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Efficacy of Digital Cognitive Behavioral Therapy for the Treatment of Insomnia Symptoms Among Pregnant Women
A Randomized Clinical Trial

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IMPORTANCE Despite the prevalence and adverse consequences of prenatal insomnia, a paucity of research is available regarding interventions to improve insomnia symptoms during pregnancy.

OBJECTIVE To test the efficacy of digital cognitive behavioral therapy for insomnia (CBT-I) compared with standard treatment among pregnant women with insomnia symptoms.

DESIGN, SETTING, AND PARTICIPANTS This randomized clinical trial enrolled pregnant women from November 23, 2016, to May 22, 2018. Of the 2258 women assessed for eligibility using an online self-report questionnaire, 208 were randomized to receive digital CBT-I (n = 105) or standard treatment (n = 103) for insomnia. Participants were pregnant up to 28 weeks' gestation, and they either had elevated insomnia symptom severity or met the criteria for insomnia caseness as determined by self-report questionnaires. Participants completed outcome measures at 10 weeks (postintervention) and 18 weeks (follow-up) after randomization. All study visits were completed remotely, and the intervention was delivered digitally. Data were analyzed between December 12, 2018, and July 2, 2019.

INTERVENTIONS Digital CBT-I consisted of 6 weekly sessions of approximately 20 minutes each. Standard treatment reflected standard care. Women receiving standard treatment had no limits placed on the receipt of nonstudy treatments, including medication and psychotherapy.

MAIN OUTCOMES AND MEASURES All outcomes were assessed remotely using self-report questionnaires administered via online survey. The primary outcome was the change in insomnia symptom severity (measured by the Insomnia Severity Index) from baseline to postintervention. Secondary outcomes were sleep efficiency and nightly sleep duration (defined by sleep diary), global sleep quality (measured by the Pittsburgh Sleep Quality Index), depressive symptom severity (measured by the Edinburgh Postnatal Depression Scale), and anxiety symptom severity (measured by the Generalized Anxiety Disorder Scale-7). For each outcome, we also examined the change from baseline to follow-up.

RESULTS The 208 participants had a mean (SD) age of 33.6 (3.7) years and a mean (SD) gestational age of 17.6 (6.3) weeks at baseline. Most of the participants were white (138 [66.3%]), married or cohabiting (196 [94.2%]), had a college degree (180 [86.5%]), and earned $100 000 or more per year (141 [67.8%]). Women randomized to receive digital CBT-I experienced statistically significantly greater improvements in insomnia symptom severity from baseline to postintervention compared with women randomized to receive standard treatment (time-by-group interaction, difference = −0.36; 95% CI, −0.48 to −0.23; $\chi^2 = 29.8$; $P < .001$; $d = -1.03$). Improvements from baseline to postintervention for all secondary outcomes, with the exception of sleep duration, were statistically significant. A similar pattern of results was evident for the change from baseline to follow-up.

CONCLUSIONS AND RELEVANCE In this trial, digital CBT was an effective, scalable, safe, and acceptable intervention for improving insomnia symptoms during pregnancy.

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Supplemental content

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Insomnia symptoms are prevalent during pregnancy, with as many as 1 in 7 pregnant women reporting moderate to severe symptoms.[1] Although sleep disturbance during pregnancy may be viewed as normative and innocuous, research indicates that it is associated with an increased risk of adverse maternal outcomes, including depression and preterm birth.[2,3] Limited research is available on interventions to improve insomnia symptoms during pregnancy. A robust body of literature documents the efficacy of cognitive behavioral therapy for insomnia (CBT-I) across a variety of populations,[4] and it is recommended as the first line treatment by the American College of Physicians.[5] Cognitive behavioral therapy for insomnia that is delivered in person by a trained clinician is effective for pregnant women diagnosed with insomnia disorder.[6] Although CBT-I is efficacious, demand for the treatment exceeds the availability of trained clinicians.[7] Clinical innovation has attempted to bridge this science-care gap with digital adaptations, which are effective among nonpregnant populations.[8,9] A digital CBT-I program may be of particular interest for pregnant women, who report a preference for mental health care that includes flexible options[10] and for whom timely intervention may be particularly important.

