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Research paper

Does treating insomnia with digital cognitive behavioural therapy (*Sleepio*) mediate improvements in anxiety for those with insomnia and comorbid anxiety? An analysis using individual participant data from two large randomised controlled trials

Alasdair L. Henry [a,b,*], Christopher B. Miller [a,b], Richard Emsley [c], Bryony Sheaves [d,e], Daniel Freeman [d], Annemarie I. Luik [f,g], Colin A. Espie [a,b]

[a] Big Health Ltd., London, UK/San Francisco, USA
[b] Sir Jules Thorn Sleep and Circadian Neuroscience Institute, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK
[c] Department of Biostatistics and Health Informatics, King's College London, Institute of Psychiatry, Psychology and Neuroscience, London, UK
[d] Department of Psychiatry, University of Oxford, Oxford, UK
[e] Oxford Health NHS Foundation Trust, Oxford, UK
[f] Department of Epidemiology, Erasmus MC University Medical Centre, Rotterdam, Netherlands
[g] Trimbos Institute, The Netherlands Institute of Mental Health and Addiction, Utrecht, Netherlands

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ABSTRACT

Background: Considerable comorbidity exists between insomnia and anxiety, and evidence shows that the benefits of CBT for insomnia extend to anxiety. Using data from two large trials of digital CBT (dCBT) for insomnia, we evaluated whether improving sleep is an effective treatment target to reduce both insomnia and anxiety symptoms in individuals with insomnia and clinically significant anxiety.

Methods: This was a controlled sub-analysis combining individual participant data from two previous randomised controlled trials of dCBT for insomnia (*Sleepio*). Participants (N = 2172) with insomnia disorder and clinically significant anxiety symptoms were included in this sub-analysis and received either dCBT or control (usual care or sleep hygiene education). Assessments were evaluated at baseline, post-intervention (week 8 or 10), and follow-up (week 22 or 24). Mediation was evaluated using structural equation models.

Results: dCBT for insomnia was superior to control at reducing both insomnia (Hedges' *g* range = 0.77–0.81; both $p < 0.001$) and anxiety symptoms (Hedges' *g* range = 0.39–0.44; both $p < 0.001$) at all time points. Baseline insomnia symptoms moderated the effects of dCBT on insomnia, however no variables moderated treatment effects on anxiety. Reductions in anxiety symptoms at follow-up were mediated by improvements in sleep at post-intervention (% mediated = 84 %), suggesting a causal pathway.

Limitations: Participants did not have a formal anxiety disorder diagnosis and so the effects of dCBT for insomnia on anxiety may differ by anxiety disorder.

Conclusions: Addressing sleep using dCBT for insomnia may serve as a treatment target from which to improve anxiety in individuals with insomnia and clinically significant comorbid anxiety.

Clinical trial registrations: Digital Insomnia therapy to Assist your Life as well as your Sleep (DIALS) - ISRCTN60530898 http://www.isrctn.com/ISRCTN60530898.

Oxford Access for Students Improving Sleep (OASIS) - ISRCTN61272251 http://www.isrctn.com/ISRCTN61272251.

1. Introduction

Significant overlap exists between sleep disturbance and mental health (Bragantini et al., 2019). Indeed, sleep disturbance is frequently experienced by patients presenting with common mental health disorders and features as a diagnostic criterion for both Major Depressive

* Corresponding author at: Big Health Ltd., London, UK
E-mail address: alasdair.henry@bighealth.com (A.L. Henry).

