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Longitudinal Study of Sleep and Internalizing Problems in Youth Treated for Pediatric Anxiety Disorders

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Abstract

The current study examined prospective bidirectional links between dysregulated sleep, and anxiety and depression severity across 4 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 4 years. Elevations in dysregulated sleep at each visit, relative to mean levels, did not predict worse anxiety or depression severity 1 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 et al. 2011) and is complexly related to a number of health and functional domains, including emotional development (Gregory and Sadeh 2012; Owens et al. 2014; Schochat et al. 2014). Indeed, sleep disturbance and internalizing problems are highly related (Alvaro et al. 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 et al. 2007; Chase and Pincus 2011; Peterman et al. 2015) and 73% to 89% in youth with major depression disorder (Liu et al. 2007; Roberts et al. 1995; Yorbik et al. 2004). Further, 35% to 59% of youth and young

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adults with sleep disturbance endorse anxiety symptoms (Calhoun et al. 2014; Peterman et al. 2015; Roane and Taylor 2008; Saxvig et al. 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 et al. 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 et al. 2014), and depressive disorders (Fichter et al. 2009; Roane and 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 et al. 2010; Shanahan et al. 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 and O'Connor 2002) and depressive symptoms (Gregory et al. 2009) did not significantly predict sleep problems over time (Gregory and 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 and Harvey 2007; Dahl and 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 and Baker 2011). In the transition from adolescence to young adulthood, research has shown decreases in time spent in bed, and sleep duration (Colrain and Baker 2011; Vela-Bueno et al. 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 et al. 2019).

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 and 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 and 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 et al. 2012; Parker and Brotchie 2010). There may also be an interaction of sex on cross-sectional associations between sleep disturbance and internalizing problems (e.g., Roane and 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 4 years of the longitudinal study and the increased risk for development of internalizing problems and sleep disturbance among women (McGuinness et al. 2012; McLean and Anderson 2009; Mong and 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 4 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 0.73 to 0.81 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 $\alpha = 0.85$ to 0.88 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 and 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 et al. 2007). In the current study, inter-rater reliability computed on a randomly selected sample ($N = 88$) of ADIS administrations was $\kappa = 0.79$.

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 and 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 regard 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 ($F(2, 316) = 5.18$, $p = 0.006$), years since CAMS ($F(2, 316) = 16.43$, $p < 0.001$), and depression severity ($F(2, 316) = 3.79$, $p = 0.024$). 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 $r = 0.20$–0.38. Dysregulated sleep was also associated with depression severity ($r = 0.33$–0.45).

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 3[1]; $f^2 = 0.39$, 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.

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 ($b = 0.83$, $SE = 0.40$, $p = 0.035$, *95% CI* [0.06, 1.61]), such that the link was stronger in males ($b = 1.64$, $SE = 0.33$, $p < 0.001$, *95% CI* [1.01, 2.28]), than females ($b = 0.81$, $SE = 0.24$, $p = 0.001$, *95% CI* [0.34, 1.28]). Sex also significantly moderated the prospective link between visit-level dysregulated sleep and next-visit depression severity ($b = -0.49$, $SE = 0.23$, $p = 0.037$, *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 ($b = -0.02$, $SE = 0.01$, $p = 0.036$, *95% CI* [−0.04, 0.00]). Although simple slopes probed at 15.2 and 22.2 years (i.e., ±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; $b = 0.15$, $SE = 0.08$, $p =$ 0.049, *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

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

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			
	Mean/N	SD/%	Mean/N	SD/%	Mean/N	SD/%	Mean/N	SD/%	Mean/N	SD/%	F / X^2	p
Sex												
Male (N, %)	42	45.65	41	45.56	38	42.22	22	46.81	143	44.83	$X^2(3) = 0.366$	0.947
Age	17.94	3.59	17.81	3.38	17.29	3.25	17.69	3.44	17.68	3.41	F(3, 315) = 0.60	0.613
Sleep	0.68	0.68	0.62	0.65	0.54	0.62	0.50	0.55	0.60	0.64	F(3, 291) = 1.09	0.354
Anxiety severity	7.58	5.79	7.80	6.18	8.36	6.22	9.45	6.41	8.13	6.12	F(3, 315) = 1.37	0.253
Depression severity	0.67	1.41	0.71	1.52	0.60	1.69	0.77	1.55	0.68	1.54	F(3, 296) = 0.23	0.879
Medication since last ax												
Yes (N, %)	59	67.05	58	66.67	47	52.81	31	65.96	195	62.70	$X^2(3) = 5.23$	0.156
Psychotherapy since last ax												
Yes (N, %)	43	50.00	48	55.81	44	49.44	29	61.70	164	53.25	$X^2(3) = 2.46$	0.483

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 %

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 and Harvey 2007; Dahl and 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 et al. 2011; Peterman et al. 2015), as well as inflammatory processes (Irwin et al. 2016; Wohleb et al. 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 et al. 2015), cognitive impairment (Thomas et al. 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 et al. 2019). 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 and 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 and Baker 2011; Vela-Bueno et al. 2009; Merikangas 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 (McMackin et al. 2019) 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 (Clarke et al. 2015) compared the combination of CBT for depression and CBT for insomnia, with the combination of

