Published in final edited form as:

J Affect Disord. 2017 June ; 215: 30–36. doi:10.1016/j.jad.2017.03.011.

Longitudinal Sleep Phenotypes among Offspring of Bipolar Parents and Community Controls

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Abstract

Background—Sleep disturbances are a prominent feature of bipolar disorder (BP). However, it remains unclear how sleep *phenotypes* may evolve among at-risk youth, and their relevance to BP onset.

Methods—Pittsburgh Bipolar Offspring Study (BIOS) offspring (ages 10–18) and their parents completed assessments approximately every two years pertaining to current psychopathology and offspring sleep habits. A latent transition analysis (LTA) identified latent sleep groups within offspring based on their ratings of six sleep domains using the School Sleep Habits Survey. Demographic and clinical characteristics were compared between sleep groups. Logistic regression tested links between sleep group and BP onset at the subsequent assessment.

Results—The LTA model identified latent groups of good, poor, and variable sleepers. We observed an overall trend of good sleep becoming variable, and then poor, as youth age. Offspring in the poor sleep group were more likely to have psychopathology. Adjusting for age and depression, poor sleepers had nearly twice the odds of developing BP relative to good (OR=1.99, CI=0.45–8.91) or variable (OR=2.03, CI=0.72–5.72) sleepers.

Limitations include the use of *proximal* sleep phenotypes to predict BP onset, and a self-report measure of sleep.

Conclusions—We found three non-overlapping sleep phenotype groups in a large sample of offspring of bipolar probands and offspring of demographically-matched community control parents. Clinicians should consider that youth will likely experience variable and/or poor sleep as

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they age, and that at-risk youth with *poor* sleep may be at increased risk of developing MDD and BP at their next assessment.

Keywords

Mood; Latent Transition Analysis; Longitudinal; At-Risk; Phenotype

Introduction

Incidence rates of bipolar disorder (BP) rise during the mid-teens and early twenties (Kessler et al., 2005), making adolescence a particularly vulnerable time for youth at clinical and familial risk for BP. As compared to adult onset BP (>18yr), the development of BP during youth is associated with a more adverse course of illness, including greater symptom severity, fewer days euthymic, comorbid psychopathology, and greater functional impairment (Perlis et al., 2009; Post et al., 2010; Suominen et al., 2007). Thus, there is a need to identify and characterize modifiable factors that contribute to BP risk in adolescents at high risk for developing the disorder. Recent work indicates that sleep disturbances play a central role in mood dysregulation and BP illness onset in those with a genetic vulnerability to the disorder (e.g., Meyer & Maier, 2006; Levenson et al., 2015). Thus, the present study examines the role of sleep behavior as a factor that increases risk of BP among youth at familial risk for the disorder.

Sleep disturbances are a prominent and complex feature of BP, which may include features of insomnia (e.g., sleep continuity disturbances), hypersomnolence (e.g., excessive sleepiness), irregular sleep-wake schedules (e.g., variable sleep timing), delayed sleep phase (e.g., late sleep schedule), or reduced sleep need (Kanady, Soehner, & Harvey, 2015). Studies of BP in adult and pediatric populations consistently show that sleep disturbances occur during acute episodes and persist between episodes in the majority of BP patients (Ng et al., 2014; Kanady et al., 2015; for review see Harvey, 2008; Harvey, Schmidt, Scarna, Semler, & Goodwin, 2005; Harvey et al., 2005; Harvey, Mullin, & Hinshaw, 2006). Moreover, sleep is significantly disturbed in individuals *at risk* for BP; for example, baseline sleep variables, such as frequent waking during the night, significantly predict the onset of BP among offspring of bipolar parents (Levenson et al., 2015). Still, findings have been inconsistent with regard to which sleep disturbances are most relevant to the onset of BP (Ritter, Marx, Bauer, Leopold, & Pfennig, 2011). Work in offspring of bipolar parents (OBP) has predominantly focused on sleep symptoms embedded within diagnostic criteria for depression and (hypo)mania (Correll et al., 2014). Since sleep disturbances in BP may include a complex combination of features, these clusters or patterns of sleep disturbances may not fit neatly into traditional diagnostic categories for sleep disorders. It remains unclear how sleep phenotypes may evolve among high-risk youth, and their relevance to the onset of BP.

