An explanatory randomised controlled trial testing the effects of improving sleep on mental health: an interventionist-causal model approach with mediation analysis.

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ABSTRACT

Background: Sleep difficulties may be a contributory causal factor in the occurrence of mental health problems. If this is true, improving sleep should benefit psychological health. Our primary objective was to determine whether treating insomnia leads to a reduction in paranoia and hallucinations. The effects on other mental health outcomes were also tested.

Methods: For our parallel group, single blinded, explanatory randomised controlled trial (called OASIS), we randomised university students with insomnia to digital cognitive behaviour therapy for insomnia or usual practice. Online assessments were at 0, 3, 10 (post-treatment), and 22 weeks. The primary outcomes were insomnia, paranoia, and hallucinatory experiences. The secondary outcomes included anxiety, depression, nightmares, and psychological well-being. The trial was registered (ISRCTN61272251).

Findings: 3,755 people were randomised between 5th March 2015 to 17th February 2016. Compared to usual practice, the sleep intervention at 10 weeks reduced insomnia, adjusted difference=4.78 (95% C.I. 4.29;5.26), p<.0001, d=1.11, paranoia, adjusted difference=-2.22 (95% C.I. -2.98;-1.45), p<.0001, d=0.19, and hallucinations, adjusted difference=-1.58 (95% C.I. -1.98;-1.18), p<.0001, d=0.24. Insomnia was a mediator of change in paranoia and hallucinations. There were improvements in other mental health outcomes. No adverse events were reported.

Interpretation: This is the largest randomised controlled trial of psychological intervention for a mental health problem. It provides strong evidence that insomnia is a causal factor in the occurrence of psychotic experiences and other mental health problems. Whether the results generalise beyond a student population requires testing. The treatment of disrupted sleep may require a higher priority in mental health provision.

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INTRODUCTION

Sleep problems are a common occurrence in patients with mental health disorders. The traditional view is that disrupted sleep is a symptom, consequence, or non-specific epiphenomenon of the disorders; the clinical result is that the treatment of sleep problems is given a low priority. An alternative perspective is that disturbed sleep is a contributory causal factor in the occurrence of many mental health disorders (1). An escalating cycle then emerges between the distress of the mental health symptoms, the impact on daytime functioning, and struggles in gaining restorative sleep. From this alternative perspective, the treatment of sleep problems attains a higher clinical importance. Our particular interest is in the putative causal relationship between disturbed sleep and psychotic experiences (2, 3). The interventionist-causal model approach to establishing a causal relationship is to manipulate the hypothesised mechanistic variable and observe the effect on the outcome of interest (4); if there is a causal relationship then the outcome variable should alter. The effects of the manipulation can then be substantiated further by use of mediation analysis (5, 6). In the current study, our principal aim was to improve sleep in individuals with insomnia in order to determine the effect on psychotic experiences. This approach therefore informs both theoretical understanding and clinical practice.

The most common form of sleep disruption is insomnia, comprising sustained difficulties in initiating and/or staying asleep that cause problems during the day. The association of insomnia with psychotic experiences in the general population has been convincingly established (3). There are multiple, independent, psychotic experiences. Each psychotic experience exists on a spectrum of severity in the general population with differing heritability and differing strength of association with insomnia (7). Paranoia and hallucinations have the strongest links with insomnia (2, 7, 8). However the effect of altering the level of sleep disruption, for example by targeted sleep treatment, on these psychotic experiences remains to be established. Clinical guidelines recommend the use of cognitive-behavioural therapy (CBT) as the first line treatment for insomnia (9). Digital forms of CBT for insomnia that require no therapist to be present have been shown to be efficacious as well (10, 11, 12). In patients with current delusions and hallucinations, our pilot randomised controlled trial has shown that insomnia can be substantially reduced with CBT (13), but the trial was underpowered to establish with sufficient precision the consequences for psychotic experiences. Therefore we wished to conduct a clinical trial that was large enough to test definitively the causal relationship between insomnia and self-reported psychotic experiences.

In order to test thousands of individuals, we conducted an online study using a digital CBT for insomnia treatment. A participant pool, university students, was selected that would be easily reachable (since we would have access to large email lists) and at an age when mental health

disorders emerge. We have previously shown in a student population that sleep problems are associated with elevated levels of paranoia, hallucinations, anxiety, depression, and manic symptoms (8). Our principal objective required a comparison between the effects of a reduction in insomnia (in a group receiving recommended treatment) to continued sleep disruption (in a group likely to be receiving little or no treatment). Clear change in sleep in one group relative to another was required to test the mechanistic hypothesis. We were disinterested here in the intervention elements that may lead to change. The primary trial hypotheses were that: CBT for insomnia, compared to a usual practice control group, will reduce insomnia by the end of treatment; CBT for insomnia, compared to a usual practice control group, will reduce paranoia and hallucinations by the end of treatment; and that changes in insomnia will mediate the changes in psychotic experiences. We also took the opportunity to determine the potential effects of sleep improvement on a wider range of mental health outcomes in this general population group. Our secondary hypotheses were that digital CBT for insomnia, compared to usual practice, will: reduce levels of depression, anxiety, nightmares, and mania; improve psychological well-being; and lead to the occurrence of fewer mental health disorders.

METHODS

The OASIS (Oxford Access to Sleep Intervention for Students) trial protocol has been published (14). The trial was registered at Current Controlled Trials ISRCTN61272251 (http://www.isrctn.com/ISRCTN61272251).

Design

The study was a parallel-group, superiority, explanatory randomised controlled trial of digital CBT versus treatment as usual (usual practice). Screening, informed consent, assessments, allocation to condition, and the delivery of the intervention were carried out online using an automated system, a specially configured instance of ‘True Colours’, an automated system for the scheduled collection of outcome measures (15). Participants in the control group were given access to the sleep intervention after their final assessment. The study received overall ethical approval from the University of Oxford Medical Sciences Inter-Divisional Ethics Committee and then local approvals at the other participating universities..

