Published in final edited form as:

J Abnorm Child Psychol. 2020 January ; 48(1): 67–77. doi:10.1007/s10802-019-00582-x.

Longitudinal study of sleep and internalizing problems in youth treated for pediatric anxiety disorders

Sunhye Bai^{1,2}, Emily J. Ricketts², Hardian Thamrin³, John Piacentini², Anne Marie Albano⁴, Scott N. Compton⁵, Golda S. Ginsburg⁶, Dara Sakolsky⁷, Courtney P. Keeton⁸, Philip C Kendall⁹, Tara S. Peris²

¹Department of Human Development and Family Studies, The Pennsylvania State University

²Division of Child and Adolescent Psychiatry, University of California, Los Angeles

³Department of Psychology, Arizona State University

⁴Department of Psychiatry, Columbia University

⁵Department of Psychiatry and Behavioral Sciences, Duke University Medical Center

⁶Child Division of Department of Psychiatry, University of Connecticut Health

⁷Department of Psychiatry, University of Pittsburgh

⁸Department of Psychiatry and Behavioral Services, Johns Hopkins University School of Medicine

⁹Department of Psychology, Temple University

Correspondence concerning this article should be addressed to Sunhye Bai, Human Development and Family Studies, The Pennsylvania State University, 216 Health and Human Development, University Park 16802, Phone: (814) 867-6488, sub1164@psu.edu.

Conflict of interest: Dr. Bai has received support from NIMH and the American Psychological Foundation. Dr. Ricketts receives grant support from NIMH, the Tourette Association of America and the TLC Foundation for Body-Focused Repetitive Behaviors. Dr. Piacentini has received support from NIMH, the TLC Foundation for Body-Focused Repetitive Behaviors, the Tourette Association of America, the Pettit Family Foundation, and Pfizer Pharmaceuticals through the Duke University Clinical Research Institute Network. He has received royalties from Guilford Press and Oxford University Press. He has served on the speakers' bureau of the Tourette Association of America, the International Obsessive-Compulsive Disorder Foundation, and the TLC Foundation for Body-Focused Repetitive Behaviors. Dr. Albano has received royalties from Oxford University Press for the Anxiety Disorders Interview Schedule, Child and Parent Versions. She has received an editor's honorarium from the American Psychological Association. Dr. Compton has received support from NIMH, NC GlaxoSmithKline Foundation, Pfizer, Neurocrine Biosciences, and Mursion, Inc. He has served as a consultant for Shire and Mursion, Inc. He has received honoraria from the Nordic Long-Term OCD Treatment Study Research Group and the Centre for Child and Adolescent Mental Health, Eastern and Southern Norway. He has served on the scientific advisory board of Tourette Association of America, Anxiety and Depression Association of America, and Mursion, Inc. He has presented expert testimony for Duke University. Dr. Ginsburg has received support from NIMH and from the US Department of Education/Institute of Education Sciences and serves as a consultant for Syneos Health. Dr. Kendall has received support from NIMH and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). He has received royalties from the sales of materials related to the treatment of anxiety disorders in youth (eg, Guilford Press; Workbook Publishing; Gyldendal Norsk; Gyldendal Akademisk). Dr. Sakolsky has received support from NIMH and NARSAD. She has served as a consultant for LEK Consulting Inc. Dr. Keeton has received support from NIMH. Dr. Peris has received support from NIMH, the Society for Clinical Child and Adolescent Psychology, and the TLC Foundation for Repetitive Behavior Disorders. She has received royalties from Oxford University Press. No other disclosures were reported.

Publisher's Disclaimer: This Author Accepted Manuscript is a PDF file of a an unedited peer-reviewed manuscript that has been accepted for publication but has not been copyedited or corrected. The official version of record that is published in the journal is kept up to date and so may therefore differ from this version.

Ethical approval: "All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards."

Abstract

The current study examined prospective bidirectional links between dysregulated sleep, and anxiety and depression severity across four years, among youth with a history of anxiety disorder. Participants were 319 youth (age 11-26 years), who previously participated in a large multisite randomized controlled trial for the treatment of pediatric anxiety disorders, Child/Adolescent Anxiety Multimodal Study (CAMS), and subsequently enrolled in a naturalistic follow-up, Child/Adolescent Anxiety Multimodal Extended Long-term Study (CAMELS), an average of 6.5 years later. They participated in four annual visits that included self-report items of dysregulated sleep and semi-structured multi-informant interviews of anxiety and depression. Dysregulated sleep was bidirectionally associated with clinician-rated anxiety and depression symptom severity across adolescence and young adulthood. However, these bidirectional relationships were attributable to youth mean levels of dysregulated sleep, and anxiety and depression severity over the four years. Elevations in dysregulated sleep at each visit, relative to mean levels, did not predict worse anxiety or depression severity one year later. Likewise visit-specific elevations in anxiety and depression severity, as opposed to average levels, did not predict higher levels of dysregulated sleep at the next visit. Having higher levels of dysregulated sleep or more severe internalizing problems across the four-year period, as opposed to reporting a relative increase in symptom severity at a particular visit, posed greater risk for poor mental health. Interventions should continue to assess and treat persistent sleep problems alongside anxiety and depression.

Keywords

sleep; anxiety; depression; treatment; adolescence

Sleep disturbance is endemic in youth (Gradisar, Gardner, & Dohnt, 2011) and is complexly related to a number of health and functional domains, including emotional development (Gregory & Sadeh, 2012; Owens et al., 2014; Schochat, Cohen-Zion, & Tzischinsky, 2014). Indeed, sleep disturbance and internalizing problems are highly related (Alvaro, Roberts & Harris, 2014), with sleep problems (e.g., insomnia, difficulty sleeping alone, nightmares, overtired, hypersomnia) present at rates of up to 90% in youth with anxiety disorders (Alfano, Ginsburg, & Kingery, 2007; Chase & Pincus, 2011; Peterman, Carper & Kendall, 2014) and 73% to 89% in youth with major depression disorder (Liu et al., 2007; Roberts, Lewinsohn, & Seeley, 1995; Yorbik, Birmaher, Williamson, & Ryan, 2004). Further, 35% to 59% of youth and young adults with sleep disturbance endorse anxiety symptoms (Calhoun, Fernandez-Mendoza, Vgontzas, Liao, & Bixler, 2014; Peterman et al., 2014; Roane & Taylor, 2008; Saxvig, Pallesen, Wilhelmsen-Langeland, Molde, & Bjorvatn, 2012) and 24% to 57% of those with sleep problems report depressive symptoms (Calhoun et al., 2014; Paavonen et al., 2002; Saxvig et al., 2012). However, the directional nature of the associations between sleep disturbance and internalizing problems is not well understood and further complicated by the presence of sleep disturbance as a diagnostic criterion for both depressive and anxiety disorders.