Understanding the evolution of sleep phenotypes across the school age years may be particularly vital for youth at-risk for BP, as sleep patterns undergo great change from childhood into adolescence even in typically developing youth (Carskadon, Acebo, & Jenni, 2004). Sleep patterns are biologically regulated by two processes: a circadian rhythm that

determines our daily sleep and wake rhythms based on structures in the hypothalamus of the brain, and a homeostatic process that determines sleep drive based on prior sleep and wakefulness of the individual (Harvey et al., 2006; Borbely, 1982). Shifts in these inter-related, but *distinct*, sleep regulatory processes during adolescence result in delayed sleep-wake patterns. These biological changes, in conjunction with psychosocial factors -- such as earlier school start times, extracurricular activities, and peer socializing -- contribute to developmental increases in insufficient sleep (Carskadon, 2011). Importantly, developmental shifts in sleep patterns overlap with those disrupted in BP, and thus may be particularly problematic for high-risk youth.

The aim of the present study was to characterize sleep phenotypes, rather than individual sleep parameters, among OBP and offspring of community controls (OC) from ages 10 through 18. The phenotypic approach allows for the identification of latent clusters of co-occurring sleep disturbances, rather than individual sleep parameters, facilitating the assessment of BP risk. To do so we used a data-driven approach that considers six core aspects of sleep. Five sleep domains included here (quality, alertness, timing, efficiency, and duration), identified in Buysse's (Buysse, 2014) recent work defining *sleep health*, were selected because they are associated with health outcomes, are continuous measures, have face validity, and can be measured across several levels of analysis (e.g., self-report, behavioral; (Buysse, 2014)). Importantly, many of these sleep dimensions demonstrate change over development and are implicated in BP (Carskadon, 2011; Harvey et al., 2006).

The longitudinal Pittsburgh Bipolar Offspring Study (BIOS) provides a unique opportunity to address these questions. BIOS prospectively assesses sleep behavior in a large sample of OBP and OC, some of whom (in both groups) had non-BP psychopathology. We aimed to extend the results of our cross-sectional study (Levenson et al., 2015), showing that baseline sleep disturbance may be a prognostic indicator of the development of BP in high-risk youth. Using data from baseline and follow-up BIOS assessments, we characterized the *longitudinal* sleep phenotypes of OBP and OC during the middle- and high-school years. Sleep groups were then compared on their clinical and demographic features at each age. Last, we examined the prospective relationship between sleep phenotype group and onset of BP among OBP.

Method

The methodology for BIOS has been described in detail in prior reports (Levenson et al., 2015; Birmaher et al., 2009). This study was approved by the University of Pittsburgh Institutional Review Board.

Participants

Parents (Probands)—Parents with BP were recruited through advertisements (65%), adult BP studies (31%), outpatient clinics (1.3%), and random digit dialing (2.6%). Parents met criteria for BP I or II according to the Diagnostic and Statistical Manual, Version-IV (DSM-IV) (American Psychiatric, 2000). Community control parents were healthy or diagnosed with non-BP psychiatric disorders, grouped-matched by age, sex, and neighborhood. Community controls were recruited using local population-based random

dialing telephone surveys based on the demographic location of the parents with BP. For community control offspring, neither biological parent could have BP and or a first-degree relative with BP. In order to recruit a sample of probands who could feasibly participate in the study, all parents were excluded for: current or lifetime diagnoses of schizophrenia; intellectual disability; mood disorders secondary to substance abuse, medical conditions, or medications; and living more than 200 miles outside the Pittsburgh area.

Offspring—Offspring ages 6-18 from each family were included. Children who were unable to feasibly participate in the research procedures (e.g., for intellectual disability or pervasive developmental disorder) were not included.

Procedures

Clinicians obtained consent from parents and assent from offspring. Parents and offspring were assessed for psychiatric disorders, sleep patterns and disturbances, and other domains of interest. Parents and offspring repeated assessments roughly every two years (mean=2.18 years, S.D.=0.16) and also completed sociodemographic characteristics and pubertal development questionnaires.

Probands' DSM-IV psychiatric disorders were assessed through structured clinical interview; parents were interviewed about their children, and children were directly interviewed for the presence of lifetime psychiatric disorders and mood symptoms. Bachelors- or masters-level interviewers completed assessments after achieving 80% agreement with a certified rater for psychiatric disorders. Independent interviewers assessed parental psychopathology and their offspring's psychopathology. All data were presented to a child psychiatrist for diagnostic confirmation, who was blinded to the psychiatric status of the parents. When necessary, offspring medical and psychiatric records were obtained and reviewed by their interviewers.