Participants

The inclusion criteria were: attending university; a positive screen for insomnia, as indicated by a score of 16 or lower on the Sleep Condition Indicator (16); and aged 18 years or older. There were no exclusion criteria. 26 UK universities took part, ensuring a range in geographical locations and academic ability. The principal method of recruitment was the sending within universities of a circular email that contained a link to the web-based screening. At the universities where a circular email was not possible, recruitment was via advertising on websites and/or displaying posters. Recruitment began on the 5th March 2015 and ended on the 17th February 2016. Final data were collected on the 28th July 2016. Figure 1 shows the flow of participants.

Figure 1 about here

Randomisation and masking

As recommended for large clinical trials (17), simple randomisation was used, with an allocation ratio of 1:1. Randomisation was carried out by the automated online system, ensuring that the research team was unable to influence randomisation. Participants completed all the assessments independently online and therefore their responses could not be influenced by the trial team.

Assessment points

Assessments took place at 0 (baseline), 3, 10 (end of therapy), and 22 weeks. The 3 week assessment comprised only the primary outcome measures in order to assess in the mediation analyses the temporal order of changes. Participants received an email prompt to complete the assessments online. The order of the assessments was consistent across time points. If participants did not complete the assessment then they received up to two email reminders two days apart.

Intervention

The CBT for insomnia intervention is called Sleepio (www.sleepio.com) (11, 18). It is provided in six sessions, lasting an average of 20 minutes each. Sessions are unlocked weekly, although participants can move at a slower pace. The full program is accessible via any web browser and all participants start the programme online. Certain tools (e.g. sleep diaries, relaxation audios) could also be accessed using the web browser of a smartphone. All of the sessions, sleep diaries, relaxation audios, and the scheduling tool could be accessed with an iPhone. Completion of an initial assessment drives the algorithms that personalize the program. For example, the assessment leads to a tailored choice of treatment goal, with progress then reviewed at each subsequent session. The treatment includes behavioural, cognitive, and educational components. The behavioural techniques include sleep restriction (i.e. reducing the sleep window to enhance sleep consolidation), stimulus control (e.g. getting out of bed after 15 to 20 minutes of wakefulness), and relaxation (e.g. tensing and relaxing muscles when in bed). The cognitive techniques include paradoxical intention (e.g. trying to stay awake), belief restructuring (e.g. targeting unrealistic expectations about sleep), mindfulness (e.g. acknowledging thoughts and feelings without dwelling on them), imagery (e.g. generating positive mental images), and putting the day to rest (e.g. setting time aside to reflect on the day). The educational component covers information about the processes of sleep and sleep hygiene. The programme is interactive, and content is presented by an animated therapist. Participants make a time for the session and are prompted via email/SMS if they do not 'attend'. Participants complete daily sleep diaries throughout the intervention, which are used by the programme to tailor the advice. Sleep restriction is introduced in the third session of the course. The animated therapist proposes a new sleep window, which is calculated from the sleep diary data, and engages with the participant to help them select the timing of the window (e.g. earlier versus later in the night). For those reporting significant physical or other mental health problems or moderate to severe sleepiness then a more lenient sleep window is used. The sleep window is regularly reviewed. If the sleep diary data indicate a sleep efficiency of 90% or higher, the animated therapist advises that 15 minutes is added to the sleep window. Throughout the course of therapy, participants had access to a moderated online community and an online library of information about sleep. Participants could also view their online 'case file' which included four sections: a progress review, a reminder of strategies, an agreed sleep schedule, and a list of further reading. Usual practice (treatment as usual) referred to the current care that the participants were receiving. The level of treatment input was likely to be minimal, with prescription of medication for a small proportion. We did not attempt to influence the current care that participants received.

Primary outcomes

The primary measure for insomnia was the Sleep Condition Indicator (SCI) (16). This is an eight item measure, validated against DSM-5 criteria, assessing sleep and its impact on daytime functioning over the past week. Scores can range from 0-32 with higher scores indicating better sleep. A clinical cut-off of less than 17 correctly identifies 89% of individuals with probable insomnia disorder. We used a version of the SCI that included one additional question, as a secondary outcome, regarding early morning waking. The internal consistency (Cronbach's alpha at baseline) of the scale in the current study was .63.

Paranoia was assessed with the Green et al Paranoid Thoughts Scale (GPTS), Part B (19). This scale assesses persecutory ideation, and the timeframe used was the past fortnight. The scale comprises 16 items, each rated on a 1 (not at all) to 5 (totally) scale. Higher scores indicate greater levels of paranoia. The internal consistencey of the scale in the current study was .94.

The measure for hallucinations was the Specific Psychotic Experiences Questionnaire (SPEQ) - Hallucinations sub-scale (20). The scale comprises nine items rated on a 0 (not at all) to 5 (more than once per day) scale. The timeframe was the past fortnight. Higher scores indicate greater levels of hallucinatory experiences. The internal consistency of the scale in the current study was .93

Secondary outcomes

The secondary outcome measures for sleep were the Insomnia Severity Index (21) (Cronbach's alpha in the current study = .67) and the Disturbing Dreams and Nightmare Severity Index (22) (Cronbach's alpha in the current study = .91). The secondary outcome measure for psychotic experiences was the 16 item version of the Prodromal Questionnaire (23) (Cronbach's alpha in the current study = .79). A score of 6 or more has 87% specificity and 87% sensitivity to correctly classify ultra-high risk for psychosis mental states in a help-seeking sample.

The measures to assess affective symptoms were the Patient Health Questionnaire (PHQ) 9 item version (24) (Cronbach's alpha in the current study = .85), the Generalised Anxiety Disorder (GAD) 7 item version (25) (Cronbach's alpha in the current study = .89), and the Altman Mania Scale (26) (Cronbach's alpha in the current study = .64). Psychological well-being was assessed with the Warwick Edinburgh Mental Wellbeing Scale (27) (Cronbach's alpha in the current study = .89), and the Work and Social Adjustment Scale (28) (Cronbach's alpha in the current study = .83).