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	0.31***															
3	Dep.	0.7	1.5	0–8	0.40***	0.23***														
4	Age	17.7	3.4	11.2–26.0	0.13*	0.09	0.16**													
Visit 2																				
5	Sleep	0.4	0.6	0–2.5	0.50***	0.26***	0.32***	0.13												
6	Anx.	7.1	5.8	0–24	0.20**	0.48***	0.22***	0.12	0.20**											
7	Dep.	0.8	1.7	0–8	0.34***	0.23***	0.43***	0.10	0.45***	0.26***										
8	Age	18.3	3.4	11.7–27.3	0.13*	0.10	0.09	1.00***	0.12	0.13	0.09									
Visit 3																				
9	Sleep	0.4	0.6	0–2.5	0.35***	0.20**	0.15*	−0.03	0.38***	0.33***	0.47***	−0.00								
10	Anx.	7.2	6.1	0–23	0.23**	0.53***	0.19**	0.06	0.30***	0.53***	0.28***	0.10	0.37***							
11	Dep.	0.7	1.6	0–6	0.25***	0.20**	0.32***	0.08	0.34***	0.21**	0.52***	0.07	0.33***	0.32***						
12	Age	19.2	3.3	12.7–28.5	0.09	0.11	0.12	1.00***	0.08	0.10	0.09	1.00***	−0.04	0.07	0.07*					
Visit 4																				
13	Sleep	0.4	0.6	0–2.8	0.42***	0.27***	0.25***	0.04	0.41***	0.22**	0.35***	0.08	0.64***	0.36***	0.31***	0.04				
14	Anx.	6.7	6.2	0–24	0.26***	0.41***	0.24***	0.01	0.27***	0.40***	0.30***	0.06	0.28**	0.65***	0.31***	0.01	0.38***			
15	Dep.	0.7	1.5	0–6	0.27***	0.20**	0.29***	0.16*	0.29***	0.23**	0.35***	0.18*	0.29***	0.22**	0.42***	0.15*	0.38***	0.23***		
16	Age	20.1	3.2	13.9–27.8	0.07	0.10	0.11	1.00***	0.09	0.13	0.15	1.00***	0.00	0.08	0.09	1.00***	0.05	0.01	0.16*	
17	Sex[a]	0.44	0.50	0 or 1	−0.15*	−0.17**	−0.01	−0.05	−0.07	−0.14*	−0.12	−0.07	−0.19**	−0.24***	−0.10	−0.09	−0.20**	−0.28***	−0.02	−0.09

* $p \leq 0.05$, ** $p \leq .01$, *** $p \leq 0.001$

[a] Sex, 0 = female, 1 = male; Anx = anxiety severity; Dep = depression severity; age in years

Table 3 Results of two-level linear regression models testing prospective links between dysregulated sleep, and anxiety and depression severity

Model 1: $Sleep_{vj}$ predicting next-visit $anxiety_{(v+1)j}$ $N = 245$, $n = 548$					
	b	SE	95% CI	z	p
$Sleep_{vj}$	−0.01	0.15	−0.31, 0.28	−0.09	0.931
$Sleep_{.j}$	1.10	0.20	0.71, 1.49	5.56	<0.001
Age	0.01	0.01	−0.02, 0.03	0.40	0.690
Sex	−0.21	0.10	−0.42, −0.01	−2.02	0.043
Model 2: $Sleep_{vj}$ predicting next-visit $depression_{(v+1)j}$ $N = 247$, $n = 549$					
	b	SE	95% CI	Z	p
$Sleep_{vj}$	−0.00	0.12	−0.23, 0.22	−0.03	0.973
$Sleep_{.j}$	0.82	0.11	0.61, 1.04	7.53	<0.001
Age	0.02	0.01	0.00, 0.03	2.16	0.031
Sex	0.02	0.06	−0.09, 0.13	0.36	0.721
Model 3: $Anxiety_{vj}$ predicting next-visit $sleep_{(v+1)j}$ $N = 235$, $n = 536$					
	b	SE	95% CI	z	p
$Anxiety_{vj}$	0.02	0.02	−0.01, 0.06	1.17	0.243
$Anxiety_{.j}$	0.11	0.02	0.07, 0.15	5.02	<0.001
Age	0.00	0.00	−0.01, 0.01	0.57	.568
Sex	−0.04	0.03	−0.10, 0.03	−1.04	0.300
Model 4: $Depression_{vj}$ predicting next-visit $sleep_{(v+1)j}$ $N = 237$, $n = 537$					
	b	SE	95% CI	z	p
$Depression_{vj}$	0.00	0.04	−0.07, 0.07	0.05	0.960
$Depression_{.j}$	0.28	0.04	0.21, 0.36	7.69	<0.001
Age	0.00	0.00	−0.01, 0.01	0.14	0.892
Sex	−0.06	0.03	−0.12, 0.00	−2.01	0.045

b = unstandardized coefficient, vj = predictor at visit v for youth j; .j = mean level of predictor for youth j; (v + 1)j = outcome at the next visit for youth j

Dysregulated sleep, anxiety and depression severity were natural log transformed (ln[x + 1]) in all analysis; All models included random intercepts, and random slopes were included in Models 2, 3 and 4; Covariates were grand mean centered age in years, sex (0 = female, 1 = male), any psychotropic medication use since last visit (0 = none, 1 = any), any psychotherapy since the last visit (0 = none, 1 = any)

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 et al. 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.

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Compliance with Ethical Standards

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;

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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."

Informed Consent Informed consent was obtained from all individual participants included in the study.

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