Cross-sectional studies revealing associations between sleep disturbance and symptoms of anxiety and depression in youth begin to inform our understanding of the pattern of relationships among sleep and internalizing problems (Gregory, Rijsdijk, Dahl, McGuffin, &

Eley, 2009; Gregory et al., 2011). However, they are limited by a snapshot of symptoms at a single point in time. Alternatively, longitudinal designs allow for detection of change in symptom course and directional relationships over time at both the group and individual level. However, at present, little is known about prospective associations between sleep disturbance and internalizing problems.

Several studies have explored sleep problems as a predictor of future internalizing problems over time, with results showing that in youth ranging from childhood to young adulthood, sleep disturbance significantly predicted both later anxiety disorders (Gregory et al., 2005) and symptoms (Jackson, Sztendur, Diamond, Byles, & Bruck, 2014), and depressive disorders (Fichter, Kohlboeck, Quadflieg, Wyschkon, & Esser, 2009; Roane & Taylor, 2008) and symptoms (Jackson et al., 2014). In studies specifically investigating directionality in prospective associations between sleep disturbance and internalizing problems, several have shown bidirectional relationships between sleep problems and internalizing symptoms, and generalized anxiety disorder and depression diagnoses among children and adolescents across time spans ranging from one to 12 years (Meijer, Reitz, Dekovic, van den Wittenboer & Stoel, 2010; Shanahan, Copeland, Angold, Bondy, & Costello, 2014). Yet, other studies testing bidirectional associations have revealed only unidirectional outcomes, finding that sleep problems in childhood predicted internalizing problems in pre-puberty or mid-adolescence, but that internalizing problems (Gregory & O'Connor, 2002) and depressive symptoms (Gregory et al., 2009) did not significantly predict sleep problems over time (Gregory & O'Connor, 2002; Gregory et al., 2009). With respect to young adult samples, a few studies have shown longitudinal bidirectional associations between insomnia and depression (i.e., major depressive episode and depressive symptoms) in young adults across durations ranging from approximately five (Gregory et al., 2016) to 20 years (Buysse et al., 2008). However, other research has shown that anxiety disorder, not depressive disorder, predicted excessive daytime sleepiness over 6 years in young adults, but excessive daytime sleepiness did not significantly predict later anxiety or depressive disorder in that sample (Hasler et al., 2005). These mixed findings indicate that further research is needed.

Sleep problems are often implicated in treatments for youth internalizing problems. The presence of sleep problems may reduce the efficacy of anxiety treatment (Wallace et al., 2017). At the same time, anxiety treatments often lead to modest improvements in sleep problems (Caporino et al., 2016; Peterman et al., 2016). Understanding longitudinal associations between sleep disturbance and internalizing problems may inform clinical decision making regarding the differential prioritizing of screening and assessment across development; and the optimal ordering of treatment components to maximize clinical benefit and decrease the likelihood of future symptom reemergence (Dahl & Harvey, 2007; Dahl & Lewin, 2002). Further, the study of longitudinal associations in adolescents and young adults is particularly important as these groups are especially susceptible to the development of sleep problems due to physiological (i.e., delaying of the circadian phase, decreases in slow wave sleep and activity), and social changes (i.e., increasing autonomy, growing social life, academic stress, balancing work and family life) occurring during physical maturation (Colrain & Baker, 2011). In the transition from adolescence to young adulthood, research has shown decreases in time spent in bed, and sleep duration (Colrain & Baker, 2011; Vela-Bueno, Fernandez-Mendoza, & Olavarrieta-Bernardino, 2009). This stage is also susceptible

to the development of emotional disturbance (particularly anxiety and depression), as adolescents experience rapid changes in functional neural connectivity, particularly between prefrontal cortex and amygdala, accompanied by changes in emotional processing and social relationships (Casey, Heller, Gee, & Cohen, 2017).

Longitudinal associations between sleep disturbance, and anxiety and depressive symptoms may be complicated by sex differences. Generally, adolescent females and women exhibit a two-fold risk of developing insomnia or other sleep problems during their lifetime relative to adolescent males and men (Mong & Cusmano, 2016). Sex differences are also present in the development of internalizing problems, such that girls and women are at greater risk for developing anxiety disorders than boys and men (McLean & Anderson, 2009). Similarly, depression is more prevalent in girls than boys, with differences emerging during adolescence and women displaying double the risk of men (McGuinness, Dyer, & Wade, 2012; Parker & Brotchie, 2010). There may also be an interaction of sex on cross-sectional associations between sleep disturbance and internalizing problems (e.g., Roane & Taylor, 2008). However, studies examining sex effects on sleep-internalizing relationships cross-sectionally are limited and little is known about the role of sex on longitudinal associations.

The current study examined prospective links between dysregulated sleep, and anxiety and depression severity among 319 adolescents and young adults who participated in a large multisite randomized controlled trial (RCT) for the treatment of pediatric anxiety disorders and an associated naturalistic follow-up (Walkup et al., 2008; Ginsburg et al., 2014; Ginsburg et al., 2018). Youth enrolled in the naturalistic follow-up an average of 6.5 years following the RCT, and participated in up to four annual visits. Using data from the four annual follow-up visits, we first tested whether dysregulated sleep at a given visit predicted increased anxiety and depression severity at the following visit. We hypothesized that greater dysregulated sleep would predict worse clinician-rated anxiety and depression severity. Second, we examined whether anxiety and depression severity predicted greater dysregulated sleep at the next annual visit, hypothesizing that greater anxiety and depression severity would predict worse sleep. Third, given the wide age range of participants across the four years of the longitudinal study and the increased risk for development of internalizing problems and sleep disturbance among women (McGuinness, Dyer, & Wade, 2012; McLean & Anderson, 2009; Mong & Cusmano, 2016), we explored the moderating effects of age and sex on these hypothesized prospective associations.

Methods

Procedures and participant characteristics.

CAMELS.—The Child/Adolescent Anxiety Multimodal Extended Long-term Study (CAMELS), is a naturalistic follow-up of 319 youth previously treated for anxiety disorders. Eligibility criteria for CAMELS included past participation in the Child/Adolescent Anxiety Multimodal Study (CAMS), the largest multisite RCT of youth anxiety treatment to date (Walkup et al., 2008). Recruitment for CAMELS took place across six geographically diverse urban sites between 2011 and 2015, via letter, social media outlets and phone.

Participating youth and their parents attended one in-person assessment (i.e., “long visit”) and one telephone assessment, per year for four years. Each family was reimbursed \$130 for the completion of a long visit, and \$50 for the completion of a telephone assessment. The current study used data from all sites from the four long CAMELS visits (i.e., Visits 1-4). Independent evaluators (IE) blinded to the original RCT condition and treatment response status led the CAMELS visits. All IEs received training to reliably administer clinician-rated measures. At each of the four long visits, parents and youth completed surveys and clinical interviews about youth anxiety, depression, and dysregulated sleep, and reported on any receipt of treatment since the last visit. Both youth and parent attended 68% of the long visits, youth alone attended 27% and parent alone attended 5%. Participants provided informed written consent and assent as appropriate, and all study sites obtained approval from their institutional review board.

