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Circadian rhythm dysfunction and psychopathology in the offspring of parents with bipolar disorder: a high-risk study in the Chinese population

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ABSTRACT

Background Understanding the evolution of circadian rhythm dysfunction and psychopathology in the high-risk population has important implications for the prevention of bipolar disorder. Nevertheless, some of the previous studies on the emergence of psychopathologies and circadian dysfunction among high-risk populations were inconsistent and limited.

Aims To examine the prevalence rates of sleep and circadian dysfunctions, mental disorders and their symptoms in the offspring of parents with (O-BD) and without bipolar disorder (O-control).

Methods The study included 191 O-BD and 202 O-control subjects aged 6–21 years from the Greater Bay Area, China. The diagnoses and symptoms of sleep/circadian rhythm and mental disorders were assessed by the Diagnostic Interview for Sleep Patterns and Disorders, and the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version, respectively. Generalised estimating equations and shared frailty proportional hazards models of survival analysis were applied to compare the outcomes in the offspring.

Results Adjusting for age, sex and region of recruitment, there was a significantly higher risk of delayed sleep phase symptoms (9.55% vs 2.58%, adjusted OR: 4.04) in O-BD than in O-control. O-BD had a nearly fivefold higher risk of mood disorders (11.70% vs 3.47%, adjusted OR: 4.68) and social anxiety (6.28% vs 1.49%, adjusted OR: 4.70), a fourfold higher risk of depressive disorders (11.17% vs 3.47%, adjusted OR: 3.99) and a threefold higher risk of mood symptoms (20.74% vs 10.40%, adjusted OR: 2.59) than O-control. Subgroup analysis revealed that O-BD children (aged under 12 years) had a nearly 2-fold higher risk of any mental and behavioural symptoms than O-control, while there was a nearly 4-fold higher risk of delayed sleep phase symptoms, a 7.5-fold higher risk of social anxiety and a 3-fold higher risk of mood symptoms in O-BD adolescents (aged 12 years and over).

Conclusions There was an increase in delayed sleep phase symptoms in O-BD adolescents compared with their control counterparts, confirming the central role of circadian rhythm dysfunction in bipolar disorder. The findings of the specific age-related and stage-related developmental patterns of psychopathologies and circadian dysfunction in children and adolescent offspring of parents with bipolar disorder paved the way to develop specific and early clinical intervention and prevention strategies.

Trial registration number NCT03656302.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ An increased prevalence of mental disorders was reported among the offspring of patients with bipolar disorder, but the evidence was inconsistent. A small number of studies have reported sleep disturbances among high-risk offspring.

WHAT THIS STUDY ADDS

⇒ The current study provided comprehensive assessments of sleep and circadian rhythm dysfunction and reported empirical evidence of the emergence of mental disorders and symptoms in Chinese high-risk bipolar offspring. Circadian rhythm dysfunction and the dimensional symptoms of psychopathology may serve as novel markers of bipolar disorder, expanding the well-known staging model of bipolar disorder.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The current study suggests that a comprehensive measurement of a spectrum of psychopathologies beyond bipolar disorder, including sleep and circadian rhythms, among the high-risk offspring population could advance the understanding of bipolar disorder. The findings of the study highlight the need to assess sleep and circadian rhythms earlier in the course of bipolar disorder and provide an important target for the early intervention and prevention of bipolar disorder.

INTRODUCTION

Bipolar disorder is one of the most severe mental disorders, characterised by recurrent (hypo)

manic and depressive episodes, affecting approximately 1% of the population worldwide.[1] In China, the weighted prevalence of bipolar disorder was approximately 0.6%.[2] Many case–control studies reported higher rates of mental disorders, sleep disturbances and circadian rhythm dysregulations among patients with bipolar disorder.[3] However, it is hard to clarify whether these factors are prodromal markers or complications of bipolar disorder due to the common comorbidities and medication use among patients with bipolar disorder.[4 5] Given bipolar disorder's heritability, which can reach up to 83%, studying high-risk offspring is a well-established method for identifying the prodromal markers or risk factors of bipolar disorder, offering a crucial window to understand the evolution of mood features and other psychopathologies in this high-risk population.[6]

Previous longitudinal investigations in the offspring of parents with bipolar disorder (O-BD) suggested the emergence of various non-mood disorders prior to the onset of bipolar disorder, including sleep and anxiety disorders in late childhood, adjustment disorders and dysthymia in early adolescence, and major depression in late adolescence.[7–9] Recently, there has been a growing consensus that sleep/circadian rhythm dysfunction may be one of the key prodromes as well as core manifestations of bipolar disorder. Existing evidence indicated that sleep alterations may serve as precursors of the initiation of bipolar disorder, and dynamic changes in sleep patterns accounted for one-third of the predictable explained variance in the multivariate psychiatric symptom outcomes.[10] Moreover, a recent investigation of dim light melatonin onset found a lower nocturnal melatonin level and a flattened melatonin secretion indicative of circadian dysfunction among unaffected O-BD than the controls.[11]

Nonetheless, several knowledge gaps exist in the field. First, the association between parental history of bipolar disorder and the emergence of various kinds of sleep and circadian dysfunction among the offspring remains largely underexplored. Second, previous findings on the risk of psychopathology among O-BD are somehow inconsistent. For example, some studies observed a higher prevalence of attention deficit hyperactivity disorder (ADHD) in O-BD than in control offspring (O-control),[12] but these findings have not been consistently replicated by other studies.[13] Third, there is limited research on the difference in the age of onset of psychopathology between O-BD and O-control. Furthermore, while a previous high-risk study has revealed important cross-national variations in psychopathology,[14] there is a dearth of evidence from the Chinese population in the bipolar disorder offspring study.

Therefore, this study aimed to comprehensively compare the differences in sleep and circadian dysfunctions, as well as mental symptoms/disorders, between the offspring of parents with and without bipolar disorder. In addition, the current study aimed to further investigate the emergence of specific patterns of sleep/circadian dysfunctions and mental problems in the childhood and adolescence periods of the offspring of parents with bipolar disorder.