Offspring ages 8-18 completed a measure of sleep behavior and circadian preference, the School Sleep Habits Survey (SSHS; (Wolfson & Carskadon, 1998) The SSHS was added to the assessment battery in November 2003--two years after BIOS started recruiting participants. As with our previous study (Levenson et al., 2015), data from the assessment time point when the SSHS was first completed by both parents and offspring was considered the baseline. Every subsequent follow-up assessment until age 18 was included. Because youth were assisted in completing the SSHS at ages 8 and 9, only SSHS data collected when the offspring were between ages 10 and 18 were included to ensure true self report (n=661, 1433 total observations). Participants had an average of 2.11 assessments (S.D.=0.995, range=1-4); among those who had 1 SSHS assessment between ages 10-18 (n=409) the assessments spanned an average of 3.63 years (SD=1.63, range = 0.94 to 7.35).

Measures

The Petersen Pubertal Developmental Scale (PDS; (Petersen, Crockett, Richards, & Boxer, 1988) and respective Tanner stages (Marshall & Tanner, 1969; Marshall & Tanner, 1970) were used to evaluate pubertal development. Pubertal status was included because of changes in sleep that occur over pubertal development (Jenni, Achermann, & Carskadon,

2005). Socio-economic status (SES) was ascertained using the Hollingshead scale (Hollingshead, 1975).

Proband's DSM-IV psychiatric disorders were ascertained through the Structured Clinical Interview-DSM-IV (SCID; (Spitzer, Gibbon, & Williams, 1995) plus several sections from the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version (K-SADS-PL; (Kaufman et al., 1997). Rates of lifetime psychiatric disorders for probands are shown in eTable 1. Offspring lifetime psychiatric disorders were assessed with the K-SADS-PL interview (the SCID was used for diagnosis of non-mood psychiatric disorders among offspring aged 18 or older). To evaluate mood disorder diagnosis, the K-SADS Mania Rating Scale (K-MRS) and the depression section of the KSADS-P (K-SADS Depression Rating Scale (K-DRS); (Frazier et al., 2007; Axelson et al., 2003) were used. A diagnosis of Bipolar Disorder Not Otherwise Specified (BP-NOS) was made using operationalized criteria from the Course and Outcome of Bipolar Youth (COBY) study (Axelson et al., 2006; Birmaher et al., 2006); this work demonstrated that youth with BPNOS have similar psychosocial impairment, suicidality, and family history of BP as youth with BP-I.

Sleep phenotype groups were assessed using an abridged version of the School Sleep Habits Survey (SSHS). Items assessing habitual sleep patterns and circadian preference were included, while other items were excluded to reduce participant burden. The SSHS asks about usual sleeping patterns over the prior two weeks on school days and weekend days, including sleep timing, continuity, duration, daytime sleepiness, quality, and circadian phase preference. The SSHS demonstrated high correlation with data obtained from sleep diaries and actigraphy, and was used in large scale community studies of children and adolescents across the world, including among youth ages 10-12 (Wolfson et al., 2003; Russo, Bruni, Lucidi, Ferri, & Violani, 2007; Bruni et al., 2015). Because an abridged version of the SSHS was administered, we were not able to utilize the subscales of the SSHS that have been developed previously (Carskadon, Vieira, & Acebo, 1993; Sleep for Science Sleep Research Lab, 2016; Kandel & Davies, 1982). Instead, we utilized the five dimensions of sleep health (Satisfaction, Alertness, Timing, Efficiency, and Duration) defined by Buysse (Buysse, 2014) and we added a measure of sleep variability. eTable 2 lists each domain name and description, and the SSHS items used to represent each domain. Sleep variables were dichotomized to fit the latent transition analysis. Without accounting for the fact that many adolescents sleep in on the weekend to make up for short sleep during the week, the calculation of weekend sleep timing may be biased. Thus, when calculating weekend sleep timing we adjusted the midpoint of sleep by half the difference in sleep duration from the weekday to the weekend ($(\text{Weekend Sleep Onset Time} + 0.5 * (\text{Weekend Sleep Duration}) - 0.5 * (\text{Weekend Sleep Duration} - \text{Weekday Sleep Duration}))$; (Roenneberg, Wirz-Justice, & Mellow, 2003)). Some measures of sleep were assessed separately for weekday and weekend in the SSHS (sleep timing, efficiency, and duration). To represent weekday and weekend in one variable, these items were weighted proportional to the days of the week ($\text{weekday} * (5/7) + \text{weekend} * (2/7)$).