To assess the development of mental health disorders, we used established cut-offs on the Prodromal Questionnaire (23), Altman Mania Scale (26), PHQ (24), and GAD-7 (25). Participants were also asked at each assessment time-point whether they were in contact with mental health services, had received a mental health diagnosis, took medication for a mental health problem, or were currently receiving any other psychological therapy.

Safety

If the trial team was informed, we recorded the occurrence of any serious adverse events in trial participants, defined as: deaths; suicide attempts; serious violent incidents; admissions to secure units; and formal complaints about the online intervention.

Analysis and sample size

An outline of the analysis strategy was provided in the published trial protocol (14) and a full statistical analysis plan was agreed before the trial analysis (see online supplement). All the analyses were validated by a second statistician. Analyses were intention to treat and were carried out at the end of the last follow-up assessments (there were no interim analyses). Each continuous outcome was analysed using a linear mixed effects regression model to account for the repeated measures over time, and binary outcomes were analysed using a logistic mixed effects model. Mixed effects models are the recommended statistical technique for analysing clinical trials when outcomes are collected at repeated time points (29), and in this trial included outcome data available on all randomised participants at 3, 10, and 22 weeks. The method has the advantage of implicitly accounting for data missing at random. The estimated (adjusted) treatment differences from these analyses are therefore reported. The linear mixed effect models included the outcome as the response variable, time point, randomised group, and baseline score as fixed effects and random effects were estimated for student within university. An interaction between time and randomised group was modelled as a fixed effect to allow estimation of treatment effect at all three time points. Gender and course level were included as covariates in the model. An unstructured variance-covariance matrix was used to model the within-subject error correlation structure. Results are presented as mean adjusted differences in scores between the randomised groups, with 95% confidence intervals (CI) and associated two-sided p-value. The normality assumption of the residuals was confirmed for each outcome. No deviations from normality were apparent and therefore maximum likelihood estimates were reported. Sensitivity analyses (pattern mixture models, inclusion of baseline covariates predictive of missing data, and imputation) were conducted for the three main outcomes, examining the

robustness of the results to different assumptions regarding missing data. Standardised effect sizes were calculated using Cohen's d, dividing the treatment effect by the shared standard deviation at baseline. Similar logistic mixed effects models were used for the secondary binary outcomes.

To test the mediation hypotheses, we determined the extent of mediation of the 3 week and 10 week insomnia scores on the 10 week paranoia and hallucination outcomes. The approach used was similar to the approach of Baron and Kenny (30, 5), but made use of linear mixed effects models at each step. The approach involved four steps and three separate model fits. In two separate linear mixed effects models, the intervention was first shown to be correlated with the outcome, and, secondly, with the mediator. Then the data were fitted to a third model with the outcome as the response and both the intervention and mediator as covariates. The parameters were extracted as per Baron and Kenny (30) to obtain the total, direct, and indirect effects, and finally the percentage mediation was determined. In all models, baseline levels of both the outcome and mediator were included as covariates. This is similar to the mediation analysis in Freeman et al (31), but made use of linear mixed effects models to account for repeated measurements, rather than through structural equation modelling.

The sample size was calculated on the basis of change in paranoia, since there should be lower change in psychotic experiences compared to insomnia. Based on the standard deviations observed from a previous study for the GPTS (SD=10.4) (32), a total sample size of 2614 (i.e. 1307 per group) would provide 90% power to detect a small effect size, a standardised mean difference of 0.15, in paranoia, whilst accounting for a high level of expected attrition (40%). In a study amendment, the sample size was increased, due to a higher than initially expected drop-out rate.

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Full details of the sample, missing data patterns, sensitivity analyses, and all other analyses are available in the online supplementary data analysis report.

The sample

The baseline characteristics of the participants are summarised in Table 1. The sample was predominately female, studying for their first university degree, and two-thirds were of White British ethnicity. One fifth of the participants were in contact with mental health services. The two randomised groups were well-matched at baseline.

During the course of the study there is a high level of drop out from the study assessments (50%), which is greater in the treatment group than in the control group, with this figure and pattern almost identical to the most comparable previous study (12). The baseline scores for the three primary outcomes (insomnia, paranoia, hallucinations) were not associated with later missingness (see Table 1 in the supplementary data analysis report). Compared with participants who remained in the study, participants who dropped out from both randomised groups were younger in age and more likely to be male. For the secondary measures, ISI, PHQ-9, AMS, and WSAS scores were slightly higher, and the WEMWBS score slightly lower, in the missing groups compared to the nonmissing groups.

Treatment uptake was also limited. In the intervention arm, 1302 (68.9%) participants logged on for at least one treatment session. 953 (50.4%) participants accessed two sessions, 672 (35.5%) participants accessed three sessions, 497 (26.3%) participants accessed four sessions, 390 (20.6%) participants accessed five sessions, and 331 (17.5%) participants accessed six sessions. Of those who started the programme, 672 (35.5%) participants accessed three or more sessions.

Table 1 about here

Primary outcomes

The outcomes for the primary measures are shown in Table 2. In comparison to the control group, the sleep treatment is associated with significant reductions, at all time points, in insomnia, paranoia, and hallucinations. After treatment the reduction in insomnia is large, while the reduction in psychotic experiences is small. After treatment, 454 (61.9%) of 733 individuals in the treatment group and 326 (28.5%) of 1142 individuals in the control group now scored outside the clinical cut-off used for trial entry. The treatment differences are robust to the three different types of sensitivity analyses for missing data that were conducted (see online data analysis report). A conservative imputation (given the general improvement in scores in both groups) of missing data was used, whereby the last available measurement for a participant was imputed for all further missing measurements of that participant. All three primary outcome differences remained significant with last observation carried forward imputations. Treatment differences also remained consistent with the primary analysis when we repeated the main analyses covarying for baseline variables which predicted missingness for each outcome. We also used pattern mixture models. Treatment differences would still be significant assuming the missing individuals in the treatment arm had outcome scores two points worse for insomnia and paranoia, and one point worse for hallucinations (predictably the hallucination scale scores are much lower than for the other two outcome variables).