CAMS.—The CAMS trial was conducted between 2002 and 2007 across the six sites. At the time of CAMS, then 7 to 17-year-old youth were randomized into one of four treatment conditions: a combination of cognitive behavioral therapy (CBT) and sertraline, sertraline only, CBT only, and a placebo drug. CAMS offered active treatment to placebo youth if they were non-responsive to the trial at post-treatment, and all participants could or seek and secure their own choice of services immediately after the trial. For additional details, see Ginsburg et al., 2014; Ginsburg et al., 2018 and Walkup et al., 2008.

Participants.—The 319 youth in the current study were between 11 and 26 years of age at enrollment ($M=17.7$ years, $SD=3.4$), 44.8% male, 81.5% White and 91.9% non-Hispanic. At enrollment, 66.4% of the 319 participants met diagnostic criteria for any DSM-IV disorder, 53.9%, for separation anxiety, social anxiety, or generalized anxiety disorder (GAD), and 7.5% for current major depressive disorder (MDD), characterized by a current episode.

Youth enrolled into CAMELS, an average of 6.5 years ($SD=1.7$, $Range=3.7-11.5$) following the CAMS baseline. Of the 319 youth in the CAMELS sample, 28.8% had received a combination therapy, 28.2% sertraline only, 28.2% CBT only, and 14.7% a placebo drug, during CAMS. At CAMELS Visit 1, about 63% reported that they took any psychotropic medications, and 53% stated that they received any psychotherapy, since the final CAMS assessment.

Measures

Dysregulated sleep.—Consistent with a prior study conducted on the original CAMS sample (Caporino et al., 2016), dysregulated sleep was assessed using four items from the Physical Symptom Checklist (PSC; March et al., 2004), a self-report questionnaire that measures the degree to which youth is bothered by physical symptoms in the past week, on a 0 = not at all to 3 = very much scale. The four items included (1) *trouble sleeping*, (2) *feeling drowsy or too sleepy*, (3) *sleeplessness*, and (4) *nightmares or very strange dreams*. Higher mean scores represented more dysregulated sleep. First derived through exploratory factor analysis of the CAMS sample, this subscale demonstrates good internal reliability (Caporino et al., 2016). In the current study, α ranges from .73 to .81 across the four visits.

Anxiety severity.—Pediatric Anxiety Rating Scale (PARS) is a clinician-administered interview of past-week anxiety symptomatology, severity and impairment (Research Units on Pediatric Psychopharmacology Anxiety Study Group, 2002). Reports from the parent and youth informed the IE's scores on the following six items, each rated on a 0 to 5 scale: (1) *overall frequency of symptoms*, (2) *overall severity of anxiety feelings*, (3) *overall severity of physical symptoms of anxiety*, (4) *avoidance of anxiety provoking situations*, (5) *interference with family*, and (6) *interference with peers, adult relationships, work or school*. Total sum scores ranged from 0 to 30, with scores above 13 indicating clinically significant levels of anxiety (Walkup et al., 2008). Widely used to evaluate symptoms, severity and impairment among youth with anxiety disorders, the PARS has internal consistency ($\alpha=0.64$) and inter-rater reliability ($r=0.97$; Research Units on Pediatric Psychopharmacology Anxiety Study Group, 2002). In the current study, internal consistency of the six items ranged from $\alpha = .85$ to $.88$ across the four visits.

We conducted sensitivity analysis using a modified PARS score composed of five items, excluding the item (3) *overall severity of physical symptoms of anxiety*, to minimize any inflation in hypothesized associations that may result from the overlap between this specific PARS item and our measure of dysregulated sleep (Ginsburg et al., 2011).

Depression severity.—Clinician-rated depression severity was assessed using the MDD section of the IE-administered semi-structured Anxiety Disorders Interview Schedule Child and Parent Version (ADIS-C/P) for DSM-IV (Silverman & Albano, 1996). Administered to parents and youth independently, this section probed current youth symptoms (i.e., within last 2 weeks) and assessed symptom-related impairment in the family, interpersonal, and school/work domains. IEs assigned a Clinician Severity Rating (CSR) from 0 to 8, considering parent and youth reports of symptomatology and related impairment. Higher numbers represented greater severity, and CSR ≥ 4 indicated a clinical diagnosis of current MDD. ADIS has good psychometric properties, including good inter-rater reliability for conditions that may co-occur with anxiety (Lyneham, Abbott, & Rapee, 2007). In the current study, inter-rater reliability computed on a randomly selected sample ($N=88$) of ADIS administrations was $\kappa=.79$.

Covariates.—Covariates were age (years, assessed at each visit) and sex (0=females, 1=males). We also controlled for any medication treatment for emotional or behavioral difficulties since the last assessment (0=none, 1=any), and any psychotherapy treatment since the last assessment (0=none, 1=any), given higher levels of dysregulated sleep and internalizing problems among those who received treatment. Years since CAMS baseline was additionally examined as a potential covariate, but excluded from the final models due to its lack of effect on the outcomes.

Data Analysis.—First, we described anxiety and depression severity, and dysregulated sleep at Visit 1 of CAMELS, and compared scores across the four CAMS treatment conditions using ANOVAs for continuous and X^2 tests for categorical variables. Second, we examined the bivariate correlations between primary variables across the four CAMELS visits. For these and all subsequent analyses, we natural log transformed dysregulated sleep, and anxiety and depression severity (i.e., $\ln[x+1]$) prior to any centering to adjust for

positive skew. All results reflect analyses run with transformed variables, with the exception of means, SDs and ranges.

To address Aims 1 and 2, we fitted two-level linear regression models with a first order autoregressive structure for the residuals, to examine the prospective within-person and between-person associations between dysregulated sleep, and anxiety and depression severity from one visit to the next (i.e., lagged effect), and vice versa. This strategy accounted for nested structure of the data (i.e., visits within individuals), calculated unbiased estimates of parameters by using all available combination of data points, and handled potential biases resulting from missing values. Models included random intercepts and random slopes for primary predictor variable whenever possible.

There were four models total: anxiety severity predicting next-visit sleep, depression severity predicting next-visit sleep, sleep predicting next-visit anxiety severity, sleep predicting next-visit depression severity. In each model, we included the youth mean score of the primary predictor variable (i.e., averaged across the four visits), and the youth mean-centered score at each visit (i.e., visit level score). The latter captured the effect of visit-specific increases or decreases from a person's own mean (Enders & Tofighi, 2007). For example, as part of Aim 1, we tested whether $anxiety_{vj}$ (i.e., at any given visit, v , for youth j) predicted $dysregulated\ sleep_{(v+1)j}$ (i.e., at the next visit, $v+1$, for youth j), over and above $anxiety_{j}$, youth j 's mean symptom level across all four visits. Covariates included sex, grand mean centered age in years assessed at each visit, and any medication use or any psychotherapy since the last visit. We additionally conducted sensitivity analysis of the bidirectional links between anxiety severity and dysregulated sleep, using a modified PARS score that excluded physical symptom severity item, to minimize any potential inflation in the association due to item overlap.