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Disorder and Generalised Anxiety Disorder (GAD; American Psychiatric Association, 2013). Insomnia has historically, and indeed falsely, been viewed simply as a corollary of these mental health conditions, and therefore was suggested to not warrant targeted treatment (Freeman et al., 2020). Although evidence shows that anxiety and depression predict insomnia onset (Jansson-Fröjmark and Lindblom, 2008), epidemiological data also indicate that insomnia is a risk factor for the development of both anxiety (OR: 3.23; Hertenstein et al., 2019; OR: 2.30; Jansson-Fröjmark and Lindblom, 2008), and depression (OR: 2.83; Hertenstein et al., 2019; OR: 3.51; Jansson-Fröjmark and Lindblom, 2008). More generally, sleep appears to play an important role in supporting emotional health (Goldstein and Walker, 2014). These data, in tandem with the changes to insomnia disorder's diagnostic status in DSM-5 and ICSD-3, have shifted clinical and scientific attention towards the potential of insomnia as a transdiagnostic therapeutic target to improve broader mental health outcomes (Dolsen et al., 2014) or even prevent onset of future mental health disorders.

Studies of Cognitive Behavioural Therapy (CBT), the guideline recommended first-line treatment for insomnia disorder, demonstrate robust effects on symptoms of comorbid mental health disorders, including anxiety and depression, beyond treating insomnia (Belleville et al., 2011; Henry et al., 2021; Hertenstein et al., 2022). Depression has, however, received substantially greater attention than anxiety in the context of insomnia, and a growing body of literature evidences the antidepressant effect of CBT for insomnia (Blom et al., 2015; Henry et al., 2021; Manber et al., 2016; Van der Zweerde et al., 2019). This includes recent work by our group demonstrating that addressing insomnia mediates 87% of the reduction in depressive symptoms in individuals with insomnia and clinically significant depressive symptoms (Henry et al., 2021), thus furthering a clinical focus upon sleep improvement as a treatment target. Whereas the effects of CBT for insomnia on co-occurring anxiety symptoms have been examined previously (e.g., Belleville et al., 2011; Pillai et al., 2015; Ye et al., 2015), studies have predominantly evaluated CBT delivered in-person, had small samples, and few studies have included individuals with clinically significant anxiety symptoms or an anxiety disorder diagnosis (Mirchandaney et al., 2022). A recent single arm trial, however, showed that CBT for insomnia led to significant improvements in insomnia and anxiety with large within-group effect sizes (Jansson-Fröjmark and Jacobson, 2021) in participants with insomnia disorder and comorbid GAD. This study, like previous research (Belleville et al., 2016), comprised a small sample size and did not have a control group. Building on this, and research by Blom et al. (2017) in depression, a recent randomised controlled trial (RCT) compared therapist-guided digital CBT (dCBT) for insomnia against therapist-guided dCBT for anxiety in individuals with insomnia disorder and clinically significant anxiety symptoms (Mason et al., 2023). Consistent with Blom et al.'s work in depression, dCBT for insomnia was more effective at improving insomnia and equally effective at reducing anxiety symptoms as dCBT for anxiety. Despite these promising findings, research to date has not evaluated the effect of fully-automated dCBT for insomnia in a comorbid population and trials have not been powered to evaluate the mediating role of sleep improvement due to relatively small sample sizes (Mirchandaney et al., 2022).

As demonstrated previously (Henry et al., 2021), recent large RCTs of dCBT are a prudent source to evaluate the effects of dCBT for insomnia on broader mental health outcomes in a treatment format that can provide greater fidelity than therapist-delivered CBT. Fully-automated dCBT has the additional benefit of being able to provide access to evidence-based insomnia treatment at scale. Using data from two large effectiveness trials (Espie et al., 2019; Freeman et al., 2017), we evaluated whether reductions in insomnia symptoms mediate reductions in anxiety symptoms in individuals with insomnia and clinically significant anxiety symptoms. We also evaluated the effects of dCBT for insomnia on anxiety and insomnia symptoms, and explored potential moderators of treatment effects.