We conducted a randomized clinical trial to evaluate digital CBT-I compared with standard treatment among 208 pregnant women with elevated insomnia symptoms. First, we hypothesized that compared with women randomized to receive standard treatment, women randomized to receive digital CBT-I would experience greater improvements from baseline to postintervention (ie, 10 weeks after randomization) in subjective sleep outcomes, including insomnia symptom severity (the primary outcome, which was measured by the Insomnia Severity Index [ISI]), diary-defined sleep efficiency and duration, global sleep quality, and insomnia caseness. Second, because poor sleep is associated with increased depressive and anxiety symptoms among perinatal women[11-13] and digital CBT-I is associated with improvements in depressive and anxiety symptoms,[14,15] we hypothesized that digital CBT-I would be effective in reducing depressive and anxiety symptoms among pregnant women. For all outcomes, we also investigated the change from baseline to follow-up (ie, 18 weeks after randomization).

Key Points

Question What is the efficacy of digital cognitive behavioral therapy compared with standard treatment among pregnant women with insomnia symptoms?

Findings In this randomized clinical trial of 208 pregnant women with insomnia symptoms, digital cognitive behavioral therapy for the treatment of insomnia was associated with statistically significantly greater improvements in insomnia symptom severity, sleep efficiency, global sleep quality, insomnia caseness, depressive symptoms, and anxiety symptoms compared with standard treatment.

Meaning Digital cognitive behavioral therapy is an effective, scalable, safe, and acceptable intervention for improving insomnia symptoms during pregnancy.

Methods

Participants

Participants were enrolled from November 23, 2016, through May 22, 2018. Pregnant women were recruited using conventional passive recruitment methods (eg, flyers hung in retail stores), a national health volunteer registry, social media advertisements, and word of mouth. In addition, patients at a university hospital were recruited via messages sent through the electronic health record and direct mail and via electronic flyers in the obstetrics and gynecology waiting rooms.

The inclusion criteria were (1) self-reported pregnancy up to 28 weeks' gestation; (2) 18 years or older; (3) met the *DSM-5* criteria for insomnia disorder, as determined by the Sleep Condition Indicator[16,17] (SCI) (women experiencing symptoms for ≥1 month were eligible, in contrast to the *DSM-5* criteria requiring symptom duration of ≥3 months, to include women whose symptoms began during pregnancy) or experienced elevated insomnia symptom severity, as determined by a total score of 11 or greater on the ISI;[18,19] and (4) had regular access to a web-enabled computer, tablet, or smart phone. The exclusion criteria were (1) probable major depression, as determined by a total score of 15 or greater on the Edinburgh Postnatal Depression Scale (EPDS);[20] (2) self-reported bipolar disorder; (3) self-reported history of psychosis; (4) active suicidality, defined as a score greater than 1 on item 10 of the EPDS, which assesses thoughts of self-harm, or report of a specific suicide plan or recent suicide attempt; and (5) a shift-work employee.

Design

Participants were randomly assigned to receive digital CBT-I or standard treatment, with a waiting list control. Although we used a 1:1 allocation ratio with blocked randomization to balance the group sizes, an error in how condition assignments were recorded resulted in 105 participants randomized to the digital CBT-I group and 103 participants randomized to the standard treatment group. For study administration purposes, staff members were unblinded. However, all outcome measures were participant-reported, potentially mitigating the consequences of staff unblinding on the outcome assessment. Participants were unblinded because of the nature of the comparison group, which was not an active comparator. The study statistician remained blinded to condition assignments for all primary analyses.

The study received approval from the institutional review board of the University of California, San Francisco, and all participants provided electronic informed consent. The trial protocol is available in Supplement 1, and changes made to the eligibility criteria after the study began are available in eMethods in Supplement 2.

Interventions

The digital CBT-I program, Sleepio (Big Health), has been described in detail in other publications.[8,21] In brief, digital CBT-I was delivered through 6 weekly sessions that were accessed

via website or iOS app. The treatment content was based on CBT-I manuals and included 5 main components: sleep restriction, stimulus control, cognitive therapy, relaxation techniques, and sleep hygiene and education.[22] The program was interactive and delivered by an animated digital therapist. Participants received automated reminders to complete each session and a daily sleep diary, and they received tailored, automated help based on their progress. Participants had access to a moderated online community and a library of sleep information.

The control group received standard care for prenatal patients with insomnia. Standard care comprised a range of nonstudy treatments, including sleep, pain, and antidepressant medications (both prescribed and over-the-counter); alternative therapy or herbal supplements; psychotherapy or counseling; and support groups. No limits were placed on the receipt of nonstudy treatments. Participants randomized to the standard treatment group received a free voucher code to access the Sleepio program at study completion.

