will be estimated using the oral disposition index (DI_o) [39]. In addition, we will use the oral minimal model to derive estimates of insulin sensitivity (S_i), β -cell responsivity, and DI_o [36].

2.4.2 Secondary outcomes

2.4.2.1 Stress-related behaviors: Disinhibited eating, physical activity/sedentary behavior, sleep disturbance

Disinhibited eating. Although adiposity may partially explain the association of depressive symptoms with low insulin sensitivity, there is preliminary evidence for effects of depressive symptoms on insulin sensitivity, independent of adiposity, through stress-related behavioral pathways [23]. Disinhibited eating refers to intake characterized by a lack of restraint over what or how much is consumed [44]. According to Affect Theory, disinhibited eating behaviors such as binge-eating occur in response to negative affect as an attempt to alleviate or escape from emotional distress [45]. Depressive symptoms in adolescents have been positively associated with, and predictive of, increases in disinhibited eating over time [46]. In separate studies, disinhibited eating has been related to markers of worsening insulin sensitivity and cardiometabolic risk in both youth and adults [47, 48].

To assess disinhibited eating behaviors in the current study, we are administering the Overeating Section of the Eating Disorder Examination (EDE) Version 14.0 [40]. The EDE is a semi-structured interview of disordered eating attitudes and behaviors. The Overeating Section of the EDE identifies the presence and frequency over the past six months of three types of disinhibited eating episodes: (1) objective binge eating – referring to eating an unambiguously large amount of food (e.g., two large pizzas and one half-gallon of ice cream) with the subjective feeling of losing control over what or how much is consumed, (2) subjective binge eating – referring to the subjective feeling of loss of control over eating without eating an unambiguously large amount as assessed by the interviewer, but viewed as excessive by the interviewee (e.g., three slices of pizza and one snickers bar), and (3) objective overeating – referring to overeating without loss of control (e.g., two large pizzas and one half-gallon of ice cream without a feeling of loss of control). The EDE is administered by a trained research assistant. Size of episodes (i.e., unambiguously or ambiguously large amount) are determined by team consensus whenever the amount is questionable. Tests of the EDE's validity and reliability, particularly with respect to objective binge eating, support its use in adolescents [40, 41].

Adolescents also report eating in response to negative affect on the Emotional Eating Scale-Adapted for Children [49]. Emotional eating has been defined as eating in response to negative emotions. Increased appetite, particularly of sweets and junk food, is one symptom of depression. On this questionnaire, participants rate the frequency of coping with negative affect in response to depression, as well as to the negative emotions of anxiety/anger/

frustration and feeling unsettled. This measure shows good internal consistency, test-re-test reliability, discriminant and convergent validity [49].

Physical activity and sedentary behavior.: Physical activity refers to all movement that increases energy use, and sedentary behavior is defined as any waking behavior characterized by very low energy expenditure (< 1 metabolic equivalents), while in a sitting, reclining, or lying posture [50]. Both insufficient physical activity and frequent sedentary behavior have negative effects on glucose homeostasis [51], and may represent another stress-related behavioral pattern that influences T2D risk, even after accounting for the effects on adiposity [52]. In early adolescence, there is a decline in girls' moderate-to-vigorous physical activity and an increase in sedentary time [53], with depressive symptoms predicting greater reductions in total physical activity [54] and increases in sedentary behavior [55] over time. Low moderate-to-vigorous physical activity and high sedentary time are both correlated with worsening insulin sensitivity in racially/ethnically diverse samples of youth [52, 56], even after accounting for BMI or adiposity [52]. Youth with recent-onset T2D have less moderate-to-vigorous physical activity and spend more time sedentary than youth with obesity but without T2D, suggesting a putative role for low levels of movement in T2D onset [57].

Habitual physical activity is measured with ActiGraph GT3X accelerometers (ActiGraph, Pensacola, FL), lightweight monitors that have well-established validity and reliability in diverse child and adolescent samples for nearly 20 years [58]. Adolescents are asked to wear the accelerometer on their right hip during waking hours for seven days and to remove it only for water-based activities that involve complete submersion (e.g., swimming). Consistent with recommended protocols, accelerometers are set to record data with a sampling frequency of 30 Hz and analyzed using 60-second epochs throughout the wear period. Adolescents are given an activity log to monitor on/off time; device wear and completion of the log are clearly and carefully described to participants and their parents/guardians by a trained research assistant.