The mediation analyses are summarised in Table 3. Change in sleep over three weeks explained 30% of the intervention effect on paranoia at 10 weeks, with change in sleep over 10 weeks accounting for 58% of the treatment effect on paranoia. Change in sleep over three weeks explained 21% of the intervention effect on hallucinations at 10 weeks, with change in sleep over ten weeks accounting for 39% of the intervention effect on hallucinations. Hence early changes in sleep explain approximately half of the total sleep mediated change in psychotic experiences by the end of treatment. In comparison, parallel analyses in the reverse direction indicated that changes in psychotic experiences explained a much smaller percentage of variation in improvements in sleep. Specifically, when paranoia and hallucinations outcomes at three weeks were set as the mediators and the sleep outcome at 10 weeks as the main outcome, paranoia symptoms mediated just 3.8% of change in sleep and hallucinations mediated 3.4% of change in sleep. This lends further support to the causal pathway hypothesis proposed in this study.

Tables 2 and 3 about here

Secondary outcomes

The outcomes for the secondary measures are shown in Table 4. The large improvement in insomnia is confirmed with the ISI assessment. The sleep treatment also led to moderate improvements in depression, and small improvements in anxiety, psychosis prodromal symptoms, nightmares, psychological well-being, and functioning. All these improvements were maintained over time. Those randomised to the sleep treatment were also less likely to meet criteria over the course of the trial for a depressive episode, anxiety disorder, or ultra high risk of psychosis. However there were no differences in contact with mental health services. Further, the sleep treatment led to a small, sustained increase in symptoms of mania. There was also a greater risk with the sleep treatment of meeting criteria for a manic episode.

Table 4 about here

Adverse events

No adverse events were reported to the trial team.

DISCUSSION

We wished to investigate the effects on mental health of reducing sleep difficulties. The first necessary stage was for the intervention to reduce insomnia. This was achieved. A large effect size reduction was found with the digital CBT intervention in a large student population. But it was the consequent effects on psychotic experiences that the trial was designed to establish. To our knowledge, OASIS is the largest randomised controlled trial of a psychological intervention for a mental health problem. Students randomised to the sleep intervention showed small, sustained reductions in paranoia and hallucinations. This is strong evidence that disrupted sleep has a contributory causal role in the occurrence of these psychotic experiences in a specific population of young adults. The mediation analyses supported this interpretation: improvements in sleep accounted for almost 60% of the change in paranoia post-treatment, for example. Insomnia may not be the largest cause of psychotic experiences but it is not an epiphenomenon.

Hence the study adds substantially to our understanding of the causes of psychotic experiences and indicates a promising route into the early treatment of psychotic problems.

The focus on a sleep intervention in a young adult population is important. Young people with incipient disorders may be very reluctant to seek help for psychiatric problems. Trouble sleeping is a common complaint with little stigma. Hence, it provides a much more acceptable focus for a first step in a care pathway. There were added benefits from the digital sleep treatment. Depression in particular, but also anxiety, psychological well-being, nightmares, and perceived functioning all improved. The effects on anxiety and depression are consistent with a recent meta-analysis (33). Those who received the sleep treatment in the trial were less likely to report symptoms at a level that met criteria for ultra high risk of psychosis, depression, or anxiety disorder. At baseline the level of positive screens for psychosis risk with the Prodromal Questionnaire was high, comparable to the rates found with this questionnaire for adolescents referred to treatment services (34); this high rate will reflect the well-established associations of sleep difficulties with psychotic experiences (2, 3, 7, 8) (i.e. that participants have been selected for insomnia and therefore will score higher on psychosis measures) but also the limitations of brief self-report questionnaires for assessing psychosis risk. However in the trial there was no evidence that the sleep treatment affected contact with mental health services. Most participants were not in contact with these services so a longer follow-up period may be needed to truly test such effects. Further, there was an increase in manic symptoms associated with the sleep treatment. This may be due to an actual increase in problematic manic symptoms or it may simply reflect the overall increase in psychological well-being in the sample since the questionnaire domains concern cheerfulness, self-confidence, reduced need for sleep, increase in activity levels, and talkativeness. The Altman scale has recently been found to correlate poorly with self-ratings of elation (35).

Are the study results generalizable beyond a student population? We consider that the results are very likely to apply to the wider adult population. We used a treatment developed for adults, which was not modified for students. The large treatment reduction in insomnia for the students is very similar to that found in trials with general adult populations (10, 11, 36), while previous studies with community samples have shown self-help sleep treatment to reduce anxiety and depression (36, 37). Nonetheless, only a direct comparison in a trial can definitively determine the generalisablilty of our findings. Although not the main objective of the study, the trial does indicate that the provision of internet-delivered CBT for insomnia to university students is likely to lead to large reductions overall in insomnia, and smaller reductions in a number of other mental health symptoms, with benefits for positive psychological well-being too. Tailoring of the

intervention specifically for this population could enhance engagement and outcome effects. Support to complete the intervention may well be helpful too.

The OASIS study is a well-powered, randomised controlled trial, informed by the causal inference literature, but there are a number of limitations. First, the study relied on self-report questionnaires, albeit validated in their development against clinical interviews. Similar change captured in rater assessed measures would have strengthened the confidence in the study results. Second, the sample tested were predominately in the non-clinical range of psychotic experiences, limiting the conclusions to the less severe end of the psychosis spectrum. Third, the participants were self-selecting in responding to the invitation, which will have affected the representativeness of the sample. Access to the study was via an Internet webpage, which is a simpler process than obtaining treatment from clinical services. The whole study could be completed in the privacy of the home, meaning that there were far fewer barriers to participation than conventional patient trials. Fourth, the extent to which the results will generalise to the rest of the general population is not known. Even within the student population we do not know the representativeness of the participants. Fifth, bias in the outcome results will have been introduced due to the high drop-out rate, especially in the treatment group, which is similar to comparable online studies (12). The results did remain robust against conservative assumptions in the sensitivity analyses about those who dropped out, but it is notable that treatment effects were greater for those who completed the sleep treatment. Finally, the causal argument rests on the plausible assumption that the sleep treatment first changes levels of insomnia, since that was the topic of the intervention, but the mediation analyses in this trial based on ten week outcomes cannot fully capture the temporal order of changes or rule out reverse causation. We were able to show a significant level of mediation based on the 3 week insomnia score as a mediator, while evidence for reverse causation was limited, which does follow the predicted temporal causal pathway. In reality, it is difficult in a clinical trial to capture potential temporal changes between mediator and outcomes, since improvement in paranoia and hallucinations is likely to closely parallel the improvement in sleep.