Outcomes

Subjective Sleep Outcomes

The primary outcome for the study was the total score on the ISI,[18,19] which is a 7-item syndromal measure of insomnia that assesses difficulty with initiating or maintaining sleep, satisfaction with sleep, impairment, distress, and the extent to which others have noticed symptoms during the previous 2 weeks. Total scores of 7 or less indicate no clinically significant insomnia, 8 to 14 indicate subthreshold insomnia, 15 to 21 indicate moderate insomnia, and 22 or greater indicate severe insomnia. A cutoff of 11 has been validated to identify participants for clinical trials.[23] As in previous research with pregnant women,[6] we defined remission as a total ISI score of 7 or less.

Daily sleep diaries were used to measure sleep efficiency and duration. Sleep efficiency was calculated by dividing the amount of time sleeping in bed by the total amount of time spent in bed and multiplying the quotient by 100. Scores ranged from 0% to 100%, with 85% or higher considered normal. Sleep duration was defined as the total amount of nightly sleep in hours. Global sleep quality was measured using the Pittsburgh Sleep Quality Index, a 19-item instrument comprised of 7 components that assess sleep duration, disturbance, latency, efficiency, quality, days of dysfunction because of sleepiness, and the need for medication to sleep.[24] Each component score ranges from 0 to 3, and the components are summed to create a Pittsburgh Sleep Quality Index global sleep quality score ranging from 0 to 21. Higher scores indicate worse global sleep quality, and scores greater than 5 indicate poor sleep. To determine whether participants met diagnostic criteria for insomnia, we used the SCI. Consistent with previous research,[25] we added a ninth item to assess early morning awakening, which is a symptom of insomnia disorder included in the *DSM-5*.

Mental Health Outcomes

Depressive symptom severity was assessed using the EPDS,[20] which is a 10-item self-report measure that omits depressive symptoms that can be conflated with normal pregnancy symptoms. It is frequently used to assess depressive symptom severity during pregnancy.[26] Total scores range from 0 to 30, with higher scores indicating greater symptom severity. Scores of 10 or greater suggest minor depression, and scores of 15 or greater suggest major depression among pregnant women.[26] Anxiety symptom severity was assessed using the Generalized Anxiety Disorder Scale-7.[27] Scores range from 0 to 21, with higher scores indicating greater anxiety symptom severity. Scores of 0 to 4 suggest minimal anxiety, 5 to 9 mild anxiety, 10 to 14 moderate anxiety, and 11 to 21 severe anxiety.

All study measures were self-reported and data was collected using Qualtrics and Research Electronic Data Capture (REDCap) online survey systems. At each time point, participants were asked about their use of the following aids to improve sleep: (1) sleep medication prescribed by a physician; (2) combination sleep aid and pain reliever; (3) over-the-counter or store-bought sleep aid; (4) alternative therapy or herbal supplement; (5) therapy or counseling; (6) alcohol, beer, or wine; (7) eye mask or ear plugs; and (8) other. Participants were also asked about their use of the following aids to improve mood: (1) antidepressant medication; (2) therapy or counseling; (3) support group; (4) alternative therapy or herbal supplement; and (5) other. Response options were rarely or never, a few nights per month, a few nights per week, and every night or almost every night. We compared the use of nonstudy treatments between groups using χ^2 tests. Owing to small sample sizes, responses were recoded to rarely or never vs a few nights per month or more.

Randomization and Procedures

The randomization sequence was generated by an independent investigator using the Sealed Envelope online randomization program with block sizes of 4, 6, and 8.[28] The randomization sequence and block sizes were concealed from study investigators and staff members. Randomization was not stratified by any baseline characteristic. The randomization sequence was stored on an electronic file that was inaccessible to the study investigators or staff members. When a participant completed baseline measures, study staff members requested the allocation assignment from the independent investigator.

Individuals interested in participating in the study completed an electronic consent form that described the screening procedures; they then completed a questionnaire battery to collect demographic information and assess their eligibility for participation. The battery included items to assess psychiatric and sleep disorder history, employment in night-shift work, and regular access to the internet. In addition, the battery included the Berlin Questionnaire[29] to assess sleep apnea symptoms and results from the ISI, SCI, and EPDS. Eligible individuals completed a demographic survey, viewed the study consent form, and received instructions to complete the sleep diaries.

For 7 consecutive mornings, participants received email requests to complete an online sleep diary. Participants indicated the time they got in bed, the amount of time it took to fall asleep, the number of awakenings, the duration of awak-

enings, the final awakening time, and the time they got out of bed. Participants who completed at least 4 diaries were invited to proceed to the orientation session.