2. Materials and methods

2.1. Participants

The data used in this sub-analysis comes from two previously published effectiveness RCTs of dCBT for insomnia (*Sleepio*). Both trials received ethical approval (ref: MS-IDREC-C2-2015-024 (Espie et al., 2019); ref MS-IDREC-C2-2014-034 (Freeman et al., 2017)) and were registered (ISRCTN60530898, ISRCTN61272251). See Espie et al. (2019) and Freeman et al. (2017) for more detailed descriptions of the study methods. In each trial, participants with probable insomnia, indicated by a score ≤ 16 on the Sleep Condition Indicator (SCI-8; Espie et al., 2014), were randomised to receive either dCBT for insomnia (Sleepio) or to usual care (Freeman et al., 2017) or sleep hygiene education (Espie et al., 2019) control. In Espie et al. (2019), the post-intervention assessment occurred 8 weeks following randomisation, and follow-up 24 weeks from randomisation. The corresponding time-points for Freeman et al. (2017) were 10 weeks and 22 weeks, respectively. For the purpose of this sub-analysis, only those who experienced clinically significant anxiety symptoms, defined by a Generalised Anxiety Disorder scale (GAD-7; Spitzer et al., 2006) score ≥ 10 at baseline were included.

2.2. Statistical analysis

Baseline values and demographics are presented using summary statistics stratified by group (i.e., dCBT and control). Insomnia symptoms were assessed using the SCI-8 (Espie et al., 2014), and the GAD-7 (Spitzer et al., 2006) was used to assess anxiety symptoms. Because the original trials were not stratified for anxiety caseness, hypothesis testing was conducted to assess for balance using *t*-tests or chi-squared tests. First, we evaluated whether dCBT led to significant improvements in insomnia and anxiety symptoms using generalised linear models with maximum likelihood estimation. Treatment, trial, baseline symptoms and an interaction between baseline symptoms and trial were included as fixed effects, and between-group effect sizes were computed using Hedges' *g*. Exploratory analyses then evaluated whether age, gender (male/female/other) or baseline SCI-8 and GAD-7 scores moderated the effect of dCBT on insomnia and anxiety symptoms by adding interactions to the linear models assessing continuous change in insomnia and anxiety symptoms. The likelihood of remission and reliable remission in anxiety symptoms at both post-intervention and follow-up were evaluated using logistic regression models. Linear structural equation models were computed to evaluate our primary objective, which was to assess the extent to which sleep improvement on the SCI-8 at post-intervention (weeks 8 and 10) causally mediated reductions in anxiety symptoms measured by the GAD-7 at follow-up (weeks 22 and 24; Dunn et al., 2015). All analyses were conducted in Stata version 17.

3. Results

Of the 5466 participants who met criteria for probable insomnia disorder included in the original RCTs, 2172 (40%) met caseness for clinically significant anxiety symptoms on the GAD-7 at baseline and were included in this sub-analysis (see Table 1 for descriptive characteristics at baseline for the included sample). Baseline SCI-8, GAD-7 and PHQ-9 scores were not significantly different between groups.

Compared with control, dCBT led to significant improvements in sleep with a large between-group effect at post-intervention (Weeks 8 and 10: $g = 0.81$), which was slightly attenuated at follow-up (Weeks 22 and 24: $g = 0.77$). Significant reductions were similarly observed in anxiety symptoms measured by GAD-7 at post-intervention with a small-to-moderate between-group effect (Weeks 8 and 10: $g = 0.44$). This difference was largely maintained at follow-up, albeit slightly attenuated (Weeks 22 and 24: $g = 0.39$). See Fig. 1 and Table 2. With respect to

Table 1
Descriptive characteristics of the sample at baseline.

Characteristic	Control n = 1036	dCBT n = 1136	Test statistic; p-value
Age, mean (SD), range (yrs)	29.1 (12.3), 18–74	29.1 (12.7), 18–81	t = 0.07; 0.944
Sex, No. (%)			Chi-square (2) = 0.0265; 0.987
Male	225 (22 %)	250 (22 %)	
Female	800 (77 %)	874 (77 %)	
Did not specify or not reported	11 (1 %)	12 (1 %)	
SCI-8, mean (SD)	7.76 (4.10)	7.88 (4.13)	t = 0.67; 0.492
GAD-7, mean (SD)	14.35 (3.29)	14.25 (3.19)	t = 0.70; 0.482
PHQ-9, mean (SD)	15.80 (5.25)	15.55 (5.13)	t = 1.11, 0.269

dCBT = digital CBT; GAD-7 = Generalised Anxiety Disorder Scale; SCI-8 = Sleep Condition Indicator; PHQ-9 = 9-item Patient Health Questionnaire; SD = Standard deviation.