Data will be reduced manually by using data output and logs to delete periods of non-wear. Per standard protocol, a full day of recording is considered to be one that includes all waking hours. Based on previous research, days of recording in which a full day of recording was possible (i.e., recording started before waking) and contained ≥ 10 hours of wear time will be considered valid. As a result, days when the monitor was handed out or returned will not be used. Adolescents with ≥ 4 valid days of data (including one weekend day) will be retained in analyses. To incentivize wear adherence, adolescents earn \$5 per day for each day of adherence. Wear adherence is checked immediately upon return of the device to the research team, and any adolescent who has not worn the device for ≥ 4 days is given an opportunity to re-wear the device (and to earn payment) the following week. Mean ActiGraph counts per minute will be classified as light physical activity, moderate-to-vigorous physical activity, total physical activity (light + moderate-vigorous activity), or sedentary time according to validated count thresholds determined by Evenson et al. [59]. Step counts also will be examined as a proxy of total ambulatory movement.

Sleep disturbance. Sleep disturbance refers to shortened, disrupted, and/or mistimed sleep and is also related to both depression and T2D [60]. In adolescents, depressive symptoms have been related to both shortened and disrupted sleep [61]. In turn, shortened sleep has been associated concurrently and longitudinally with lower insulin sensitivity in adolescents, after accounting for BMI [62, 63]. These patterns are consistent with adult data indicating that short and mistimed sleep relate to acute and long-term declines in insulin sensitivity, β -cell function, and T2D onset [60].

Actiwatch (Spectrum Plus, Phillips), a small device worn on the wrist continuously for seven days, is used to objectively quantify key dimensions of sleep disturbance, including sleep duration, timing of sleep onset and sleep wake, and sleep efficiency. Following standard guidelines to increase compliance, participants maintain a sleep log in conjunction with the daily physical activity log. Actiwatch has good concordance with polysomnography and has less participant burden than laboratory sleep assessment [64]. Objective sleep measures have been related to both depressive symptoms [61] and insulin sensitivity [62] in adolescents. As with the ActiGraph device, adolescents are compensated for each day of Actiwatch wear and given an opportunity to re-wear the device if at least four days of wear is not achieved.

2.4.2.3 Stress-related cortisol physiology: From a neurohumoral framework, stress physiology is posited to explain the effect of depression on insulin sensitivity and deterioration in β -cell function [65]. Prolonged psychosocial stress repeatedly stimulates activation of the hypothalamic-pituitary-adrenocortical (HPA) axis. The HPA axis is the critical neuroendocrine system that, in conjunction with the autonomic nervous system, governs the body's peripheral physiologic response to stress [66]. Over-activation of the HPA axis results in subtle elevations of the stress hormone cortisol [66]. Individuals with elevated depressive symptoms and MDD have higher total daily cortisol output [67], more heightened cortisol awakening response [68], and flattened diurnal rhythm [69] than individuals without depression. Animal and human studies demonstrate that hypercortisolism promotes selective accumulation of visceral fat, insulin resistance, metabolic syndrome, and β cell dysfunction [65]. Beyond the impact of excess cortisol on decreased insulin sensitivity through visceral adiposity, cortisol also directly increases hepatic glucose release, diminishes cellular glucose uptake, and decreases β -cell insulin secretion [70]. Consistent with these data, total daily cortisol output in adolescents has been associated with lower insulin sensitivity [71] and predicts worsening of insulin sensitivity over time [72], even after adjusting for fat mass or visceral adiposity.

Cortisol awakening response/diurnal rhythm. Post-awakening cortisol and diurnal cortisol rhythm are assessed with salivary samples collected in the participant's home environment on one weekday and one weekend day overlapping with the same at-home collection period of devices to measures activity and sleep. Samples are obtained with an oral swab (Sarstedt, Newton, NC) placed under the tongue for 120 seconds upon awakening, 15, 30, and 45 minutes after awakening, 4:00 pm, and bedtime. Participants are instructed to refrain from eating, drinking (other than water), or brushing their teeth until after completion of the 45-minute post-wake sample and for 15-minutes prior to afternoon and bedtime samples. Completion of a participant log is used to encourage adherence, and we also use screw-top

bottles that automatically, electronically record opening times to improve accuracy of collection timing, given its high importance. Participants are also reimbursed \$5 per day for completion of samples. Salivary cortisol is a well-accepted non-invasive indicator of circulating physiologically active free plasma cortisol [73]. Latent growth models will be used to express non-linear change in cortisol across two days as awakening response and diurnal rhythm.