Aim 3 tested (1) sex moderation, (2) age moderation, and (3) sex and age moderation. We expanded on models for Aims 1 and 2 to include the moderator and the interaction between the moderator and primary predictor at the visit level and youth mean level. First, we tested only sex as a potential moderator, with age as a covariate. Second, we tested age as a potential moderator, with sex as a covariate. Third, we examined the three-way interaction between sex, age and the primary predictor.

Results

Attrition.

Among 319 youth who participated in Visit 1, 240 youth (75.2%) completed Visit 2, 220 (69.0%) completed Visit 3, and 209 (65.5%) completed Visit 4. Youth who completed all four visits ($N=168$) did not differ from those who completed Visit 1 only ($N=43$) or those who completed 2 or 3 visits ($N=108$), in regards to race, sex, CAMS treatment condition, medication use, psychotherapy, anxiety, and dysregulated sleep reported at Visit 1. Significant between-group differences were detected for age ($F(2, 316)=5.18, p=.006$), years since CAMS ($F(2, 316)=16.43, p<.001$), and depression severity ($F(2, 316)=3.79, p=.024$). Post-hoc pairwise comparisons of significant group differences showed that youth who completed all four visits were younger ($M=17.15$ years, $SD=3.22$) at Visit 1 than those who

completed Visit 1 only ($M=18.83$ years, $SD=3.78$, respectively). Youth who completed all four visits had the shortest time lapse between their participation in CAMS and CAMELS Visit 1 ($M=6.09$ years, $SD=1.34$), followed by youth who completed 2 or 3 visits ($M=6.78$ years, $SD=1.73$), then by youth who completed only Visit 1 ($M=7.53$ years, $SD=1.96$). Youth who completed only Visit 1 reported greater depression severity at CAMELS Visit 1 ($M=1.33$, $SD=2.18$) compared to youth who completed two or three visits ($M=0.59$, $SD=1.43$), and youth who completed all four visits ($M=0.57$, $SD=1.37$). Of the 168 participants who completed all four visits, 119 (71%) had complete data. At the visit level, 91% of participants had complete data at Visit 1, 86% at Visit 2, 87% at Visit 3, and 87% at Visit 4.

Descriptive statistics.

Table 1 describes CAMELS Visit 1 characteristics across the four CAMS treatment conditions. Key variables did not differ by former CAMS treatment condition. All youth reported low levels of dysregulated sleep ($M=0.60$, $SD=0.64$, $Range=0-3$). Mean anxiety score on the PARS was 8.13 ($SD=6.12$, $Range=0-24$), and the average youth scored in the non-depressed range ($M=0.68$, $SD=1.54$, $Range=0-8$).

Table 2 shows the bivariate associations between dysregulated sleep, anxiety severity, depression severity and age within and between the four CAMELS visits. Dysregulated sleep ($r=0.35-0.64$; $ICC=0.50$), anxiety severity ($r=0.40-0.65$; $ICC=0.48$) and depression severity ($r=0.29-0.52$; $ICC=0.41$) were moderately stable across time. Within each visit, dysregulated sleep was correlated with anxiety severity, with correlations ranging from $r=.20-.38$. Dysregulated sleep was also associated with depression severity ($r=.33-.45$).

Links between dysregulated sleep, anxiety severity and depression severity.

First, we examined dysregulated sleep at the visit level as a predictor of anxiety and depression severity at the next visit, over and above youth mean level of dysregulated sleep, and other covariates. As shown in Table 3, dysregulated sleep predicted worse anxiety ($f^2=0.05$, Model 1) and depression severity ($f^2=0.41$, Model 2). Between-person differences in dysregulated sleep, as opposed to within-person increases from each youth's own mean at the visit level, accounted for these results.

We examined sleep at the next visit as an outcome, predicted by anxiety and depression severity. Anxiety and depression severity predicted more dysregulated sleep ($f^2=0.25$, Model 3¹; $f^2=0.39$, Model 4, respectively). In both models, mean level of internalizing problems, as opposed to visit levels, was associated with dysregulated sleep. Sensitivity analysis conducted using a more conservative version PARS score that excludes the physical symptom severity replicated findings reported in Table 3, Models 1 and 3.

¹Random slope effect of anxiety on sleep was excluded from the effect size calculations to improve convergence of comparable full, restricted and null models

Role of sex and age.

Of the four tests of sex moderation, two were significant. Sex moderated the association between youth mean levels of dysregulated sleep and anxiety severity ($b=0.83$, $SE=0.40$, $p=.035$, $95\% CI[0.06, 1.61]$), such that the link was stronger in males ($b=1.64$, $SE=0.33$, $p<.001$, $95\% CI[1.01, 2.28]$), than females ($b=0.81$, $SE=0.24$, $p=.001$, $95\% CI[0.34, 1.28]$). Sex also significantly moderated the prospective link between visit-level dysregulated sleep and next-visit depression severity ($b=-0.49$, $SE=0.23$, $p=.037$, $95\% CI[-0.94, -0.03]$), but the simple slopes for males and females did not reach statistical significance in post-hoc analyses. When included as covariates, males had lower levels of anxiety (Model 1) and lower levels of dysregulated sleep (Model 4). Of the four tests of age moderation, age significantly moderated the prospective link between visit-level depression severity and next-visit dysregulated sleep ($b=-0.02$, $SE=0.01$, $p=.036$, $95\% CI[-0.04, 0.00]$). Although simple slopes probed at 15.2 and 22.2 years (i.e., $\pm 1SD$ from the mean age) did not reach statistical significance, an analysis of the region of significance suggested that visit-level depression severity may predict sleep problems in early adolescence (< 12.2 years; $b=0.15$, $SE=0.08$, $p=.049$, $95\% CI[0.00, 0.30]$). None of the four tests of three-way interactions between age, sex and predictor variables were statistically significant.

Discussion

The current study found bidirectional links between dysregulated sleep and internalizing problems in 11 to 26-year-old youth with histories of anxiety disorders, assessed over four annual visits. Higher levels of dysregulated sleep were associated with greater clinician-rated anxiety and depression severity. Moreover, higher levels of anxiety and depression severity were associated with greater levels of dysregulated sleep. Specifically, stable between-person differences in dysregulated sleep was associated with internalizing problems, as opposed to within-person increases or decreases relative to a person's own mean. Likewise, youth mean levels of internalizing problems predicted dysregulated sleep at each visit, over and above the effects of within-person fluctuations in symptomatology. Notably, all youth received state-of-the-art treatment for pediatric anxiety disorders an average of 6.5 years prior to their enrollment in the current study. Furthermore, over 50% endorsed receiving psychotherapy or psychopharmacologic treatments for emotional or behavioral problems in between assessments. Despite this treatment history, participants showed a bidirectional link between sleep and internalizing problems across adolescence and young adulthood. The study findings, in the context of the sample characteristics, highlight the importance of treating sleep alongside illness (Dahl & Harvey, 2007; Dahl & Lewin, 2002).