moderation, only baseline SCI-8 score significantly moderated treatment effects, such that those with more severe insomnia at baseline experienced significantly greater improvements in sleep at both post-intervention and follow-up. No variables moderated the effect of dCBT on anxiety symptoms (See Table S1 for moderation results).

At post-intervention (weeks 8 and 10), participants in the dCBT group were 2.2 times more likely to reach remission (GAD-7 < 10; OR = 2.24 (0.30); <0.001 (1.72, 2.91)) and reliable remission (GAD-7 < 10 and a reduction of ≥5; OR = 2.24 (0.30); <0.001 (1.73, 2.89)) of their anxiety compared to the control group. These results were maintained at follow-up (weeks 22 and 24; Table 3).

The results of the mediation analyses are presented in Table 4. Improvements in sleep at post-intervention (weeks 8 and 10) mediated 84% of the effect of dCBT on anxiety symptoms at follow-up (weeks 22 and 24; $p < 0.001$). See Fig. 2 for a path diagram of the mediation analysis.

4. Discussion

Here, we show that improvements in sleep resulting from fully-automated dCBT for insomnia (*Sleepio*) mediate improvements in symptoms of anxiety in those with insomnia comorbid with anxiety. Results expand upon previous findings (e.g., Henry et al., 2021; Jansson-Fröjmark and Jacobson, 2021; Mason et al., 2023), and show that, in those with insomnia and clinically significant anxiety symptoms, the effects of fully-automated dCBT for insomnia extend to reducing anxiety symptoms. Importantly, reductions in insomnia symptoms resulting from dCBT mediate reductions in anxiety, as predicted temporally, suggesting a causal relationship. This furthers the idea that addressing sleep may serve as a transdiagnostic treatment target to improve mental health outcomes in those with insomnia and co-presenting anxiety and, as previously demonstrated, in those with comorbid clinically significant depressive symptoms (Henry et al., 2021). The effect sizes observed for anxiety symptoms here are comparable to those observed for depressive symptoms in those with insomnia and clinically significant depressive symptoms (Henry et al., 2021). Our approach using individual participant data from two RCTs with mediation analysis using sequential timepoints helps us understand whether treating insomnia first is useful for anxiety. Together, these results and those of others (Blom et al., 2017; Mason et al., 2023) provide testable hypotheses for future prospective studies evaluating treatment sequencing in those with insomnia and comorbid mental health complaints.

The clinical value of addressing anxiety in the context of insomnia with dCBT is underscored by the doubled odds of anxiety remission