METHODS

Participants

This is a case–control high-risk offspring study of bipolar disorder conducted in the Greater Bay Area (Hong Kong Special Administrative Region (SAR) and Guangdong) in China. Parents with bipolar disorder who served as case probands were recruited from psychiatric clinics, while parents without bipolar disorder who served as control probands were recruited from other research projects and communities. The inclusion criteria for case offspring were: (1) aged 6–21 years and (2) having at least one biological parent with bipolar disorder-I/II. The inclusion criteria for control offspring were: (1) aged 6–21 years, (2) having no biological parent with bipolar disorder-I/II and (3) age/sex matched with case offspring. The exclusion criteria for offspring participants were: (1) having any severe medical diseases or neuropsychiatric disorders, (2) being unable to accomplish the measurements or (3) being shift workers. All eligible offspring participants from the same family were recruited. Informed consent was obtained from participants. Assent was also obtained from the parents of offspring under 18 years old. Offspring participants were recruited from 11 February 2017 to 16 January 2020. Statistical analyses were conducted from March 2022 to July 2022.

Measurements and procedures

Probands and their spouses were invited to a clinical interview based on the Diagnostic and Statistical Manual of Mental Disorders[15]—Fourth Edition (DSM-IV)[16] conducted by psychiatrists and psychologists. The families with at least one biological parent diagnosed with bipolar disorder were regarded as case families, while the families without any biological parent with bipolar disorder were regarded as control families (figure 1).

The diagnoses and symptoms of sleep and circadian rhythm dysfunction of offspring were ascertained by face-to-face interviews using the Chinese Version of the Diagnostic Interview for Sleep Patterns and Disorders (DISP).[17] The original DISP was developed according to the International Classification of Sleep Disorders, Second Edition criteria, while the DISP applied in the current study was further adapted to align with the International Classification of Sleep Disorders, Third Edition (ICSD-3).[18] In addition, we have further adapted the items of DISP to meet the diagnostic criteria of sleep and circadian disorders among children and adolescents. Compared with the clinician diagnosis, DISP has classification accuracies of 0.63–0.96 and κ coefficients of 0.20–0.79.[17] In this study, data were excluded if they were not collected in accordance with ICSD-3 criteria. In order to capture the emergence of psychopathologies in childhood and adolescence comprehensively, the diagnoses and symptoms of mental disorders among the offspring were assessed by the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADSPL), with high inter-rater agreements ranging from 0.93 to 1.00 and high κ coefficients of 0.63 to 1.00.[19] Mental, sleep and circadian rhythm disorders were defined according

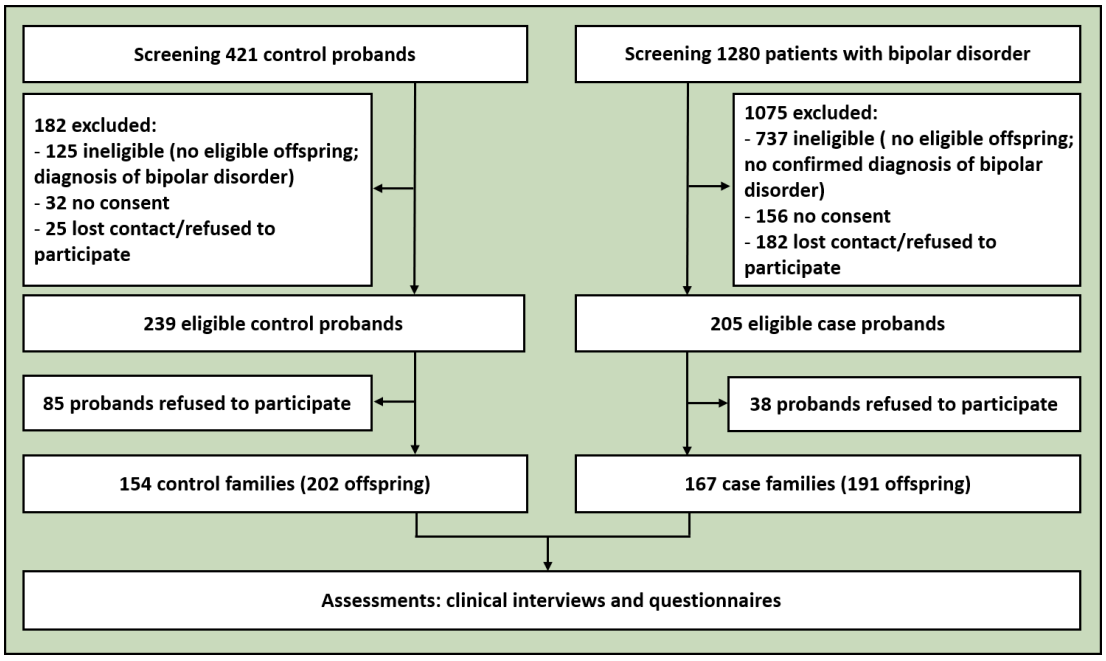

Figure 1 Flowchart of the current study[a]. [a]Probands were excluded if they (1) had severe medical diseases/problems; (2) did not have offspring aged between 6 and 21 years; and (3) were unwilling to take part in this study.

to DSM-IV criteria and ICSD-3 criteria, respectively. In other words, the disorder would need to fulfil the symptom criteria, duration criteria and functional impairments. On the other hand, the study also elicited sleep/circadian dysfunction and psychopathologies at the symptom level. Participants answering in the affirmative on the symptom-related items were considered to have the specific symptoms in their lifetime. Mental symptoms were defined by the key symptoms of the clusters of related disorders, based on K-SADSPL according to DSM-IV. For instance, we defined mood symptoms by key symptoms of depression and bipolar disorder, while anxiety symptoms by key symptoms of panic disorder, agoraphobia, separation anxiety disorder, social anxiety, generalised anxiety disorder, specific phobia and obsessive-compulsive disorder. In terms of sleep and circadian dysfunction, the offspring with the key symptoms of delayed sleep phase disorder, advanced sleep phase disorder, insomnia disorder, restless legs syndrome and nightmares would be considered as suffering from the respective symptoms based on the DISP interview according to ICSD-3.