Daily cortisol output. Adolescents also collect urine for one 24-hour period to estimate urinary free cortisol, normalized to urine creatinine, a well-accepted measure of total daily cortisol output [74]. Adolescents earn \$10 for collecting their urine to support adherence.

2.4.3 Other variables

2.4.3.1 Depressive symptoms: Depressive symptoms are assessed as a continuous measure of symptoms and as the presence or absence of a MDD episode. Participants complete the 20-item version of the CES-D [75] for depressive symptoms, with higher scores reflecting more elevated depressive symptoms.

The Computerized Schedule for Affective Disorders and Schizophrenia for School-Age Children (COMP K-SADS) [76] is administered to determine if adolescents meet full criteria for current MDD (past two weeks) or another psychiatric disorder. At baseline, we assess the past one-year for possible exclusionary diagnoses of current bipolar disorder, psychosis, panic disorder, obsessive-compulsive disorder, eating disorders, conduct disorder, substance abuse disorder, or post-traumatic stress disorder. At the follow-up visits, we administer only the depression module to determine onset of MDD episodes. The K-SADS is a reliable, valid semi-structured diagnostic interview with good inter-rater reliability [76]. A clinical psychologist or a trained research assistant administers the adolescent-only portion of the K-SADS.

2.4.3.2 Body measurements: BMI (kg/m^2) is derived from height in triplicate by stadiometer and fasting weight by calibrated digital scale. BMI z-score, BMI percentile, and BMI 120th percentile are computed. Dual-energy x-ray absorptiometry (DXA) scans are conducted to assess total fat, as well as total lean mass, using Hologic QDR Discovery A (S/N81337; Bedford, MA). DXA is a gold-standard for fat distribution assessment with strong predictive validity for youths' obesity co-morbidities [77].

2.4.3.3 Health status, treatment history, and puberty: A brief psychiatric and medical health history, including T2D, of the participant and family is obtained by a trained research staff member with a parent/guardian. At the follow-up visits, medical and behavioral treatment history is assessed. While adolescents currently in psychotherapy or on medication affecting mood/insulin will not be enrolled at baseline, it is possible that youth and their families may initiate an alternative treatment during the intervention phase or one-year follow-up phase. We will track initiation of psychotherapy and/or medication status at each follow-up so that this information can be evaluated in sensitivity analyses.

A study pediatric endocrinologist or pediatric nurse practitioner conducts a physical exam including blood pressure in triplicate and waist circumference is measured to evaluate health

status. Fasting labs (lipid panel, alanine aminotransferase [ALT], aspartate aminotransferase [AST]) are collected to measure obesity-related comorbidities. Tanner staging for breast and pubic hair is performed by a study pediatric endocrinologist or pediatric nurse practitioner [42].

2.5 Safety monitoring

In addition to Institutional Review Board requirements pertaining to annual reviews and reporting of adverse events, we also have formed a data safety and monitoring board (DSMB) comprised of three investigators who are not part of the research study and who each contribute experience in clinical trials. The DSMB Chair is a pediatric endocrinologist with expertise in adolescent obesity and T2D; the second DSMB member is a clinical psychologist with expertise in adolescent obesity, T2D, and depression; the third DSMB member is a statistician experienced in clinical trials of adolescents with and at-risk for T2D. At an initial meeting of the investigative team and DSMB, we established a charter by reviewing the protocol inclusion and exclusion criteria, study methods, all risks and protections to participants, timeline for adverse events reporting, and stopping rules for safety and validity. A DSMB report is prepared and reviewed every six months.

2.6 Sample size justification

Sample size was determined based on the difference in the primary outcome of insulin sensitivity derived from whole body insulin sensitivity index (WBISI) between CBT and Health Ed over one-year observed in preliminary data. One-year WBISI was adjusted for baseline WBISI as well as change in DXA body fat. To find a statistical difference between groups with 80% power and 95% confidence, we estimated that we would require a sample size of 75 per group (total $N = 150$), anticipating a difference in mean change in standard deviation units from baseline of 0.38 and a SD ~ 0.7 units between both conditions and attrition of 30% by the end of the study. Additionally, we estimate that the planned sample size provides adequate power ($>80\%$) to detect small-to-moderate indirect effects, accounting for attrition (Aims 2 and 3).

2.7 Statistical analysis

Aims will be examined with multilevel modeling, a flexible approach for repeated assessments within individuals using multiple imputation to handle missing data in SAS V9.4 (SAS Inc., Cary, NC). The co-primary outcomes are insulin sensitivity (WBISI) and β -cell function (DI_0). Time (baseline, post-treatment, one-year) will be tested as linear and non-linear. To evaluate the primary efficacy hypotheses, we will test significant change across time between group conditions. The independent variables will be group condition (CBT versus Health Ed), time, and the interaction of group condition $\times$ time, and the dependent variable will be insulin sensitivity or β -cell function. Modeling will include participant-specific random intercepts and slopes of each outcome. We will control for baseline and change in DXA body fat, to test our hypothesis, that the group condition effect on outcomes is independent of adiposity, and consider other covariates of age, race/ethnicity, and puberty, though groups should be reasonably well-matched for these based on initial randomization.

Consistent with recommendations for the analysis of mediation in randomized controlled trial studies [78], we will evaluate if improvements in insulin sensitivity and β -cell function at one year are mediated by changes from baseline to post-treatment in stress-related behaviors (decreased disinhibited eating, increased physical activity, decreased sedentary time, decreased sleep disturbance) and changes from baseline to post-treatment in cortisol physiology (cortisol awakening response, diurnal cortisol, total daily cortisol output). We first will determine if adolescents assigned to CBT show greater improvements than Health Ed in the proposed mediators by evaluating a model with group condition, time, and the interaction of group condition $\times$ time as independent variables. The dependent variables will be disinhibited eating, physical activity/sedentary time, sleep disturbance, cortisol awakening response, diurnal cortisol, or total daily cortisol output. Participant-specific random intercepts and slopes of the respective dependent variable will be included in the model. Next, we will evaluate if baseline to posttreatment changes in the mediators predict one-year changes in insulin sensitivity and β -cell function, and whether these associations are moderated by group condition (CBT versus Health Ed). The model will include main and interactional effects of time and disinhibited eating, physical inactivity, sleep, cortisol awakening response, diurnal cortisol, or total daily cortisol output. The dependent variable will be insulin sensitivity or β -cell function. Participant-specific random intercepts and slopes of insulin sensitivity or β -cell function will be included. Then, using a moderated mediation model, we will evaluate the indirect effects of decreases in depressive symptoms on insulin sensitivity and β -cell function through disinhibited eating, physical activity/sedentary time, sleep, cortisol awakening response, diurnal cortisol, and total daily cortisol output (mediators), with group condition as the moderator. Indirect effects will be tested with a product of coefficients approach. Bias-corrected bootstrap confidence intervals will be generated for the product of α = group condition effect on the mediator and β = mediator effect on the dependent variable. We initially will conduct modeling separately by mediator and separately by dependent variable, and then follow up on significant outcomes in a more parsimonious, multiple mediation model that will permit evaluation of the unique contribution of each proposed behavioral mediator. Covariates considered in these models will include body fat, race/ethnicity, age, and puberty. Multiple imputation will be used to handle missing data.

3. Discussion

The manifestation of T2D in adolescents is a serious public health concern [4]. Although youth-onset T2D remains a rare disease, the presentation of T2D during adolescence is growing in prevalence, particularly in girls and in adolescents from historically disadvantaged racial/ethnic groups [4]. Youth-onset T2D appears to be distinguished by serious health comorbidities and an aggressive disease course [7]. Treatment of T2D in adolescents involves a combination of medication and lifestyle intervention [7]. Unfortunately, current treatment options show insufficient effectiveness, with only ~55% of treated adolescents with T2D achieving good glycemic control [79]. Treatment adherence is a major obstacle. Adherence is complicated by the serious and chronic psychosocial realities that youth with T2D frequently face, including household dysfunction, poverty, maltreatment, and other major stressful and adverse life experiences [5, 7, 80].

Approximately 70% of adolescents with T2D report at least one major life stressor, and one-third report three or more [80]. The number of stressful life events that adolescents with T2D endorse relates to poorer treatment adherence [80].

Such challenges to the treatment of youth-onset T2D underscore the need for effective prevention efforts. T2D is preventable. The Diabetes Prevention Program (DPP) found that in adults at risk for T2D, an intensive, structured lifestyle intervention addressing physical activity and eating behavior led to a lower likelihood of developing T2D through adults' sustained weight loss that lessened insulin resistance and preserved insulin secretory capacity [81, 82]. Similar efforts in adolescents that involve intensive, structured lifestyle intervention (e.g., three times per week for six months) have shown some success in lessening T2D risk by decreasing severity of obesity/adiposity, and consequently, insulin resistance [83, 84]. Unfortunately, these effects generally have not been as robust as in adults. This approach also is costly, time intensive, and adherence is especially challenging for adolescents, and for racial/ethnic minority teenagers in particular [14, 15, 85]. Moreover, lifestyle interventions usually do not address the psychosocial challenges faced by many adolescents who are at risk for developing T2D. Such psychosocial factors likely interfere with adherence, and in and of themselves may contribute to worsening insulin resistance and T2D onset.

In the MIND Project, we are testing an alternative, targeted approach to prevention of T2D. The primary goal of the MIND Project is to determine to what extent intervening with depressive symptoms affects insulin sensitivity and β -cell function over time in adolescents at risk for T2D with elevated depressive symptoms. Many theoretical perspectives on depression purport that depressive symptoms arise in response to major environmental stressors in individuals who are vulnerable (e.g., genetically and/or biologically) to depression [86]. In adolescents and adults, depressive symptoms are related to insulin resistance, predict worsening insulin sensitivity over time, and heighten the risk for the onset of T2D [20–24, 87]. These effects are, at least partially, independent of obesity/adiposity, raising important questions about the mechanisms connecting depression and T2D risk.

The MIND Project is innovative because no prior approach to T2D prevention has explicitly addressed underlying psychosocial stressors as a risk factor for worsening insulin sensitivity. The conceptual foundation of the study relies on interdisciplinary prevention science and adolescent development. Although most research on depression and T2D focuses upon the comorbidity of depressive disorders and T2D in adults after these chronic disorders have developed, adolescence offers a potential window of opportunity to intervene with depressive symptoms in order to lessen the risk of developing T2D [10]. Interventions timed during adolescence have the possibility of altering the dynamic biological, behavioral, and socioemotional systems of adolescence, in order to impact trajectories of depressed mood and insulin resistance and secretion into adulthood. The use of a randomized controlled trial design permits experimental testing of the role of depression in T2D etiology, as well the putative mediating role of a comprehensive set of stress-related behavioral mechanisms and hypercortisolism. Moreover, the MIND Project results pertaining to mechanisms may inform revisions to depression interventions to enhance effectiveness for lessening T2D risk. In future directions, a brief CBT-based intervention could be revised or augmented to more

explicitly address mechanisms that emerge as significant explanatory factors, including the potential mediators of disinhibited eating, moderate-to-vigorous physical activity, sedentary time, sleep disturbance, and/or hypercortisolism.

One practical limitation to this study is the one-year length of follow-up. Following program participants beyond one year would be ideal in order to track longer-term insulin action and β -cell function and the emergence (or prevention) of youth-onset T2D, which remains relatively rare even among adolescents with overweight/obesity and a T2D family history. The comparison of CBT to a Health Ed control group also has drawbacks. Health Ed is an attention-matched comparison condition but not an active experimental comparator. If the current comparison yields positive effects for CBT as compared to Health Ed, future efficacy trials that evaluate CBT in comparison to an active intervention such as a dose-matched exercise or lifestyle-based intervention could yield valuable information. Likewise, evaluating the additive benefit of CBT as an adjunct to interventions in adolescents with overweight/obesity and/or prediabetes/T2D and depressive symptoms is an alternative design that offers merit. In the current study, we focus upon adolescent girls based upon the rationale that girls are at higher risk than boys for both depression and youth-onset T2D [4, 28]. We also focused on youth with elevated depressive symptoms, but not MDD, in part because MDD ethically necessitates more intervention than a non-clinical Health Ed program. Adolescents in psychotherapy, structured weight loss counseling, or drug treatment for depression or insulin resistance are not enrolled in this trial. Although this approach helps to isolate the efficacy of CBT for improving key outcomes, these sample characteristics limit generalizability. Youth who have already progressed to behavioral or medication treatment of depression and insulin resistance could potentially benefit from the programs being evaluated, particularly CBT. Future work may involve extending the approach to at-risk boys; more intensive, comparative efficacy adaptations to address adolescents and young adults whose symptoms reach the MDD threshold; and/or studies of CBT's effectiveness in at-risk youth who already may be receiving some form of treatment for depression, insulin resistance, or obesity.

In spite of these design considerations, the MIND Project has the potential to make a valuable contribution to our understanding of the relationship between depression and T2D in adolescents. A CBT depression group, known to decrease depressive symptoms in adolescents with elevated depressive symptoms [30–33, 78] is brief, likely to be cost-effective, and ultimately has high potential for dissemination. If a stand-alone CBT group also lessens T2D risk, it has the potential to have a significant impact on our healthcare approach to intervening with the relatively large number of adolescents at risk for T2D with elevated depressive symptoms [18].