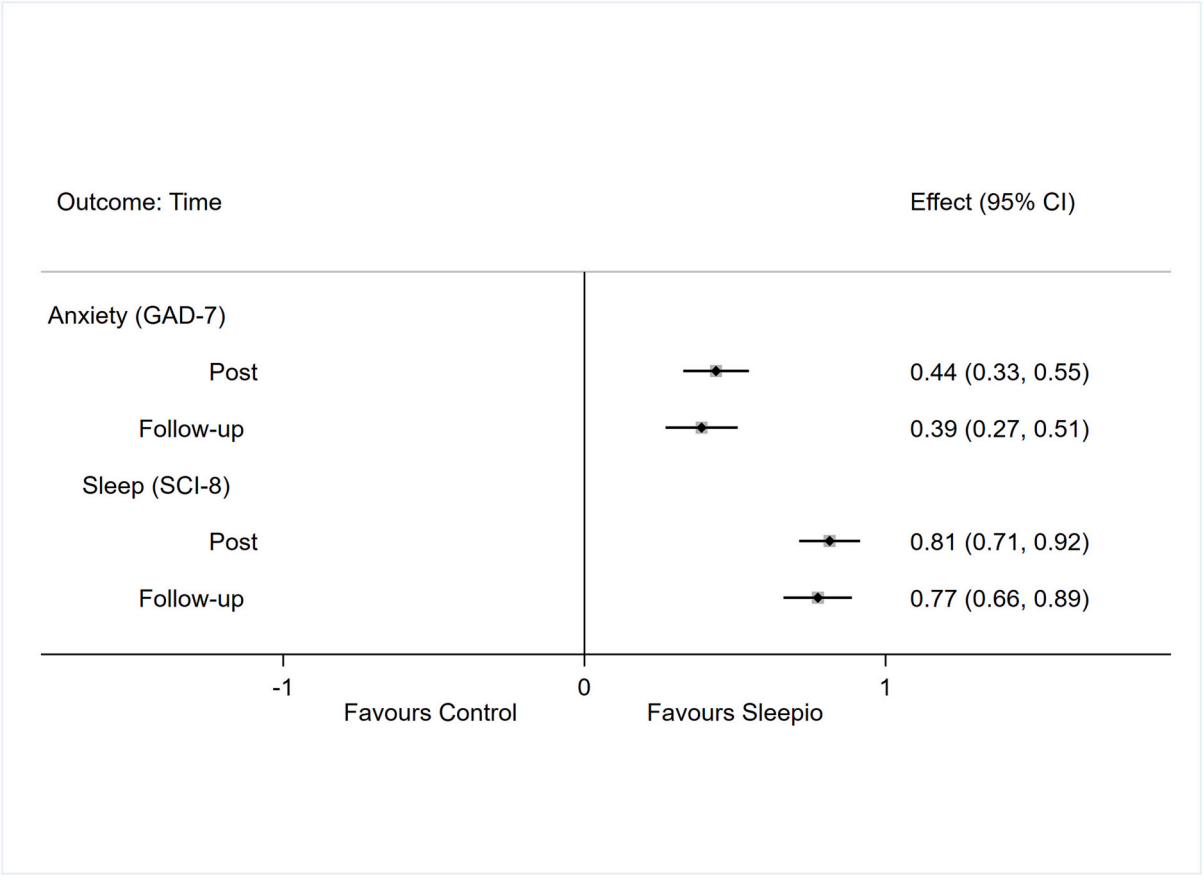

Fig. 1. Forest plot showing the between-group effect sizes (g) for anxiety symptoms (GAD-7) and insomnia symptoms (SCI-8) at post-intervention and follow-up.

Table 2
Effects of dCBT versus control (usual care and Sleep Hygiene Education) on insomnia symptoms (SCI-8) and anxiety symptoms (GAD-7).

Assessment	Unadjusted mean (SD); *n*		Adjusted difference (95 % CI)	Hedges' g	*p* Value
	Control (n = 1036)	dCBT (n = 1136)			
GAD-7					
Baseline	14.35 (3.29)	14.25 (3.19)			
Post-intervention (Weeks 8 and 10)	11.63 (5.63); 625	8.84 (5.54); 439	−2.51 (−3.14, −1.89)	0.44	<0.001
Follow-up (Weeks 22 and 24)	10.65 (5.88); 534	8.24 (5.42); 353	−2.27 (−2.97, −1.56)	0.39	<0.001
SCI-8[a]					
Baseline	7.76 (4.10)	7.88 (4.13)			
Post-intervention (Weeks 8 and 10)	11.28 (6.18); 629	16.93 (6.51); 444	5.62 (4.92, 6.32)	0.81	<0.001
Follow-up (Weeks 22 and 24)	12.27 (6.83); 535	18.16 (7.29); 357	5.88 (5.01, 6.74)	0.77	<0.001

[a] Higher score indicates better sleep / fewer insomnia symptoms
CI = Confidence Interval; GAD-7 = Generalised Anxiety Disorder Scale; SCI-8 = Sleep Condition Indicator; SD = Standard deviation.