The uncertain responses in the clinical interviews were defined as missing data. When there was disagreement between the child and parent about the presence of symptoms, the parental report of observed behaviour and the offspring's report of subjective symptoms were adopted. By combining the clinical interviews and medical records, the best estimate strategy was applied.

For the offspring, pubertal status was assessed by the self-reported Tanner Scale which has been validated locally.[20] In addition, the Montgomery-Asberg Depression Rating Scale and the Young Mania Rating Scale were used to measure the severity of depressive and manic symptoms of probands, respectively. The Montgomery-Asberg Depression Rating Scale has a mean intraclass correlation of 0.95 and Cronbach's α of 0.96,[21] while the Young Mania Rating Scale has inter-rater reliability ranging from 0.66 to 0.95 and high validity, reaching up to 0.89.[22] Demographic data, including age, sex and region of recruitment, were collected for all the participants.

Quality control and inter-rater reliability

All interviewers had at least 3 years of clinical experience in psychiatry. The training and standardisation of diagnostic interviews were conducted in a workshop prior to the collection of data. Each interviewer was supervised by experienced interviewers for at least five cases before he/she could independently conduct the clinical interviews. Kendall's coefficient of concordance values ranged from 0.65 to 0.73, which suggested a high level of consistency among interviewers.

Sample size estimation

To achieve a power of 90%, a type I error of 0.05, setting the proportions of 52.1% and 29.1% in the two groups, referring to the largest offspring cohort of bipolar disorder,[23] we estimated that the minimum sample size required for this study would be 199 offspring to detect significant differences between the two groups. The sample size was estimated by G*Power V.3.1.9.7.

Statistical analysis

The demographics of all the participants have been presented as the mean (SD) for continuous variables and percentages for categorical variables. Generalised estimating equations (GEEs) were applied to compare the demographics between O-BD and O-control. The prevalence of sleep/circadian rhythm dysfunction and psychopathologies was presented as percentages, and the differences between groups were calculated by GEE, logistic regression and Mann-Whitney

U test where appropriate. Because of the data issue related to the inclusion of siblings from the same families, GEE was deemed to be the suitable statistical method for the main analysis.[24] Only when the number of cases was insufficient for the use of GEE, logistic regression and Mann-Whitney U test would be used. Survival analysis was used to estimate the relationship between parental history of bipolar disorder and the emergence of sleep/circadian rhythm dysfunction and psychopathologies, including sleep and circadian rhythm disorders, mental disorders and their key symptoms. Two shared frailty proportional hazards models were performed with years from birth as the time-varying covariate. Model 1 is unadjusted. Age at recruitment, sex and region of recruitment were adjusted in model 2. Kaplan-Meier survival plots were used to depict the cumulative events. Subgroup analysis stratified by age was conducted. All the analyses were conducted with IBM SPSS Statistics for Windows, V.26.0 (IBM Corp) and the R project (V.3.6.1, R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/).

RESULTS

In the current study, 321 probands and their offspring were recruited. The probands with bipolar were slightly younger than the control probands (42.30 (9.79) vs 45.10 (8.81), t=3.50, p=0.001). There were 96 and 55 female probands in the bipolar group and control group, respectively (57.49% vs 35.71%, χ^2=15.24, p<0.001). There were fewer control probands (Mainland China: 40.26%, Hong Kong SAR: 59.74%) and more probands with bipolar disorder (Mainland China: 68.86%, Hong Kong SAR: 31.13%) recruited in Mainland China when compared with Hong Kong SAR (figure 1).

A total of 191 O-BD (age: 11.88 (4.36) years; 46.07% female) and 202 O-control (age: 11.54 (3.35) years; 49.25% female) were included, with comparable body mass index, pubertal stage and rates of two-parent family between the two groups. There were fewer O-BD recruited in Hong Kong SAR (O-BD: 28.27% in Hong Kong SAR and 71.73% in Mainland China, O-control: 60.89% in Hong Kong SAR and 39.11% in Mainland China, Wald χ^2=27.02, p<0.001). The parental probands of the O-BD had a lower education level (college and above: 37.68% vs 52.26%, Wald χ^2=4.01, p=0.045) and employment rate (64.93% vs 87.74%, Wald χ^2=12.59, p<0.001). There were 3.50% of the parental probands of the O-BD meeting the criteria of current (hypo)mania. The parental probands of the O-BD group had a higher level of current depression (39.13% vs 12.83%, Wald χ^2=19.33, p<0.001) than the probands of the O-control group (table 1).

Mental disorders and symptoms in O-BD

As shown in table 1, O-BD had a higher lifetime prevalence of mental disorders and symptoms compared with their control counterparts. After adjustment for age, sex and region of recruitment, O-BD had a nearly twofold higher rate of any mental disorders (40.31% vs 26.24%, adjusted OR: 1.87, 95% CI 1.14 to 3.10), a nearly fivefold higher rate of mood disorders (11.70% vs 3.47%, adjusted OR: 4.68, 95% CI 1.30 to 16.86), a fourfold higher rate of depressive disorders (11.17% vs 3.47%, adjusted OR: 3.99, 95% CI 1.11 to 14.34) and a nearly fivefold higher rate of social anxiety (6.28% vs 1.49%, adjusted OR: 4.70, 95% CI 1.21 to 18.18), when compared with their counterparts. Besides, O-BD had a marginally insignificant 2.5 times higher rate of anxiety disorders (12.63% vs 4.95%, adjusted OR: 2.45, 95% CI 0.97 to 6.23). Likewise, there were significantly higher risks of mental symptoms among O-BD than their counterparts. O-BD had higher rates of any mental symptoms (60.73% vs 43.07%, adjusted OR: 2.14, 95% CI 1.37 to 3.33) and mood symptoms (20.74% vs 10.40%, adjusted OR: 2.59, 95% CI 1.24 to 5.44), when compared with O-control. In addition, O-BD had a marginally significant higher rate of behavioural symptoms (36.96% vs 27.86%, adjusted OR: 1.60, 95% CI 0.97 to 2.63). The two groups showed comparable rates of other mental disorders and symptoms.