Statistical Analyses

All analyses were performed with SAS version 9.4. PROC LTA was used to perform a latent transition analysis (LTA) to identify latent sleep groups over time, based on participants' ratings for the six sleep domains. A LTA allows for the identification of latent sleep groups based on multiple categorical variables. We fit LTA models with 2-5 latent groups (using 20 randomly generated starting seeds to locate a global solution) and compared the models based on the interpretability of their fitted latent groups and fit statistics (e.g. AIC and BIC). This number of latent groups was initially chosen because allowing for 6 or more groups would not enhance the interpretability or generate new data than using the original 6 sleep variables identified. Because we were interested in the longitudinal characteristics of sleep, after identifying the latent groups we used the LTA to examine transitions between sleep groups from one time point to the next. Participant assessments were put into 'bins' by age at time of the assessment: 10-12, then 12-14, 14-16, and 16-18. If a participant had multiple assessments within one age 'bin' due to scheduling restrictions (e.g., one at age 12.2, one at age 13.9), we used the worst rating for each sleep variable for each person during the bin. Chi-square, ANOVA, and Fisher's exact tests were used to compare the latent groups on demographic and clinical characteristics. Since we intended to use the imputed latent group assignments for predicting the development of BP, we used only the observations *preceding* BP conversion for any participant; thus the 49 offspring with BP at baseline were excluded from this analysis. If a participant did not develop BP, all observations between ages 10-18 were used.

To test if sleep phenotype is predictive of the development of BP among OBP, we used a 'proximal' model with latent sleep group as the main predictor of BP conversion at the subsequent BIOS assessment during the 12-20 age range. We utilized a logistic regression model with a random intercept for family membership to model the association between proximal sleep group/covariates and the development of BP (BPI, II, or NOS) at the next assessment. For every participant at every time point, we computed their posterior probability (probability of correct assignment) to each latent group given his/her sleep ratings at that time point, and then assigned him/her to the latent group with the highest posterior probability. For participants who developed BP, we used their latent group membership at the visit preceding BP onset; for participants who did not develop BP, we used their latent group membership from the visit preceding their final visit in the 10-20 age range (the 'proximal' visit). We first compared demographic and clinical characteristics between the proximal latent sleep groups using chi-square, Fisher's exact, and ANOVA tests where appropriate. All hypothesis tests were two-sided with the significance level set to 0.05.

Results

Sample Selection and Descriptive Characteristics

Of the original 661 participants (with 1433 observations) who completed the SSHS between the ages of 10 and 18, n=49 were diagnosed with BP at the time of their first SSHS assessment. After excluding these participants from the analyses (and their associated observations), our sample included 1293 observations from 612 participants. Of these 612

participants (335 OBP, 687 observations; 277 OC, 606 observations), half were female (50.2%) and 57.8% lived with both of their biological parents at intake. Mean age at their first SSHS assessment was 12.81 years (S.D.=2.25) and nearly 36% were at advanced pubertal status (Tanner stage 4 or 5). The majority of participants were Caucasian (80.9%), and on average middle class (mean Hollingshead rating 36.32 (S.D.=14.23)). At their first SSHS assessment 16.2% were using any psychotropic medication, and 6.5% were using stimulants specifically. Among these 612 participants, 36 converted to BP during the study, with an average age of BP onset of 17.23 years (S.D.=3.01y).

Sleep Phenotype Groups

The LTA model with three latent groups balanced the best performance of AIC (1821.88) and BIC (1989.72; eTable 3) and produced interpretable, non-redundant sleep groups. Table 1 shows the estimated probability of having each sleep disturbance within each latent group. Based on these probabilities, the three groups were characterized as: 1) **good sleepers**: very low incidence (< 0.20) of sleep deficiencies over the six sleep domains; 2) **poor sleepers**: moderate (~ 0.40) to high (> 0.70) incidence of sleep deficiencies in nearly all of the sleep domains; and 3) **variable sleepers**: high incidence (0.94) of weekend-to-weekday sleep variability and low incidence (≤ 0.20) of sleep deficiencies over all other sleep domains. Each participant was then assigned to the latent group with the highest posterior probability at each time point.

It is possible that youth may have fit into one sleep phenotype group at one assessment point, but another group at a later point. eTable 4 shows the estimated group membership probabilities at each age bin. The variable sleep group was the most common across all time points. Membership in the good sleep group decreased over time from 0.40 during the 10-12 age range to 0.08 during the 16-18 age range, while membership in the poor sleep group increased from 0.16 during the 10-12 age range to 0.46 during the 16-18 age range.