Table 3
Effects of dCBT vs. control on binary outcomes for GAD-7.

Assessment	No. (% of group)		OR (SE); *p*-value (95 % CI)
	Control	dCBT	
Post-intervention remission - Yes	240 (38)	256 (58)	2.24 (0.30); <0.001 (1.72, 2.91)
No	385 (62)	183 (42)	
Post-intervention reliable remission - Yes	187 (30)	217 (49)	2.24 (0.30); <0.001 (1.73, 2.89)
No	438 (70)	222 (51)	
Follow-up remission - Yes	240 (45)	219 (62)	2.11 (0.32); <0.001 (1.57, 2.84)
No	294 (55)	134 (38)	
Follow-up reliable remission - Yes	190 (36)	186 (53)	2.03 (0.29); <0.001 (1.54, 2.68)
No	344 (64)	167 (47)	

CI = Confidence Interval; dCBT = digital CBT; GAD-7 = Generalised Anxiety Disorder Scale; OR = Odds Ratio; SCI-8 = Sleep Condition Indicator; SE = Standard Error.

following treatment with dCBT relative to control. Small-to-medium between-group effects were observed for anxiety outcomes at post-intervention and follow-up, which is consistent with previous meta-analyses of both therapist-delivered (Belleville et al., 2011), and dCBT for insomnia broadly (Ye et al., 2015). Importantly, neither demographic characteristics (age and gender), *nor* baseline anxiety or insomnia severity moderated the effects of dCBT (*Sleepio*) on anxiety symptoms, thereby supporting the generalisability of treatment effects across groups. It should be noted, however, that the effect sizes for insomnia symptoms reported in this paper are smaller than found in the original RCT publications (d = 1.51: Espie et al., 2019; d = 1.11: Freeman et al., 2017). It is plausible, therefore, that clinically significant anxiety symptoms attenuate the effects of dCBT on sleep outcomes. This would need to be evaluated in a full sample of patients with insomnia and in those with clinical and subclinical to no symptoms of anxiety (i.e., not in a limited subsample of those with anxiety and insomnia). Nevertheless, this hypothesis is supported by Jansson-Fröjmark and Jacobson (2021) who found lower insomnia remission rates in participants with insomnia and comorbid GAD than in studies evaluating the same CBT protocol in individuals who did not have comorbid GAD.

Although we were unable to evaluate specific mechanisms underlying the causal pathway between sleep improvement and subsequent reductions in anxiety, improvements in both cognitive and behavioural processes such as insomnia-related worry, dysfunctional beliefs about sleep, sleep-related threat monitoring and safety behaviours and time in bed may explain the broader benefits to both sleep and anxiety (Jansson-Fröjmark and Jacobson, 2021). Indeed, the techniques comprising CBT for insomnia may readily translate to anxiety symptoms given that worry features as a common symptom across both disorders (Dolsen et al., 2014). Effects on other putative transdiagnostic factors including arousal, mental events and stimulus control may also be critical components underlying the benefits to both anxiety and sleep. Real world evidence has shown that treatment of anxiety and depression through Improving Access to Psychological Therapies (IAPT) can be augmented by improving sleep with dCBT for insomnia. Stott et al. (2021) showed higher remission rates for anxiety and depression and a lower need for high-intensity intervention in NHS IAPT settings with *Sleepio* compared to those who did not receive *Sleepio*. A further clinical consideration is whether dCBT for insomnia may prevent or reduce the risk of developing future anxiety disorders. Relatedly, given the frequent comorbidity between insomnia, anxiety and depression (e.g., Bard et al., 2023), the effects of dCBT for insomnia should next be evaluated in those with both clinically significant depression and anxiety alongside insomnia to evaluate whether sleep remains an appropriate treatment target in this clinical presentation.