The bidirectional link between sleep and internalizing problems is well-established in research (Alvaro et al., 2014; Gregory et al., 2011). However, relatively few studies have examined these links in a longitudinal design, which can more adequately identify both individual-level and time-variant risk factors for symptom relapse. There are several mechanisms that may contribute to the comorbidity. Physiologically, sleep and internalizing problems are both regulated by the serotonergic system (Harvey, Murray, Chandler & Soehner, 2011; Peterman et al., 2015), as well as inflammatory processes (Irwin, Olmstead

& Carrole, 2016; Wohleb, Franklin, Iwata & Duman, 2016). Dysregulation in either of these systems may give rise to a stable association between internalizing and sleep problems. Furthermore, dysregulated sleep often leads to poor self-control (Meldrum, Barnes & Hay, 2015), cognitive impairment (Thomas, Monahan, Lukowski & Cauffman, 2015), and emotion dysregulation (Harvey et al., 2011), which also contribute to internalizing problems. As a construct, sleep has several facets, including satisfaction, timing, efficiency and duration (Buysse, 2014). Considering subjective reports of nightly sleep, the bidirectional relationship between sleep and internalizing problems may be related to youth with internalizing problems having a higher and less attainable demand for nightly sleep duration (Fuligni, Bai & Krull, 2018). Dysregulated sleep, as measured in the current study, may also reflect individual differences in sleep physiology. The various stages and waves of sleep have distinct roles in memory consolidation, which may influence mental health in adolescents (Alfano, 2018; McMakin & Alfano, 2015). Future research should test specific and potentially modifiable facets of sleep that contribute to the link between sleep and internalizing problems.

The current study detected bidirectional, longitudinal links between sleep and internalizing problems in a sample of youth who had previously met diagnostic criteria for an anxiety disorder and received treatment. In contrast to past research (Colrain & Baker, 2011; Vela-Bueno et al., 2009; Merikanga et al., 2010), we detected few sex and age-related developmental trends. Depression severity may contribute to worse sleep in early adolescents, and the linkage between dysregulated sleep and anxiety severity is particularly prominent in males. Unlike relatively healthy youth, age may be a less prominent correlate of changes in levels of internalizing or sleep problems in clinical youth with history of anxiety disorder. Although CBT for pediatric anxiety disorders and depression secondarily improves dysregulated sleep at post-intervention (Alfano, 2018; Caporino et al, 2016), youth with greater levels of dysregulated sleep relative to others continue to be at high risk for anxiety and depression. An integrated and sequential treatment strategy that targets both conditions may more effectively address the risk for symptom relapse. For example, McMackin and colleagues (2018) found that providing a sleep-focused intervention following anxiety treatment significantly improved sleep disturbance, whereas providing anxiety treatment alone resulted in small sleep reductions. Likewise, Clarke and colleagues (2015) compared the combination of CBT for depression and CBT for insomnia, with the combination of CBT for depression and sleep hygiene psychoeducation, and found the former to more effectively treat targeted problems. Although these studies show promising results, the long-term effects of such interventions on mental illness and sleep are unknown. More research examining the most effective sequence of treatment modules for relapse prevention can help to reduce levels of co-morbidity.

Potential limitations of this study include our measure of sleep, which was subjective and not psychometrically validated. More standardized measures, including the Pittsburgh Sleep Quality Inventory (Buysse, Reynolds, Monk, Berman & Kupfer, 1989), sleep diaries (Carney et al., 2012) and actigraphy could provide more nuanced information about the within-person variance in sleep. Second, although standardized, our anxiety and depression measures include sleep-related items, which may have inflated our findings. However, this potential limitation is offset by our multi-method assessment strategy and sensitivity

analysis, conducted with a measure of anxiety that excludes items that overlap with sleep problems. Third, as a naturalistic follow-up, time elapsed since participation in the RCT varied, which prohibits us from drawing conclusions about the effects of original CAMS trial. Nonetheless, the inclusion of years since enrollment in CAMS as a potential covariate, did not affect study results. Other participant characteristics, such as race/ethnicity and socioeconomic status may be important moderators, and present findings may not generalize to more diverse groups.

Despite these limitations, the current study demonstrates the clear role of sleep on internalizing problems, and of internalizing problems on sleep from early adolescence to young adulthood. Interventions that tackle sleep problems alongside mental illness may help to reduce relapse over the long-term. Such strategies, with a focus on sequencing treatment components to not only target but prevent future problems are an important area of ongoing research.

Acknowledgments

Funding: This work was supported by the National Institute of Mental Health (R01MH064089, R01MH064003, R01MH64088, R01MH64092, R01MH64107, R01MH063747, T32MH073517).

References

- Alfano CA (2018). (Re) Conceptualizing sleep among children with anxiety disorders: Where to next? *Clinical Child and Family Psychology Review*, 21, 482–499. doi: 10.1007/s10567-018-0267-4 [PubMed: 30136070]
- Alfano CA, Ginsburg GS, & Kingery JN (2007). Sleep-related problems among children and adolescents with anxiety disorders. *Journal of the American Academy of Child and Adolescent Psychiatry*, 46, 224–232. doi: 10.1097/01.chi.0000242233.06011.8e [PubMed: 17242626]
- Alvaro PK, Roberts RM, & Harris JK (2014). The independent relationships between insomnia, depression, subtypes of anxiety, and chronotype during adolescence. *Sleep Medicine*, 15, 934–941. doi: 10.1016/j.sleep.2014.03.019 [PubMed: 24958244]
- Buyse DJ (2014). Sleep health: can we define it? Does it matter? *Sleep*, 37, 9–17. doi: 10.5665/sleep.3298 [PubMed: 24470692]
- Buyse DJ, Angst J, Gamma A, Ajdacic V, Eich D, & Rössler W (2008). Prevalence, course, and comorbidity of insomnia and depression in young adults. *Sleep*, 31, 473–480. doi: 10.1093/sleep/31.4.473 [PubMed: 18457234]
- Buyse DJ, Reynolds CF III, Monk TH, Berman SR, & Kupfer DJ (1989). The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Psychiatry Research*, 28, 193–213. doi: 10.1016/0165-1781(89)90047-4 [PubMed: 2748771]
- Calhoun SL, Fernandez-Mendoza J, Vgontzas AN, Liao D, & Bixler EO (2014). Prevalence of insomnia symptoms in a general population sample of young children and preadolescents: Gender effects. *Sleep Medicine*, 15, 91–95. doi: 10.1016/j.sleep.2013.08.787 [PubMed: 24333223]
- Caporino NE, Read KL, Shiffrin N, Settapani C, Kendall PC, Compton SN, ... Albano AM (2016). Sleep-related problems and the effects of anxiety treatment in children and adolescents. *Journal of Clinical Child & Adolescent Psychology*, 46, 675–685. doi: 10.1080/15374416.2015.1063429
- Carney CE, Buysse DJ, Ancoli-Israel S, Edinger JD, Krystal AD, Lichstein KL, & Morin CM (2012). The consensus sleep diary: standardizing prospective sleep self-monitoring. *Sleep*, 35, 287–302. doi: 10.5665/sleep.1642 [PubMed: 22294820]
- Casey BJ, Heller AS, Gee DG, & Cohen AO (2019). Development of the emotional brain. *Neuroscience Letters*, 693, 29–34. doi: 10.1016/j.neulet.2017.11.055 [PubMed: 29197573]