Because the probability of membership in each group changed over time, we examined the likelihood of transitioning from one sleep group to another over time. The diagonal entries in eTable 5 denote the estimated probability of *remaining* in a latent sleep group over consecutive time points. Membership in the poor sleep group is close to stationary over time (> 0.90 for all transitions), members of the good sleep group were more likely to transition to another sleep group at the next age than remain in the good sleep group (< 0.45), and membership in the variable sleep group exhibited moderate stability over time (> 0.75).

Demographic and Clinical Characteristics of Each Sleep Phenotype Group

Clinical characteristics related to psychiatric diagnoses reflect *lifetime ratings* (intake assessment through the last assessment completed within each age bin). At ages 10-12 (eTable 6) participants in each sleep group differed only on likelihood of being diagnosed with MDD, with youth in the poor sleep group significantly more likely to have MDD than the other two groups ($p < 0.03$). At ages 12-14 and 14-16 (eTables 7-8) the poor sleep group was significantly more likely to have MDD than the other two groups (all $p < 0.05$), and at ages 16-18 the poor and variable groups were significantly more likely to have MDD than the good sleep group (all $p < 0.04$). With respect to parental status, the proportion of youth in

each sleep group who had a parent with BP did not significantly differ at ages 10-12 or 12-14. At middle adolescence (ages 14-16; eTable 8), youth in the poor sleep group were significantly more likely to have a parent with BP than those in the variable sleep group ($p=0.007$), while at ages 16-18 (eTable 9) youth in the poor sleep group were significantly more likely to have a parent with BP than those in the good sleep group ($p=0.017$). No additional significant differences were observed at ages 10-12 or 12-14. As youth aged into middle adolescence (ages 14-16, eTable 8), a greater proportion of the poor sleep group was diagnosed with an anxiety disorder and DBD as compared to the other two groups (all $p<0.03$), and a greater proportion of the poor sleep group was diagnosed with a substance use disorder than the variable sleep group ($p=0.017$). At ages 16-18 the poor sleep group was significantly more likely to have an anxiety disorder, DBD, and substance use disorder (all $p<0.05$) than those in the variable sleep group. Last, we found no differences between groups on level of psychotropic medication use, stimulant use, and season in which participants were assessed (school-year vs. summer) at any age point (results available upon request).

Proximal Model Analyses

To estimate the risk of developing BP among at-risk youth, we examined data from the 227 OBP offspring with sufficient data who were included in the LTA, of whom 25 developed BP. We identified the latent sleep groups at the time of the 'proximal' visit and compared the groups on demographic and clinical characteristics (Table 2). For youth who did not develop BP, the proximal time point was the visit preceding their final visit in the 10-20 age range. The proximal latent sleep groups differed significantly on pubertal status, age, and likelihood of having MDD. Because pubertal status and age were highly correlated ($r=0.65$), we included only age as a covariate in the regression analyses. eTable 10 shows the estimated probability of having each sleep disturbance within each latent group at the proximal assessment.

Using the logistic regression model with a random intercept for family membership described above, Table 3 shows that after controlling for age and MDD, those in the poor sleep group had nearly twice the odds of developing BP as those in the good (OR=1.99) and variable sleep group (OR=2.03). Those in the variable sleep group were just as likely to develop BP as those in the good sleep group (OR=0.98). These differences were not statistically significant at the $p<0.05$ level. After controlling for psychotropic medications and, separately, stimulants, the effect sizes increased. For example, the poor sleep group had more than four times the odds of developing BP as those in the good sleep group (OR=4.25), though results remained marginally non-significant. This may suggest that these variables were initially minimizing the differences between sleep groups on their likelihood of developing BP. Controlling for whether the sleep assessment occurred during school or non-school months had little effect on the odds ratios as compared to the model controlling only for age.

Because major depressive episodes have been shown to predict the onset of BP among at-risk youth (Axelson et al., 2015), we chose to examine whether latent sleep group predicted the onset of major depressive disorder (MDD), which then predicted BP. Unfortunately,

sufficient data were not available to test this model. Instead, we examined the association between proximal sleep group/covariates and development of MDD at the next assessment (see eTable 12 for demographic and clinical comparisons of groups at the proximal MDD timepoint). After controlling for age, lifetime DBD, and whether youth live with both parents at intake, those in the poor sleep group had nearly five times the odds of developing MDD as those in the good (OR=4.71; $p=0.022$) and nearly four times the odds of developing MDD as those in the variable sleep group (OR=3.99; $p=0.004$).