The orientation session was conducted by phone. The primary goal of this session was to promote participant retention by discussing the importance of the clinical trial, the required commitments, what to expect if randomized to receive digital CBT-I or standard treatment, the rationale for having a control condition and random assignment, and the consequences of attrition bias.[30]

Participants completed baseline measures on the Qualtrics online survey system. At completion, study staff members requested the condition assignment from the independent investigator, who generated the randomization sequence. Participants were informed of their condition assignment by phone and email.

Participants completed all study measures at postintervention (ie, 10 weeks after randomization), and all study measures with the exception of sleep diaries at follow-up (ie, 18 weeks after randomization). The change from baseline to postintervention was the primary outcome. Participants were sent $10 electronic gift cards for completing the baseline assessment and each follow-up assessment.

Information about the effect size used in the sample size calculations is available in eMethods in Supplement 2. We used GPower software to perform an analysis of variance of repeated measures with a within-between interaction, which estimated that a sample of 128 participants was required to have 80% power to detect a small to medium effect size (d = 0.3), with α = .01 for a within-between interaction. Participant attrition in web-based CBT-I programs ranges from 4% to 22%.[8,31,32] However, a meta-analysis of computer-based treatments for depression estimated attrition rates of 38.4% in programs that offer administrative support.[33] We used the higher attrition estimate of 38%, yielding a required sample of 208 participants (104 women per intention-to-treat group).

Statistical Analysis

We compared baseline characteristics between groups using 2-sample t tests for continuous variables and χ^2 tests for categorical variables. The objective of the statistical analysis was to assess the within-women rates of change in outcomes during the study, specifically the amount of change per week and the differences in these weekly rates of change between women in the digital CBT-I and standard treatment groups. We assessed whether within-woman changes in sleep and mental health outcomes differed between the digital CBT-I and standard treatment groups using linear mixed-effects models.[34] These models included the sleep outcomes (diary-defined sleep efficiency and duration as well as results from the ISI, the SCI, and the Pittsburgh Sleep Quality Index) and mental health outcomes (results from the EPDS and the Generalized Anxiety Disorder Scale-7) as the dependent variables, along with time in weeks, intervention group, and time-by-group interactions as the explanatory variables. The models also included random intercepts to accommodate the correlation among the repeated responses within women.

The regression coefficients of time-by-group interactions measure the differences in the rate of within-woman change in the outcomes between the 2 intervention groups. We assessed the statistical significance of the time-by-group interaction using likelihood ratio χ^2 tests, with statistical significance set at P = .05. We fit the mixed models using routines in Stata software (StataCorp). The primary analysis assessed differences in changes in insomnia symptom severity from baseline to postintervention, with time measured in weeks. Secondary analyses of additional sleep and mental health outcomes used the same time scale. In addition, we examined change from baseline to follow-up. For a sensitivity analysis, we fit mixed models that used a categorical indicator of time point, as opposed to a continuous measure of time. More details are available in the eMethods, eResults, and eTable in the Supplement. Data were analyzed between December 12, 2018, and July 2, 2019.

In addition to performing statistical tests, we assessed the magnitude of differences in within-woman change between groups using 95% CIs for the time-by-group interaction effect, and we calculated Cohen d effect sizes by dividing the between-group postintervention (or follow-up) differences by the baseline pooled SD for continuous outcomes. The absolute Cohen d values of 0.2, 0.5, and 0.8 corresponded with small, medium, and large effect sizes. For binary outcomes (eg, insomnia caseness), estimated odds ratios were used as a standard measure of association magnitude.

Results

Participant Enrollment and Characteristics

Of the 2258 women assessed for eligibility using an online self-report questionnaire, 1762 did not meet the eligibility criteria. The 3 most common reasons for ineligibility were (1) the woman was more than 28 weeks pregnant (n = 463); (2) the woman did not meet the criteria for an insomnia case or have elevated insomnia symptoms (n = 371); and (3) after the modification to the eligibility criteria, the woman did not identify her race as black (n = 488). Among the 96 women who declined to participate, the most common reason was noncompletion of the study consent form for unknown reasons after completion of the screening procedures (n = 85). Among the 192 participants who were excluded for other reasons, most did not complete at least 4 of 7 daily sleep logs (n = 85; **Figure**).

