Supplemental information

Treating insomnia with high risk of depression using therapist-guided digital cognitive, behavioral and circadian rhythm support interventions to prevent worsening of depressive symptoms: a randomized controlled trial

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Supplementary background

Specific insomnia subtypes with increased risk of MDD

Insomnia Disorder (ID) is a primary risk factor for the development of major depressive disorder (MDD) [1-3]. However, heterogeneity has made it difficult to predict whom among insomniacs are most likely to develop MDD and who will be spared. Recently, five previously unrecognized subtypes of ID were discovered, distinguished by their profile of life history and stable traits of affect and personality [4]. Profiling requires people with insomnia to fill out a survey that combines multiple validated questionnaires. Online assessment takes about 20-25 minutes and can completed by the patient without guidance. A free multilingual implementation will be available as of 1/1/2022 on https://insomniatype.org.

An important finding is that this extensive trait profiling can determine who among people with ID are most, versus least, likely to develop MDD. ID subtypes differ strongly in their lifetime risk of MDD, with prevalence estimates varying from 8% in the least vulnerable ID subtypes up to even 54% in the most vulnerable ID subtypes [4]. While two subtypes did not show an increased lifetime risk of MDD as compared to people without sleep complaints, this risk was increased threefold in two other subtypes and fivefold in a fifth subtype. The latter three subtypes score high on complaints that can be typical of depression, such as negative affect and reduced positivity. Details are provided in Blanken et al. [4]. Subtype 1 scores high on several other distressful characteristic including severe pre-sleep arousal. Subtypes 2 and 3 score moderately on most other distressful characteristics. While subtype 2 is furthermore characterized by a strong sleep disruption in response to stress, subtype 3 is better characterized by insensitivity to reward. Intervention studies aiming at prevention of first-onset depression or relapse can be performed more efficiently by including participants selected on having a subtype with increased risk of depression. Given an annual incidence estimate of 3% in the general population, prevention trials would require a very large sample size without such preselection [5].

Table S1. Distribution of the three high-risk insomnia subtypes across the four intervention conditions. Subtype 2 is more prevalent than subtypes 1 and 3, as reported before [4]. A Fisher Exact test showed effective randomization of subtypes across intervention groups.

	Mean (SD) or N (%)				P-value
	NT N = 35	CRS N = 34	CBT-I N = 31	CBT-I + CRS N = 32	
Insomnia					0.925
Subtype 1	10 (28.6%)	6 (17.6%)	8 (25.8%)	7 (21.9%)	
Subtype 2	17 (48.6%)	21 (61.8%)	18 (58.1%)	18 (56.3%)	
Subtype 3	8 (22.9%)	7 (20.6%)	5 (16.1%)	7 (21.9%)	

Our RCT focused on high-risk insomnia. However, in order to validate the expected increased risk in our subtype-selected participants, we in parallel assessed the time course of depressive symptoms at T0-T4 in 30 people with insomnia of a subtype without increased risk of depression (67% female, age = 52.6, SD = 10.9). Indeed, in this untreated low-risk group, depressive symptom severity during follow-up (T1-T4) did not differ significantly from baseline (-0.2 [95% CI -1.7 to 1.4] IDS-SR points, d = -0.03, p = 0.830).

According to the CIDI assessment at T4, only 2/30 participants (6.7%) in this parallel untreated low-risk group had experienced an episode with depressive symptom severity meeting the criteria for a clinical diagnosis of MDD during the past year, versus 4/35 (11.4%) of untreated participants in the high-risk group. As mentioned, these numbers are too small to lead to statistically significant group differences: sensitivity of repeated IDS-SR assessments outperformed the single retrospective CIDI assessment.

Supplementary Methods

Description therapist-guided digital interventions

Overview of implementation

Sessions are provided online and include text, pictures and videos with examples of fictional patients. The sequence of sessions is fixed and straightforward, without using artificial intelligence methods for individual tailoring like conditional presentations or questions. Active participation is promoted by requesting answers to questions and providing instructions for assignments like adhering to bedtimes, filling out sleep diaries, performing physical activity, exposing oneself to bright light, etc. Participants spend up to approximately 30-60 minutes each session on working through the material provided, and subsequently each day on completing the assignments. Therapy guidance takes approximately 45 minutes per participant per week. Therapy guidance is provided via a one-to-one message board on the internet platform of the Netherlands Sleep Registry. When participants do not complete a treatment session, the supervising therapist sends an email asking the participant to visit the message board, which contains a reminder. Participants who do not respond to the reminder are contacted by telephone.

Circadian Rhythm Support (CRS)

Participants received therapist-guided digital CRS (i-Cycle) consisting of five sessions five weekly sessions to be completed within six weeks [6]. The sessions address: 1) psychoeducation about circadian rhythms and light exposure including daily use of a provided Philips EnergyUp HF3430/01 light, scheduled shortly after awakening for 30 minutes at a distance of 40 cm (from eye to light); 2) consolidating the light schedule and commencing with physical activity for at least 30 minutes to be performed at least 4 times a week at a fixed time of day; 3) consolidating scheduled physical activity and increasing its intensity; 4) 30 minutes of body warming in the interval 3 to 2 h before bedtime, by use of a warm bath with a temperature of 37- 39°C (or a hot shower if no bath is available), for approximately 3 times a week; 5) revisiting schedules to optimize feasibility to secure continuation. As part of i-Cycle, participants completed a daily activities diary to assess compliance.

Cognitive Behavioral Therapy for Insomnia (CBT-I)

Participants received therapist-guided digital CBT-I (i-Sleep), as extensively described before [7-9]. In brief, i-Sleep consists of five sessions to be completed within six weeks. The sessions address: 1) psychoeducation and sleep hygiene; 2) stimulus control and sleep restriction targeting 85% sleep efficiency; 3) worrying and relaxation; 4) erroneous cognitions about sleep; and 5) relapse prevention. As part of i-Sleep, participants completed a sleep diary (Consensus Sleep Diary [10]) every day.

Combined CBT-I and CRS

Participants received both CBT-I and CRS as described above. The i-Sleep and i-Cycle sessions are designed in a way that allows for parallel use.

Therapy guidance

Participants randomized to the active intervention conditions were guided by trained psychologists. After each completed session, the participant received a personal feedback report commenting on the participant's own evaluation of previous instructions, on their proposed plans, and on information participants provided on questions asked during the session. Guidance included answering participant's questions and providing motivation support (e.g., motivating the participants to adhere to the requested behavioral changes). Communication was primarily in written form through the one-to-one message board of the internet platform of the Netherlands

Sleep Registry (www.slaapregister.nl), and could be extended by telephone in case of nonresponse to messages.

Table S2. Checklist of Methodological Recommendations for Trials of Psychological Interventions, Guidi et al. (2018) [11]

Recommendations from Guidi et al. (2018)	Addressed
1. In addition to the cross-sectional assessment of the DSM-5, the longitudinal development of the disorder (acute, residual, chronic, etc.) should be described according to staging methods.	Staging of depression was performed according to Cosci and Fava [12] with a refinement according to Verduijn et al. [13] to optimally utilize the IDS-SR information about symptom severity to distinguish absence of current or past MDD versus possible prodromal depression. See results section, and Table 2.
2. Current or past treatment with psychotropic medications needs to be detailed, specifying the medications that were involved; staging methods may be used.	Table S3 shows the medication status in detail. Past use of medication was queried at inclusion as part of the DSISD structured interview [14]. Current use of medication (i.e. in the preceding 3 months) was assessed at baseline and at 1-year follow-up using the TIC-P questionnaire. See results section, and Table S3.
3. In parallel treatment designs, the limitations of the use of waiting list or treatment as usual or other treatment control groups should be acknowledged; "attention placebo" and "clinical management" provide more reliable control groups, as long as the patient receives the same amount of time and attention from a professional figure that occurs with the experimental group without any specific interventions).	We carefully considered the type of control groups in our study design. No-treatment-, waiting-list- and care-as-usual control all have their disadvantages [11], which we tried to mitigate in the following ways. First, this RCT was part of a larger multimodal investigation including, e.g., sleep EEG, MRI and ambulatory monitoring [15]. Consequently, participants of all four groups received a considerable and equal amount of attention from researchers, which outnumbered the additional attention time specific to the intervention. Second, based on previous findings [6], next to the NT control condition, CRS can be considered as active control condition. CRS requires the same amount of time and attention as CBT-I, but is expected to initially be devoid of therapeutic effectiveness for sleep during the intervention. See Methods and Results sections.
4. Adaptive and dismantling designs may provide valuable insights into the incremental role of psychological interventions.	A third point related to the choice of control groups (see above) is that our four-arms design includes a dismantling design allowing to obtain insights into the incremental role of CBT-I and the initially ineffective CRS, i.e. stand-alone and in combination. See Methods section.
5. All potential treatment ingredients that were found to yield significant effects in controlled trials should be detailed in the description of psychological treatments, including the order of administration of therapeutic components.	A detailed description of the interventions is provided. See Supplement page 4.
6. Assessment should be performed under blind conditions not only before and after treatment but also at some time during follow-up to verify long-term outcomes.	Assessments were performed under blind conditions not only before and after treatment but also three more times during follow-up to verify long-term outcomes up to one year. See Methods section.
7. Each distinct modality of measurement should deliver a unique increase in information in order to qualify for inclusion (incremental validity).	Respecting the importance of incremental validity, our primary and secondary outcome measures were carefully selected on the criterion that they would increase the information resulting from our study [11, 16-18]. A few examples are mentioned here. The application of the insomnia type questionnaire during screening to led to a better prediction of the risk of an increase in depressive symptom severity [4]. The use of a sleep diary complementary to the insomnia severity index adds sleep duration measures, which are of added and interactive importance in determining health consequences of insomnia disorder [19]. Repeated follow-ups using the IDS-SR allow for the detection of short-lived episodes characterized by increased depressive symptom severity. The reliable change index allows for an evaluation of the clinical meaningfulness of changes in the primary outcome measure. The use of a CIDI next to the primary outcome allows for comparison of our findings with previous studies. Assessment of medication use allows for investigation of, e.g., iatrogenic modification of treatment effects. See Methods section.
8. A combination of observer- and self-rated tools (patient-reported outcome measures) is recommended.	The study adhered to the recommended combination of observer- and self-rated tools (patient-reported outcome measures). See Methods section.
9. Assessment of side effects of psychotherapy should be performed using suitable methods of evaluation.	Side effects were assessed in two ways. First, participants were instructed to report any suspect mild or serious adverse events serious adverse reactions and other problems by email. Second, a validated questionnaire [20] assessed all-year common complaints retrospectively, and compared it with the same assessment at baseline. No participant emailed about adverse effects. The active inquiry about common complaints indicated no time-by-treatments effects as mentioned in the Results section, and detailed in Table S4.
10. The number of participants who display deterioration after treatment according to the methods that were used for defining response or remission should be indicated.	The number of participants who deteriorated in each intervention condition according to the reliable change index (RCI) are reported. The percentage was lower in all intervention groups as compared to no treatment. See Results section, Table 3, and Figure 3.

Table S3. Overview of psychotropic medication used in the past, at baseline and at 12 months in the four intervention groups. To investigate possible iatrogenic effects of prior psychotropic medication, the mixed effect regression models on the effect of time and treatment were extended. We failed to find significant main or interaction effects of psychotropic medication status in the past and/or at baseline or on the change in IDS-SR from baseline to follow-ups (p>0.32), neither did medication status alter intervention effects (all p>0.18). Iatrogenic effects cannot strictly be excluded, since the current study was not powered to demonstrate their absence, which would require a much larger sample size.

	NT	CRS	CBT-I	CBT-I+CRS
Any psychotropic medication				
past[a]	8 (22.9%)	9 (26.5%)	6 (19.4%)	11 (34.4%)
baseline[b]	7 (20.0%)	8 (24.3%)	5 (16.1%)	7 (21.9%)
12 months[b]	2 (5.7%)	3 (9.1%)	4 (13.8%)	3 (9.7%)
Antidepressants				
past[a]	4 (11.4%)	5 (14.7%)	2 (6.5%)	4 (12.5%)
baseline[b]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
12 months[b]	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.2%)
Anti-psychotics				
past[a]	1 (2.9%)	0 (0.0%)	1 (3.2%)	0 (0.0%)
baseline[b]	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%)
12 months[b]	1 (2.9%)	1 (3.0%)	0 (0.0%)	2 (6.5%)
Stimulants				
past[a]	1 (2.9%)	1 (2.9%)	1 (3.2%)	1 (3.1%)
baseline[b]	0 (0.0%)	1 (3.0%)	0 (0.0%)	1 (3.1%)
12 months[b]	0 (0.0%)	2 (6.1%)	1 (3.4%)	1 (3.2%)
Benzodiazepines/ Z-drugs/ Melatonin				
past[a]	4 (11.4%)	5 (14.7%)	3 (9.7%)	7 (21.9%)
baseline[b]	7 (20.0%)	7 (20.6%)	5 (16.1%)	6 (18.8%)
12 months[b]	2 (5.7%)	1 (3.0%)	3 (10.3%)	0 (0.0%)

NT, No treatment; CRS, Circadian Rhythm Support; CBT-I, Cognitive Behavioral Therapy for Insomnia; CBT-I+CRS, Cognitive Behavioral Therapy for Insomnia combined with Circadian Rhythm Support; [a] past medication users, but no current use; from Duke Structural Interview for Sleep Disorders; [b] from Trimbos and iMTA questionnaire on Costs associated with Psychiatric Illness

Supplementary results

Table S4. Common complaints during baseline and 12-month follow-up for each intervention condition from Trimbos and iMTA questionnaire on Costs associated with Psychiatric Illness. There were no significant time (all $p>0.46$) or time by treatment (all $p>0.32$) effects in common complaints.

	NT	CRS	CBT-I	CBT-I+CRS
Cardiovascular problems				
baseline	4 (11.4%)	2 (5.9%)	4 (12.9%)	3 (9.4%)
12 months	3 (8.6%)	3 (9.1%)	4 (13.8%)	1 (3.2%)
Gastrointestinal problems				
baseline	6 (17.1%)	4 (11.8%)	1 (3.2%)	3 (9.4%)
12 months	5 (14.3%)	3 (9.1%)	0 (0.0%)	2 (6.5%)
Respiratory problems and allergies				
baseline	4 (11.4%)	7 (20.6%)	7 (22.6%)	3 (9.4%)
12 months	5 (14.3%)	6 (18.2%)	5 (17.2%)	4 (12.9%)
Musculoskeletal problems				
baseline	14 (40.0%)	10 (29.4%)	8 (25.8%)	12 (37.5%)
12 months	14 (40.0%)	10 (30.3%)	6 (20.7%)	10 (32.3%)
Headache				
baseline	2 (5.7%)	5 (14.7%)	3 (9.7%)	4 (12.5%)
12 months	2 (5.7%)	4 (12.1%)	2 (6.9%)	2 (6.5%)
Endocrinal problems				
baseline	1 (2.9%)	2 (5.9%)	0 (0.0%)	4 (12.5%)
12 months	1 (2.9%)	2 (6.1%)	0 (0.0%)	2 (6.5%)
Injuries				
baseline	5 (14.3%)	6 (17.6%)	4 (12.9%)	0 (0.0%)
12 months	3 (8.6%)	1 (3.0%)	2 (6.9%)	3 (9.7%)

NT, No treatment; CRS, Circadian Rhythm Support; CBT-I, Cognitive Behavioral Therapy for Insomnia; CBT-I+CRS, Cognitive Behavioral Therapy for Insomnia combined with Circadian Rhythm Support

Ancillary analyses

IDS-SR at individual follow-ups

When investigating the trajectory of the four individual follow-up assessments versus baseline separately (see Table S5, Fig. 2), CBT-I induced a reduction in the severity of depressive symptoms at T1, T2 and T3 (d = -0.73 to -1.11, all $p < 0.031$) rather than the increase observed in the NT group. At T4, the difference just dropped below significance (d = -0.51, p = 0.087). CBTI-I+CRS induced even somewhat larger effects on depressive symptoms compared to NT, and at all follow-up assessments including T4 (d = -0.73 to -1.35, all $p \leq 0.012$). CRS as standalone treatment on the other hand did not significantly reduce the severity of depressive symptoms compared to NT at any of the follow-up measurements (all $p > 0.158$). Although the additional effect of combining CRS with CBT-I, compared to CBT-I, did not reach significance on any of the individual follow-up measurements (all $p < 0.204$, see Table S6), beneficial effects seemed to last longer for the combined intervention, indicated by larger effect sizes for CBT-I combined with CRS at 9 and 12 months (respectively d = -1.35; d = -0.73), than for standalone CBT-I (d = -0.73; d = -0.51).

An adapted IDS-SR score excluding sleep items

A sensitivity analysis was performed to evaluate whether the intervention benefits for depressive symptoms might merely reflect beneficial effects on the three insomnia items of the IDS-SR ("falling asleep", "sleep during the night", "waking up too early"). Similar results were found when removing these three insomnia items from the total IDS-SR depression score, see Table S7, indicating that results on depressive symptom severity were not driven by group differences in changes in sleep complaints.

IDS-SR sensitivity analyses

Models including covariates used for covariate-adaptive randomization (i.e., age, sex, insomnia subtype, insomnia severity at baseline, time of year [a circular variable linearized by the average day length and the rate of change in daylength at baseline], mild restless legs syndrome, mild sleep apnea, and the use of sleep medication) did not change nor confound our results (see Table S7). Per-protocol analyses including only the participants who fully completed the intervention (N = 124; CBT-I = 29, CRS = 31, CBT-I+CRS = 29, NT = 35), also resulted in similar effect estimates (see Table S7).

ISI at individual follow-ups

When investigating the trajectory of the four individual follow-up assessments versus baseline separately (see Table S5, Fig. S1), CBT-I induced a significant stronger reduction in insomnia severity than changes observed in the NT group at T1, T2 and T3 (d = -0.86 to -1.54, all $p < 0.007$), but not anymore at T4 (d = -0.56, p = 0.074). CBT-I+CRS induced a significant stronger reduction in insomnia severity than changes observed in the NT group at T1 and T3 (d = -0.97 to -1.22, all $p < 0.001$), but not at T2 and T4 (d = -0.41 to -0.61, all $p > 0.078$). CRS as standalone treatment induced a significant reduction in insomnia severity at T1 (d = -0.65, p = 0.018), but not at any of the other follow up measurements (all $p > 0.079$). There was no additional effect of combining CRS with CBT-I, compared to standalone CBT-I (see Table S6).

Sleep diary variables at individual follow-ups

When investigating the trajectory of the two individual follow-up assessments versus baseline separately, sleep efficiency increased more between T0 and T1 after CBT-I and CBT-I+CRS than after NT (respectively d = 0.51, p = 0.016; d = 0.55, p = 0.005, see Fig. S2). At T4, the increase in sleep efficiency remained significantly stronger for CBT-I+CRS than for NT (d = 0.56, p = 0.026), while benefits of standalone CBT-I over NT were no longer significant (d = 0.33, p = 0.091). Similarly, between T0 and T1, wake after sleep onset decreased more after CBT-I and CBT-I+CRS than after NT (respectively d = -0.56, p = 0.012; d = -0.59, p = 0.005, see Fig. S5). At T4, the decrease in wake after

sleep onset remained significantly stronger for CBT-I+CRS than for NT (d = -0.56, p = 0.030), while benefits of standalone CBT-I over NT were no longer significant (d = -0.38, p = 0.090).

Table S5. Group means, standard deviation (SD) and mixed model regression estimates for primary and secondary outcomes

	Mean (SD) for each group								Intervention effect (compared to NT)									
	NT		CRS		CBT-I		CBT-I+CRS		CRS				CBT-I				CBT-I + CRS			
	n	mean (SD)	n	mean (SD)	n	mean (SD)	n	mean (SD)	Estimate[a] (95% CI)	*d*	*p*		Estimate[a] (95% CI)	*d*	*p*		Estimate[a] (95% CI)	*d*	*p*	
Depressive symptom severity (IDS-SR)																				
pre	34	19.4 (6.2)	34	19.1 (7.9)	31	19.5 (8.2)	32	18.7 (7.5)												
post (all 4 follow-ups)		21.4 (7.6)		19.4 (9.1)		15.6 (9.9)		14.0 (7.7)	-2.0 (-5.1 to 1.1)	-0.24	0.199		-5.6 (-8.8 to -2.4)	-0.80	**0.001**		-6.3 (-9.5 to -3.1)	-0.95	**<0.001**	
7 weeks	34	21.7 (7.5)	34	19.1 (8.5)	29	13.6 (7.4)	32	14.8 (8.2)	-2.5 (-6.0 to 1.0)	-0.33	0.158		-7.9 (-11.6 to -4.3)	-1.11	**<0.001**		-6.3 (-9.9 to -2.8)	-0.88	**0.001**	
6 months	35	21.5 (7.0)	31	20.0 (8.6)	29	15.1 (8.9)	30	14.5 (8.0)	-1.9 (-5.6 to 1.8)	-0.16	0.320		-6.1 (-10.0 to -2.3)	-0.87	**0.002**		-6.0 (-9.7 to -2.2)	-0.90	**0.002**	
9 months	34	22.4 (7.9)	33	19.6 (10.0)	29	17.1 (12.8)	28	12.3 (7.0)	-2.6 (-6.9 to 1.7)	-0.34	0.229		-4.9 (-9.4 to -0.5)	-0.73	**0.031**		-7.9 (-12.3 to -3.5)	-1.35	**0.001**	
12 months	35	20.1 (7.9)	33	19.0 (9.5)	29	16.4 (9.9)	31	14.3 (7.7)	-1.1 (-4.9 to 2.7)	-0.11	0.567		-3.4 (-7.3 to 0.5)	-0.51	0.087		-4.9 (-8.7 to -1.1)	-0.73	**0.012**	
Inomnia severity (ISI)																				
pre	35	16.0 (4.2)	34	15.8 (3.5)	31	16.4 (4.1)	32	15.9 (3.5)												
post (all 4 follow-ups)		14.1 (4.0)		12.3 (4.2)		10.4 (4.0)		11.0 (4.2)	-1.6 (-3.5 to 0.4)	-0.39	0.109		-3.9 (-6.0 to -1.9)	-0.98	**<0.001**		-3.0 (-5.0 to -1.0)	-0.79	**0.003**	
7 weeks	34	15.2 (4.7)	34	12.5 (4.8)	29	9.1 (3.2)	32	11.3 (5.1)	-2.5 (-4.6 to -0.4)	-0.65	**0.018**		-6.3 (-8.5 to -4.1)	-1.54	**<0.001**		-3.8 (-5.9 to -1.7)	-0.97	**<0.001**	
6 months	35	13.5 (4.9)	31	11.9 (5.3)	29	10.2 (5.0)	30	10.9 (5.1)	-1.6 (-4.1 to 0.9)	-0.34	0.201		-3.5 (-6.0 to -0.9)	-0.86	**0.007**		-2.3 (-4.8 to 0.3)	-0.61	0.078	
9 months	34	14.5 (4.9)	32	12.2 (5.0)	29	10.8 (6.6)	29	9.6 (4.5)	-2.1 (-4.5 to 0.2)	-0.55	0.079		-3.8 (-6.2 to -1.3)	-0.97	**0.003**		-4.5 (-6.9 to -2.0)	-1.22	**<0.001**	
12 months	35	13.4 (4.8)	33	13.1 (5.1)	29	11.4 (5.9)	31	11.6 (5.5)	-0.2 (-2.5 to 2.0)	-0.03	0.837		-2.2 (-4.5 to 0.2)	-0.56	0.074		-1.6 (-3.9 to 0.7)	-0.41	0.180	
Subjective sleepparameters from sleep dairy[b]																				
Sleep Efficiency (%)																				
pre	35	73.9 (11.2)	34	77.1 (10.0)	31	74.7 (14.0)	32	73.2 (13.2)												
post (all 2 follow-ups)		76.4 (12.2)	66	79.9 (8.2)	58	82.7 (8.8)	62	81.9 (10.4)	0.2 (-4.4 to 4.8)	0.03	0.925		5.5 (0.8 to 10.2)	0.42	**0.023**		6.7 (2.0 to 11.4)	0.50	**0.005**	
7 weeks	35	76.3 (12.8)	34	78.9 (11.8)	29	83.7 (9.8)	32	82.4 (11.2)	-0.1 (-5.4 to 5.3)	-0.05	0.975		6.7 (1.2 to 12.2)	0.51	**0.016**		7.9 (2.4 to 13.3)	0.55	**0.005**	
12 months	35	76.5 (12.5)	32	80.3 (9.6)	29	81.6 (9.8)	30	82.8 (10.2)	0.3 (-4.5 to 5.1)	0.05	0.892		4.2 (-0.7 to 9.1)	0.33	0.091		5.5 (0.7 to 10.4)	0.56	**0.026**	
Total Sleep Time (min)																				
pre	35	350.0 (57.0)	34	370.3 (52.4)	31	361.3 (75.4)	32	343.8 (65.4)												
post (all 2 follow-ups)		366.5 (58.2)	66	393.5 (42.8)	58	380.1 (47.5)	62	367.3 (55.8)	5.6 (-16.7 to 28.0)	0.12	0.621		4.6 (-18.2 to 27.5)	0.03	0.692		9.8 (-13.1 to 32.6)	0.11	0.401	
7 weeks	35	359.1 (62.2)	34	382.1 (60.0)	29	372.5 (53.5)	32	356.4 (55.0)	2.9 (-22.4 to 28.3)	0.05	0.821		4.7 (-21.0 to 30.4)	0.03	0.720		7.2 (-18.6 to 33.0)	0.06	0.584	
12 months	35	373.7 (59.3)	32	401.6 (54.7)	29	388.0 (49.7)	30	385.5 (56.8)	7.7 (-17.2 to 32.6)	0.14	0.544		5.0 (-20.4 to 30.3)	0.05	0.701		12.7 (-12.7 to 38.2)	0.29	0.327	
Sleep Onset Latency (min)																				
pre	35	34.6 (24.5)	34	36.2 (27.1)	31	34.7 (24.7)	32	33.9 (24.3)												
post (all 2 follow-ups)		30.5 (18.0)	66	32.8 (25.3)	58	25.2 (18.6)	62	23.2 (16.5)	0.3 (-8.6 to 9.2)	0.03	0.944		-5.9 (-15.1 to 3.2)	-0.22	0.202		-8.4 (-17.5 to 0.7)	-0.27	0.071	
7 weeks	35	28.7 (18.3)	34	33.5 (29.9)	29	23.5 (17.3)	32	22.1 (18.3)	1.4 (-8.5 to 11.2)	0.12	0.788		-5.9 (-15.8 to 4.1)	-0.21	0.249		-7.9 (-17.9 to 2.1)	-0.24	0.122	
12 months	35	32.1 (21.9)	32	34.1 (29.3)	29	27.4 (23.0)	30	22.9 (16.6)	-0.8 (-11.0 to 9.4)	0.02	0.871		-5.8 (-16.2 to 4.6)	-0.19	0.276		-8.9 (-19.3 to 1.6)	-0.35	0.095	
Wake After Sleep Onset (min)																				
pre	35	90.0 (57.8)	34	72.8 (36.7)	31	86.9 (56.6)	32	92.7 (56.6)												
post (all 2 follow-ups)		85.1 (66.7)	66	67.9 (35.8)	58	55.2 (32.0)	62	56.8 (43.4)	0.2 (-21.8 to 22.2)	0.00	0.988		-26.6 (-49.2 to -4.0)	-0.46	**0.021**		-31.4 (-53.8 to -8.9)	-0.53	**0.006**	
7 weeks	35	84.6 (66.2)	34	68.6 (49.8)	29	48.9 (37.0)	32	53.2 (43.0)	1.0 (-23.9 to 25.9)	0.02	0.937		-32.7 (-58.3 to -7.2)	-0.56	**0.012**		-36.4 (-61.7 to -11.0)	-0.59	**0.005**	
12 months	35	86.9 (73.5)	32	65.5 (41.4)	29	61.6 (38.9)	30	57.1 (48.5)	-1.2 (-24.8 to 22.4)	-0.08	0.922		-20.9 (-45.0 to 3.3)	-0.38	0.090		-26.7 (-50.7 to -2.6)	-0.56	0.030	

NT, No treatment; CRS, Circadian Rhythm Support; CBT-I, Cognitive Behavioral Therapy for Insomnia; CBT-I+CRS, Cognitive Behavioral Therapy for Insomnia combined with Circadian Rhythm Support; IDS-SR, Inventory of Depressive Symptomatology- Short Form; ISI, Insomnia Severity Index. [a] estimated between-group difference in the change from baseline to follow-up, relative to this change in NT. [b] means (SD) were computed by aggregating each participant's daily assessments across each timepoint (T0, T1, T4). Boldface p-values survived multiple comparison correction for the sleep diary outcomes, with a critical p-value below 0.027 according to the Sidak with D/AP adjustment for correlated data (mean r = 0.54).

Table S6. Mixed model regression estimates comparing CBT-I + CRS versus CBT-I

	Mean (SD) for each group						
	CBT-I		CBT-I + CRS		Intervention effect CBT-I + CRS (compared to CBT-I)		
	n	mean (SD)	n	mean (SD)	Estimate[a] (95% CI)	*d*	*p*
Depressive symptom severity (IDS-SR)							
pre	31	19.5 (8.2)	32	18.7 (7.5)			
post (all 4 follow-ups)		15.6 (9.9)		14.0 (7.6)	-0.7 (-4.0 to 2.6)	-0.10	0.679
7 weeks	29	13.6 (7.4)	32	14.8 (8.2)	1.6 (-2.0 to 5.3)	0.25	0.381
6 months	29	15.1 (8.9)	30	14.5 (8.0)	0.2 (-3.8 to 4.1)	0.02	0.931
9 months	29	17.1 (12.8)	28	12.3 (7.0)	-3.0 (-7.6 to 1.6)	-0.51	0.204
12 months	29	16.4 (9.9)	31	14.3 (7.7)	-1.5 (-5.5 to 2.5)	-0.17	0.460
Inomnia severity (ISI)							
pre	31	16.4 (4.1)	32	15.9 (3.5)			
post (all 4 follow-ups)		10.4 (4.0)		11.0 (4.2)	0.9 (-1.1 to 3.0)	0.26	0.377
7 weeks	29	9.1 (3.2)	32	11.3 (5.1)	2.5 (0.3 to 2.5)	0.69	0.028
6 months	29	10.2 (5.0)	30	10.9 (5.1)	1.2 (-1.4 to 1.2)	0.31	0.360
9 months	29	10.8 (6.6)	29	9.6 (4.5)	-0.7 (-3.3 to -0.7)	-0.19	0.570
12 months	29	11.4 (5.9)	31	11.6 (5.5)	0.6 (-1.9 to 0.6)	0.19	0.646
Subjective sleepparameters from sleep dairy[b]							
Sleep Efficiency (%)							
pre	31	74.7 (14.0)	32	73.2 (13.2)			
post (all 2 follow-ups)		82.7 (8.8)		81.9 (10.4)	1.3 (-3.6 to 6.3)	0.05	0.612
7 weeks	29	83.7 (9.8)	32	82.4 (11.2)	1.2 (-4.5 to 6.8)	0.02	0.689
12 months	29	81.6 (9.8)	30	82.8 (10.2)	1.3 (-3.7 to 6.4)	0.19	0.607
Total Sleep Time (min)							
pre	31	361.3 (75.4)	32	343.8 (65.4)			
post (all 2 follow-ups)		380.1 (47.5)		367.3 (55.8)	5.2 (-18.5 to 28.8)	0.07	0.669
7 weeks	29	372.5 (53.5)	32	356.4 (55.0)	2.5 (-24.1 to 29.1)	0.02	0.854
12 months	29	388.0 (49.7)	30	385.5 (56.8)	7.8 (-18.6 to 34.1)	0.21	0.563
Sleep Onset Latency (min)							
pre	31	34.7 (24.7)	32	33.9 (24.3)			
post (all 2 follow-ups)		25.2 (18.6)		23.2 (16.5)	-2.5 (-11.9 to 7.0)	-0.05	0.607
7 weeks	29	23.5 (17.3)	32	22.1 (18.3)	-2.0 (-12.4 to 8.3)	-0.03	0.699
12 months	29	27.4 (23.0)	30	22.9 (16.6)	-3.1 (-13.9 to 7.7)	-0.15	0.574
Wake After Sleep Onset (min)							
pre	31	86.9 (56.6)	32	92.7 (56.6)			
post (all 2 follow-ups)		55.2 (32.0)		56.8 (43.4)	-4.8 (-28.1 to 18.6)	-0.07	0.689
7 weeks	29	48.9 (37.0)	32	53.2 (43.0)	-3.6 (-29.9 to 22.6)	-0.03	0.786
12 months	29	61.6 (38.9)	30	57.1 (48.5)	-5.8 (-30.8 to 19.2)	-0.18	0.650

CBT-I, Cognitive Behavioral Therapy for Insomnia; CBT-I+CRS, Cognitive Behavioral Therapy for Insomnia combined with Circadian Rhythm Support; IDS-SR, Inventory of Depressive Symptomatology - Short Form; ISI, Insomnia Severity Index. [a] estimated between-group difference in the mean change from baseline to follow-up (change in CBT-I + RS minus change in CBT-I). [b] means (SD) were computed by aggregating each participant's daily assessments across each timepoint (T0, T1, T4)

Table S7. Sensitivity analyses: effect of intervention on depressive symptom severity without insomnia items, models including covariates, and per protocol analysis.

	Mean (SD) for each group								Intervention effect (compared to NT)							
	NT		CRS		CBT-I		CBT-I+CRS		CRS			CBT-I			CBT-I + CRS		
	n	mean (SD)	n	mean (SD)	n	mean	n	mean (SD)	Estimate[a] (95% CI)	*d*	*p*	Estimate[a] (95% CI)	*d*	*p*	Estimate[a] (95% CI)	*d*	*p*
Depressive symptom severity (IDS-SR) without insomnia items																	
pre	34	14.6 (6.0)	34	14.3 (7.0)	31	14.9 (7.5)	32	13.9 (7.4)									
post (all 4 follow-ups)		17.1 (7.5)		15.2 (8.2)		12.2 (9.6)		10.7 (7.3)	-1.8 (-4.8 to 1.1)	-0.24	0.215	-4.9 (-7.9 to -1.8)	-0.75	**0.002**	-5.4 (-8.3 to -2.4)	-0.83	**<0.001**
7 weeks	34	17.6 (7.9)	34	15.0 (7.6)	29	11.0 (7.7)	32	11.9 (7.5)	-2.5 (-5.7 to 0.7)	-0.36	0.126	-6.7 (-10.0 to -3.4)	-1.01	**<0.001**	-5.2 (-8.4 to -2.0)	-0.74	**0.002**
6 months	35	17.3 (6.8)	31	15.6 (7.7)	29	11.6 (8.9)	30	10.6 (7.7)	-1.9 (-5.5 to 1.6)	-0.21	0.282	-5.8 (-9.4 to -2.1)	-0.88	**0.002**	-5.8 (-9.3 to -2.2)	-0.88	**0.002**
9 months	34	17.6 (7.8)	33	15.3 (8.9)	29	13.3 (12.3)	28	9.1 (6.3)	-2.1 (-6.2 to 1.9)	-0.31	0.297	-4.2 (-8.3 to 0.0)	-0.67	**0.048**	-6.5 (-10.7 to -2.4)	-1.15	**0.002**
12 months	35	15.7 (7.7)	33	14.8 (8.9)	29	12.9 (9.4)	31	11.0 (7.3)	-0.8 (-4.4 to 2.8)	-0.10	0.654	-2.8 (-6.5 to 1.0)	-0.45	0.147	-3.9 (-7.6 to -0.3)	-0.60	**0.035**
Depressive symptom severity (IDS-SR) including covariates																	
pre	34	19.4 (6.2)	34	19.1 (7.9)	31	19.5 (8.2)	32	18.7 (7.5)									
post (all 4 follow-ups)		21.5 (6.2)		19.1 (7.8)		15.6 (8.5)		14.7 (7.1)	-2.0 (-5.2 to 1.1)	-0.24	0.210	-5.4 (-8.7 to -2.1)	-0.80	**0.001**	-6.3 (9.5 to -3.1)	-0.95	**<0.001**
7 weeks	34	21.7 (7.5)	34	19.1 (8.5)	29	13.6 (7.4)	32	14.8 (8.2)	-2.5 (-6.0 to 1.0)	-0.33	0.161	-7.7 (-11.4 to -4.1)	-1.11	**<0.001**	-6.3 (-9.8 to -2.7)	-0.88	**0.001**
6 months	35	21.5 (7.0)	31	20.0 (8.6)	29	15.1 (8.9)	30	14.5 (8.0)	-1.9 (-5.6 to 1.8)	-0.16	0.320	-5.9 (-9.7 to -2.1)	-0.87	**0.002**	-5.9 (-9.7 to -2.1)	-0.90	**0.002**
9 months	34	22.4 (7.9)	33	19.6 (10.0)	29	17.1 (12.8)	28	12.3 (7.0)	-2.6 (-6.9 to 1.7)	-0.34	0.233	-4.8 (-9.2 to -0.3)	-0.73	**0.036**	-8.0 (-12.4 to -3.5)	-1.35	**<0.001**
12 months	35	20.1 (7.9)	33	19.0 (9.5)	29	16.4 (9.9)	31	14.3 (7.7)	-1.1 (-4.8 to 2.7)	-0.11	0.576	-3.2 (-7.1 to 0.7)	-0.51	0.105	-4.9 (-8.7 to -1.1)	-0.73	**0.012**
Depressive symptom severity (IDS-SR) per-protocol analysis																	
pre	34	19.4 (6.2)	31	19.5 (7.9)	29	18.9 (7.9)	29	18.7 (7.8)									
post (all 4 follow-ups)		21.4 (7.6)		19.5 (9.0)		15.6 (9.9)		13.4 (7.3)	-2.2 (-5.3 to 0.9)	-0.27	0.163	-5.4 (-8.5 to -2.2)	-0.74	**0.001**	-7.2 (-10.3 to -4.1)	-1.02	**<0.001**
7 weeks	34	21.7 (7.5)	31	18.6 (8.3)	29	13.6 (7.4)	29	13.8 (7.9)	-3.3 (-6.7 to 0.2)	-0.43	0.065	-7.7 (-11.2 to -4.2)	-1.06	**<0.001**	-7.3 (-10.8 to -3.8)	-1.01	**<0.001**
6 months	35	21.5 (7.0)	30	19.8 (8.6)	29	15.1 (8.9)	29	13.7 (6.9)	-2.0 (-5.6 to 1.6)	-0.24	0.284	-5.9 (-9.5 to -2.2)	-0.81	**0.002**	-7.0 (-10.7 to -3.3)	-0.98	**<0.001**
9 months	34	22.4 (7.9)	30	20.1 (9.8)	29	17.1 (12.8)	28	12.3 (7.0)	-2.6 (-6.9 to 1.8)	-0.33	0.248	-4.7 (-9.1 to -0.3)	-0.66	**0.036**	-8.8 (-13.3 to -4.4)	-1.32	**<0.001**
12 months	35	20.1 (7.9)	30	19.5 (9.7)	29	16.4 (9.9)	29	13.8 (7.7)	-0.9 (-4.8 to 2.9)	-0.09	0.637	-3.2 (-7.1 to 0.7)	-0.44	0.109	-5.6 (-9.5 to -1.7)	-0.79	**0.005**

NT, No treatment; CRS, Circadian Rhythm Support; CBT-I, Cognitive Behavioral Therapy for Insomnia; CBT-I+CRS, Cognitive Behavioral Therapy for Insomnia combined with Circadian Rhythm Support; IDS-SR, Inventory of Depressive Symptomatology - Short Form; ISI, Insomnia Severity Index. [a] estimated between-group difference in the mean change from baseline to follow-up (change in active intervention condition minus change in NT)

Supplementary Figures

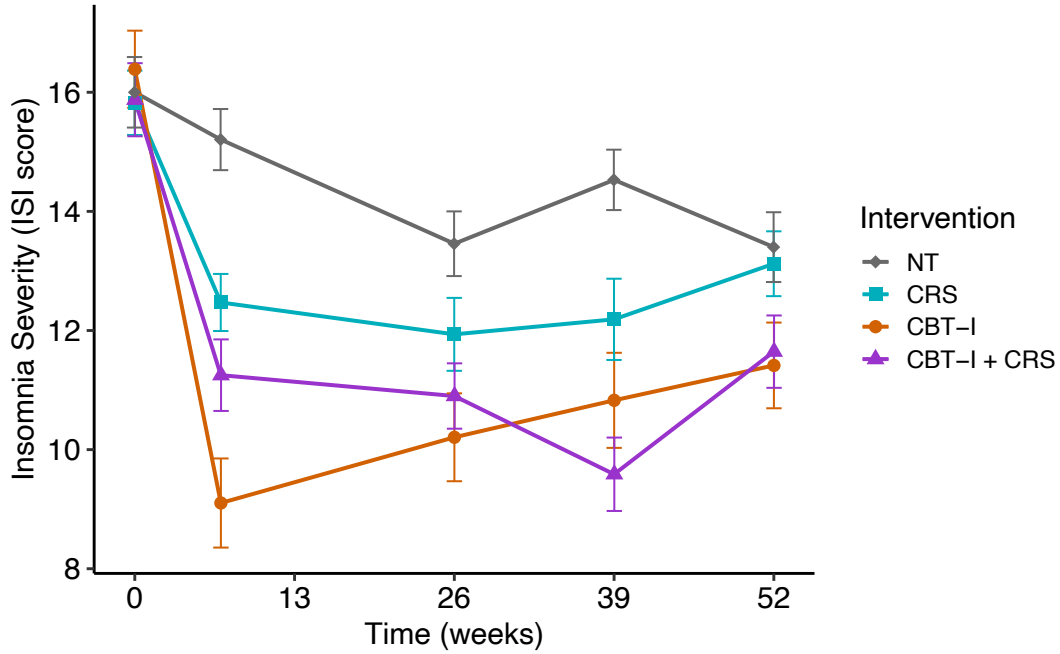

Figure S1. Mean insomnia severity scores for each treatment condition at individual follow-ups. Error bars represent the standard error. NT, no treatment; CRS, Circadian Rhythm Support; CBT-I, Cognitive Behavioral Therapy for Insomnia; CBT-I+CRS; combined Cognitive Behavioral Therapy for Insomnia with Circadian Rhythm Support.

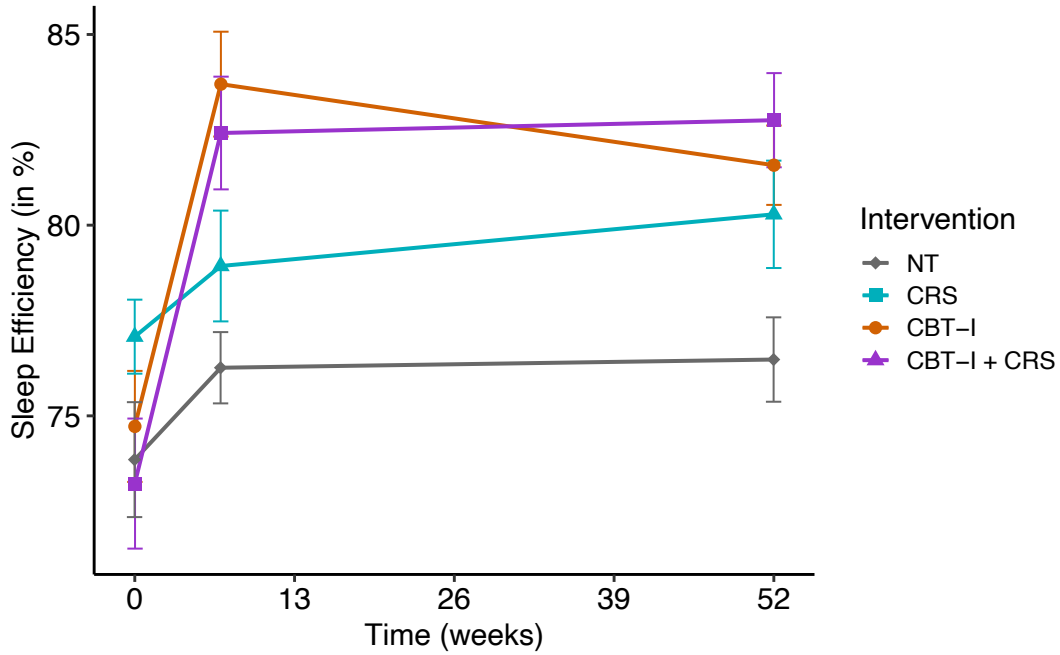

Figure S2. Subjective sleep efficiency (in %) derived from sleep diaries for each treatment condition at individual follow-ups. Error bars represent the standard error. NT, no treatment; CRS, Circadian Rhythm Support; CBT-I, Cognitive Behavioral Therapy for Insomnia; CBT-I+CRS; combined Cognitive Behavioral Therapy for Insomnia with Circadian Rhythm Support.

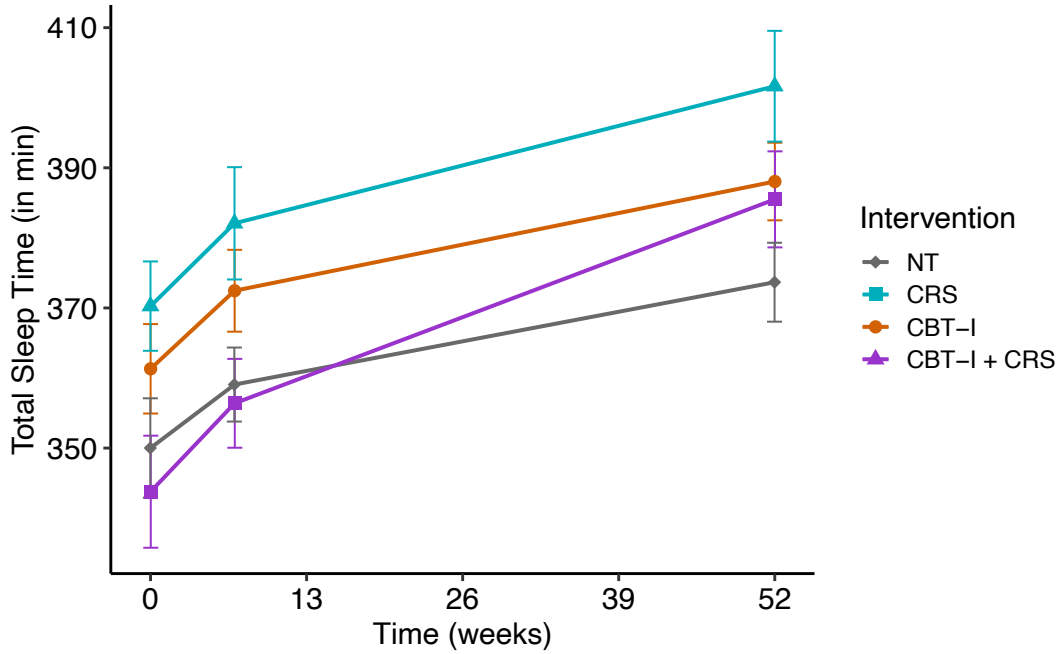

Figure S3. Subjective total sleep time (in minutes) derived from sleep diaries for each treatment condition at individual follow-ups. Error bars represent the standard error. NT, no treatment; CRS, Circadian Rhythm Support; CBT-I, Cognitive Behavioral Therapy for Insomnia; CBT-I+CRS; combined Cognitive Behavioral Therapy for Insomnia with Circadian Rhythm Support.

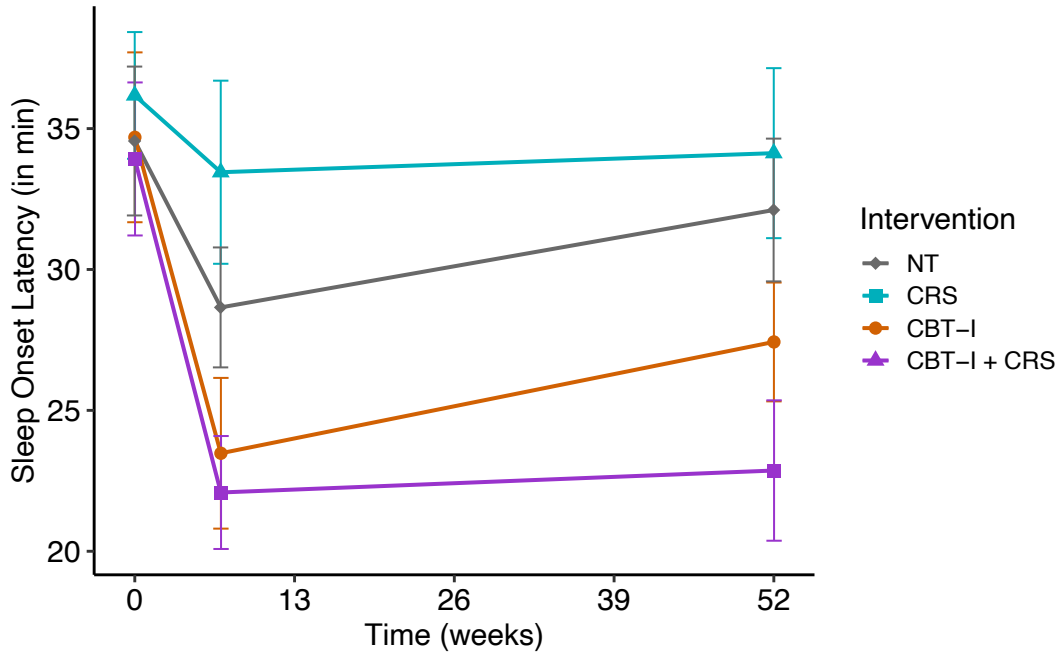

Figure S4. Subjective sleep onset latency (in minutes) derived from sleep diaries for each treatment condition at individual follow-ups. Error bars represent the standard error. NT, no treatment; CRS, Circadian Rhythm Support; CBT-I, Cognitive Behavioral Therapy for Insomnia; CBT-I+CRS; combined Cognitive Behavioral Therapy for Insomnia with Circadian Rhythm Support.

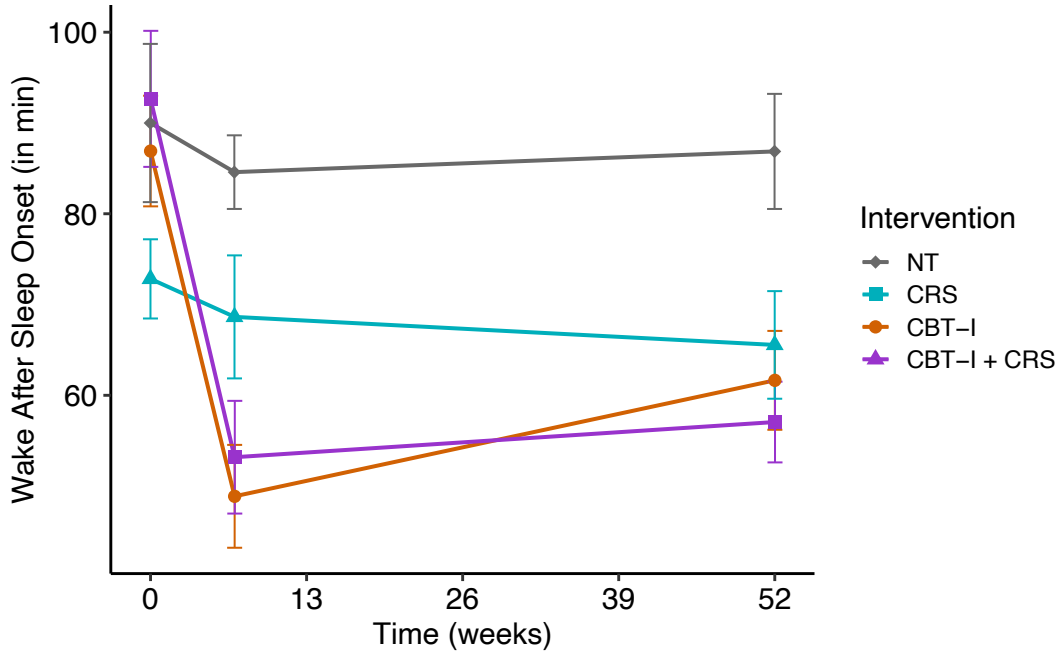

Figure S5. Subjective wake after sleep onset (in minutes) derived from sleep diaries for each treatment condition at individual follow-ups. Error bars represent the standard error. NT, no treatment; CRS, Circadian Rhythm Support; CBT-I, Cognitive Behavioral Therapy for Insomnia; CBT-I+CRS; combined Cognitive Behavioral Therapy for Insomnia with Circadian Rhythm Support.

Supplementary Discussion

Comparing effect sizes to previous meta-analyses

Insomnia Severity Index

The most comprehensive meta-analysis on digital CBT-I to date [21] reported mean differences (rather than Cohen's *d* or Hedges' *g*) with the control condition on the ISI of -5.0 post-intervention, -4.0 at short-term follow-up and -3.5 at long-term follow-up. Corresponding mean differences in our study were, respectively, -6.5, -3.7 and -2.4, so not that different overall - possibly somewhat stronger initially and weaker at long-term follow-up.

Since Soh et al. [21] report no effect size, we refer to an older meta-analysis [22] which reported *g* = 0.89 post-intervention and *g* = 0.50 at short term (±6-month) follow-up. In our study, the corresponding effect sizes were *d*=-1.54 and d = -0.86, both comparing favorably.

Since 1-yr follow-up effect sizes are not included in meta-analyses specifically on digital CBT-I, we refer to 1-yr follow-up findings in a meta-analysis including mostly face-to-face CBT-I [23]. This meta-analysis reported the effect of CBT-I on insomnia severity to wane over time to *g*=0.25 at 12 months). In our study, the corresponding effect size was *d* = -0.56, also comparing favorably .

The lack of immediate effects of standalone CRS on insomnia severity is consistent with a previous study [6]. While evidence supports the use of bright light, exercise and to a lesser extent warm baths at a fixed time of day to improve sleep quality in other populations, few studies applied these interventions specifically in insomnia disorder. So far, only the effect of exercise on sleep in insomnia disorder has been meta-analyzed, indicating very low-quality evidence of a clinically irrelevant 3-point decrease on the insomnia severity index [24]. We are not aware of meta-analyses on the effects of bright light or warm baths specifically in insomnia disorder.

Sleep diary variables

Post-treatment effects on sleep diary variables can be compared with a meta-analysis on digital CBT-I reporting both mean differences and effect sizes [22]. Long-term follow-up 12 months was not included in this meta-analysis.

The post-treatment effect of CBT-I on sleep efficiency (mean difference 6.6%, *d*=0.51) was identical to what was reported by meta-analysis (mean difference 6.7%, *d*=0.49), while the effect on WASO (mean difference -32.6 min, *d* =0.56) even compared favorably to the meta-analysis (mean difference -16.6 min, *d*=0.21). On the other hand, we did not find significant effects on SOL (mean difference -5.3 min, *d*=0.21, ns) and TST (mean difference 2.0 min, *d*=0.03, ns) while meta-analysis did (respectively 16.8 and 20.6 minutes, *d* =0.34 and *d*=0.24). Future studies may address whether our selected insomnia subtypes respond differently to CBT-I than insomnia subtypes without increased risk of depression. No meta-analyses are available to compare our other interventions.

Depressive symptoms

A recent meta-analysis specifically evaluated the effect of self-help CBT-I (mostly digital) on depressive symptoms and reported an effect size of *g* = 0.35 [25]. Our post-treatment effect size compares favorably (*d* = -1.11 for CBT-I).

A recent individual patient data network meta-analysis makes it possible to compare our post-treatment effects as well with effects of guided digital CBT targeting depressive symptoms rather than insomnia [26]. Based on the pooled standard deviation of the total sample of that study, the reported mean differences can be converted to an estimated Cohen's *d* = -0.29 compared to treatment as usual and *d* = -0.57 compared to waitlist control. Again, our results compare favorably.

References

1. Paunio T, Korhonen T, Hublin C, Partinen M, Kivimaki M, Koskenvuo M, et al. Longitudinal study on poor sleep and life dissatisfaction in a nationwide cohort of twins. Am J Epidemiol. 2009 Jan 15;169(2):206-13.
2. Baglioni C, Battagliese G, Feige B, Spiegelhalder K, Nissen C, Voderholzer U, et al. Insomnia as a predictor of depression: A meta-analytic evaluation of longitudinal epidemiological studies. J Affect Disord. 2011 Feb 5;135:10-19.
3. Paunio T, Korhonen T, Hublin C, Partinen M, Koskenvuo K, Koskenvuo M, et al. Poor sleep predicts symptoms of depression and disability retirement due to depression. J Affect Disord. 2015 Feb 01;172:381-89.
4. Blanken TF, Benjamins JS, Borsboom D, Vermunt JK, Paquola C, Ramautar J, et al. Insomnia disorder subtypes derived from life history and traits of affect and personality. Lancet Psychiatry. 2019 Feb;6(2):151-63.
5. Ferrari AJ, Somerville AJ, Baxter AJ, Norman R, Patten SB, Vos T, et al. Global variation in the prevalence and incidence of major depressive disorder: a systematic review of the epidemiological literature. Psychol Med. 2013;43(3):471-81.
6. Dekker K, Benjamins Jeroen S, Maksimovic T, Filardi M, Hofman Winni F, van Straten A, et al. Combined internet-based cognitive-behavioral and chronobiological intervention for insomnia: A randomized controlled trial. Psychother Psychosom. 2020;89(2):117-18.
7. van Straten A, Emmelkamp J, de Wit J, Lancee J, Andersson G, van Someren EJW, et al. Guided Internet-delivered cognitive behavioural treatment for insomnia: a randomized trial. Psychol Med. 2014 May;44(7):1521-32.
8. van der Zweerde T, van Straten A, Effting M, Kyle SD, Lancee J. Does online insomnia treatment reduce depressive symptoms? A randomized controlled trial in individuals with both insomnia and depressive symptoms. Psychol Med. 2019 Feb;49(3):501-09.
9. Van der Zweerde T, Lancee J, Slottje P, Bosmans JE, Van Someren EJW, van Straten A. Nurse-guided internet-delivered cognitive behavioral therapy for insomnia in general practice: Results from a pragmatic randomized clinical trial. Psychother Psychosom. 2020;89(3):174-84.
10. Carney CE, Buysse DJ, Ancoli-Israel S, Edinger JD, Krystal AD, Lichstein KL, et al. The consensus sleep diary: standardizing prospective sleep self-monitoring. Sleep. 2012 Feb 1;35(2):287-302.
11. Guidi J, Brakemeier EL, Bockting CLH, Cosci F, Cuijpers P, Jarrett RB, et al. Methodological recommendations for trials of psychological interventions. Psychother Psychosom. 2018;87(5):276-84.
12. Cosci F, Fava GA. Staging of mental disorders: systematic review. Psychother Psychosom. 2013;82(1):20-34.
13. Verduijn J, Milaneschi Y, van Hemert AM, Schoevers RA, Hickie IB, Penninx BW, et al. Clinical staging of major depressive disorder: an empirical exploration. J Clin Psychiatry. 2015 Sep;76(9):1200-8.
14. Edinger J, Kirby A, Lineberger M, Loiselle M, Wohlgemuth W, Means M. The Duke Structured Interview Schedule for DSM-IV-TR and International Classification of Sleep Disorders, Second Edition (ICSD-2) Sleep Disorder Diagnoses. Durham, NC: Duke University Medical Center; 2004.
15. Leerssen J, Foster-Dingley JC, Lakbila-Kamal O, Dekkers LMS, Albers ACW, Ikelaar SLC, et al. Internet-guided cognitive, behavioral and chronobiological interventions in depression-prone insomnia subtypes: protocol of a randomized controlled prevention trial. BMC Psychiatry. 2020 April 15;20(1):163.
16. Hunsley J, Meyer GJ. The incremental validity of psychological testing and assessment: Conceptual, methodological, and statistical issues. Psychol Assessment. 2003;15(4):446-55.

17. Fava GA, Rafanelli C, Tomba E. The clinical process in psychiatry: a clinimetric approach. J Clin Psychiatry. 2012;73(2):177-84.
18. Carrozzino D, Patierno C, Guidi J, Berrocal Montiel C, Cao J, Charlson ME, et al. Clinimetric Criteria for Patient-Reported Outcome Measures. Psychother Psychosom. 2021;90(4):222-32.
19. Vgontzas AN, Fernandez-Mendoza J, Liao D, Bixler EO. Insomnia with objective short sleep duration: the most biologically severe phenotype of the disorder. Sleep Med Rev. 2013 Aug;17(4):241-54.
20. Hakkaart-van Roijen L, Straten A, Tiemens B, C. H. Donker M. Manual Trimbos/iMTA Questionnaire for Costs Associated with Psychiatric Illness (TIC-P) (in Dutch). 2002.
21. Soh HL, Ho RC, Ho CS, Tam WW. Efficacy of digital cognitive behavioural therapy for insomnia: a meta-analysis of randomised controlled trials. Sleep Med. 2020 2020/11/01/;75:315-25.
22. Zachariae R, Lyby MS, Ritterband LM, O'Toole MS. Efficacy of internet-delivered cognitive-behavioral therapy for insomnia - A systematic review and meta-analysis of randomized controlled trials. Sleep Med Rev. 2015 Oct 24;30:1-10.
23. van der Zweerde T, Bisdounis L, Kyle SD, Lancee J, van Straten A. Cognitive behavioral therapy for insomnia: a meta-analysis of long-term effects in controlled studies. Sleep Med Rev. 2019.
24. Banno M, Harada Y, Taniguchi M, Tobita R, Tsujimoto H, Tsujimoto Y, et al. Exercise can improve sleep quality: a systematic review and meta-analysis. PeerJ. 2018 2018/07/11;6:e5172.
25. Ho FY-Y, Chan CS, Lo W-Y, Leung JC-Y. The effect of self-help cognitive behavioral therapy for insomnia on depressive symptoms: An updated meta-analysis of randomized controlled trials. J Affect Disord. 2020;265:287-304.
26. Karyotaki E, Efthimiou O, Miguel C, Bermpohl FMg, Furukawa TA, Cuijpers P, et al. Internet-Based Cognitive Behavioral Therapy for Depression: A Systematic Review and Individual Patient Data Network Meta-analysis. JAMA psychiatry. 2021;78(4):361-71.