Discussion

In this paper we used latent transition analyses to characterize the naturally-occurring sleep phenotypes among OBP and OC during the middle and high school years, examined demographic and clinical differences among the groups, and tested whether at-risk youth with a particular sleep phenotype were more likely to develop BP. Participants' report of sleep across six domains best fit into three non-overlapping latent sleep phenotype groups, and those with poor sleep at their proximal assessment were more likely to develop BP at the next assessment than those with good or variable sleep, though this difference did not reach statistical significance.

Upon identifying the three sleep phenotype groups, we observed general group membership trends over time, such that the likelihood of being in the good sleep group became rare by the 16-18 age point, while being in the poor sleep group became increasingly likely over time. These developmental sleep trends may be explained by normative biological changes to sleep from childhood into adolescence. For example, homeostatic sleep pressure accumulates more slowly during this time (Jenni et al., 2005) and endogenous circadian phase is delayed (Crowley, Acebo, & Carskadon, 2007; Carskadon, 2011), making it harder for adolescents to fall asleep. While the likelihood of being in the variable sleep group in our sample was relatively stable (~50% at all ages), this rate is higher than the 26-44% of youth who go to bed at least 2 hours later on the weekends than on school nights reported by the National Sleep Foundation (National Sleep Foundation poll task force, 2006). This difference may be accounted for by the fact that our measure of variability included at least 2 hours difference in bedtime or wake time. In addition, the likelihood of transitioning from one group to another at adjacent time points differed by group, as did the direction of each transition. For example, participants whose sleep started as good tended to experience variable or poor sleep at the next time point. Further research is needed to fully understand the clinical implications of these transitions with age.

We did find several demographic and clinical differences among the sleep groups at each age. Youth in the poor sleep group were more likely to have MDD than those in the other groups, and by middle adolescence (ages 14-16) those in the poor group were also more likely to have an anxiety disorder and DBD. Because sleep disturbances are diagnostic criteria for MDD (American Psychiatric Association, 2013), and frequently occur in anxiety disorders and DBD (Cox & Olatunji, 2016; Aronen, Lampenius, Fontell, & Simola, 2014), it may be that those youth were identified as poor sleepers as a *consequence* of this psychopathology, just as much as poor sleep may have *contributed* to the likelihood of having these disorders. While we are unable to determine the direction of effect in these

analyses because assessments at each age are cross-sectional, future longitudinal work should aim to do so. If poor sleep contributes to the likelihood of developing these psychiatric disorders, our findings suggest that the consequences of poor sleep may have the greatest impact at this developmental stage.

Additionally, starting at age 14-16, participants in the poor sleep group were more likely to have a parent with BP, suggesting that by middle adolescence being at-risk for BP increases the likelihood of having poor sleep, either directly or indirectly by virtue of having a non-BP psychiatric disorder. The ages of 14-16 also correspond with the beginning of high school for many adolescents, a time when school start times shift significantly earlier in the morning, while, biologically, youth experience a slower buildup of the homeostatic sleep drive and delay of circadian phase (Carskadon, 2011). These biological changes in sleep may have contributed to increasing membership in the poor sleep phenotype group at this developmental stage. Moreover, this mismatch of circadian phase and schedule demands, in conjunction with consequent insufficient or fragmented sleep, may confer even higher risk for BP among youth who are biologically vulnerable to the disorder by virtue of having a parent with BP.

Last, those with poor sleep at their proximal assessment had twice the odds of developing BP at the next assessment point than those with good or variable sleep, after controlling for age and MDD. These differences were *not statistically significant*, likely due to small sample size and/or low base rate of BP conversion, contributing to low power to detect our effect and/or the relatively large confidence interval. Indeed, our observed rate of BP conversion among the sample included in our analyses (25 out of 227 or 11%) is consistent with the rate of BP among offspring who have at least one parent with BP observed in other studies (5-15%) (Birmaher et al., 2009; Lapalme, Hodgins, & LaRoche, 1997; Zappitelli et al., 2011). Assuming that our effect size of 2.74 reflects the true odds of developing BP based on being in the poor vs. good sleep group, and given that the rate of BP conversion seen here is consistent with that observed in the literature, our power to detect a significant effect was roughly 59% (power estimated at 58.6% for a true odds ratio of 2.5 and a 10% probability of conversion). While low power may have contributed to statistically non-significant effects, we cautiously speculate that these findings carry clinical significance. The high risk of developing BP among the poor sleepers may be due to having a comorbid MDD diagnosis, however our analyses controlled for MDD, suggesting that poor sleep increases vulnerability to BP at the next assessment point, *over and above* the risk conferred from MDD. Those in the poor sleep group had significantly greater odds of developing MDD, but due to limited data, we were unable to examine whether the development of MDD then led to BP onset. Future work should test this model, as well as to build on recent findings that dimensional measures of mood lability predict BP onset (Hafeman et al., 2016). For example, future work could examine whether latent sleep group predicts worsening mood lability and subsequent BP onset.