The final sample comprised 208 pregnant women, with a mean (SD) age of 33.6 (3.7) years and a mean (SD) gestational age of 17.6 (6.3) weeks at baseline. Most of the participants were white (138 women [66.3%]), married or cohabiting (196 women [94.2%]), had a college degree (180 women [86.5%]), and earned $100 000 or more per year (141 women [67.8%]). **Table 1** presents baseline demographic and clinical characteristics by condition. Information about baseline differences is available in eResults in Supplement 2. Of the 105 participants who were randomized to receive digital CBT-I, 68 women (64.8%) completed all 6 of the sessions, taking a mean (SD) period of 7.97 (2.08) weeks to complete the 6 sessions. A total of 33 women (31.4%) returned to the program for refresher ses-

Figure. CONSORT Diagram

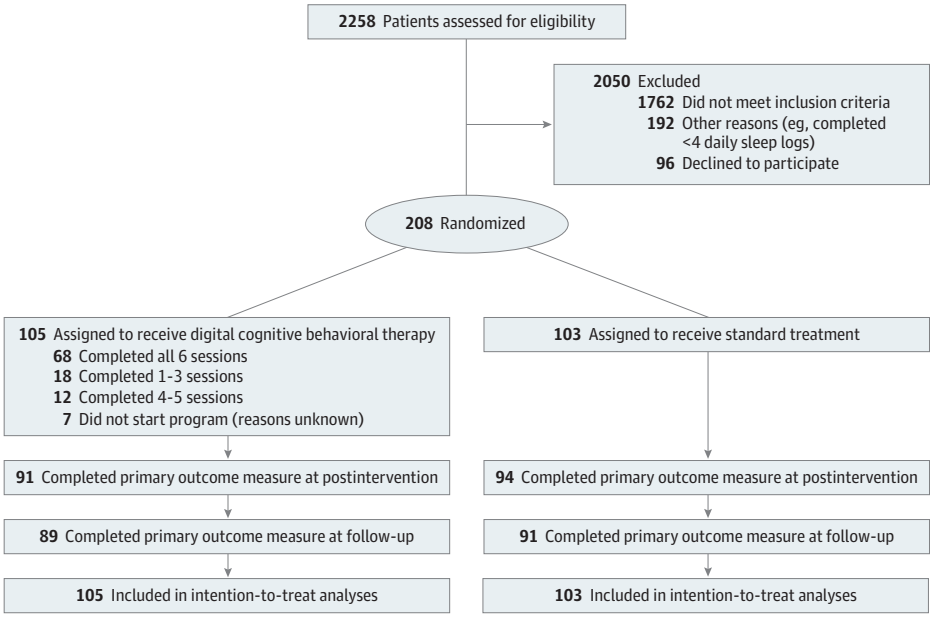

Table 1. Participant Baseline Demographic and Clinical Characteristics by Condition

Characteristic	No. (%) Standard Treatment (n = 103)	Digital CBT-I (n = 105)	Test Statistic	*P* Value
Age, mean (SD), y	33.2 (4.0)	33.90 (3.38)	−1.35[a]	.18
Race/ethnicity				
White	65 (63.1)	73 (69.5)	1.0[b]	.33
Hispanic	10 (9.7)	5 (4.8)	1.9[b]	.17
Graduated from 4-y college	88 (85.4)	92 (87.6)	0.2[b]	.64
Income ≥$100 000	70 (68.0)	71 (67.6)	0.003[b]	.96
Married or cohabiting	96 (93.2)	100 (95.2)	0.4[b]	.53
Gestational age at screening, mean (SD), wk	18.07 (6.3)	17.1 (6.4)	1.11[a]	.27
Primiparous	66 (64.1)	46 (43.8)	8.6[b]	.003
Sleep outcomes				
Insomnia symptom severity, mean (SD)[c]	14.19 (3.72)	14.52 (3.26)	−0.68[a]	.50
Sleep efficiency, mean (SD)[d]	74.19 (11.96)	72.22 (12.35)	1.17[a]	.24
Nightly sleep duration, mean (SD)[d]	6.84 (1.23)	6.68 (1.13)	0.97[a]	.33
Global sleep quality, mean (SD)[e]	9.47 (3.02)	9.52 (2.74)	−0.14[a]	.89
Insomnia caseness[f]	41 (39.8)	54 (51.4)	2.8[b]	.09
Mental health outcomes				
Depressive symptom severity, mean (SD)[g]	7.24 (3.77)	7.79 (4.05)	−1.01[a]	.31
Anxiety symptom severity, mean (SD)[h]	4.81 (3.23)	5.43 (3.55)	−1.32[a]	.19

Abbreviation: CBT-I, cognitive behavioral therapy for insomnia.