The work can be taken forward. Determining the mechanisms linking insomnia to psychotic experiences will shed further light on the causes of psychosis and potentially enable treatment improvement (3, 13). Of great clinical interest will be the evaluation of the effects of improving sleep for patients attending clinical services with ultra high risk of psychosis, or established clinical psychotic experiences, or at the early stages of relapse. Our experience is that patients with psychosis value their sleep difficulties being appropriately addressed, that this enhances

engagement with other treatments, and that better sleep can contribute to a reduction in psychotic experiences. Further, there is a challenge in mental health services regarding intervention for early, relatively non-specific presentations and proper sleep treatment may prove a sensible first response. Overall, this trial indicates to us the importance of sleep difficulties for mental health in the general population and the need for a reconsideration in clinical services of the priority given to improving sleep.

Research in context

Evidence before this study

If insomnia is a contributory cause of psychotic experiences then the key test is whether improving sleep leads to a reduction in psychotic experiences. We therefore searched for randomised controlled studies that set out to reduce insomnia and examine the effects on psychotic experiences. On the 23rd June 2017 we searched the entire archive (i.e. using no date restrictions) of PubMed (https://www.ncbi.nlm.nih.gov/pubmed) for: (Sleep OR Insomnia) AND (Delus* OR Hallucinat* OR Psychosis OR Psychotic OR Schizophren*) AND (CBT OR hypnotic OR medication) AND (Random* OR RCT). 130 papers were identified. There were only two randomised controlled trials that tested the effects of sleep treatment on psychotic experiences, with the larger of the trials being our own with 50 patients with schizophrenia or related disorders. These trials were underpowered to determine with any precision the potential link between insomnia and psychotic experiences.

Added value of this study

We conducted what may be the largest randomised controlled test to date of a psychological treatment. It is the first study adequately powered to determine the effects of treating sleep dysfunction on psychotic experiences. It shows very clearly that treating insomnia in students leads to a reduction in psychotic experiences. A mediation analysis supports this interpretation. Further, the trial is consistent with a small number of other randomised controlled trials that indicate multiple other benefits for mental health of treating sleep problems.

Implications of all the available evidence

Sleep disruption may have a contributory causal role in the occurrence of psychotic experiences and a wide range of other mental health problems. Adequately powered tests in other

populations would be helpful, but research is accumulating indicating that the treatment of disrupted sleep requires a higher priority in mental health provision.

Declaration of interests

CAE is Co-founder and Chief Medical Officer of the digital CBT for insomnia programme (Sleepio/Big Health Ltd) and AL receives funding from Big Health Ltd. The University of Oxford has a Memorandum of Understanding with Sleepio Ltd for the conduct of joint research. BS provides monthly support for an online discussion forum run by Sleepio. The present study was conducted by the University of Oxford Sleep and Circadian Neuroscience Institute, with a grant from the Wellcome Trust, and was not directly funded by Sleepio, although the programme was provided to all the trial participants by Sleepio at no cost. GMG is a NIHR senior investigator; the views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health. No other investigators have conflicts of interest.

Author contributions

DF was the chief investigator, conceived of the study, led the design, and drafted the paper. BS was the trial co-ordinator and contributed to the design. GG conceived of the study and contributed to the design. LMY contributed to the design and was responsible for the main statistical outcome analyses. AN carried out the trial analyses. PH conceived of the study and contributed to the design. RE oversaw the statistical mediation analysis. AL was responsible for the digital therapy programme. VW was responsible for the computer programming that carried out the screening, assessments, and links to the digital intervention. RF contributed to the design of the trial. CHi was responsible for the development and coordination of the underlying True Colours platform. CE conceived of the study, contributed to the design, and was responsible for the digital therapy programme. Other authors led the research at their university site. All authors commented upon and approved the final manuscript.