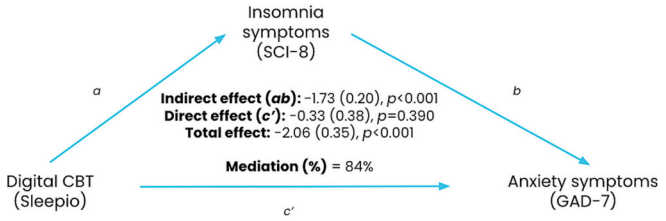

Fig. 2. Path diagram displaying the mediating role of sleep improvement on anxiety symptoms.

Table 4
Mediating effect of sleep improvement at post-intervention on anxiety symptom reduction at follow-up.

		Total effect		Direct effect		Indirect effect		Mediation (%)
Assessment	Mediator	Effect (SE)	*p* value	Effect (SE)	*p* value	Effect (SE)	*p* value	
GAD-7								
Follow-up (weeks 22 and 24)	SCI-8 (weeks 8 and 10)	−2.06 (0.35)	<0.001	−0.33 (0.38)	0.390	−1.73 (0.20)	<0.001	84%

GAD-7 = Generalised Anxiety Disorder Scale; SCI-8 = Sleep Condition Indicator; SE = Standard Error.

5. Limitations

In light of these findings, a number of limitations should be considered. Firstly, the subsample of participants in this analysis was not included based on having a clinical diagnosis of an anxiety disorder, nevertheless participants scored above an established symptom threshold on a validated measure. Further work should, however, be conducted in a sample with a comorbid anxiety disorder diagnosis. Secondly, whilst these findings build upon previous literature (e.g., Belleville et al., 2016; Jansson-Fröjmark and Jacobson, 2021) by using a controlled design and a large sample size, the effects of dCBT for insomnia on anxiety in a large real-world sample of patients still needs to be evaluated, including within primary care settings. Finally, as there was no formal clinical diagnosis of an anxiety disorder in this study it may be that treatment effects on anxiety vary depending on the anxiety disorder in question. Beyond clinical efficacy, additional work, building upon Stott et al. (2021) must be conducted to evaluate how best to implement such a treatment in current care pathways.

6. Conclusion

Our results show that addressing sleep through fully-automated dCBT for insomnia is an effective transdiagnostic treatment target to reduce anxiety symptoms in individuals with insomnia disorder and clinically significant anxiety symptoms. Improvements in sleep by way of reductions in insomnia symptoms associated with dCBT mediated improvements in anxiety. Given insomnia and anxiety commonly co-present, increasing accessibility to fully-automated dCBT for insomnia may therefore serve as an appropriate first-line intervention for some individuals with insomnia and comorbid anxiety.

CRediT authorship contribution statement

ALH and CAE conceived the study question. CAE, AIL, DF and BS collected data in the original trials. RE performed the statistical analysis. All authors performed statistical interpretation. ALH, CBM and CAE wrote the paper. All authors critically edited the paper. All authors agreed to submission.

Declaration of competing interest

The authors declare no Competing Non-Financial Interests but the following Competing Financial Interests. ALH is employed by Big Health Ltd. (Sleepio), receives a salary and is a shareholder. CBM, is employed by Big Health Ltd. and is salaried by the company. CAE is the Co-Founder and Chief Scientist of Big Health Ltd. and is a shareholder, and is salaried by the company. BS offered clinical consultancy to Big Health Ltd. during the course of the OASIS trial. RE is a paid consultant of Big Health Ltd. AIL held a position at the University of Oxford funded by Big Health Inc. when the DIALS trial was being conducted. The digital CBT intervention was made available to all participants at no cost. No other investigators report conflicts of interest. Both original studies were conducted at the University of Oxford, Sleep & Circadian Neuroscience Institute and Department of Psychiatry.

Data availability

The data used to create the dataset for this trial are available from the corresponding authors of the original trials upon reasonable request and subject to review and contract with the University of Oxford.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2023.06.053.

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