- Chase RM, & Pincus DB (2011). Sleep-related problems in children and adolescents with anxiety disorders. *Behavioral Sleep Medicine*, 9, 224–236. doi: 10.1080/15402002.2011.606768 [PubMed: 22003976]
- Clarke G, McGlinchey EL, Hein K, Gullion CM, Dickerson JF, Leo MC, & Harvey AG (2015). Cognitive-behavioral treatment of insomnia and depression in adolescents: a pilot randomized trial. *Behaviour Research and Therapy*, 69, 111–118. doi: 10.1016/j.brat.2015.04.009 [PubMed: 25917009]
- Colrain IM, & Baker FC (2011). Changes in sleep as a function of adolescent development. *Neuropsychological Review*, 21, 5–21. doi: 10.1007/s11065-010-9155-5
- Dahl RE, & Harvey AG (2007). Sleep in children and adolescents with behavioral and emotional disorders. *Sleep Medicine Clinics*, 2, 501–511. doi: 10.1016/j.jsmc.2007.05.002
- Dahl RE, & Lewin DS (2002). Pathways to adolescent health sleep regulation and behavior. *Journal of Adolescent Health*, 31, 175–184. doi: 10.1016/S1054-139X(02)00506-2 [PubMed: 12470913]
- Fichter MM, Kohlboeck G, Quadflieg N, Wyschkon A, & Esser G (2009). From childhood to adult age: 18-year longitudinal results and prediction of the course of mental disorders in the community. *Social Psychiatry and Psychiatric Epidemiology*, 44, 792–803. doi: 10.1007/s00127-009-0501-y [PubMed: 19212695]
- Enders CK, & Tofighi D (2007). Centering predictor variables in cross-sectional multilevel models: a new look at an old issue. *Psychological methods*, 12, 121–138. doi: 10.1037/1082-989X.12.2.121 [PubMed: 17563168]
- Fuligni AJ, Bai S, Krull JL, & Gonzales NA (2017). Individual differences in optimum sleep for daily mood during adolescence. *Journal of Clinical Child & Adolescent Psychology*. doi: 10.1080/15374416.2017.1357126
- Ginsburg GS, Keeton CP, Drazdowski TK, & Riddle MA (2011). The utility of clinicians ratings of anxiety using the Pediatric Anxiety Rating Scale (PARS). *Child & Youth Care Forum*, 40, 93–105. doi: 10.1007/s10566-010-9125-3
- Ginsburg GS, Becker EM, Keeton CP, Sakolsky D, Piacentini J, Albano AM, ... & Peris T (2014). Naturalistic follow-up of youths treated for pediatric anxiety disorders. *JAMA psychiatry*, 71, 310–318. doi: 10.1016/j.jaac.2018.03.017 [PubMed: 24477837]
- Ginsburg GS, Becker-Haimes EM, Keeton C, Kendall PC, Iyengar S, Sakolsky D, ... & Piacentini J (2018). Results from the Child/Adolescent Anxiety Extended Long-Term Study (CAMELS): Primary anxiety outcomes. *Journal of the American Academy of Child & Adolescent Psychiatry*, 57, 471–480. doi: 10.1016/j.jaac.2018.03.017 [PubMed: 29960692]
- Gradisar M, Gardner G, & Dohnt H (2011). Recent worldwide sleep patterns and problems during adolescence: A review and meta-analysis of age, region, and sleep. *Sleep Medicine*, 12, 110–118. doi: 10.1016/j.sleep.2010.11.008 [PubMed: 21257344]
- Gregory AM, Buysse DJ, Willis TA, Rijsdijk FV, Maughan B, Rowe R, ... Eley TC (2011). Associations between sleep quality and anxiety and depression symptoms in a sample of young adult twins and siblings. *Journal of Psychosomatic Research*, 71, 250–255. doi: 10.1016/j.jpsychores.2011.03.011 [PubMed: 21911103]
- Gregory AM, Caspi A, Eley TC, Moffitt TE, O'Connor TG, & Poulton R (2005). Prospective longitudinal associations between persistent sleep problems in childhood and anxiety and depression disorders in adulthood. *Journal of Abnormal Child Psychology*, 33, 157–163. doi: 10.1007/s10802-005-1824-0 [PubMed: 15839494]
- Gregory AM, & O'Connor TG (2002). Sleep problems in childhood: a longitudinal study of developmental change and association with behavioral problems. *Journal of the American Academy of Child & Adolescent Psychiatry*, 41, 964–971. doi: 10.1097/00004583-200208000-00015 [PubMed: 12162632]
- Gregory AM, Rijsdijk FV, Eley TC, Buysse DJ, Schneider MN, Parsons M, & Barclay NL (2016). A longitudinal twin and sibling study of associations between insomnia and depression symptoms in young adults. *Sleep*, 39, 1985–1992. doi: 10.5665/sleep.6228 [PubMed: 27634812]
- Gregory AM, Rijsdijk FV, Lau JY, Dahl RE, & Eley TC (2009). The direction of longitudinal associations between sleep problems and depression systems: A study of twins aged 8 and 10 years. *Sleep*, 32, 189–199. doi: 10.5665/sleep/32.2.189 [PubMed: 19238806]