[a] The t_{206} statistic.

[b] The χ^2_1 statistic.

[c] Measured by the Insomnia Severity Index.

[d] Measured by sleep diary.

[e] Measured by the Pittsburgh Sleep Quality Index.

[f] Measured by the Sleep Condition Indicator.

[g] Measured by the Edinburgh Postnatal Depression Scale.

[h] Measured by the Generalized Anxiety Disorder Scale-7.

sions after completing the initial 6 sessions. Seven women (6.7%) never logged in to the digital CBT-I program for unknown reasons. Among the 30 women (28.6%) who started but did not complete the program, the reasons for noncompletion were unknown (21 women [70%]), experienced a miscarriage (3 women [10%]), decided the program was not a good fit for their needs (4 women [13.3%]), started taking an antihistamine medication and experienced improvement in symptoms (1 woman [3.3%]), and was unable to make the time commitment (1 woman [3.3%]).

Baseline to Postintervention and Follow-up

Table 2 presents the results of the mixed-effects analysis comparing rates of change from baseline to postintervention in the primary and secondary outcomes between the digital CBT-I and standard treatment groups. Women in the digital CBT-I group had greater reductions in their insomnia symptom severity scores than women in the standard treatment group, with a weekly change in scores of −0.59 compared with −0.23, respectively (time-by-group interaction, χ^2 = 29.8; difference = −0.36; 95% CI, −0.48 to −0.23); the difference between these rates was statistically sig-

Table 2. Linear Mixed-Effects Analysis of Change From Baseline to Postintervention by Group Interaction

Outcome	Weekly Change for Digital CBT-I[a]	Weekly Change for Standard Treatment[a]	Effect Size Difference Between Groups	95% CI for Time-by-Group Interaction	Interaction χ^{2b}	*P* Value	Cohen *d*
Insomnia symptom severity	−0.59	−0.23	−0.36	−0.48 to −0.23	29.8	<.001	−1.03
Sleep efficiency	0.84	0.08	0.76	0.39 to 1.14	15.4	.001	−0.51
Sleep duration	0.03	0.002	0.028	−0.002 to 0.67	3.4	.07	0.16
Global sleep quality	−0.31	−0.02	−0.29	−0.37 to −0.21	43.8	<.001	1.04
Insomnia caseness	−0.26	−0.02	−0.24	−0.35 to −0.12	20.2	<.001	NA
Depressive symptom severity	−0.22	−0.01	−0.21	−0.30 to −0.11	16.3	<.001	−0.39
Anxiety symptom severity	−0.19	−0.002	−0.188	−0.26 to −0.10	19.0	<.001	−0.42

Abbreviations: CBT-I, cognitive behavioral therapy for insomnia; NA, not applicable.

[a] Change is per week from baseline to postintervention.

[b] The χ^2 is from a likelihood ratio test.

Table 3. Linear Mixed-Effects Analysis of Change From Baseline to Follow-Up by Group Interaction

Outcome	Weekly Change for Digital CBT-I[a]	Weekly Change for Standard Treatment[a]	Effect Size Difference Between Groups	95% CI for Time-by-Group Interaction	Interaction χ^{2b}	*P* Value	Cohen *d*
Insomnia symptom severity	−0.31	−0.17	−0.14	−0.22 to −0.05	9.7	.002	−0.54
Global sleep quality	−0.13	−0.05	−0.08	−0.13 to −0.02	7.5	.006	−0.34
Insomnia caseness	−0.16	−0.04	−0.12	−0.18 to −0.06	15.7	<.001	NA
Depressive symptom severity	−0.13	0.003	−0.133	−0.20 to −0.07	16.9	<.001	−0.48
Anxiety symptom severity	−0.10	0.02	−0.12	−0.18 to −0.07	20.1	<.001	−0.46

Abbreviations: CBT-I, cognitive behavioral therapy for insomnia; NA, not applicable.

[a] Change is per week from baseline to follow-up.

[b] The χ^2 is from a likelihood ratio test.

nificant ($P < .001$), and the magnitude of the effect size was large ($d = -1.03$). Remission rates, defined as ISI scores of 7 or less, were significantly higher among those in the digital CBT-I group (30 women [44.0%]) vs those in the standard treatment group (21 women [22.3%]; $\chi^2_1 = 9.8$; $P = .002$). The secondary sleep outcomes of sleep efficiency, global sleep quality, and insomnia caseness also exhibited statistically significant time-by-group interactions, with greater reductions in the digital CBT-I group than in the standard treatment group. The time-by-group interaction for sleep duration did not achieve statistical significance (0.03 vs 0.002; difference = 0.028 [95% CI, −0.002 to 0.67]; $P = .07$).

