STUDY PROTOCOL

Sleep optimization to improve glycemic control in adults with type 1 diabetes: study protocol for a randomized controlled parallel intervention trial

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Abstract

Background: Despite improvements in treatment regimens and technology, less than 20% of adults with type 1 diabetes (T1D) achieve glycemic targets. Sleep is increasingly recognized as a potentially modifiable target for improving glycemic control. Diabetes distress, poor self-management behaviors, and reduced quality of life have also been linked to sleep variability and insufficient sleep duration. A significant gap of knowledge exists regarding interventions to improve sleep and the effects of sleep optimization on glycemic control in T1D. The purpose of this study is to determine the efficacy of a T1D-specific sleep optimization intervention (Sleep-Opt) on the primary outcomes of sleep variability, sleep duration, and glycemic control (A1C); other glycemic parameters (glycemic variability, time-in-range [TIR]); diabetes distress; self-management behaviors; quality of life; and other patient-reported outcomes in adults with T1D and habitual increased sleep variability or short sleep duration.

Methods: A randomized controlled parallel-arm study will be employed in 120 adults (aged 18 to 65 years) with T1D. Participants will be screened for habitual sleep variability (> 1 h/week) or insufficient sleep duration (< 6.5 h per night). Eligible subjects will be randomized to the Sleep-Opt intervention group or healthy living attention control group for 12 weeks. A 1-week run-in period is planned, with baseline measures of sleep by actigraphy (sleep variability and duration), glycemia (A1C and related glycemic measures: glycemic variability and TIR using continuous glucose monitoring), and other secondary outcomes: diabetes distress, self-management behaviors, quality of life, and additional patient-reported outcomes. Sleep-Opt is a technology-assisted behavioral sleep intervention that we recently developed that leverages the rapidly increasing public interest in sleep tracking. Our behavioral intervention employs four elements: a wearable sleep tracker, didactic content, an interactive smartphone application, and brief telephone counseling. The attention control group will participate in a healthy living information program. Baseline measures will be repeated at midpoint, program completion, and post-program (weeks 6, 12, and 24, respectively) to determine differences between the two groups and sustainability of the intervention.

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Background
Sleep variability and insufficient sleep duration have negative health consequences in the general population. These include changes in appetite and eating patterns [1–3], obesity [4], insulin resistance [5], increased systemic inflammation [6], metabolic syndrome [7], dysglycemia [8], risk for incident diabetes [3], depression [9], and a higher prevalence of cardiovascular disease [10]. Sleep times of less than 5 h have been associated with up to four times the mortality risk of those with greater than 5 h [11, 12]. Each hour of increased sleep variability, as measured by standard deviation (SD) of sleep duration, was associated with a 27% higher odds of metabolic syndrome in a multi-ethnic population [7]. Work commitments, family and social obligations, and general stress have also been linked with poor sleep [13, 14]. Negative health consequences of insufficient and irregular sleep may be amplified for persons with type 1 diabetes (T1D), who must cope with the added burden of managing a chronic condition [15].

Up to 40% of adults with T1D had insufficient sleep (sleep duration < 6–6.5 h/night) either by self-report or objectively assessed [16–24]. Insufficient sleep is a predictor of poor glycemic control in T1D [16, 25]. Increased insulin resistance likely plays a central role; one night of experimental sleep restriction (4 h) in seven persons with T1D was associated with decreased peripheral insulin sensitivity, compared to normal sleep duration (7.8 h) [26]. In our recent meta-analysis, adults with T1D who reported sleeping > 6 h had 0.24% lower A1C levels than those sleeping ≤ 6 h [16].