The results reported here have potentially meaningful clinical implications. First, while variability in sleep across the week is not rare among youth (the likelihood of having variable sleep without other sleep disturbances rises to about 50% by late adolescence), having variable sleep *on its own* is not substantially associated with elevated risk of

developing BP among at-risk youth. Rather, at-risk youth with *poor* sleep (i.e., variable sleep *and* other sleep problems) may be at increased risk of developing MDD and BP at their next assessment. While it was outside the scope of the current study to evaluate which aspects of poor sleep differentiate poor sleepers from the other two groups, future work should aim to identify relevant sleep variables within each domain at this level of detail. Second, clinicians and parents should be aware of the association between poor sleep and the development of MDD and BP among at-risk youth, particularly among those who may already be primed for the onset of BP by virtue of having other psychopathology. Third, it is likely that youth will experience variable and/or poor sleep as they age. However, since sleep problems may be malleable risk factors among at-risk youth (Goldstein et al., 2014), future work should continue to apply sleep interventions in the service of preventing or delaying BP among OBP who show disturbed sleep.

This study is unique in use of LTA, a data driven analytic approach that allows for the identification of sleep disturbances that are most likely to present together and participant movement between sleep phenotype groups. To do so, we relied on Buysse's *Sleep Health* framework, which guided the selection of sleep dimensions to obtain an overall comprehensive representation of sleep, and the SSHS, which assesses usual sleeping patterns and collects a variety of sleep-related variables.

Limitations

The present analyses have important limitations. We were not able to use distal longitudinal predictors of sleep to predict the development of BP among at-risk youth. Rather, we relied on each participant's sleep phenotype at the assessment *proximal* to BP onset. Future studies should aim to better understand longitudinal trajectories of sleep and how these influence the onset of BP and other psychiatric illnesses. Indeed, when additional waves of data from the BIOS study are available, it will be useful to replicate the current analyses to determine whether transitions from one sleep phenotype to the next over time are predictive of onset of BP. While sleep assessments were completed roughly every two years, allowing for multiple sleep assessments for many participants included in the analysis, sleep patterns may have changed during the inter-assessment interval. If so, these changes likely were not captured by our assessments, since the SSHS inquires about sleep over the last two school weeks. Moreover, the sleep patterns reflected in the proximal sleep assessment may have been collected up to two years prior to BP conversion, again calling into question the clinical significance of the sleep parameters in the prediction of BP onset. Future studies should aim for more frequent assessment of sleep, perhaps using daily diary or actigraphy, to obtain greater specificity in understanding the impact of each sleep phenotype on the onset of BP and other psychiatric disorders. Indeed, our study relied on a self-report assessment of sleep, which may have limited the objectivity of the sleep measurement and constitutes a relative weakness of the study. Still, the SSHS demonstrated high correlation with data obtained from sleep diaries and actigraphy. While we controlled for syndromal MDD in our analysis of latent sleep group predicting the onset of BP, another potential limitation is the possibility that youth may have reported subsyndromal mood symptoms that did not constitute a full mood disorder, but nevertheless may have contributed to the risk of developing BP among the poor sleepers. The sleep of parents diagnosed with non-BP psychiatric disorders

(including OC) may be disrupted as a consequence of the psychopathology they report (proband lifetime psychopathology seen in eTable 1). The presence of these disorders in the parents may not only affect parents' *own* sleep, but may have presented a genetic and/or environmental risk for disturbed sleep in the offspring included in our sample. While it is outside the scope of this paper to address this question, future work should focus efforts here to further understand the impact of parent psychopathology on youth sleep and risk for BP. Last, the relatively small number of at-risk participants developing BP during the study period may have contributed to the lack of statistically significant differences among sleep groups in their likelihood of developing BP. Future studies may choose to focus on those at 'ultra-high-risk' for BP (Hafeman et al., 2016) by virtue of having several key predictors, to examine the nature and role sleep in the development of BP in this sample.