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Table 1.

Overview of content in the cognitive-behavioral therapeutic (CBT) Blues Program depression prevention group intervention and content in the health education control group

Session	CBT	Health Education
1	Introduction; interrelationships among thoughts, feelings, and behaviors; identifying negative thoughts; scheduling fun activities	Introduction; domestic violence; intimate partner violence
2	Challenging negative thoughts with “What’s the Alternative?”; rewarding oneself for behavior change	Alcohol; drugs; tobacco
3	Challenging negative thoughts with “Where’s the Evidence?”; rewarding oneself behavior change	Nutrition; body image
4	Challenging negative thoughts with “What if it’s True?”; problem-solving negative coping ruts	Depression; suicide
5	Cope ahead strategies for daily hassles; scheduling future fun activities	Gang violence; non-violent conflict resolution
6	Cope ahead strategies for major life events; planning multiple cope ahead strategies; program review; graduation	Sun safety; program review; graduation

Table 2.

Overview and schedule of primary and secondary outcomes assessed as part of the Mood and Insulin Resistance to prevent Diabetes (MIND) Project clinical trial

Construct	Measurement	Description	Intervals Assessed	Reference
<u>Primary Outcomes</u>				
Insulin sensitivity	WBISI, S_i	7-sample, 2-hour oral glucose tolerance test to estimate insulin sensitivity	Baseline, Post, 1-Year	[35, 36]
β -cell function	DI_o , β -cell responsivity	7-sample, 2-hour oral glucose tolerance test to estimate insulin secretory capacity of β -cells relative to insulin sensitivity	Baseline, Post, 1-Year	[36–39]>
<u>Secondary Outcomes</u>				
Disinhibited eating	EDE Emotional eating	Semi-structured interview to assess disordered eating including objective binge, subjective binge, and objective overeating Assessed by teen self-report through the EES-C	Baseline, Post, 1-Year Baseline, Post, 1-Year	[40, 41] [40, 41]
Physical activity	ActiGraph GT3X+	Body-worn accelerometer to measure 7 days of habitual physical activity including step counts, light and moderate-vigorous intensity, and sedentary	Baseline, Post, 1-Year	[53]
Sleep disturbance	Actiwatch	Home sleep monitoring device to measure 7 nights of total sleep duration, sleep onset, wake time, and sleep efficiency	Baseline, Post, 1-Year	[55, 56, 58]
Cortisol awakening	Saliva	2, 15, 30, and 45 minutes postawakening weekday and weekend saliva samples 2 days collected at home by cotton swabs under the tongue to measure cortisol awakening	Baseline, Post, 1-Year	[62, 67]
Diurnal cortisol	Saliva	4:00 pm and bedtime weekday and weekend saliva samples 2 days collected at home by cotton swabs under the tongue to measure diurnal cortisol	Baseline, Post, 1-Year	[63, 67]
Daily cortisol output	Urine	24-hour home urine collection to measure daily cortisol output	Baseline, Post, 1-Year	[61, 65, 68]
<u>Other Variables</u>				
Depressive symptoms	CES-D	20-item version of the scale administered to assess depressive symptoms	Baseline, Post, 1-Year	[69]
Body composition	BMI indices Body fat	Height and weight measured to calculate BMI DXA conducted to measure body composition including total fat and lean mass	Baseline, Post, 1-Year Baseline, Post, 1-Year	[23] [71]
Health status	Family history Physical exam	Family history interview administered by trained study staff to assess medical health and family history of diabetes Physical exam administered by study pediatric endocrinologist to assess overall physical health status	Baseline & 1-Year Baseline & 1-Year	[25]
Puberty	Tanner staging	Staging for breast and pubic hair performed by study pediatric endocrinologist or nurse practitioner	Baseline & 1-Year	[42]

Abbreviation: Post=refers to an immediate post-treatment assessment interval occurring within two weeks of the last intervention session; WBISI = whole body insulin sensitivity index [35]; S_i = insulin sensitivity [38]; DI_o = oral disposition index [37–39]; BMI = body mass index (kg/m^2 , z-score, percentile, 120th percentile) [23]; EDE = eating disorder examination [44, 45]; EES-C = emotional eating scale- adapted for children [46]; CES-D = center for epidemiologic studies- depression scale [69]; DXA = dualenergy x-ray absorptiometry [71].