- Gregory AM, & Sadeh A (2012). Sleep, emotional and behavioral difficulties in children and adolescents. *Sleep Medicine Reviews*, 16, 129–136. doi: 10.1016/j.smrv.2011.03.007 [PubMed: 21676633]
- Harvey AG, Murray G, Chandler RA, & Soehner A (2011). Sleep disturbance as transdiagnostic: consideration of neurobiological mechanisms. *Clinical Psychology Review*, 31, 225–235. doi: 10.1016/j.cpr.2010.04.003 [PubMed: 20471738]
- Hasler G, Buysse DJ, Gamma A, Ajdacic V, Eich D, Rössler W, & Angst J (2005). Excessive daytime sleepiness in young adults: A 20-year prospective community study. *The Journal of Clinical Psychiatry*, 66, 521–529. [PubMed: 15816796]
- Irwin MR, Olmstead R, & Carroll JE (2016). Sleep disturbance, sleep duration, and inflammation: a systematic review and meta-analysis of cohort studies and experimental sleep deprivation. *Biological Psychiatry*, 80, 40–52. doi: 10.1016/j.biopsych.2015.05.014 [PubMed: 26140821]
- Jackson ML, Sztendur EM, Diamond NT, Byles JE, & Bruck D (2014). Sleep difficulties and the development of depression and anxiety: a longitudinal study of young Australian women. *Archives of Women's Mental Health*, 17, 189–198. doi: 10.1007/s00737-014-0417-8
- Kendall PC, Compton S, Walkup J, Birmaher B, Albano AM, Sherrill J, Ginsburg G, Rynn M, McCracken J, Gosch E, Keeton C, Bergman L, Sakolsky D, Suveg C, Iyengar S, March J, & Piacentini J (2010). Clinical characteristics of anxiety disorder youth. *Journal of Anxiety Disorders*, 24, 360–365. doi: 10.1016/j.janxdis.2010.01.009 [PubMed: 20206470]
- Liu X, Buysse DJ, Gentzler AL, Kiss E, Mayer L, Kapornai K, ... Kovacs M (2007). Insomnia and hypersomnia associated with depressive phenomenology. *Sleep*, 30, 83–90. doi: 10.1093/sleep/30.1.83 [PubMed: 17310868]
- Lyneham HJ, Abbott MJ, & Rapee RM (2007). Interrater reliability of the Anxiety Disorders Interview Schedule for DSM-IV: child and parent version. *Journal of the American Academy of Child & Adolescent Psychiatry*, 46, 731–736. doi: 10.1097/chi.0b013e3180465a09 [PubMed: 17513985]
- March J, Silva S, Petrycki S, Curry J, Wells K, Fairbank J, ... TADS Study Team. (2004). Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for adolescents with depression study (TADS) randomized controlled trial. *Journal of the American Medical Association*, 292, 807–820. doi: 10.1001/jama.292.7.807 [PubMed: 15315995]
- McGuinness TM, Dyer JG, & Wade EH (2012). Gender differences in adolescent depression. *Journal of Psychosocial Nursing and Mental Health Services*, 50, 17–20. doi: 10.3928/02793695-20121107-04
- McLean CP, & Anderson ER (2009). Brave men and timid women? A review of the gender differences in fear and anxiety. *Clinical Psychology Review*, 29, 496–505. doi: 10.1016/j.cpr.2009.05.003 [PubMed: 19541399]
- McMakin DL, & Alfano CA (2015). Sleep and anxiety in late childhood and early adolescence. *Current Opinion in Psychiatry*, 28, 483–489. doi: 10.1097/YCO.0000000000000204 [PubMed: 26382163]
- McMakin DL, Ricketts EJ, Forbes EE, Silk JS, Ladouceur CD, Siegle GJ, ... & Harvey AG (2018). Anxiety treatment and targeted sleep enhancement to address sleep disturbance in pre/early adolescents with anxiety. *Journal of Clinical Child & Adolescent Psychology*, 48, S284–S297. doi: 10.1080/15374416.2018.1463534 [PubMed: 29873503]
- Meijer AM, Reitz E, Deković M, Van Den Wittenboer GL, & Stoel RD (2010). Longitudinal relations between sleep quality, time in bed and adolescent problem behaviour. *Journal of Child Psychology and Psychiatry*, 51, 1278–1286. doi: 10.1111/j.1469-7610.2010.02261.x [PubMed: 20456533]
- Meldrum RC, Barnes JC, & Hay C (2015). Sleep deprivation, low self-control, and delinquency: A test of the strength model of self-control. *Journal of Youth and Adolescence*, 44, 465–477. doi: 10.1007/s10964-013-0024-4 [PubMed: 24085558]
- Merikangas KR, He JP, Burstein M, Swanson SA, Avenevoli S, Cui L, ... & Swendsen J (2010). Lifetime prevalence of mental disorders in US adolescents: results from the National Comorbidity Survey Replication-Adolescent Supplement (NCS-A). *Journal of the American Academy of Child & Adolescent Psychiatry*, 49, 980–989. doi: 10.1016/j.jaac.2010.05.017 [PubMed: 20855043]
- Mong JA, & Cusmano DM (2016). Sex differences in sleep: Impact of biological sex and sex steroids. *Philosophical Transactions of the Royal Society B*, 371, 1–11. doi: 10.1098/rstb.2015.0110

- Owens J, & the Adolescent Sleep Working Group, Committee on Adolescence. (2014). Insufficient sleep in adolescents and young adults: An update on causes and consequences. *Pediatrics*, 134, e921–e932. doi:10.1542/peds.2014-1696 [PubMed: 25157012]
- Paavonen EJ, Almqvist F, Tamminen T, Moilanen I, Piha J, Räsänen E, & Aronen ET (2002). Poor sleep and psychiatric symptoms at school: An epidemiological study. *European Child & Adolescent Psychiatry*, 11, 10–17. doi: 10.1007/s007870200002 [PubMed: 11942422]
- Parker G, & Brotchie H (2010). Gender differences in depression. *International Review of Psychiatry*, 22, 429–436. doi: 10.3109/09540261.2010.492391 [PubMed: 21047157]
- Peterman J, Carper M, Elkins R, Pincus D, Comer J, & Kendall PC (2016). The effects of cognitive behavioral therapy for youth anxiety on sleep problems. *Journal of Anxiety Disorders*, 37, 78–88. doi: 10.1016/j.janxdis.2015.11.006 [PubMed: 26735330]
- Peterman JS, Carper MM, & Kendall PC (2015). Anxiety disorders and comorbid sleep problems in school-aged youth: review and future research directions. *Child Psychiatry & Human Development*, 46, 376–392. doi: 10.1007/s10578-014-0478-y [PubMed: 24962165]
- Roane BM, & Taylor DJ (2008). Adolescent insomnia as a risk factor for early adult depression and substance abuse. *Sleep*, 31, 1351–1356. doi: 10.5665/sleep/31.10.1351 [PubMed: 18853932]
- Research Units on Pediatric Psychopharmacology Anxiety Study Group. (2002). The pediatric anxiety rating scale (PARS): Development and psychometric properties. *Journal of the American Academy of Child & Adolescent Psychiatry*, 41, 1061–1069. doi: 10.1097/00004583-200209000-00006 [PubMed: 12218427]
- Roberts RE, Lewinsohn PM, & Seeley JR (1995). Symptoms of DSM-III-R major depression in adolescence: evidence from an epidemiological survey. *Journal of the American Academy of Child and Adolescent Psychiatry*, 34, 1608–1617. doi: 10.1097/00004583-199512000-00011 [PubMed: 8543532]
- Saxvig IW, Pallesen S, Wilhelmsen-Langeland A, Molde H, & Bjorvatn B (2012). Prevalence and correlates of delayed sleep phase in high school students. *Sleep Medicine*, 13, 193–199. doi: 10.1016/j.sleep.2011.10.024 [PubMed: 22153780]
- Schochat T, Cohen-Zion M, & Tzischinsky O (2014). Functional consequences of inadequate sleep in adolescents: A systematic review. *Sleep Medicine Reviews*, 18, 75–87. doi: 10.1016/j.smr.2013.03.005 [PubMed: 23806891]
- Shanahan L, Copeland WE, Angold A, Bondy CL, & Costello EJ (2014). Sleep problems predict and are predicted by generalized anxiety/depression and oppositional defiant disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, 53, 550–558. doi: 10.1016/j.jaac.2013.12.029 [PubMed: 24745954]
- Silverman WK, & Albano AM (1996). *The Anxiety Disorders Interview Schedule for Children for DSM-IV (Child and Parent Versions)*. San Antonio, TX: Psychological Corporation.
- Steinberg LD (2017). *Adolescence* (11th ed.). New York, NY: McGraw-Hill Education.
- Thomas AG, Monahan KC, Lukowski AF, & Cauffman E (2015). Sleep problems across development: A pathway to adolescent risk taking through working memory. *Journal of Youth and Adolescence*, 44, 447–464. doi: 10.1007/s10964-014-0179-7 [PubMed: 25213135]
- Vela-Bueno A, Fernandez-Mendoza J, & Olavarrieta-Bernardino S (2009). Sleep patterns in the transition from adolescence to young adulthood. *Sleep Medicine Clinics*, 4, 77–85. doi: 10.1016/j.jsmc.2008.12.003
- Walkup JT, Albano AM, Piacentini J, Birmaher B, Compton SN, Sherrill JT, Ginsburg GS, ... Kendall PC (2008). Cognitive behavior therapy, sertraline, or a combination in childhood anxiety. *The New England Journal of Medicine*, 359, 2753–2766. doi: 10.1056/NEJMoa0804633 [PubMed: 18974308]
- Wallace M, McMakin D, Tan P, Rosen D, Forbes E, Cecile D, Ladouceur C, Ryan N, Siegle G, Dahl R, Kendall P, Mannarino A, & Silk J (2017). The role of day-to-day emotions, sleep, and social interactions in pediatric anxiety treatment. *Behaviour Research and Therapy*, 90, 87–95. doi: 10.1016/j.brat.2016.12.012 [PubMed: 28013054]
- Waloszek JM, Schwartz O, Simmons JG, Blake M, Blake L, Murray G, ... & Trinder J (2015). The SENSE Study (Sleep and Education: learning New Skills Early): a community cognitive-behavioural therapy and mindfulness-based sleep intervention to prevent depression and improve