Conclusion

In summary, we found three non-overlapping sleep and circadian phenotype groups in a large sample of OBP and offspring of demographically-matched community control parents. Among all youth, we observed an overall trend of good sleep becoming variable, and then poor, as youth age. Future studies will be required to fully understand the clinical implications of the transitions across development and to explore the direction of these effects (e.g., whether poor sleep is a cause or consequence of psychopathology at each age bin). Future work is needed to understand the biopsychosocial processes by which disturbed sleep contributes to the onset of BP.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

1. The LTA model identified latent groups of good, poor, and variable sleepers.
2. We observed a trend of good sleep becoming variable, and then poor, as youth age.
3. Poor sleepers had twice the odds of developing BP than good and variable sleepers.
4. Poor sleepers were more likely to have psychopathology than other groups.

Table 1

Estimated Probability of Sleep Deficiencies Given Latent Group Membership

	Latent Sleep Group		
	Good	Poor	Variable
Frequent Awakenings	0.11	0.39	0.11
Inadequate Sleep	0.15	0.71	0.20
Short Sleep Duration	0.04	0.40	0.10
Daytime Sleepiness	0.03	0.39	0.01
Large Sleep Variability	0.00	0.87	0.94
Late Midsleep Time	0.02	0.28	0.16

Table 2

Demographic/Clinical Comparisons at Proximal BIOS Assessment

	Latent Sleep Group			Test Stat	p-value
	Good Sleep	Poor Sleep	Variable Sleep		
	n=34	n=78	n=115		
Demographic Factors					
Gender (% Female)	15 (44.127%)	41 (52.6%)	58 (50.4%)	0.68	0.7118
Lives with both bio parents (% yes)	19 (57.6%)	27 (36.5%)	47 (41.6%)	4.20	0.1222
Puberty (% Tanner stage 4 or 5)	6 (18.2%) ^{ab}	60 (79%) ^a	79 (70.5%) ^b	40.1	<0.0001
Race (% White)	30 (88.2%)	62 (79.5%)	96 (83.5%)	1.34	0.5105
Age, mean (SD)	12.37 (2.1) ^{ab}	15.81 (1.8) ^{ac}	14.85 (2.2) ^{bc}	33.16	<0.0001
SES, mean (SD)	38.38 (16.7)	36.33 (13.3)	35.52 (14.5)	0.52	0.5969
Lifetime Diagnostic History					
Major Depressive Disorder	3 (9.1%) ^a	22 (28.2%) ^{ac}	16 (14.2%) ^c	8.28	0.0159
Any Anxiety Disorder	10 (30.3%)	29 (37.2%)	36 (31.9%)	0.76	0.6831
ADHD	10 (30.3%)	24 (30.8%)	35 (31%)	0.01	0.9973
Disruptive Behavior Disorder	6 (18.2%)	21 (26.9%)	18 (15.9%)	3.56	0.1685
Non-BP Axis I d/o in Proband	31 (91.2%)	74 (94.9%)	105 (91.3%)	0.96	0.6198

Superscripts ^a, ^b, and ^c denote pairwise comparisons that are significant at 0.05 level.

Table 3

Likelihood of Developing BP as a Function of Sleep Phenotype at Proximal Assessment

Sleep Group Comparison	Control for age		Control for age, depression		Control for age, psychotropic meds		Control for age, stimulants		Control for age, season	
	Odds Ratio	p-value	Odds Ratio	p-value	Odds Ratio	p-value	Odds Ratio	p-value	Odds Ratio	p-value
Poor vs. Good	2.74(0.62,12.11)	0.1794	1.9 (0.45,8.91)	0.3617	4.2 (0.89,20.34)	0.0692	3.4 (0.74,15.87)	0.1154	2.7 (0.61,12.03)	0.188
Variable vs. Good	1.22 (0.31,4.78)	0.7722	0.9 (0.25,3.92)	0.9802	1.6 (0.40,6.61)	0.4984	1.3 (0.33,5.42)	0.6771	1.2 (0.30,4.75)	0.7929
Poor vs. Variable	2.25 (0.83,6.10)	0.1100	2.03 (0.72,5.72)	0.1782	2.63 (0.95,7.27)	0.0619	2.55 (0.91,7.11)	0.0737	2.26 (0.83,6.15)	0.1106