In addition to insufficient sleep, sleep variability (a potential marker of circadian misalignment) can impact glycemic control. Up to 73% of adults with T1D have sleep variability (> 1 h) [17, 27]. The circadian system plays an important role in glucose metabolism, and experimental circadian misalignment results in impaired glucose tolerance [28, 29]. Thus, sleep variability could be detrimental to glycemic control. Supporting this hypothesis, recent studies have reported that sleep variability is an independent predictor of glycemic control in T1D [17, 30, 31]. Sleep variability (SD of sleep duration as objectively measured by actigraphy) explained 8.2% to 15.8% of the variance in glycemic control [17, 30]. In our study of 41 working-age adults with T1D, those with SD of sleep duration > 1 h had significantly higher A1C than those with SD sleep duration ≤ 1 h (median 7.2% vs. 7.8%, p = 0.008). Sleep variability was also associated with increased daily insulin requirement, suggesting more insulin resistance in these individuals [17]. These findings were reproducible: another study in 65 adolescents with T1D also found that greater SD of sleep duration was significantly associated with higher A1C [30], and in a study of 191 German adolescents with T1D, greater variability of sleep timing between work and free days was associated with higher insulin requirements [32]. Persons with T1D lack endogenous insulin secretion; varying degrees of insulin resistance could lead to increased glycemic variability (within-day glucose fluctuations), a factor reported to be associated with increased microvascular complications and cardiovascular events in T1D [33, 34]. Indeed, our pilot data in 30 adults with T1D revealed that greater SD of sleep duration was associated with greater glycemic variability as measured by continuous glucose monitoring (CGM) [27].

These data strongly suggest that sleep variability and insufficient sleep duration affect glycemic control and glycemic variability, with the effect size similar to some standard treatments for T1D [35, 36]. Despite recognition that sleep patterns should be assessed in individuals with diabetes [37], few studies have been conducted to evaluate strategies to improve sleep. Those conducted have primarily evaluated interventions in children [38, 39]. Perfect et al. conducted a short-term pilot RCT using sleep extension in 79 adolescents with T1D for 1 week [40]. The sleep extension intervention included didactic information on topics such as the importance of sleep, sleep hygiene principles, control of environmental conditions, management of competing activities, and stress reduction, as well as use of a sleep log and actigraphy monitoring [40]. The preliminary results revealed that glucose levels as measured by CGM in extension participants differed from the fixed-sleep-duration group by 17 mg/dl points (p = .003) during the sleep modification week. Sleep extension resulted in 11 h more spent in the glucose target range than those in the fixed-sleep condition [41]. In a pilot trial of 39 children, aged 5–9, and their parents, sleep-promoting intervention (relaxation and mindfulness, setting a bedtime, and combating bedtime resistance/nighttime waking) was compared with usual care [38]. The program was well accepted, but there was no difference in children’s total sleep time, sleep efficiency, or A1C at 3 months. However, when excluding children with A1C < 7% at baseline, there was a possible small effect of sleep coach vs. usual care on A1C (~0.3%). A similar intervention was compared...
to usual care in 39 adolescents with T1D [39]. The study showed excellent feasibility, and teens in the sleep coach group had an increase in sleep duration by 48 min and were less likely to report poor sleep quality compared with control group. However, no change in A1C was observed. This emerging evidence supports the feasibility and efficacy of sleep optimization, as well as a possible dose-response relationship between optimized sleep and changes in metabolic control.

Because sleep is linked to possible mediators of glycemic control (including diabetes distress [42–44], diabetes self-management behavior [45, 46], and quality of life [QoL] [47]), those mediators’ influence on glycemic control during sleep optimization need to be examined also. Diabetes distress pertains to the emotional burdens and worries associated with the complexities of managing diabetes [48]. Moderate to high distress levels are experienced by up to 54% of those with T1D [48]. Concern over blood glucose levels (particularly fear of hypoglycemia) is a major source of distress at night that impacts sleep [49]. In a study of 267 adults with T1D, diabetes distress was found to be significantly higher in those adults who reported poor sleep quality. Those with poor sleep quality also experienced greater daytime sleepiness and diabetes regimen burdens [15].

Poor sleep has also been linked directly to self-management behavior. In a cross-sectional study of 45 adolescents, a significant relationship was found between sleep duration and self-management behavior [50]. Specifically, a 15- and 20-min increase in sleep was associated with one additional blood glucose check and one additional insulin bolus, respectively [50]. In addition, sleep variability (SD of sleep duration) was found to be a significant predictor of self-management behavior, explaining 6.1% of the variance in the frequency of blood glucose monitoring [30]. Thus, improving sleep variability and duration could potentially improve self-management behavior.

In summary, we found no published studies that explored the effects of sleep optimization (strategies to improve sleep duration and variability) on glycemic control in adults with T1D. These data are needed and could have a large clinical impact, given the current state of suboptimal glycemic control and increasing incidence of T1D. Wearable sleep trackers provide a critical opportunity to engage short or variable sleepers. Over the past few years, the public’s interest in monitoring sleep has increased immensely, providing an important opportunity to affect sleep in public health. Our intervention uses data from a wearable sleep tracker (Fitbit) to personalize feedback and promote interaction with remote coaches.

Enhancing adherence to technology-assisted behavioral interventions is key to improvements. Many technology interventions suffer from high rates of non-adherence [51]. Coached interventions typically show larger effect sizes than unguided interventions, likely due to improved adherence [52]. The process by which human support enhances adherence to behavioral intervention technologies has been termed “Supportive Accountability” [53] and draws on broad empirical literature, including clinical and organizational psychology [54, 55] and motivation theory [56, 57]. Accountability is defined as knowing that one will have to justify use or non-use to another individual at some future time [54]. The model involves qualities of the coach, including legitimacy, trustworthiness, and helpfulness. We designed and tested a coaching protocol around these principles (Duffey, Kinsingre, Ludman & Mohr, Brief Telephone Support Program to Enhance Adherence to Technology Assisted Behavioral Interventions Therapist Manual, unpublished protocol) that demonstrated the capacity to enhance adherence in a sleep extension intervention.

Methods

Objectives

The goal of this study is to improve glycemic control (A1C) by reducing sleep variability and improving insufficient sleep duration. The specific aims are:

1) Determine the effect of the Sleep-Opt intervention (compared to an attention control group) on sleep variability, sleep duration, and glycemic control (primary outcomes)
2) Determine if Sleep-Opt will result in improved psychological and behavioral outcomes, including diabetes distress, diabetes self-management behavior, QoL, fatigue, mood, and subjective sleep quality compared to the healthy living attention control group
3) Determine the contribution of changes in sleep variability and sleep duration during the intervention to changes in glycemic parameters (A1C, glycemic variability, TIR). We hypothesize that Sleep-Opt will result in improved sleep and glycemic control, lower diabetes distress, and improve self-management behavior and QoL. Reduction in variability and improved sleep duration will correlate with improvement in glycemic parameters (Fig. 1)

Design

A randomized controlled parallel-arm design will be used. Following a baseline run-in phase, 120 subjects will be randomized to the Sleep-Opt or healthy living attention control group for 12 weeks.
Setting
The study will be conducted remotely with participants in their free-living environment living in the United States. Due to changes instituted with COVID-19, data collection was converted to remote collection using mail services and videoconferencing.

Recruitment
Participants will be recruited through two Midwestern medical centers, diabetes clinics, diabetes websites, and organizations, using flyers, e-announcements, recruitment letters, listservs, and ResearchMatch (www.researchmatch.org).

Participant eligibility criteria
Inclusion criteria consist of adults 18–65 years old with a clinical diagnosis of T1D for at least 1 year who report habitual sleep variability (1 h/week or more) or sleep duration < 6.5 h/night during work- or weekdays (confirmed with actigraphy) who have a desire to improve sleep and who own a smartphone compatible with Fitbit.

Exclusion criteria consist of insomnia symptoms defined as severe as assessed by the Insomnia Severity Index [58] (score ≥ 15), being at high risk for obstructive sleep apnea as assessed by the STOP Questionnaire [59], history of severe hypoglycemia (defined as hypoglycemic episodes that result in loss of consciousness within the last 6 months, seizures, or requiring emergency room visits or hospitalization), A1C > 10%, rotating shift or night shift work, use of sleep medications/ aids, significant renal impairment (estimated glomerular filtration rate < 45 ml/min/1.73 m²), significant medical morbidities (such as congestive heart failure, cirrhosis, chronic obstructive pulmonary disease requiring oxygen, active treatment for cancer, restless leg syndrome, depression [8-item Patient Health Questionnaire PHQ-8 score greater than or equal to 10], history of stroke with neurological deficits), or breast feeding, pregnant, or planning pregnancy.

Consent procedures
Potentially eligible interested participants will be screened by trained study personnel for inclusion and exclusion criteria. Written informed consent will be obtained online (Research Data Capture [REDCap]) prior to performing any research procedures. The informed consent process will begin when potential subjects are contacted. The researcher will explain the study purpose, procedures, benefits, risks, confidentiality, and research subject’s rights. After all questions have been answered and the subject verbally agrees to participate, written consent will be obtained. A copy of the signed consent will be provided to the participant.

Study procedures
Following pre-screening by phone for eligibility and informed consent, those who meet initial study criteria will be scheduled for a video conference appointment for the start of the 1-week run-in period (week 0) to obtain baseline measures, confirm eligibility (A1C, urine pregnancy [if appropriate], and actigraphy for sleep), supervise the application of a CGM device, review instructions on its care, and review instructions for completion of questionnaires using REDCap. Prior to the video conference appointment, study staff will mail study materials (pregnancy test strips, measurement tape, CGM [Free-Style Libre Pro CGM and Reader, or Dexcom], Actiwatch [Phillips Spectrum Plus], sleep log, A1C kit, and post-age-paid package to return supplies) to subjects’ home (Table 1).

Randomization, allocation, and masking
Following the 1-week run-in period and a confirmation of objective sleep criteria (variability [≥ 1 h] or mean sleep duration [< 6.5 h/night] during work- or weekdays), A1C results, and other inclusion criteria, participants will be randomly assigned to the Sleep-Opt intervention or healthy living attention control group. We will use permuted blocks of 4, arranged in random order and stratified by sex, A1C (cats), and age (cats). The randomization model will be developed by the study statistician and executed through the REDCap data management system. Although the statistician created the allocation schedule for two groups, they are not aware of group identifiers and will remain blinded until after main effect models are finalized.

All study staff are unaware of future treatment allocations through restrictions in REDCap permissions. Only study staff members who are designated to obtain the allocation assignment have access to this function and do this only when an eligible participant is ready for randomization. They will then communicate the assignment...
to the respective interventionist (coach). All investigators and study staff who collect or have access to outcome data are masked to participant allocation. If needed, the project director would be able to unmask allocation assignment and communicate allocation assignment to the appropriate personnel.

**Sleep-opt intervention**
The goal of the intervention will be to decrease sleep variability by at least 30 min and/or increase time in bed by at least 30 min. The intervention will take place over 12 weeks and be conducted remotely by phone call/video conference (Webex) at participants’ preference. Participants who are randomized to Sleep-Opt will receive the following four components: (1) a wearable sleep tracker; (2) a smartphone application with interactive feedback and tools; (3) didactic content via email lessons, reminders, and notifications; and (4) brief telephone coaching. The components are described below.

**Wearable sleep tracker**
Participants assigned to the sleep intervention will receive a Fitbit wearable sleep tracker to allow them to track their sleep and share results with the coach. Data support that consumer sleep trackers provide an estimation of sleep but are less precise than validated actigraphy devices [60, 61]. Therefore, sleep sufficiency will be measured with actigraphy, which is validated but does not currently provide real-time feedback to the wearer [62]. Fitbit data will be used in coaching sessions and for providing weekly reports.

**Smartphone application**
We will use a commercial sleep tracking application to provide participants feedback on their sleep behaviors. Participants will download the Fitbit smartphone application on their smartphone and participate in a brief training in the intervention orientation session. Participants will be trained to review and edit their Fitbit sleep log each day, thus increasing the validity of the data. Although the Fitbit application has developed the ability to enter sleep goals, these features will not be set on participants’ applications. In addition, participants will be able to use other features (e.g., step goals) but not trained or instructed on the use of these application features as part of the intervention.

**Intervention content**
Participants will receive automated content including didactic lessons for 8 of the 12 weeks, with gap weeks included beginning at week 5 for participants to work on behavior change (Table 2). The intervention content was developed by members of the team with advanced training in sleep and behavior change and has been piloted in initial user testing. The eight didactic lessons (estimated duration 8–10 min) of written and video didactic content will be delivered via email using REDCap and can be viewed on smartphone, desktop, or tablet. Content from the lessons will be reinforced in the telephone coaching sessions.

**Coaching**
All participants will be assigned to an interventionist who will be a sleep coach to monitor their progress during the study and provide telephone coaching sessions related to their sleep-related goals. The coaches will establish legitimacy by their knowledge of sleep and basic counseling principles. They will establish goals with the participants based on the participants’ values and beliefs, including the sleep-related goals and usage

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**Table 1** Study procedures

| Study period | Enrollment | Intervention | Follow-up |
|--------------|------------|--------------|-----------|
| Week         | 0          | 1            | 2 3 4 5 6 8 10 12 24 |
| Informed consent | X          |              |           |
| Eligibility screen | X          |              |           |
| Actigraphy   | X          | X            | X X       |
| CGM          | X          |              | X X       |
| A1C          | X          |              | X X       |
| Questionnaires | X         |              | X X       |
| Randomization | X          |              |           |
| SleepOpt     | X X X X X  | X X X X     | X X X X   |
| Control      | X X X X    | X X X X     | X X       |
| Post-program evaluation | X          |              |           |
goals (e.g., number of days wearing the sleep tracker). Performance monitoring will be completed through an online dashboard visible to the coaches. The first coaching session will be a 20-min engagement session, which includes introductions, rationale for the program, clarifying roles of the coach, and the participants’ goals for the program. Coaches will provide feedback to the participants based on wearable sleep tracker data. For subsequent coaching sessions, the coach and participant will also have weekly brief (5–10 min) follow-up support calls to troubleshoot any problems with the application or wearable sleep tracker, review progress, problem solve barriers to progress, and set goals. Between sessions, the coaches will be available (mostly via email) to troubleshoot any problems with the application or wearable sleep tracker. All coaching sessions, text, and email communication will be recorded, and a selection of sessions will be coded for intervention fidelity.

Healthy living attention control
The design of the 12-week control group is intended to control for the coach contact in the intervention group, so that we can test the intervention-related components contained in Sleep-Opt. Participants assigned to the healthy living control group will be provided eight scheduled emails with health content (e.g., dental health, handwashing, stretching exercises; 8–10 min in length) with content written at the 4th grade level or below. Participants will receive eight brief (5–10 min) telephone contact from the coach (see schedule Table 2) to determine if they received the information and if they had any questions about the materials. The schedule will mirror that of the intervention group. Coaches will not provide counseling or goal setting but may clarify terms or concepts. Participants in the healthy living control group will be instructed not to change their sleep behavior. They will be eligible to receive the sleep intervention at the end of the study. After completion of the study, they will receive a Fitbit wearable fitness tracker as part of study compensation.

Measures
Measures will be obtained at baseline (week 0), midpoint of intervention (week 6), end of intervention (week 12), and post-program (week 24; Table 3).

Primary outcomes
- Sleep variability
- Sleep duration
- Glycemic control: hemoglobin A1C

Secondary outcomes
- Diabetes distress
- Diabetes self-management
- Quality of life (QoL)
- Fatigue
- Depressive mood
- Subjective sleep quality

Glycemic assessment
1) Glycemic control will be assessed using hemoglobin A1C blood spot (A1C; Home Access Health Corp.). A1C is a gold standard marker of glycemic control in T1D, reflecting average glucose levels in the previous 90 days.
2) Glycemic variability using CGM will be conducted using FreeStyle Libre Pro glucose sensor or Dexcom (FDA-approved). The system captures interstitial glucose and records the data every 5–15 min. Variables to be derived from the CGM are mean glucose level, standard deviation (SD), coefficient of variation (CV), percentage of time spent in range (70–180 mg/dL), percentage of time < 70 mg/dl, and percentage of time ≥ 180 mg/dl [65, 66]. Interstitial glucose measurements with FreeStyle Libre and Dexcom were found to be accurate compared with capillary blood glucose reference values, with a mean absolute relative difference (MARD) of 12% and 9% (respectively) compared to the gold standard YSI measure of blood glucose [77]. Accuracy of 10% MARD has been approved for self-adjustment of insulin doses in clinical practice [78].

### Table 3 Measures

| Variables                                      | Measures                                                                 | Frequency          |
|------------------------------------------------|--------------------------------------------------------------------------|--------------------|
| Demographic and health information, caffeine, and sleep aid use | Demographic, health questionnaire, hypoglycemia unawareness, Clark Scale [63], menopausal status (STRAW+10 in women ≥ 40 years) [64], caffeine, sleep aid use | Week 0             |
| Primary measures: Objective sleep indices      | Sleep duration, sleep variability, sleep and wake timing (Respironics Actiwatch Spectrum Plus®). Confirmed with sleep diary (bedtime, disruptions, wake time). | Weeks 0, 6, 12, 24 |
| Glycemic indices                               | A1C                                                                      |                    |
| Glycemic control                               | CGM (Abbott Libre® or Dexcom®): glucose variability, coefficient of variation (CV%), time-in-range [65, 66] |                    |
| Secondary measures:                            |                                                                          |                    |
| Diabetes distress                              | T1D Diabetes Distress Scale [67]                                         | Weeks 0, 6, 12, 24 |
| Diabetes self-management                       | Self-Management Questionnaire-R [68]                                     |                    |
| Quality of life                                | Diabetes Quality of Life Scale (DQOL) [69]                               |                    |
| Fatigue                                        | PROMIS Fatigue Scale [70]                                               |                    |
| Depressed mood                                 | Center for Epidemiological Studies Depression Scale (CES-D) [71]        |                    |
| Subjective sleep quality                       | Pittsburgh Sleep Quality Index [72]                                      |                    |
| Important patient-related variables            |                                                                          |                    |
| Sleep onset                                    | Pittsburgh Sleep Quality Index [72]                                      |                    |
| Sleep offset                                    |                                                                          |                    |
| Sleep duration                                  |                                                                          |                    |
| Mid-sleep time                                  |                                                                          |                    |
| SD of sleep duration                           |                                                                          |                    |
| Sleep offset, sleep duration, mid-sleep time   |                                                                          |                    |
| (time point between sleep onset and wake time) |                                                                          |                    |
| SD of sleep duration                           |                                                                          |                    |

### Sleep assessment

Participants will wear an Actiwatch Spectrum Plus (Respironics, USA) on their non-dominant wrist for 1 week for assessment at baseline and weeks 6, 12, and 24. Data will be collected in 30-s epochs. Subjects will be asked to keep a daily sleep log and press an event marker on the Actiwatch at bedtime and wake-up time. Data will be downloaded and reviewed with each participant to clarify inconsistencies when the Actiwatch is returned. Bedtime and wake time will be set by researchers considering event markers, times on sleep logs, light, and activity signals as previously described [79]. Using the Immobile Minutes algorithm in the Actiware 6 software, we will derive the following variables: sleep onset, sleep offset, sleep duration, mid-sleep time (time point between sleep onset and wake time), and SD of sleep duration, an indicator of sleep variability which we previously showed to be related to glucose metabolism [17].

### Secondary outcomes: diabetes distress, self-management behavior, quality of life, fatigue, depressive mood, subjective sleep quality

Diabetes distress will be measured with the Type 1 Diabetes Distress Scale [67]: This 28-item, 6-point Likert scale measures seven subscales (powerlessness, management distress, hypoglycemia distress, negative social perceptions, eating distress, physician distress, and friend/family distress) and provides an overall total distress scale score.

Self-management behavior will be measured with the Diabetes Self-Management Questionnaire-Revised (DSMQ-R) [68]. This 27-item, 4-point Likert scale measures aspects of self-management behavior and has questions that are specific to those using rapid-acting insulin.

Quality of life will be measured with the Diabetes Quality of Life Scale (DQOL), a 46-item, 5-point Likert scale that measures four subscales (satisfaction, impact, social/vocational worry, and diabetes-related worry) [69]. The scales chosen have strong psychometric properties and have been validated in people with T1D.

Fatigue will be measured with the PROMIS Short Form 8a Fatigue Scale [70]. This 8-item, 5-point Likert scale measures the level of fatigue over the past 7 days. It uses item-response theory and has been validated for use across all populations.

Depressive mood will be measured with the Center for Epidemiological Studies Depression Scale (CES-D) [71].
This 20-item, 4-point Likert scale measures emotions over the past week. Scores range from 0 to 60. The scale has been validated in adult populations. A score ≥ 16 indicates a depressive mood.

Subjective sleep quality will be measured with the Pittsburgh Sleep Quality Index (PSQI) [72]. The PSQI measures seven domains of sleep—quality, latency, duration, efficiency, disturbances, use of sleep medications, and daytime dysfunction—over the past month. The scale provides an overall summary score. Scores of 5 or more indicate poor overall sleep quality. The scale has been psychometrically validated in a variety of adult populations, including those with diabetes.

Additional important patient-related variables
Self-efficacy, anxiety, fear of hypoglycemia, and daytime sleepiness will be measured with validated instruments: Self-Efficacy for Diabetes Scale [80], General Anxiety Disorder – 7-item (GAD-7) [74], Hypoglycemia Fear Scale II [75], and Epworth Sleepiness Scale [76]. Because menopausal status can affect sleep, we will use the STRAW+10 (Stages of Reproductive Aging Workshop+10) criteria for staging menopause for women aged 40 and over [64]. Physical activity will be obtained by activity counts from actigraphy recordings.

Sample size calculation
We conservatively estimated the minimal detectable difference between treatment arms to be 0.4 to 0.6 standard deviations for our target sample size of 60 per group (after attrition) at the 12-week post-treatment measurement based on a two-groups pre-post design, α = 0.02, two-sided, 80% power, and assuming correlations between time points of 0.5 to 0.8 [81]. Standard deviations from pilot data for A1C (1.07%), sleep variability (30 min), and sleep duration (49 min), and the correlation between measurements (r = 0.56 to 0.85) were used for sample size determination. Our minimal detectable difference represents a modest but clinically important change (e.g., 20-min increase in sleep duration, 0.43% change in A1C).

Data analysis
Aim 1: Determine the effect of Sleep-Opt (compared to a healthy living attention control group) on the primary outcomes of sleep variability, sleep duration, and glycemic control (A1C).

We will conduct mixed-effect models for repeated measures (MMRM) using change from baseline for our outcome regressed onto categorical fixed effects for treatment arm, time, their interaction, and the initial baseline measure of the outcome. We will use an unstructured covariance structure to model within-person errors. If convergence problems occur, we will select the best fitting model from among several options, including random coefficients with residual covariance patterns such as autoregressive or exchangeable structure [82, 83]. In addition to A1C, we will estimate separate models for parameters from CGM (glycemic variability, TIR). Sex will be included as a covariate and tested for moderation of the treatment effect. We will also control for BMI, A1C (for other glucose measures), and method of insulin delivery. If treatment arms are found to differ in the distribution of baseline characteristics despite randomization, we will conduct sensitivity analyses including these variables as covariates. The primary endpoint will be change differences between groups at 12 weeks, based on least square means using a two-sided test with α = .05. We will also assess differences in change from baseline to the 24-week endpoint to assess sustainability of effect.

Aim 2: Determine if Sleep-Opt will result in improved psychological and behavioral secondary outcomes, including diabetes distress, diabetes self-management behavior, and QoL. Secondary outcomes will be analyzed with the same approach used in aim 1

Aim 3: Determine the contribution of changes in sleep variability and sleep duration during the intervention to changes in glycemic parameters (A1C, glycemic variability, TIR)

Sleep-Opt is designed to reduce sleep variability and extend sleep and duration, and we expect these changes to mediate change in glycemic control. In the context of the Aim 1 models, we will add time-varying sleep parameters—considering the average levels per person and the variation at each time point—to understand contributions of between- and within-person differences. We will also examine additional covariates predicting sleep parameters, because level and change in sleep parameters (while influenced by randomized treatment arm) are not experimentally controlled [84]. In addition, we will test moderation of within-person mechanisms by sex, distress, method of insulin delivery, and A1C level using interaction terms. Successful completion of this aim will inform how aspects of sleep are related to the various aspects of glycemic control in general; which glycemic control parameters show reactivity to within-person fluctuations in sleep; and which personal characteristics may be more associated with this reactivity. This will explicate key mechanisms of change and suggest who may benefit most from sleep optimization.

Methods to address missing data
While missing data will be minimized through careful procedures, some missing data are inevitable with longitudinal studies. We will handle missing data using the full information maximum likelihood (FIML) approach
that is appropriate for data missing at random [85]. We will use inclusive models with auxiliary variables related to missingness among covariates collected at baseline, if needed, to support the missing-at-random assumption [86]. Multiple imputation will be considered if excessive data are missing among predictor variables (e.g., change in sleep parameters for Aim 3) [86]. Sensitivity analyses such as pattern mixture models will be employed if data are suspected to be missing not at random [82].

Data safety monitoring committee composition and function, reporting of adverse events
The Data Safety Monitoring Committee (DSMC) will be an independent committee, composed of five senior faculty members whose roles include a statistician, endocrinologist, and sleep and trials specialists. The DSMC will meet annually but will be consulted more frequently if needed. An annual summary report will be provided to the principal investigator, IRB, and funding organization. Adverse and unanticipated events will be reported to the IRB and sponsor according to IRB protocol and a summary provided to the DSMC.

Frequency and plans for monitoring trial conduct
The principal investigator (PI) will have overall responsibility for day-to-day support of the trial. A trial steering committee (SC) will be composed of all investigators and study staff (see title page for members). The SC will meet monthly and review recruitment, enrollment, retention, completion, and intervention fidelity reports.

A trial management committee, comprised of the PI, project manager and research specialist will meet weekly to monitor study plans, weekly recruitment and enrollment processes, randomization, progress of study participants, supply and equipment purchases, preparation of agenda and materials for SC and DSMC meetings.

Intervention fidelity will be evaluated quarterly by study personnel and reported to the SC. All coaching sessions (Sleep-Opt and healthy living attention control) will be recorded for training and fidelity monitoring. Approximately 10% of conducted sessions will be reviewed and coded for adherence using previously developed rating scales [87]. A manual of operations will be developed, and staff will be trained on study procedures. All interactions with participants will be scripted when possible. Fidelity less than 88% will trigger retraining.

Ten percent of actigraphy recordings will be reviewed for congruence in scoring by one of the study co-investigators who is not involved in data collection. Congruence less than 88% will trigger retraining.

Participant retention strategy
We expect to randomize 144 subjects to obtain complete data on 120 subjects. This estimate is based on our previous work, with a 17% attrition rate expected. All efforts will be made to retain participants and reduce burden of participation. Assessment visits and coaching calls will be flexibly scheduled according to participant needs. Participants will be compensated for participation incrementally across visits. Participant sleep and glucose data will be provided at the end of the study. Participants will also be allowed to keep the Fitbit device as an additional incentive for program completion. Those in the attention control group will receive a Fitbit at the end of the study.

Discussion
Despite improvements in treatment regimens and technology, less than 20% of adults with T1D achieve glycemic targets [88]. Sleep is increasingly recognized as a potentially modifiable target for improving glycemic control. Research is limited as to how to optimize sleep among persons with T1D and whether such interventions improve important outcomes, including glycemic control, diabetes distress, and QoL. The proposed study will determine the efficacy of a T1D-specific sleep optimization intervention (Sleep-Opt) in reducing sleep variability and insufficient sleep duration and improving glycemic control, other glucose parameters, diabetes distress, self-management, QoL, and other important patient-reported outcomes. If the intervention is determined to be beneficial, sleep optimization could be incorporated as a component of standard medical care of T1D.

Trial status
Protocol number version 10, November 2021. The first participant was randomized on January 19, 2021. The trial will complete recruitment on April 30, 2025.

IRB Protocol #2020-0374
All protocol amendments will be submitted for approval by the IRB prior to implementation of any changes. Any changes to the study aims will require approval by the funding organization prior to implementation. Written informed consent to participate will be obtained from all participants.

Abbreviations
T1D: Type 1 diabetes; QoL: Quality of life; SD: Standard deviation; REDCap: Research electronic data capture; CGM: Continuous glucose monitoring; DQOL: Diabetes Quality of Life Scale; CES-D: Center for Epidemiologic Studies Depression Scale; PSQI: Pittsburgh Sleep Quality Index; PROMIS: Patient-Reported Outcomes Measurement Information System; GAD-7: Generalized Anxiety Disorder Scale-7-item; STRAN-10: Stage of Reproductive Aging+10,
CV: Coefficient of variation; TIR: Time-in-range; MMRM: Mixed-effect models for repeated measures; MARD: Mean absolute relative difference; FIML: Full information maximum likelihood; DSMQ-R: Diabetes Self-Management Questionnaire-Revised; DSMC: Data Safety Monitoring Committee; SC: Trial steering committee; PI: Principle investigator.

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Authors’ contributions
PMN, JD, LQ, SR, AS, and KB were involved in the conception and study design, study set-up, and study conduct. AS developed the statistical analysis plan and randomization procedures. LB set up REDCap and assisted with study start-up procedures. With the implementation of the study, RP, MP, SA, DM, and PMN were involved with recruitment. RP and MP are responsible for enrolling participants and data collection. MCW, GAI, PMN, JD, LQ, SR, AS, KB, RP, MP, and PMN are involved with execution of the protocol. All authors were involved with final approval of the manuscript.

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Declarations
Ethics approval and consent to participate
This trial was approved by the University of Illinois Chicago, Office for the Protection of Research Subjects; Institutional Review Board (Protocol 2020-0374). Initial approval obtained April 3, 2020. Amendments are submitted to the Institutional Review Board for approval prior to institution of any changes in the protocol.

Competing interests
The authors declare that they have no competing interests.

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