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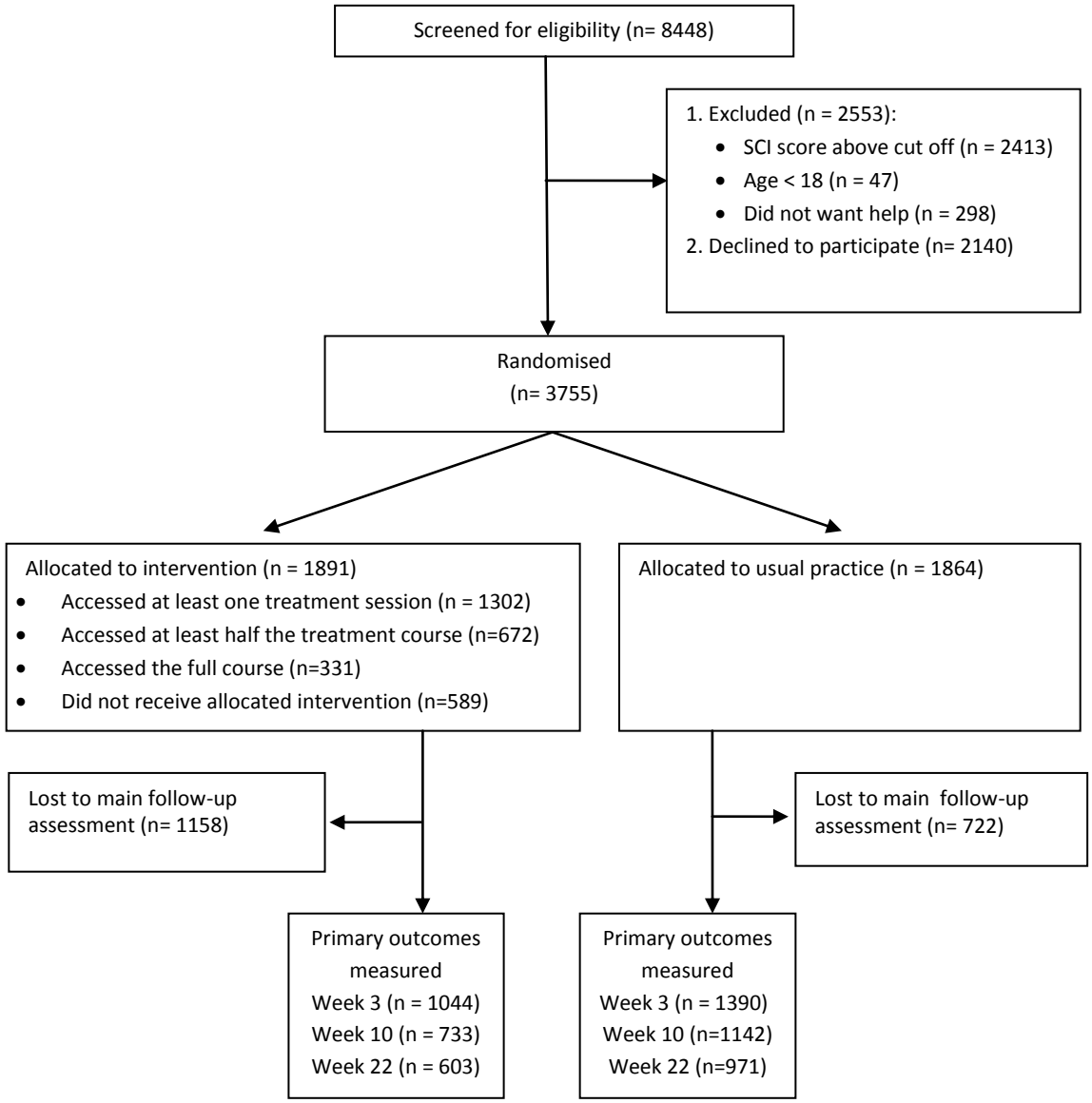
Figure

Figure 1. CONSORT Flow Diagram



Table

Table 1. Baseline information.

Baseline Characteristics	***Control (n= 1864)***	***Treatment (n=1891)***
Mean age in Years (SD)	24.6 (7.6)	24.8 (7.7)
Mean total UCAS points (SD)	753.0 (517.3)	720.8 (456.3)
Male	530 (28.4%)	513 (27.1%)
Female	1315 (70.6%)	1361 (72.0%)
Other	19 (1.0%)	17 (0.9%)
Undergraduate student	1352 (72.5%)	1389 (73.5%)
Postgraduate student	480 (25.8%)	473 (25.0%)
Other	32 (1.7%)	29 (1.5%)
White British	1212 (65.0%)	1265 (66.9%)
White Irish	32 (1.7%)	27 (1.4%)
White Other	284 (15.3%)	261 (13.8%)
Mixed – White/Caribbean	13 (0.7%)	11 (0.6%)
Mixed – White/African	9 (0.5%)	13 (0.7%)
Mixed – White/Asian	31 (1.7%)	27 (1.4%)
Mixed- Other	36 (1.9%)	29 (1.5%)
Asian Indian	26 (1.4%)	43 (2.3%)
Asian Pakistani	23 (1.2%)	22 (1.2%)
Asian Bangladeshi	9 (0.5%)	7 (0.4%)
Asian – Chinese	95 (5.1%)	73 (3.9%)
Asian – Other	25 (1.3%)	32 (1.7%)
Black – African	26 (1.4%)	23 (1.2%)
Black – Caribbean	10 (0.5%)	17 (0.9%)
Black – Other	2 (0.1%)	3 (0.2%)
Arab	12 (0.6%)	14 (0.7%)
Other	19 (1%)	24 (1.3%)
Insomnia (SCI-8) mean score (SD)	10.1 (4.3)	9.9 (4.3)
Paranoia (GPTS) mean score (SD)	24.8 (11.6)	25.4 (11.9)
Hallucinations (SPEQ) mean score (SD)	5.3 (6.9)	5.3 (6.4)
Insomnia (SCI-9) mean score (SD)	12.1 (4.9)	11.9 (4.8)
Insomnia (ISI) mean score (SD)	15.3 (4.0)	15.4 (3.9)
Nightmares (DDNSI) mean score (SD)	8.1 (8.2)	7.7 (7.8)
Prodromal psychosis (PQ-16) mean score (SD)	4.9 (3.4)	4.8 (3.3)
Depression (PHQ-9) mean score (SD)	12.7 (5.9)	12.9 (5.8)
Anxiety (GAD-7) mean score (SD)	9.0 (5.6)	9.4 (5.6)
Mania (Altman) mean score (SD)	3.5 (3.0)	3.5 (3.0)
Functioning (WSAS) mean score (SD)	17.7 (7.6)	17.6 (7.6)
Well-being (WEMWBS) mean score (SD)	37.9 (8.8)	37.8 (8.5)
Ultra high risk of psychosis (PQ-16) Cut-off (6+)		
Above	706 (37.9%)	711 (37.6%)
Below	1158 (62.1%)	1180 (62.4%)
Depressive disorder (PHQ-9) Cut-off (10+)		
Above	1238 (66.4%)	1286 (68.0%)
Below	626 (33.6%)	605 (32.0%)
Anxiety disorder (GAD-7) Cut-off (10+)		
Above	781 (41.9%)	880 (46.5%)
Below	1083 (58.1%)	1011 (53.5%)
Mania disorder (Altman) Score Cut-off (6+)		
Above	422 (22.6%)	413 (21.8%)
Below	1442 (77.4%)	1478 (78.2%)
Contact with mental health services		
Yes	328 (17.6%)	346 (18.3%)

No	1536 (82.4%)	1545 (81.7%)
Any psychiatric Diagnosis		
Yes	590 (31.7%)	641 (33.9%)
No	1274 (68.3%)	1250 (66.1%)
Previous diagnosis of a sleep disorder		
Yes	93 (5.0%)	96 (5.1%)
No	1771 (95.0%)	1795 (94.9%)
Any psychiatric Medication		
Yes	433 (23.2%)	460 (24.3%)
No	1431 (76.8%)	1431 (75.7%)
Specific medication for a sleep disorder		
Yes	51 (2.7%)	55 (2.9%)
No	1813 (97.3%)	1836 (97.1%))
Psychological Therapy		
Yes	146 (7.8%)	135 (7.1%)
No	1718 (92.2%)	1756 (92.9%)

Table 4. Secondary outcome results.