cardiac health in adolescence. *BMC psychology*, 3, 39–50. doi: 10.1186/s40359-015-0096-x [PubMed: 26537175]

Wohleb ES, Franklin T, Iwata M, & Duman RS (2016). Integrating neuroimmune systems in the neurobiology of depression. *Nature Reviews Neuroscience*, 17, 497–508. doi: 10.1038/nrn.2016.69 [PubMed: 27277867]

Yorbik O, Birmaher B, Axelson D, Williamson DE, & Ryan ND (2004). Clinical characteristics of depression severity in children and adolescents with major depressive disorder. *Journal of Clinical Psychiatry*, 65, 1654–1659. doi: 10.4088/JCP.v65n1210 [PubMed: 15641870]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 1

Descriptive statistics at Visit 1, by CAMS treatment condition

	COMB N=92		SRT N=90		CBT N=90		PBO N=47		Total N=319		p
	Mean/N	SD/%	Mean/N	SD/%	Mean/N	SD/%	Mean/N	SD/%	Mean/N	SD/%	
Sex											
Male(N, %)	42	45.65	41	45.56	38	42.22	22	46.81	143	44.83	.947
Age	17.94	3.59	17.81	3.38	17.29	3.25	17.69	3.44	17.68	3.41	.613
Sleep	0.68	0.68	0.62	0.65	0.54	0.62	0.50	0.55	0.60	0.64	.354
Anxiety severity	7.58	5.79	7.80	6.18	8.36	6.22	9.45	6.41	8.13	6.12	.253
Depression severity	0.67	1.41	0.71	1.52	0.60	1.69	0.77	1.55	0.68	1.54	.879
Medication since last ax											
Yes(N, %)	59	67.05	58	66.67	47	52.81	31	65.96	195	62.70	.156
Psychotherapy since last ax											
Yes(N, %)	43	50.00	48	55.81	44	49.44	29	61.70	164	53.25	.483

CAMS treatment conditions: COMB = Combination therapy, SRT = sertraline only, CBT=cognitive behavior therapy, PBO=placebo ax = assessment

Numeric values represent means and SD unless otherwise specified as N and %.

Table 2

Descriptive statistics and bivariate correlations between dysregulated sleep, and anxiety and depression severity across four CAMELS visits

	M	SD	Range	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Visit 1																			
1 Sleep	0.6	0.6	0 - 2.8																
2 Anx.	8.1	6.1	0 - 24	.31***															
3 Dep.	0.7	1.5	0 - 8	.40***	.23***														
4 Age	17.7	3.4	11.2 - 26.0	.13*	.09	.16**													
Visit 2																			
5 Sleep	0.4	0.6	0 - 2.5	.50***	.26***	.32***	.13												
6 Anx.	7.1	5.8	0 - 24	.20**	.48***	.22***	.12	.20**											
7 Dep.	0.8	1.7	0 - 8	.34***	.23***	.43***	.10	.45***	.26***										
8 Age	18.3	3.4	11.7 - 27.3	.13*	.10	.09	1.00***	.12	.13	.09									
Visit 3																			
9 Sleep	0.4	0.6	0 - 2.5	.35***	.20**	.15*	-.03	.38***	.33***	.47***	-.003								
10 Anx.	7.2	6.1	0 - 23	.23**	.53***	.19**	.06	.30***	.53***	.28***	.10	.37***							
11 Dep.	0.7	1.6	0 - 6	.25***	.20**	.32***	.08	.34***	.21**	.52***	.07	.33***	.32***						
12 Age	19.2	3.3	12.7 - 28.5	.09	.11	.12	1.00***	.08	.10	.09	1.00***	-.04	.07	.07*					
Visit 4																			
13 Sleep	0.4	0.6	0 - 2.8	.42***	.27***	.25***	.04	.41***	.22**	.35***	.08	.64***	.36***	.31***	.04				
14 Anx.	6.7	6.2	0 - 24	.26***	.41***	.24***	.01	.27***	.40***	.30***	.06	.28**	.65***	.31***	.01	.38***			
15 Dep.	0.7	1.5	0 - 6	.27***	.20**	.29***	.16*	.29***	.23**	.35***	.18*	.29***	.22**	.42***	.15*	.38***	.23***		
16 Age	20.1	3.2	13.9 - 27.8	.07	.10	.11	1.00***	.09	.13	.15	1.00***	.00	.08	.09	1.00***	.05	.01	.16*	
17 Sex ^a	0.44	0.50	0 or 1	-.15*	-.17**	-.01	-.05	-.07	-.14*	-.12	-.07	-.19**	-.24***	-.10	-.09	-.20**	-.28***	-.02	-.09

* p .05,

**

p .01,

p .001

S_{sex} , 0=female, 1=male; Anx = anxiety severity; Dep = depression severity; age in years

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript