

Meta-analysis of digital cognitive behavioral therapy for insomnia

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Severance

- Insomnia can be defined by symptoms such as
 - difficulty in initiating, maintaining sleep, and early-morning awakenings which impair the ability for daily functioning
- Prevalence among adults in general population
 - Insomnia disorder: 10~30%
 - Insomnia symptoms: 33% ~50%
- **Bidirectional relationship** between insomnia and depression/anxiety
- Cognitive behavioral therapy for insomnia (CBT-I)
 - Sleep restriction, stimulus control, sleep hygiene education, relaxation, and cognitive restructuring
 - First-line treatment for insomnia
 - **Considered an effective approach for managing depression and anxiety**

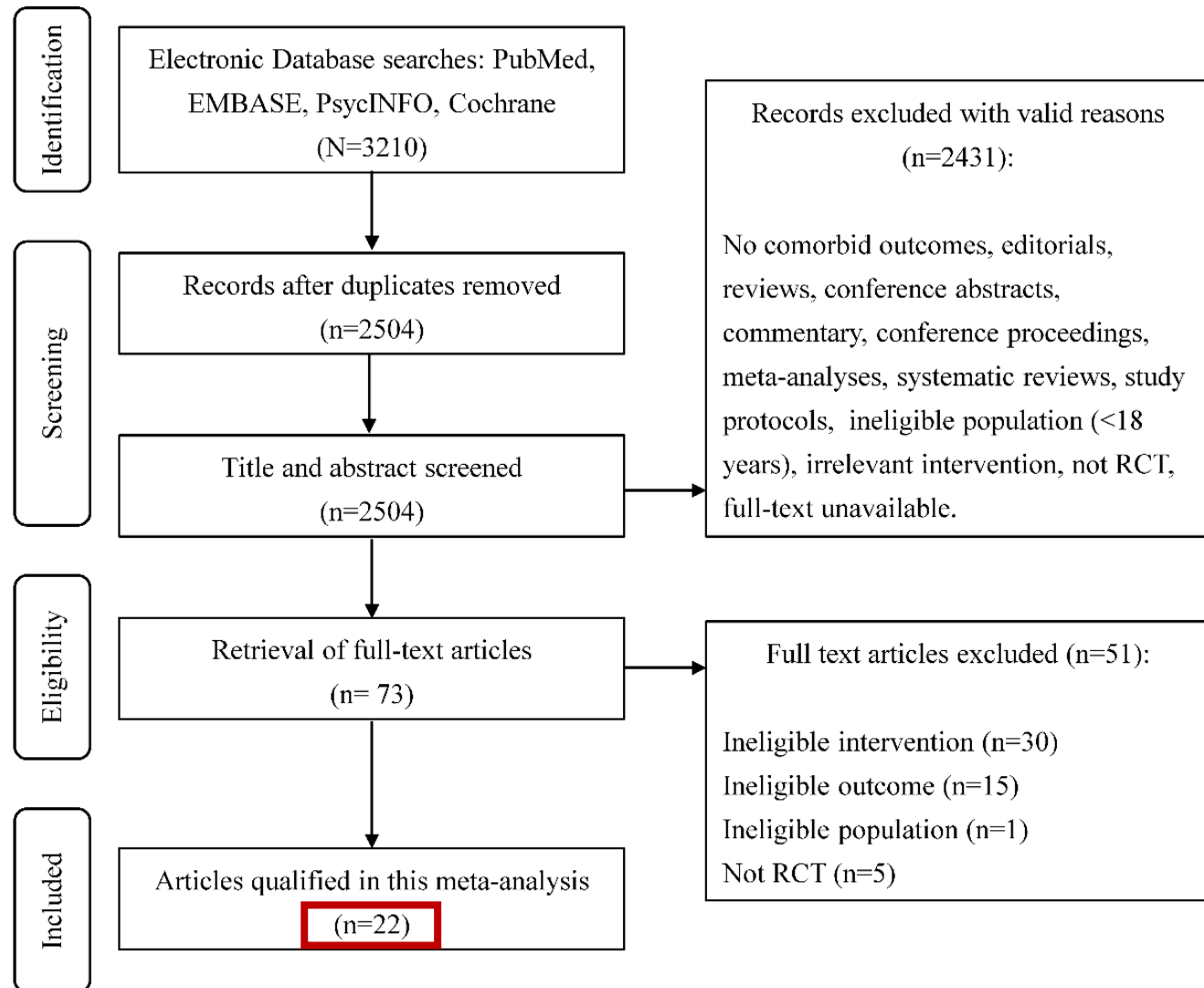
- Certain limitations of traditional CBT-I
 - Lack of therapists, time and geographical limitations, lack of scalability, high costs
- **Digital CBT-I (dCBT-I)**
 - Reflecting contemporary spectrum of digital technology (e.g., computers, the internet, smartphone applications, and other devices in health care)
 - Effective treatment alternative for insomnia
 - Lack of effectiveness in comparison to the traditional methods of face-to-face CBT-I
 - **Adherence** remains a critical predictor of treatment outcome
- Further studies are needed to evaluate the outcomes of dCBT-I on insomnia and the comorbid factors depression and anxiety
 - Conducted under controlled conditions
 - Lacking real-world applicability

- The present meta-analysis aimed to assess the effects of dCBT-I on depression and anxiety symptoms as well as insomnia and other sleep parameters by pooling published randomized control trials (RCTs).
- A subgroup analysis for the **adherence** of participants was performed to evaluate the efficacy of dCBT-I.

- **Systematic Reviews and Meta-Analysis**
- PubMed, Embase, PsycINFO, and Cochrane databases from inception to January 15th, 2022
- **Search strategy**
 - **Population**
 - Age ≥ 18
 - Formally diagnosed with *DSM, ICSD, or ICD or having self-reported symptoms of insomnia
 - Reported measures of depressive or anxiety symptoms
 - **Intervention: dCBT-I intervention**
 - consisted of multimodal components with at least one key cognitive and one key behavioral strategy
 - **Comparison: active controls, waitlist, treatment as usual (TAU)**
 - **Outcomes**
 - self-reported insomnia-related measures and sleep diary outcomes (*TST, SE, WASO, SOL)
 - measures of symptoms of depression and anxiety
 - **Study design: RCTs**

- **Assessment of risk of bias (RoB):** The revised Cochrane RoB for RCTs (RoB 2.0)
 - Domains in RoB: randomization process, deviation from intended interventions, missing outcome data, measurement of the outcome, selection of the reported result
- **Data synthesis and analysis**
 - Comprehensive Meta-Analysis (CMA) version 3
 - Treatment efficacy - the standardized mean difference (SMD)
 - Random-effects model
 - Overall between-group SMDs - based on the difference in the post-intervention outcome measures
 - Heterogeneity – Cochrane Q test ($p < 0.05$), I^2 statistics
 - Publication bias – Funnel plot, Egger's test
- **Subgroup analysis**
 - Dividing the groups using dCBT-I completer studies for the adherence of participants
 - Threshold of 65% for completion – based on prior researches (Horsch, C. et al., 2015; Matthews, E. et al., 2013)

• PRISMA Flow Diagram



- Summary of the characteristics of the included studies.

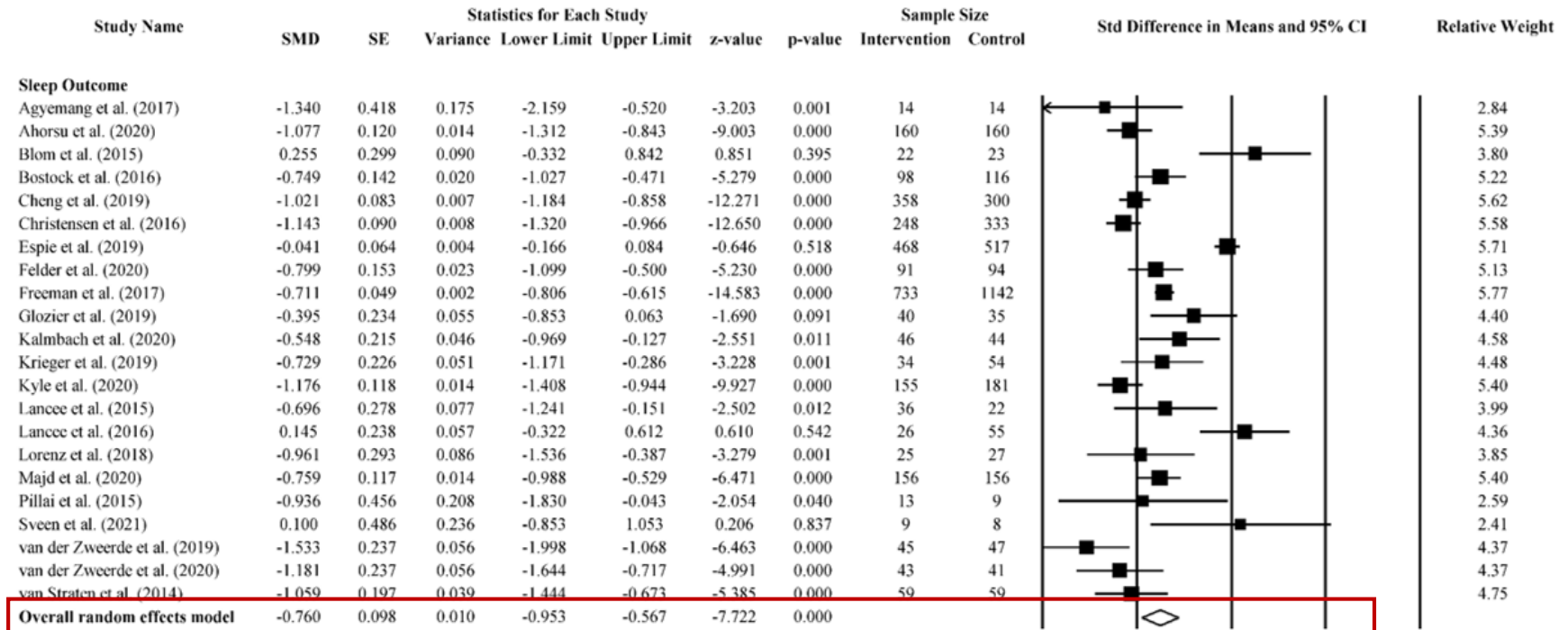
Author	Year	Country	Total sample size (%Female)	Mean age, years (SD)	Study design	dCBTi components	No. of sessions	Time point of post-assessment	Insomnia outcome measurement	Depression outcome measurement	Anxiety outcome measurement
Agyemang et al. ¹⁰	2017	United States	28 (78.6)	dCBTi: 43 (10.2) TAU: 50 (10.4)	2 parallel arms (dCBTi, TAU)	SRT, SC, CR, SHE	6	9-10 weeks	ISI, TST, SE, SOL, WASO	PHQ-9	GAD-7
Ahorsu et al. ¹¹	2020	Iran	320 (58.4)	dCBTi: 38.37 (13.45) Sleep education: 37.99 (9.88)	2 parallel arms (dCBTi, sleep education)	SHE, RE, CR, SRT, SC	6	10 weeks	ISI, TST, SE, WASO, SOL, PSQI	HADS	HADS
Blom et al. ¹²	2015	Sweden	48 (47.9)	dCBTi: 56.1 (10.2) GCBT: 52.6 (16.6)	2 parallel arms (dCBTi, GCBT)	SRT, SC, SHE, CR, RE, RP	8	8 weeks	ISI, TST SE, SOL	MADRS-S	-
Bostock et al. ¹³	2016	United Kingdom	270 (33.3)	dCBTi: 33.9 (6.41) WL: 33.3 (5.59)	2 parallel arms (dCBTi, WL)	SRT, SC, CR, RE, SHE	6	8 weeks	SCI	PHQ-2	GAD-2
Cheng et al. ¹⁴	2018	United States	1385 (78.9)	dCBTi: 44.5 (15.8) Online sleep education: 45.7 (15.1)	2 parallel arms (dCBTi, online sleep education)	SRT, SC, CR, PI, RE, SHE	6	12 weeks	ISI	QIDS	-
Christensen et al. ¹⁵	2016	Australia	1149 (73.5)	dCBTi: 42.95 (12.17) Online attention-matched placebo: 42.51 (12.24)	2 parallel arms (dCBTi, online attention-matched placebo)	SRT, SC, CR, SHE, RP	6	6 weeks	ISI	PHQ-9	GAD-7
Espie et al. ¹⁶	2019	United Kingdom	1711 (77.7)	dCBTi: 48.4 (13.9) SHE: 47.7 (13.6)	2 parallel arms (dCBTi, SHE)	SRT, SC, RE, CR, PI, PE, SHE	6	8 weeks	SCI	PHQ-9	GAD-7
Freeman et al. ¹⁷	2017	United Kingdom	3755 (71.3)	dCBTi: 24.8 (7.7) TAU: 24.6 (7.6)	2 parallel arms (dCBTi, TAU)	SRT, SC, RE, CR, PI, SHE, MI, IM	6	10 weeks	ISI	PHQ-9	GAD-7
Felder et al. ¹⁸	2020	United States	208 (100)	dCBTi: 33.90 (3.38) TAU: 33.2 (4.0)	2 parallel arms (dCBTi, TAU)	SRT, SC, CR, RE, SHE	6	10 weeks	ISI, PSQI, SE	EPDS	GAD-7
Glozier et al. ¹⁹	2019	Australia	87 (0)	dCBTi: 58.6 (6.3) Online PE: 58.1 (6.1)	2 parallel arms (dCBTi, Online PE)	SRT, SC, SHE, CR, RP	6	12 weeks	ISI	CES-D	STPI
Kalmbach et al. ⁴⁰	2020	United States	91 (100)	dCBTi: 28.91 (28.91) digital sleep education: 29.16 (4.11)	2 parallel arms (dCBTi, digital sleep education)	SRT, SC, CR, PI, RE, SHE	6	7 weeks	ISI, PSQI	EPDS	-
Krieger et al. ⁴¹	2019	Switzerland	104 (68.3)	dCBTi: 42.17 (12.4) SRT: 46.59 (17.52) TAU: 45.24 (12.40)	3 parallel arms (MCT+ TAU, SRT + TAU, TAU)	PE, SRT, RE, CR, SHE, RP	8	8 weeks	ISI, PSQI, SE	ADS-K	-
Kyle et al. ⁴²	2020	United Kingdom	410 (86.6)	dCBTi: 52.5 (11.2) WL: 52.4 (11.7)	2 parallel arms (dCBTi, WL)	SRT, SC, CR, SHE, RE	6	10 weeks	ISI, PSQI	PHQ-9	GAD-2

- Summary of the characteristics of the included studies.

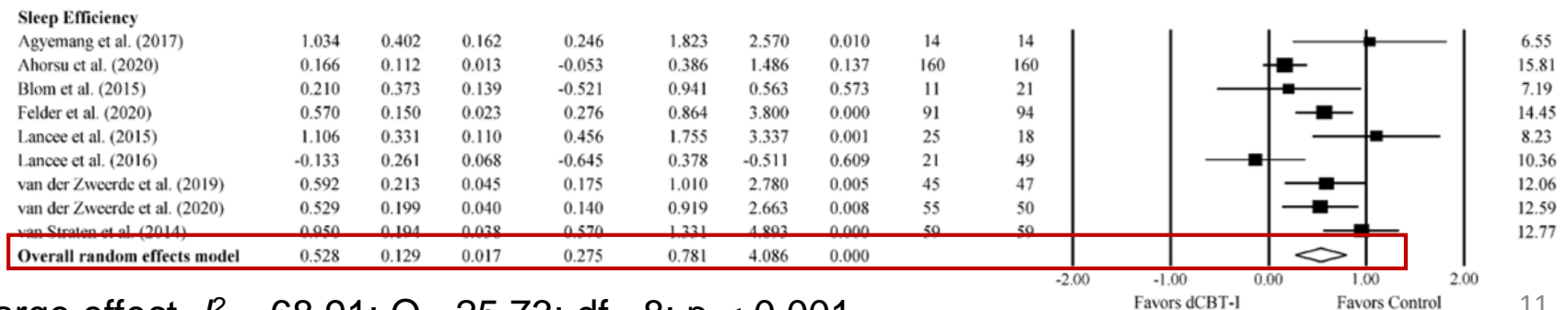
Author	Year	Country	Total sample size (%Female)	Mean age, years (SD)	Study design	dCBTi components	No. of sessions	Time point of post-assessment	Insomnia outcome measurement	Depression outcome measurement	Anxiety outcome measurement
Lancee et al. ⁴³	2015	Netherlands	63 (79.4)	dCBTi: 47.47 (14.37) WL: 49.98 (13.71)	2 parallel arms (dCBTi, WL)	PE, RE, SRT, SHE, CR	6	12 weeks	ISI, TST, SE, WASO, SOL	CES-D	HADS
Lancee et al. ⁴⁴	2016	Netherlands	90 (81.1)	dCBTi: 41.2 (14.1) fif: 38.5 (13.1) WL: 45.1 (13.7)	3 parallel arms (dCBTi, fif, WL)	PE, RE, SHE, SRT, CR	6	12 weeks	ISI, TST, SE	CES-D	HADS
Lorenz et al. ⁴⁵	2018	Switzerland	56 (69.6)	dCBTi: 41.72 (17.31) WL: 44.04 (20.05)	2 parallel arms (dCBTi, WL)	PE, SRT, SC, RE, SHE, RP, CR	6	6 weeks	ISI, TST, SE, WASO, SOL	BDI-II	BSI-Anxiety
Majd et al. ⁴⁶	2020	Iran	312 (55.8)	dCBTi: 36.21 (5.81) Sleep education: 35.29 (5.76)	2 parallel arms (dCBTi, sleep education)	SHE, SC, RE, CR, SRT, PI	6	10 weeks	ISI	HADS	HADS
Pillai et al. ⁴⁷	2015	United States	21 (62.5)	dCBTi: 53.2 (12.2) Sleep education: 44.0 (13.2)	2 parallel arms (dCBTi, sleep education)	SRT, SC, CR, PI, RE, SHE	6	7 weeks	ISI, TST, SOL	-	BAI
Sveen et al. ⁴⁸	2021	Sweden	21 (66.7)	dCBTi: 49.9 (5.8) Sleep education: 45.6 (5.5)	2 parallel arms (dCBTi, sleep education)	SRT, SC, ST, CR, SHE	8	9 weeks	ISI	MADRS	GAD-7
van der Zweerde et al. ⁴⁹	2019	Netherlands	104 (81.7)	dCBTi: 44.64 (13.12) SM: 46.29 (15.07)	2 parallel arms (dCBTi, SM)	SHE, SR, SC, RE, CR, RP	5	9 weeks	ISI, TST, SE, WASO, SOL	PHQ-9	HADS
van der Zweerde et al. ⁵⁰	2020	Netherlands	134 (64.9)	dCBTi: 51.7 (15.77) TAU: 49.4 (16.01)	2 parallel arms (dCBTi, TAU)	SHE, SRT, SC, CR, RP, RE	5	8 weeks	ISI, TST, SE, SOL, WASO	HADS	HADS
van Straten et al. ⁵¹	2014	Netherlands	118 (70.3)	dCBTi: 48.7 (13.8) WL: 50.1 (11.9)	2 parallel arms (dCBTi, WL)	PE, SHE, SRT, SC, RE, CR	6	6 weeks	PSQI, TST, SOL, SE	CES-D	HADS

- Total 10,486 participants
 - 5,494 were randomized to the dCBT-I group
 - median study size of 111 participants (range 21-3755)
- The overall mean age
 - dCBT-I group: 43.8 ± 8.7 years
 - Control group: 43.6 ± 8.3 years
- The average completion rate of dCBT-I sessions: 59.7%
- The overall risk of bias was low for 8 studies, moderate for 10, and high for the remaining 4 studies
 - Studies utilizing self-rating questionnaires as primary outcomes and blinding of participants and research personnel

- The effect of dCBT-I on sleep outcome and sleep efficiency

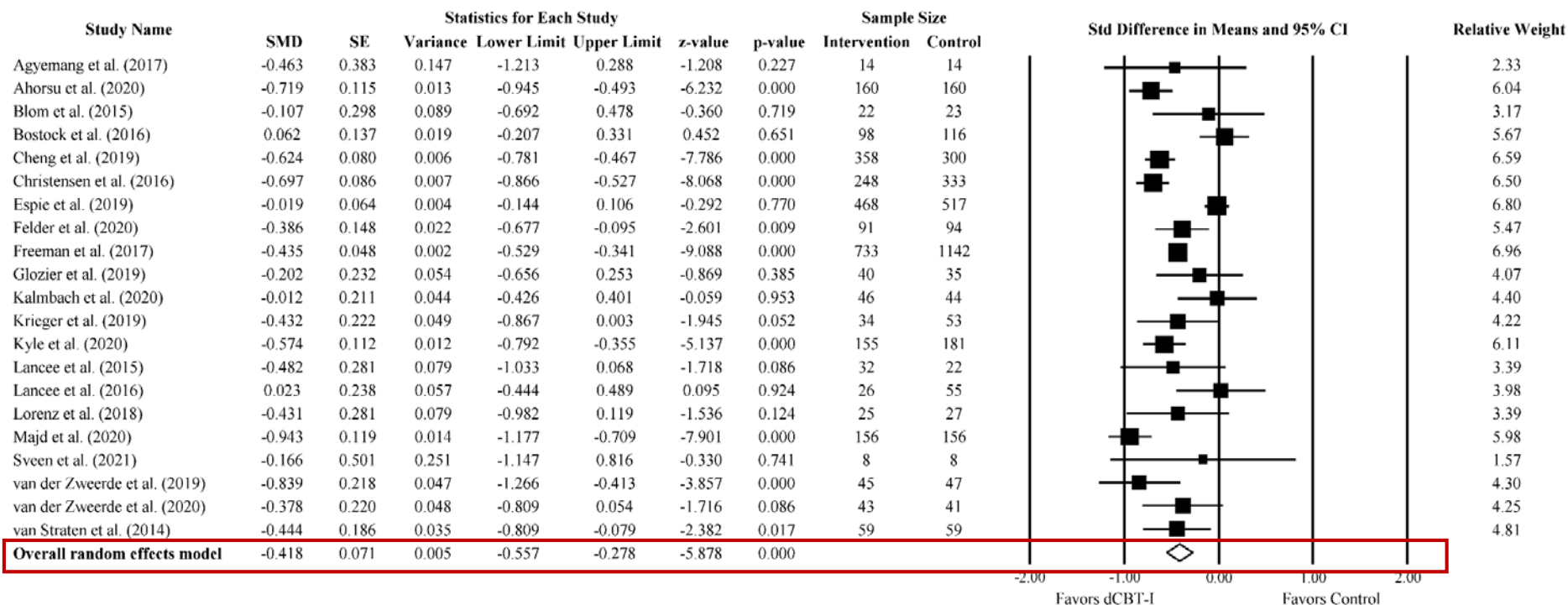


Large effect, $I^2 = 90.59$; $Q = 223.04$; $df = 21$; $p < 0.001$



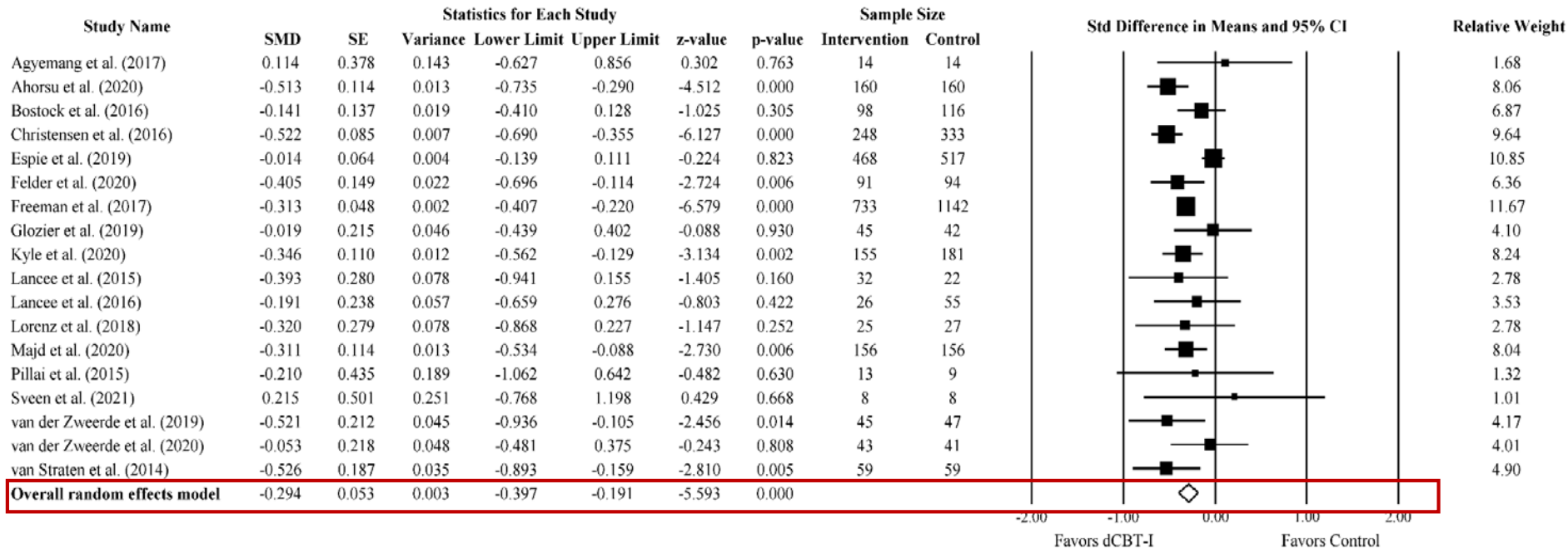
Large effect, $I^2 = 68.91$; $Q = 25.73$; $df = 8$; $p < 0.001$

- The effect of dCBT-I on depression



- $I^2 = 81.79$; $Q = 109.85$; $df = 20$; $p < 0.001$

- The effect of dCBT-I on anxiety



- $I^2 = 57.75$; $Q = 40.24$; $df = 17$; $p < 0.001$

- Subgroup analysis- The effect of dCBT-I among dCBT-I completers (>65%)**

Study Name	SMD	SE	Statistics for Each Study				z-value	p-value	Sample Size		Std Difference in Means and 95% CI	Relative Weight
			Variance	Lower Limit	Upper Limit	Intervention			Control			
Depression												
Agyemang et al. (2017)	-0.463	0.383	0.147	-1.213	0.288	-1.208	0.227	14	14			2.93
Cheng et al. (2019)	-0.624	0.080	0.006	-0.781	-0.467	-7.786	0.000	358	300			66.81
van der Zweerde et al. (2019)	-0.839	0.218	0.047	-1.266	-0.413	-3.857	0.000	45	47			9.07
van der Zweerde et al. (2020)	-0.378	0.220	0.048	-0.809	0.054	-1.716	0.086	43	41			8.85
van Straten et al. (2014)	-0.444	0.186	0.035	-0.809	-0.079	-2.382	0.017	59	59			12.35
Overall random effects model	-0.595	0.066	0.004	-0.723	-0.466	-9.079	0.000					
Anxiety												
Agyemang et al. (2017)	0.114	0.378	0.143	-0.627	0.856	0.302	0.763	14	14			12.51
van der Zweerde et al. (2019)	-0.521	0.212	0.045	-0.936	-0.105	-2.456	0.014	45	47			28.12
van der Zweerde et al. (2020)	-0.053	0.218	0.048	-0.481	0.375	-0.243	0.808	43	41			27.19
van Straten et al. (2014)	-0.526	0.187	0.035	-0.893	-0.159	-2.810	0.005	59	59			32.17
Overall random effects model	-0.316	0.149	0.022	-0.607	-0.024	-2.124	0.034					
Sleep Outcome												
Agyemang et al. (2017)	-1.340	0.418	0.175	-2.159	-0.520	-3.203	0.001	14	14			4.15
Cheng et al. (2019)	-1.021	0.083	0.007	-1.184	-0.858	-12.271	0.000	358	300			55.28
van der Zweerde et al. (2019)	-1.533	0.237	0.056	-1.998	-1.068	-6.463	0.000	45	47			11.95
van der Zweerde et al. (2020)	-1.181	0.237	0.056	-1.644	-0.717	-4.991	0.000	43	41			12.02
van Straten et al. (2014)	-1.059	0.197	0.039	-1.444	-0.673	-5.385	0.000	59	59			16.60
Overall random effects model	-1.121	0.087	0.008	-1.291	-0.951	-12.917	0.000					

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Favors dCBT-IFavors Control

- For the **non-adherent group**, the treatment effects were also significant but effect sizes were smaller than those in adherent groups for **depression** (SMD = **-0.35**; 95% CI: -0.57, -0.14; $p = 0.001$; $I^2 = 88.71$; $k = 7$), **anxiety** (SMD = **-0.28**; 95% CI: -0.45, -0.11; $p = 0.001$; $I^2 = 82.34$; $k = 6$), and **sleep outcomes** (SMD = **-0.69**; 95% CI: -1.05, -0.34; $p < 0.001$; $I^2 = 95.82$; $k = 7$).

- **Effects of fully automated dCBT-I**

- Additional subgroup analysis on 15 studies using **fully automated version of dCBT-I without support of human therapists**
- The treatment effects were significant for depression (SMD = -0.43; 95% CI: -0.60, -0.27; $p < 0.001$; $I^2 = 87.15$; $k = 14$), anxiety (SMD = -0.29; 95% CI: -0.41, -0.17; $p = 0.001$; $I^2 = 68.46$; $k = 12$), and sleep outcomes (SMD = -0.81; 95% CI: -1.03, -0.59; $p < 0.001$; $I^2 = 92.13$; $k = 15$).

- **Publication bias**

- Visual inspection of funnel plots and Egger's tests for asymmetry in funnel plots were used to estimate publication bias.
- The Egger's tests were not significant for depression ($t = 0.03$, $df = 19$, $p = 0.98$), anxiety ($t = 0.02$, $df = 16$, $p = 0.98$), and insomnia ($t = 0.63$, $df = 20$, $p = 0.54$), indicating no significant publication bias.

- dCBT-I yielded significant effects at post-treatment on alleviating depressive and anxiety symptoms as well as insomnia symptoms and sleep diary outcomes (SE, TST, SOL, WASO).
- Extending the finding of previous meta-analysis (Ye et al., 2016)
 - Larger sample size (10 → 22 RCTs)
 - Demonstrating effectiveness of fully automated dCBT-I and treatment adherence on improving depression and anxiety
- A study of a fully automated dCBT-I integrated into an existing UK-based clinical service showed effectiveness in alleviating depression, anxiety, and insomnia (Luik et al., 2017).
 - Lack of published studies on the fully automated dCBT-I implementations in real-world environments

- In this study, the pooled effects of dCBT-I on depressive and anxiety symptoms is small to moderate, which are possibly due to heterogeneity.
 - the diversity of participants recruited, outcome measures, the delivery format of CBT-I, and baseline severity levels of depression and anxiety
- The majority of the studies had subclinical depression and anxiety samples, suggesting that dCBT-I interventions are **beneficial in reducing subclinical depression and anxiety symptoms.**
- This study showed the **importance of treatment adherence** and implications on increasing the treatment efficacy.
 - Investigating factors for improving adherence using digital therapeutics is warranted.

- Twelve out of 22 studies had a small sample size of <50.
- Long-term outcomes were difficult to evaluate between studies.
- The baseline severity of depression and anxiety of the participants were not considered.
- The majority of the included studies compared the dCBT-I group with the waitlist, treatment as usual, and psychoeducation, not face-to-face individual CBT-I.

- dCBT-I is effective for patients with depressive and anxiety symptoms, as well as insomnia.
- Future studies are needed to
 - provide the sufficient clinical evidence of effectiveness in the fully automated version in comparison to the traditional methods of face-to-face CBT-I
 - improve our understanding of optimizing adherence using digital tools, regarding the adherence is a potential predictor of treatment effectiveness



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THANK YOU