	Insomnia (ISI) 10 Weeks		**Insomnia (ISI) 22 Weeks**	
	Control n=1142	**Treatment n=733**	**Control n=970**	**Treatment n=603**
Unadjusted mean (standard deviation)	12.95 (5.27)	9.23 (5.18)	12.17 (5.29)	8.62 (5.48)
Adjusted difference* (95% confidence interval), d†	-3.72 (-4.16; -3.29), 0.94		-3.40 (-3.87; -2.93), 0.86	
p-value	<0.0001		<0.0001	
	Nightmares (DDNSI) 10 Weeks		**Nightmares (DDNSI) 22 Weeks**	
	TAU n=1142	**Treatment n=733**	**TAU n=963**	**Treatment n=599**
Unadjusted mean (standard deviation)	7.35 (7.85)	5.47 (6.91)	7.32 (7.93)	5.09 (6.66)
Adjusted difference* (95% confidence interval), d†	-1.63 (-2.16; -1.10), 0.20		-1.84 (-2.41; -1.26), 0.23	
p-value	<0.0001		<0.0001	
	Prodromal psychosis (PQ-16) 10 Weeks		**Prodromal psychosis (PQ-16) 22 Weeks**	
	TAU n=1142	**Treatment n=733**	**TAU n=971**	**Treatment n=603**
Unadjusted mean (standard deviation)	4.35 (3.71)	3.37 (3.29)	4.05 (3.83)	3.14 (3.24)
Adjusted difference* (95% confidence interval), d†	-0.81 (-1.03; -0.60), 0.24		-0.74 (-0.98; -0.51), 0.22	
p-value	<0.0001		<0.0001	
	Depression (PHQ-9) 10 Weeks		**Depression (PHQ-9) 22 Weeks**	
	TAU n=1142	**Treatment n=733**	**TAU n=971**	**Treatment n=602**
Unadjusted mean (standard deviation)	11.27 (6.72)	8.44 (6.16)	10.34 (6.79)	8.00 (6.54)
Adjusted difference* (95% confidence interval), d†	-2.83 (-3.30; -2.35), 0.48		-2.44 (-2.95; -1.94), 0.42	
p-value	<0.0001		<0.0001	
	Anxiety (GAD-7) 10 Weeks		**Anxiety (GAD-7) 22 Weeks**	
	TAU n=1142	**Treatment n=733**	**TAU n=971**	**Treatment n=603**
Unadjusted mean (standard deviation)	8.35 (6.06)	6.53 (5.40)	7.67 (6.10)	6.14 (5.41)
Adjusted difference* (95% confidence interval), d†	-1.86 (-2.29; -1.43), 0.33		-1.56 (-2.01; -1.10), 0.28	
p-value	<0.0001		<0.0001	
	Mania (Altman) 10 Weeks		**Mania (Altman) 22 Weeks**	
	TAU n=1142	**Treatment n=733**	**TAU n=971**	**Treatment n=603**
Unadjusted mean (standard deviation)	2.97 (3.03)	3.77 (3.33)	2.92 (3.06)	3.57 (3.41)
Adjusted difference* (95% confidence interval), d†	0.93 (0.67; 1.19), -0.31		0.75 (0.46; 1.03), -0.25	
p-value	<0.0001		<0.0001	

	Functioning (WSAS) 10 Weeks		Functioning (WSAS) 22 Weeks	
	TAU n=1142	**Treatment n=733**	**TAU n=971**	**Treatment n=603**
Unadjusted mean (standard deviation)	15.92 (8.89)	11.43 (8.37)	14.92 (9.17)	10.25 (8.30)
Adjusted difference* (95% confidence interval), d†	-4.36 (-5.03; -3.69), 0.58		-4.33 (-5.05; -3.62), 0.57	
p-value	<0.0001		<0.0001	
	Well-being (WEMWBS) 10 Weeks		**Well-being (WEMWBS) 22 Weeks**	
	TAU n=1142	**Treatment n=733**	**TAU n=971**	**Treatment n=603**
Unadjusted mean (standard deviation)	38.73 (9.78)	40.92 (9.63)	39.63 (10.19)	42.12 (10.36)
Adjusted difference* (95% confidence interval), d†	2.47 (1.72; 3.22), 0.29		2.78 (1.97; 3.60), 0.32	
p-value	<0.0001		<0.0001	
Dichotomous outcomes				
	Ultra high risk of psychosis (PQ16) 10 Weeks		**Ultra high risk of psychosis (PQ16) 22 Weeks**	
	TAU n=1142	**Treatment n=733**	**TAU n=971**	**Treatment n=603**
Adjusted odds ratio‡ (95% confidence interval)	0.26 (0.15; 0.46)		0.33 (0.18; 0.59)	
p-value	<0.0001		0.00026	
	Mania (Altman) 10 Weeks		**Mania (Altman) 22 Weeks**	
	TAU n=1142	**Treatment n=733**	**TAU n=971**	**Treatment n=603**
Adjusted odds ratio‡ (95% confidence interval)	2.01 (1.48; 2.73)		1.89 (1.34; 2.66)	
p-value	<0.0001		0.00027	
	Depressive disorder (PHQ-9) 10 Weeks		**Depressive disorder (PHQ-9) 22 Weeks**	
	TAU n=1142	**Treatment n=733**	**TAU n=971**	**Treatment n=603**
Adjusted odds ratio‡ (95% confidence interval)	0.21 (0.14; 0.32)		0.32 (0.21; 0.48)	
p-value	<0.0001		<0.0001	
	Anxiety disorder (GAD-7) 10 Weeks		**Anxiety disorder (GAD-7) 22 Weeks**	
	TAU n=1142	**Treatment n=733**	**TAU n=971**	**Treatment n=603**
Adjusted odds ratio‡ (95% confidence interval)	0.32 (0.21; 0.48)		0.42 (0.27; 0.64)	
p-value	<0.0001		<0.0001	
	Contacted Mental Health Services 10 Weeks		**Contacted Mental Health Services 22 Weeks**	
	TAU n=1142	**Treatment n=733**	**TAU n=971**	**Treatment n=603**
Adjusted odds ratio‡ (95%	1.19 (0.70; 2.04)		0.98 (0.55; 1.75)	

confidence interval)				
p-value	0.52		0.94	
	Mental health diagnosis 10 Weeks		**Mental health diagnosis 22 Weeks**	
	TAU n=1142	**Treatment n=733**	**TAU n=971**	**Treatment n=603**
Adjusted odds ratio‡ (95% confidence interval)	1.33 (0.75; 2.37)		1.43 (0.78; 2.63)	
p-value	0.33		0.25	
	Psychiatric medication 10 Weeks		**Psychiatric medication 22 Weeks**	
	TAU n=1142	**Treatment n=733**	**TAU n=971**	**Treatment n=603**
Adjusted odds ratio‡ (95% confidence interval)	0.77 (0.47; 1.26)		0.96 (0.58; 1.59)	
p-value	0.30		0.86	
	Psychological Therapy 10 Weeks		**Psychologial Therapy 22 Weeks**	
	TAU n=1142	**Treatment n=733**	**TAU n=971**	**Treatment n=603**
Adjusted odds ratio‡ (95% confidence interval)	1.27 (0.48; 3.35)		0.41 (0.11; 1.58)	
p-value	0.63		0.20	

* Linear mixed effects model adjusted for gender, student status, week and interaction of week with randomisation, and including a random effect for student within university. Covariance matrix of within subject measurements unstructured.

† d = standardised effect size (Cohen's d)

‡ Logistic mixed effects model adjusted for gender, student status, week and interaction of week with randomisation, and including a random effect for student within university. Covariance matrix of within subject measurements unstructured.

Table

Table 2. Primary outcome results.

	Control n=1398	Treatment n=1044	Control n=1142	Treatment n=733	Control n=971	Treatment n=603
	Insomnia (SCI-8) 3 Weeks		**Insomnia (SCI-8) 10 Weeks**		**Insomnia (SCI-8) 22 Weeks**	
Unadjusted mean (standard deviation)	12.34 (5.85)	14.96 (5.80)	13.31 (6.45)	18.08 (6.66)	14.43 (6.71)	19.27 (7.13)
Adjusted difference* (95% C.I.), d†	2.62 (2.19; 3.06), 0.61		4.78 (4.29; 5.26), 1.11		4.81 (4.29; 5.33), 1.12	
p-value*	<0.0001		<0.0001		<0.0001	
	Paranoia (GPTS) 3 Weeks		**Paranoia (GPTS) 10 Weeks**		**Paranoia (GPTS) 22 Weeks**	
Unadjusted mean (standard deviation)	24.63 (11.82)	22.61 (9.89)	23.84 (12.16)	21.06 (9.08)	23.84 (12.68)	20.75 (9.19)
Adjusted difference* (95% C.I.), d†	-1.81 (-2.49; -1.13), 0.15		-2.22 (-2.98; -1.45), 0.19		-2.78 (-3.60; -1.96), 0.24	
p-value*	<0.0001		<0.0001		<0.0001	
	Hallucinations (SPEQ) 3 Weeks		**Hallucinations (SPEQ) 10 Weeks**		**Hallucinations (SPEQ) 22 Weeks**	
Unadjusted mean (standard seviation)	5.06 (6.89)	4.06 (5.84)	4.89 (7.24)	3.12 (5.12)	4.71 (7.43)	2.87 (5.45)
Adjusted difference* (95% C.I.), d†	-0.79 (-1.15; -0.42), 0.12		-1.58 (-1.98; -1.18), 0.24		-1.56 (-1.99; -1.14), 0.23	
p-value*	<0.0001		<0.0001		<0.0001	

* Linear mixed effects model adjusted for gender, student status, week and interaction of week with randomisation, and including a random effect for student within university. Covariance matrix of within subject measurements unstructured.

† d = standardised effect size (Cohen's d)

Table

Table 3. Mediation analysis* results (n=1718).

		Total Effect		Direct Effect		Indirect Effect		Percent mediated
Outcome at week 10	**Mediator (SCI)**	**Effect size - adjusted treatment difference (95% confidence interval)**	**p**	**Effect size - adjusted treatment difference (95% confidence interval)**	**p**	**Effect size - adjusted treatment difference (95% confidence interval)**	**p**	
Paranoia (GPTS)	**Insomnia at Week 3**	-2.27 (-3.03; -1.51)	<0.0001	-1.85 (-2.66; 1.04)	<0.0001	-0.67 (-0.86; -0.48)	<0.0001	29.5%
	Insomnia at Week 10	-2.27 (-3.03; -1.51)	<0.0001	-0.97 (-1.80; -0.14)	<0.0001	-1.31 (-1.60; -1.02)	<0.0001	57.8%
Hallucinations (SPEQ)	**Insomnia at Week 3**	-1.60 (-2.00; -1.20)	<0.0001	-1.36 (-1.79; -0.94)	<0.0001	-0.33 (-0.43; -0.23)	<0.0001	20.7%
	Insomnia at Week 10	-1.60 (-2.00; -1.20)	<0.0001	-0.90 (-1.34; -0.46)	<0.0001	-0.62 (-0.78; -0.46)	<0.0001	38.6%

*Outcome and mediators modelled by means of linear mixed effects models and the total, direct, and indirect effects determined using the Baron and Kenny (30) approach. The effect size is the adjusted treatment difference (i.e. non-standardised treatment difference).