Women in the digital CBT-I group had greater reductions in depressive symptom severity and anxiety symptom severity than women in the standard treatment group, and these differences were statistically significant (for depressive symptom severity, −0.22 vs −0.01; difference = −0.21 [95% CI, −0.30 to −0.11]; $P < .001$; for anxiety symptom severity, −0.19 vs −0.002; difference = −0.188 [95% CI, −0.26 to −0.10; $P < .001$).

Table 3 presents the results of the mixed-effects analysis to compare rates of change from baseline to follow-up between the digital CBT-I and standard treatment groups. Results of the rates of change from baseline to follow-up were consistent with those from baseline to postintervention; statistically significant time-by-group interactions in the primary outcome, insomnia symptom severity, and all of the secondary sleep and mental health outcomes were observed. Remission rates were also significantly higher among women in the digital CBT-I group (38 women [42.7%]) vs the standard treatment group (26 women [28.6%]; $\chi^2_1 = 3.9$; $P = .048$).

Adverse Events

Three participants randomized to receive standard treatment experienced adverse events (1 stillbirth and 2 miscarriages). These events were determined to be unrelated to study participation because participants in the standard treatment group were free to receive the care they would have typically received if they had not participated in the study, and their health care was in no way restricted. These participants received no study intervention and had no study contact between the time they were notified of their condition assignment and the time of the adverse event.

Three participants randomized to receive digital CBT-I experienced adverse events (3 miscarriages in the first trimester). These events were determined to be possibly related to study participation. It was impossible to rule out a connection between the adverse event and study participation, although an alternative cause was more likely. Two participants had started the digital CBT-I program and reported improved sleep, and 1 participant experienced a miscarriage before beginning the program.

Use of Nonstudy Treatments

Data regarding the use of nonstudy treatments were available from 183 participants (88%) at postintervention and 178

participants (85.6%) at follow-up. At postintervention, significantly more participants receiving standard treatment compared with CBT-I reported using a sleep medication prescribed by a physician (9 participants [9.6%] vs 2 participants [2.2%], respectively; $\chi^2_1 = 4.3$; $P = .04$) or an alternative therapy or herbal supplement to improve sleep at least a few nights per month (15 participants [16%] vs 5 participants [5.6%], respectively; $\chi^2_1 = 5.0$; $P = .03$). No significant differences were observed in the use of other aids to improve sleep at the postintervention or follow-up time points. No condition differences were found in the use of nonstudy treatments to improve mood at either time point.

Discussion

The primary goal of this study was to evaluate the efficacy of digital CBT-I among pregnant women. We found strong support for our hypothesis that digital CBT-I treatment would be associated with significant improvement in insomnia symptoms compared with standard care. During the 10-week study period, insomnia severity scores decreased more than twice as much for participants randomized to receive digital CBT-I compared with participants randomized to receive standard treatment. In addition, women who received digital CBT-I treatment reported greater reductions in the amount of time they lay awake in bed and greater improvements in global sleep quality. Of note, the benefit of digital CBT-I treatment was maintained approximately 2 months after the postintervention time point. In terms of clinical significance, substantially more women randomized to receive digital CBT-I experienced symptom remission compared with women randomized to receive standard treatment.

Our findings add to an emerging body of research suggesting that CBT-I treatment is an effective nonpharmacological approach for treating insomnia symptoms during pregnancy.[6,35,36] Our clinical trial extends this literature to indicate that CBT-I treatment can also be effective for subthreshold insomnia symptoms, which are prevalent during pregnancy.[1] Moreover, a digital intervention that women can access at their convenience may be particularly attractive to pregnant women, who experience competing demands on their time and energy.

Although the use of sleep medication was rare in this sample, participants randomized to receive standard treatment were more likely to use prescription medication for sleep at the postintervention time point (eResults in Supplement 2). A paucity of research is available using randomized clinical trials to evaluate the efficacy and safety of pharmacotherapy for insomnia during pregnancy, but observational studies suggest risks for adverse birth outcomes. Medications frequently prescribed for insomnia in the general population, such as benzodiazepines and zolpidem, are associated with an increased risk of spontaneous abortion, low birth weight, preterm birth, small size for gestational age, and cesarean delivery.[37,38] Pregnant women prefer nonpharmacological treatments for insomnia,[39] and our research indicates that digital CBT-I treatment is an effective and safe intervention for reducing insomnia symptoms.

A secondary goal of this study was to evaluate the efficacy of digital CBT-I treatment for depressive and anxiety symptoms among pregnant women. We found that participants randomized to receive digital CBT-I experienced significantly greater improvements in subclinical depressive and anxiety symptom severity compared with participants randomized to receive standard treatment. Participants entered this study with mild depressive and anxiety symptoms, and it seems that research is needed to evaluate whether CBT-I is effective for treating or preventing perinatal depression or anxiety in those with elevated symptom severity. It is possible that a treatment that improves depressive and anxiety symptoms indirectly may be a less stigmatized entry point for improving perinatal mental health.

We believe this study revealed that pregnant women are highly interested in an intervention that may improve sleep; more than 2000 women completed the eligibility survey. However, one of the most common reasons women were ineligible to participate was that they did not meet the threshold for clinically significant insomnia symptoms. It is important that future research examines interventions to improve less severe sleep disturbances given their high prevalence[1] and consequences.[11,40-46] Although more women randomized to receive digital CBT-I experienced remission in insomnia symptoms compared with those randomized to receive standard treatment, most women continued to experience at least subthreshold symptoms. We feel future research should examine whether targeting pregnancy-specific sleep disturbances, such as nocturia and discomfort, helps more women achieve symptom remission. Mindfulness-based and acceptance-based approaches that focus on increasing acceptance of physical symptoms that may be difficult to eliminate may be particularly well suited for pregnancy-related poor sleep.

Limitations

The study had several limitations. First, because we were interested in investigating a scalable intervention format, insomnia outcomes were based on self-reported symptom severity rather than a clinical diagnostic interview. Second, we did not use objective sleep measures because insomnia diagnosis is determined by subjective report of symptoms rather than by objective measures (eg, behavioral assessment using wrist actigraphy).[47] Third, we did not use an active control comparator group because our primary research question was whether digital CBT-I treatment outperformed a clinically relevant comparator. Finally, the sample was predominantly wealthy, white, and highly educated; future research should examine whether the current findings can be generalized to more diverse populations, who may be disproportionately affected by poor sleep.[48]

Conclusions

To our knowledge, this study was the first randomized clinical trial of digital CBT-I treatment in pregnancy. We found that CBT-I treatment was effective for improving insomnia as well as subclinical anxiety and depressive symptoms. Given the widespread nature of insomnia in pregnancy, the scalability of this intervention, its low-risk profile, and its demonstrated efficacy, digital CBT-I has great promise as a treatment for insomnia in pregnant women.

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Author Contributions: Dr Felder had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Felder, Epel, Prather.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Felder, Neuhaus, Krystal.
Critical revision of the manuscript for important intellectual content: Felder, Epel, Neuhaus, Prather.
Statistical analysis: Felder, Neuhaus.
Obtained funding: Felder.
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Supervision: Epel, Krystal, Prather.

Conflict of Interest Disclosures: Dr Felder reported receiving voucher codes for Sleepio, the digital cognitive behavioral therapy for insomnia intervention, from Big Health. All authors reported receiving grants from the National Institutes of Health during the conduct of the study. Dr Krystal reported receiving grants from Janssen Pharmaceuticals, Axsome Therapeutics, Reveal Biosensors, and the National Institutes of Health and personal fees from Adare, Axsome Therapeutics, Eisai, Ferring Pharmaceuticals, Galderma, Harmony Biosciences, Janssen Pharmaceuticals, Jazz Pharmaceuticals, Millennium Pharmaceuticals, Merck, Neurocrine Biosciences, Otsuka Pharmaceuticals, Pernix, Reveal Biosensors, and Takeda outside the submitted work. Dr Prather reported receiving grants from Headspace outside the submitted work. Dr Epel reported that she is a scientific advisor to Meru Health. No other disclosures were reported.

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Additional Contributions: Alison Hartman, BA, of the Center for Health and Community at the University of California, San Francisco, and Esperanza Castillo, MS, and Brianne Taylor, AA, of the California Preterm Birth Initiative at the University of California, San Francisco, were project coordinators and assisted with recruitment, enrollment, and data collection. Danielle Roubinov, PhD, of the Department of Psychiatry at the University of California, San Francisco, generated the randomization sequence. Alinne Barrera, PhD, of Palo Alto University, served as an independent safety officer. We are deeply grateful for the women who volunteered their time to participate in this research. No compensation was received.

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