We further divided the offspring into two subgroups: those under 12 years old (childhood) and those aged 12 years and over (adolescence). In childhood, O-BD had a 1.91-fold higher risk of any mental disorders when compared with O-control. Also, O-BD had nearly twofold higher risks of having any mental symptoms (58.25% vs 41.18%, adjusted OR: 2.12, 95% CI 1.21 to 3.72) and behavioural symptoms (48.54% vs 30.69%, adjusted OR: 2.13, 95% CI 1.14 to 3.95) than O-control after further adjustment. In adolescence, there were 88 O-BD (47.73% female) who were slightly older (15.94 (2.68) vs 14.32 (2.05), Wald χ^2=21.72, p<0.001) and more mature in pubertal maturation (pre/early puberty: 29.89% vs 54.00%, Wald χ^2=10.59, p=0.001) than the 100 O-control (52.00% female). The O-BD group had a 7.49-fold higher risk of social anxiety (11.36% vs 2.00%, adjusted OR: 7.49, 95% CI 1.33 to 42.20) compared with the O-control group. In addition, there were increased mood symptoms (36.05% vs 16.00%, adjusted OR: 3.00, 95% CI 1.14 to 7.92) in the O-BD group. Four O-BD adolescent subjects but none of the O-control reported substance use problems (z=–1.86, p=0.063) (table 2).

Sleep and circadian rhythm disorders and symptoms in O-BD

A total of 179 O-BD (age: 11.85 years (4.39); 45.51% female) and 194 O-control (age: 11.63 years (3.34); 49.74% female) were included in the analyses, with comparable pubertal maturation. Table 3 shows that O-BD had a significantly higher prevalence of delayed sleep phase disorder than O-control in the unadjusted model (5.62% vs 1.03%, OR: 5.71, 95% CI 1.21 to 27.04), but the significance was attenuated after adjustment (adjusted OR: 3.06, 95% CI 0.44 to 21.47). There was no difference in other sleep and circadian rhythm disorders including insomnia between the two groups. On the other hand, there was a significantly higher risk of delayed sleep phase symptoms (9.55% vs 2.58%, adjusted OR: 4.04, 95% CI 1.23 to 13.28) in O-BD than in the controls, which persisted after further adjustment.

In terms of age, there were different circadian patterns between children and adolescents. In childhood, O-BD

Table 1 Demographics and lifetime prevalence of psychopathologies of offspring of parents with (O-BD) and without bipolar disorder (O-control)

	O-control (n=202)	O-BD (n=191)	Unadjusted OR (95% CI)/p value	Adjusted OR (95% CI)*
Demographics				
Age, mean (SD)	11.54 (3.35)	11.88 (4.36)	0.41	NA
Female, n (%)	99 (49.25)	88 (46.07)	0.52	NA
BMI, mean (SD)	18.35 (3.82)	18.15 (3.81)	0.66	NA
Pre/early puberty, n (%)	155 (77.11)	129 (67.89)	0.051	NA
Region of recruitment, n (%)			<0.001	NA
Hong Kong SAR, n (%)	123 (60.89)	54 (28.27)		NA
Mainland China, n (%)	79 (39.11)	137 (71.73)		NA
Two-parent family, n (%)	140 (99.29)	124 (90.51)	0.96	NA
Proband characteristics, n (%)				
Education (college and above)	81 (52.26)	52 (37.68)	0.045	NA
Employment	136 (87.74)	87 (64.93)	<0.001	NA
Current (hypo)mania (YMRS >12)	0 (0.00)	5 (3.50)	0.010†	NA
Current depression (MADRS >6)	24 (12.83)	54 (39.13)	<0.001	NA
Mental disorders, n (%)				
Any mental disorders	53 (26.24)	77 (40.31)	1.90 (1.21 to 2.97)	**1.87 (1.14 to 3.10)**
Mood disorders	7 (3.47)	22 (11.70)	3.69 (1.54 to 8.88)	**4.68 (1.30 to 16.86)**
Depressive disorders	7 (3.47)	21 (11.17)	3.50 (1.45 to 8.47)	**3.99 (1.11 to 14.34)**
Bipolar disorders	1 (0.50)	5 (2.63)	5.43 (0.63 to 46.65)	7.12 (0.38 to 131.95)
Psychotic disorders	1 (0.50)	3 (1.58)	3.23 (0.33 to 31.22)	3.68 (0.38 to 36.00)
Anxiety disorders	10 (4.95)	24 (12.63)	2.78 (1.26 to 6.11)	2.45 (0.97 to 6.23)
Social anxiety	3 (1.49)	12 (6.28)	4.45 (1.24 to 15.92)	**4.70 (1.21 to 18.18)**
Generalised anxiety disorder	3 (1.49)	11 (5.76)	4.05 (1.12 to 14.67)	4.07 (0.79 to 21.03)
Post-traumatic stress disorder	0 (0.00)	2 (1.05)	0.14†	NA
Elimination disorders	1 (0.50)	3 (1.63)	3.33 (0.34 to 32.26)	2.77 (0.28 to 27.75)‡
Eating disorders	0 (0.00)	0 (0.00)	NA	NA
Behavioural disorders	40 (19.80)	45 (24.46)	1.30 (0.79 to 2.14)	1.41 (0.79 to 2.50)
Attention deficit hyperactivity disorder	39 (19.31)	42 (22.83)	1.24 (0.75 to 2.04)	1.33 (0.75 to 2.34)
Tic disorders	7 (3.48)	11 (5.98)	1.76 (0.63 to 4.95)	1.62 (0.46 to 5.71)
Autism spectrum disorders	1 (0.50)	2 (1.07)	2.16 (0.20 to 23.86)	4.95 (0.40 to 60.65)‡
Substance use disorders	0 (0.00)	3 (1.59)	0.073†	NA
Suicide	19 (9.69)	32 (17.49)	1.97 (1.07 to 3.63)	1.26 (0.60 to 2.63)
Non-fatal self-harm	8 (4.08)	12 (6.49)	1.63 (0.66 to 4.04)	1.20 (0.38 to 3.76)
Mental symptoms, n (%)				
Any mental symptoms	87 (43.07)	116 (60.73)	2.04 (1.36 to 3.08)	**2.14 (1.37 to 3.33)**
Mood symptoms	21 (10.40)	39 (20.74)	2.24 (1.26 to 3.97)	**2.59 (1.24 to 5.44)**
Psychotic symptoms	3 (1.49)	4 (2.11)	1.43 (0.32 to 6.41)	1.98 (0.45 to 8.75)
Anxiety symptoms	34 (16.83)	47 (24.74)	1.64 (0.99 to 2.70)	1.55 (0.89 to 2.72)
Trauma and stress-related symptoms	5 (2.48)	6 (3.16)	1.29 (0.39 to 4.29)	1.20 (0.30 to 4.73)
Elimination symptoms	2 (0.99)	8 (4.34)	4.57 (0.97 to 21.63)	4.08 (0.83 to 20.17)‡
Eating symptoms	4 (1.98)	0 (0.00)	0.051†	NA
Behavioural symptoms	56 (27.86)	68 (36.96)	1.53 (0.99 to 2.38)	1.60 (0.97 to 2.63)
Tics	7 (3.48)	15 (8.15)	2.46 (0.90 to 6.70)	2.31 (0.71 to 7.54)
Autistic symptoms	3 (1.50)	3 (1.61)	1.08 (0.22 to 5.39)	1.93 (0.34 to 10.88)‡

Continued

Table 1 Continued

	O-control (n=202)	O-BD (n=191)	Unadjusted OR (95% CI)/p value	Adjusted OR (95% CI)*
Substance use	0 (0.00)	5 (2.63)	0.021†	NA

Because missing data were not imputed, the denominators used to calculate the percentages in this table are the valid data. Significant adjusted OR values (with their 95% CIs) are highlighted in bold.
*Adjusted for age at recruitment, sex and region.
†Mann-Whitney U test was applied.
‡Logistic regression was applied.
BMI, body mass index; MADRS, Montgomery-Asberg Depression Rating Scale; NA, not applicable; SAR, Special Administrative Region; YMRS, Young Mania Rating Scale.

was similar to O-control in both circadian disorder and symptom levels. When O-BD reached adolescence, they reported a higher risk of delayed sleep phase disorder (12.50% vs 2.02%, OR: 6.93, 95% CI 1.44 to 33.42) and delayed sleep phase symptoms (20.00% vs 5.05%, OR: 4.70, 95% CI 1.63 to 13.56) than the O-control group. After adjustment for age at recruitment, sex and region, the statistical significance of delayed sleep phase symptoms remained (adjusted OR: 3.83, 95% CI 1.11 to 13.16), but not at the disorder level. Interestingly, both groups had similar risks of insomnia (disorder and symptom level) in both childhood and adolescence (table 4).

Survival analyses

Survival analysis was used to estimate the longitudinal associations between the parental history of bipolar disorder and the emergence of psychopathologies and sleep/circadian rhythm dysfunction. The findings of shared frailty proportional hazards models indicated that the parental history of bipolar disorder was associated with increased risks of any mental disorders (adjusted HR: 1.83, 95% CI 1.15 to 2.92), mood disorders (adjusted HR: 14.97, 95% CI 2.68 to 83.67), depressive disorders (adjusted HR: 11.39, 95% CI 2.18 to 59.37) and social anxiety disorder (adjusted HR: 6.17, 95% CI 1.07 to 35.58), after adjusting for age at recruitment, sex and region. Besides, the parental history of bipolar disorder increased the lifetime prevalence of anxiety disorders, but the HR was attenuated to marginal significance after adjustment (HR: 3.21, 95% CI 1.12 to 9.19; adjusted HR: 2.88, 95% CI 0.99 to 8.32) (see online supplemental table 1 and figure 2).

In terms of the emergence of symptoms, there was a marginally significant association of parental history of bipolar disorder with delayed sleep phase symptoms (adjusted HR: 4.97, 95% CI 0.97 to 25.45) but not delayed sleep phase disorder (adjusted HR: 6.74, 95% CI 0.71 to 64.15) (see online supplemental table 1 and figure 2).

DISCUSSION

Main findings

To our knowledge, this is the first case–control study of the offspring of parents with and without bipolar disorder, encompassing a comprehensive assessment of sleep and circadian rhythm disorders and symptoms, as well as the empirical evidence of mental disorders and symptoms in the Chinese population. We found further evidence for the specificity of familial patterns of mood disorders/symptoms and circadian rhythm dysfunction in O-BD compared with O-control. The age-related developmental pattern of progressive occurrence of psychopathologies was reflected in the differential occurrence of behavioural symptoms in O-BD under age 12 years and social anxiety disorder, mood symptoms and delayed sleep phase symptoms in O-BD adolescents aged 12 years and over.

While sleep alteration has been frequently reported in patients with bipolar disorder, only a few studies of sleep and circadian rhythm dysfunction suggested that O-BD have higher rates of sleep disorders and evening chronotype than controls.[7 25] In this study, there was a higher risk of delayed sleep phase symptoms among O-BD which started to emerge in adolescence, whereas there was no increased risk of insomnia in both O-BD children and adolescents. Thus, it is probable that circadian rhythm dysfunction rather than insomnia may underlie the core sleep–wake pathologies among the high-risk O-BD population.[11] Previous studies have indicated that eveningness and insomnia symptoms were independently associated with mood disorders and other psychopathologies.[26 27] Hence, there may be an interesting postulation that delayed sleep phase symptoms could be the major prodrome of bipolar disorder, while insomnia might reflect subsequent effects of depression, circadian or other comorbidities.

Earlier findings in both patients with bipolar disorder and O-BD suggested that a broader dysregulation of circadian rhythm may underlie this condition.[11] Our previous report of dysregulation of melatonin secretion further suggested that suppressed melatonin secretion might reflect genetic susceptibility conferring increased sensitivity of melatonin suppression to environmental light exposure.[11] Excessive electronic media use, especially before bedtime (which may enhance light exposure at night), has been associated with sleep and circadian problems and poor mental health.[28] Thus, appropriate guidelines and interventions for the appropriate use of electronic media are needed among adolescents, especially in high-risk adolescents with a family history of bipolar disorder as suggested by our study.

Another contribution of this study is the collection of information on symptoms and subthreshold manifestations of mental and sleep disorders beyond the diagnostic criteria. Our findings replicate the results of earlier bipolar disorder high-risk studies showing that O-BD tend to have an earlier onset of mood and anxiety disorders than the controls.[29] Furthermore, the findings suggest that there is

Table 2 Lifetime prevalence of psychopathologies among offspring of parents with (O-BD) and without bipolar disorder (O-control) in childhood and adolescence

	O-control	O-BD	Unadjusted OR (95% CI)/p value	Adjusted OR (95% CI)*
Children (offspring <12 years old)	**n=102**	**n=103**		
Age, mean (SD)	8.81 (1.76)	8.41 (1.69)	0.086	NA
Female, n (%)	47 (46.53)	46 (44.66)	0.78	NA
Pre/early puberty, n (%)	102 (100.00)	103 (100.00)	NA	NA
Mental disorders, n (%)				
Any mental disorders	26 (25.49)	41 (39.81)	1.93 (1.05 to 3.55)	**1.91 (1.00 to 3.63)**
Mood disorders	0 (0.00)	4 (3.92)	0.044 †	NA
Depressive disorders	0 (0.00)	3 (2.94)	0.082†	NA
Bipolar disorders	0 (0.00)	2 (1.96)	0.16†	NA
Psychotic disorders	0 (0.00)	1 (0.98)	0.32†	NA
Anxiety disorders	3 (2.94)	5 (4.85)	1.68 (0.39 to 7.30)	1.54 (0.31 to 7.72)
Social anxiety	1 (0.98)	2 (1.94)	2.00 (0.18 to 22.51)	1.37 (0.64 to 2.96)‡
Generalised anxiety disorder	0 (0.00)	1 (0.97)	0.320†	NA
Post-traumatic stress disorder	0 (0.00)	0 (0.00)	NA	NA
Elimination disorders	1 (0.98)	3 (2.91)	3.03 (0.31 to 29.43)	2.73 (0.28 to 27.16)‡
Eating disorders	0 (0.00)	0 (0.00)	NA	NA
Behavioural disorders	22 (21.78)	36 (34.95)	1.93 (1.02 to 3.64)	1.92 (0.96 to 3.82)
Attention deficit hyperactivity disorder	22 (21.57)	33 (32.04)	1.71 (0.91 to 3.25)	1.65 (0.83 to 3.28)
Tic disorders	5 (4.95)	6 (5.83)	1.19 (0.31 to 4.50)	1.04 (0.28 to 3.89)
Autism spectrum disorders	1 (0.99)	1 (0.97)	0.98 (0.06 to 15.95)	1.38 (0.07 to 26.11)
Substance use disorders	0 (0.00)	0 (0.00)	NA	NA
Suicide	8 (7.92)	6 (5.88)	0.73 (0.24 to 2.18)	0.60 (0.20 to 1.87)‡
Non-fatal self-harm	2 (1.98)	4 (3.92)	2.02 (0.36 to 11.30)	1.91 (0.32 to 11.44)
Mental symptoms, n (%)				
Any mental symptoms	42 (41.18)	60 (58.25)	1.99 (1.16 to 3.43)	**2.12 (1.21 to 3.72)**
Mood symptoms	5 (4.90)	8 (7.84)	1.65 (0.53 to 5.16)	2.18 (0.59 to 7.96)
Psychotic symptoms	0 (0.00)	1 (0.98)	0.32†	NA
Anxiety symptoms	15 (14.71)	18 (17.48)	1.23 (0.58 to 2.58)	1.20 (0.57 to 2.55)
Trauma and stress-related symptoms	0 (0.00)	1 (0.98)	0.32†	NA
Elimination symptoms	2 (1.96)	8 (7.77)	4.21 (0.89 to 19.96)	4.13 (0.81 to 22.01)
Eating symptoms	1 (0.98)	0 (0.00)	0.32†	NA
Behavioural symptoms	31 (30.69)	50 (48.54)	2.13 (1.19 to 3.82)	**2.13 (1.14 to 3.95)**
Tics	5 (4.95)	9 (8.74)	1.84 (0.53 to 6.37)	1.64 (0.47 to 5.67)
Autistic symptoms	3 (2.97)	2 (1.94)	0.65 (0.11 to 3.98)	1.21 (0.17 to 8.79)‡
Substance use	0 (0.00)	1 (0.98)	0.320†	NA
Adolescence (offspring ≥12 years old)	**n=100**	**n=88**		
Age, mean (SD)	14.32 (2.05)	15.94 (2.68)	<0.001	NA
Female, n (%)	52 (52.00)	42 (47.73)	0.560	NA
Pre/early puberty, n (%)	54 (54.00)	26 (29.89)	0.001	NA
Mental disorders, n (%)				

Continued

Table 2 Continued

Adolescence (offspring ≥12 years old)	n=100	n=88		
Any mental disorders	27 (27.00)	36 (40.91)	1.87 (1.00 to 3.50)	1.46 (0.64 to 3.33)
Mood disorders	7 (7.00)	18 (20.93)	3.52 (1.39 to 8.92)	2.60 (0.69 to 9.78)
Depressive disorders	7 (7.00)	18 (20.93)	3.52 (1.39 to 8.92)	2.60 (0.69 to 9.78)
Bipolar disorders	1 (1.00)	3 (3.41)	3.49 (0.36 to 34.36)	1.35 (0.03 to 67.55)
Psychotic disorders	1 (1.00)	2 (2.27)	2.30 (0.21 to 25.69)	1.26 (0.26 to 6.08)
Anxiety disorders	7 (7.00)	19 (21.84)	3.71 (1.46 to 9.45)	2.86 (0.92 to 8.96)
Social anxiety	2 (2.00)	10 (11.36)	6.28 (1.36 to 29.12)	**7.49 (1.33 to 42.20)**
Generalised anxiety disorder	3 (3.00)	10 (11.36)	4.15 (1.11 to 15.51)	3.54 (0.57 to 22.16)
Post-traumatic stress disorder	0 (0.00)	2 (2.27)	0.13†	NA
Elimination disorders	0 (0.00)	0 (0.00)	NA	NA
Eating disorders	0 (0.00)	0 (0.00)	NA	NA
Behavioural disorders	18 (18.00)	9 (11.11)	0.57 (0.24 to 1.35)	0.81 (0.22 to 2.93)
Attention deficit hyperactivity disorder	17 (17.00)	9 (11.11)	0.61 (0.26 to 1.46)	0.99 (0.29 to 3.45)
Tic disorders	2 (2.00)	5 (6.17)	3.22 (0.61 to 17.06)	3.71 (0.23 to 60.91)
Autism spectrum disorders	0 (0.00)	1 (1.20)	0.27†	NA
Substance use disorders	0 (0.00)	3 (3.41)	0.063†	NA
Suicide	11 (11.58)	26 (32.10)	3.61 (1.69 to 7.72)	2.26 (0.80 to 6.42)
Non-fatal self-harm	6 (6.32)	8 (9.64)	1.58 (0.53 to 4.75)	0.86 (0.17 to 4.25)
Mental symptoms, n (%)				
Any mental symptoms	45 (45.00)	56 (65.64)	2.14 (1.16 to 3.94)	1.78 (0.83 to 3.83)
Mood symptoms	16 (16.00)	31 (36.05)	2.96 (1.48 to 5.91)	**3.00 (1.14 to 7.92)**
Psychotic symptoms	3 (3.00)	3 (3.41)	1.14 (0.23 to 5.68)	1.57 (0.41 to 5.97)
Anxiety symptoms	19 (19.00)	29 (33.33)	2.13 (1.08 to 4.22)	2.35 (0.98 to 5.65)
Trauma and stress-related symptoms	5 (5.00)	5 (5.68)	1.15 (0.32 to 4.09)	0.84 (0.18 to 3.93)
Elimination symptoms	0 (0.00)	0 (0.00)	NA	NA
Eating symptoms	3 (3.00)	0 (0.00)	0.10†	NA
Behavioural symptoms	25 (25.00)	18 (22.22)	0.86 (0.42 to 1.74)	0.80 (0.29 to 2.23)
Tics	2 (2.00)	6 (7.41)	3.92 (0.72 to 21.42)	4.04 (0.30 to 54.40)
Autistic symptoms	0 (0.00)	1 (1.20)	0.27†	NA
Substance use	0 (0.00)	4 (4.55)	0.032†	NA

Because missing data were not imputed, the denominators used to calculate the percentages in this table are the valid data. Significant adjusted OR values (with their 95% CIs) are highlighted in bold.
*Adjusted for age at recruitment, sex and region.
†Mann-Whitney U test was applied.
‡Logistic regression was applied.
NA, not applicable.

a developmental trajectory reflected by an increased risk of behavioural symptoms in childhood, followed by the emergence of social anxiety and mood symptoms in adolescence. The significant effects of symptoms rather than disorders for some conditions suggest that dimensional symptom scales might be a more sensitive indicator of the evolving risk of bipolar disorder, especially when most of the offspring are in their childhood and adolescence.[30]

The elevated rates of mood, anxiety and delayed sleep phase in O-BD youth are likely to reflect genetic susceptibility to bipolar disorder, which is known for its high heritability among major mental disorders.[31] There is a convergence of evidence that bipolar disorder may reflect dysregulation of motor activity and sleep, with shifts to later day peak activity and later sleep onset time.[32] Our compelling data on delayed sleep symptoms and disorders confirm these adult data and

Table 3 Lifetime prevalence of sleep and circadian rhythm disorders/symptoms among offspring of parents with (O-BD) and without bipolar disorder (O-control)

	O-control (n=194)	O-BD (n=179)	Unadjusted OR (95% CI)/p value	Adjusted OR (95% CI)*
Age, mean (SD)	11.63 (3.34)	11.85 (4.39)	0.59	NA
Female, n (%)	96 (49.74)	81 (45.51)	0.41	NA
Pre/early puberty, n (%)	147 (76.17)	123 (69.49)	0.15	NA
Sleep and circadian rhythm disorders, n (%)				
Any sleep and circadian rhythm disorders	32 (16.49)	29 (16.20)	0.98 (0.56 to 1.72)	1.04 (0.54 to 2.01)
Delayed sleep phase disorder	2 (1.03)	10 (5.62)	5.71 (1.21 to 27.04)	3.06 (0.44 to 21.47)
Advanced sleep phase disorder	1 (0.52)	0 (0.00)	0.34†	NA
Insomnia	14 (7.22)	12 (6.74)	0.93 (0.40 to 2.14)	0.86 (0.30 to 2.42)
Restless legs syndromes	7 (3.61)	5 (2.81)	0.77 (0.24 to 2.45)	0.65 (0.15 to 2.91)
Nightmare	16 (8.25)	8 (4.73)	0.55 (0.23 to 1.31)	0.88 (0.33 to 2.36)
Sleep and circadian rhythm symptoms, n (%)				
Any sleep and circadian rhythm symptoms	53 (27.32)	49 (27.37)	1.00 (0.63 to 1.59)	1.21 (0.74 to 1.98)
Delayed sleep phase symptoms	5 (2.58)	17 (9.55)	3.99 (1.42 to 11.19)	**4.04 (1.23 to 13.28)**
Advanced sleep phase symptoms	1 (0.52)	0 (0.00)	0.34†	NA
Insomnia symptoms	31 (15.98)	25 (14.04)	0.86 (0.49 to 1.52)	0.93 (0.50 to 1.74)
Restless legs syndrome symptoms	9 (4.64)	5 (2.81)	0.59 (0.20 to 1.79)	0.48 (0.12 to 1.87)
Nightmare symptoms	28 (14.43)	15 (8.88)	0.58 (0.30 to 1.11)	0.92 (0.47 to 1.79)

Because missing data were not imputed, the denominators used to calculate the percentages in this table are the valid data. Significant adjusted OR value (with its 95% CI) is highlighted in bold.
*Adjustment for age at recruitment, sex and region.
†Mann-Whitney U test was applied.
NA, not applicable.

further demonstrate that these shifts may manifest as early as in adolescence. The emergence of behavioural, mood, anxiety and sleep/circadian disturbances in late childhood and adolescence could further interact with environmental exposure or adverse events,[33] resulting in increased stress that will lead to greater impairment in functioning.[34]

Some discrepant results of our study are also noteworthy. First, the lack of differences in the rates of ADHD in the two risk groups is inconsistent with prior research that reported an elevated risk of ADHD in O-BD.[23] Nevertheless, O-BD had an increased risk of behavioural symptoms. The findings suggest that behavioural dysfunction may emerge in childhood among high-risk offspring. Thus, clinicians should focus not only on the categorical ADHD diagnosis but also on the general behavioural symptoms. Interestingly, we found a substantially lower rate of substance use disorders than other similar studies in Canada and the USA.[7 35] This might reflect the stringent drug-control policy in China and the relatively young age of the cohort (mean age of 12 years in the current study). Nevertheless, there was an emergence of substance use in the adolescent O-BD group, although the reported prevalence rate was still low.

The inclusion of a wide age range of high-risk subjects from children to adolescents with a comprehensive assessment of mental disorders as well as sleep/circadian assessment at both the symptom and disorder levels among the high-risk offspring allowed us to confirm and extend the preclinical staging model of bipolar disorder among O-BD, as exemplified by the Canadian High-Risk Offspring Cohort.[7] In summary, behavioural symptoms start to occur in childhood followed by the emergence of a delayed sleep phase, social anxiety and mood symptoms in early adolescence. We predicted that major mood disorders may emerge in middle/late adolescence and early adulthood before the full-blown development of bipolar disorder. Prospective follow-up is necessary to elucidate the trajectories of these early manifestations of the bipolar spectrum and their transition to mood disorders in late adolescence and early adulthood.

Limitations

The current study has several limitations. First, despite being one of the largest studies of offspring of parents with and without bipolar disorder, the sample size for younger people with certain specific disorders, such as post-traumatic stress disorder, is still insufficient for multivariate data analysis. Second, the wide age range of offspring may introduce potential heterogeneity in psychopathologies and circadian rhythm assessment because of the age-specific development of these systems. Nevertheless, investigating the emergence of both symptoms and disorders across this developmental transition is critical for understanding the evolution and variations in phenotypical patterns associated with bipolar disorder. Hence, the subgroup analyses provided an opportunity to investigate the specific patterns in childhood and adolescence, respectively. Third, although there were some apparent deviations in the age appropriateness of the

Table 4 Lifetime prevalence of sleep and circadian rhythm disorders/symptoms among offspring of parents with (O-BD) and without bipolar disorder (O-control) in childhood and adolescence

	O-control	O-BD	Unadjusted OR (95% CI)/p value	Adjusted OR (95% CI)*
Children (offspring <12 years old)	**n=95**	**n=98**		
Age, mean (SD)	8.84 (1.78)	8.44 (1.71)	0.110	NA
Female, n (%)	44 (46.81)	43 (43.88)	0.68	NA
Pre/early puberty, n (%)	95 (100.00)	98 (100.00)	NA	NA
Sleep and circadian rhythm disorders, n (%)				
Any sleep and circadian rhythm disorders	9 (9.47)	10 (10.20)	1.09 (0.42 to 2.81)	1.07 (0.40 to 2.87)
Delayed sleep phase disorder	0 (0.00)	0 (0.00)	NA	NA
Advanced sleep phase disorder	0 (0.00)	0 (0.00)	NA	NA
Insomnia	3 (3.16)	4 (4.08)	1.31 (0.28 to 6.04)	1.25 (0.27 to 5.83)
Restless legs syndrome	4 (4.21)	3 (3.06)	0.72 (0.16 to 3.29)	0.62 (0.12 to 3.25)
Nightmare	3 (3.16)	5 (5.49)	1.78 (0.41 to 7.70)	1.92 (0.43 to 8.49)
Sleep and circadian rhythm symptoms, n (%)				
Any sleep and circadian rhythm symptoms	21 (22.11)	22 (23.45)	1.02 (0.51 to 2.04)	1.10 (0.53 to 2.26)
Delayed sleep phase symptoms	0 (0.00)	1 (1.02)	0.32†	NA
Advanced sleep phase symptoms	0 (0.00)	0 (0.00)	NA	NA
Insomnia symptoms	12 (12.63)	13 (13.27)	1.06 (0.46 to 2.45)	1.14 (0.47 to 2.73)
Restless legs syndrome symptoms	5 (5.26)	3 (3.06)	0.57 (0.13 to 2.45)	0.48 (0.10 to 2.38)
Nightmare symptoms	9 (9.47)	11 (12.09)	1.31 (0.52 to 3.32)	1.50 (0.58 to 3.87)
Adolescence (offspring ≥12 years old)	**n=99**	**n=81**		
Age, mean (SD)	14.30 (2.06)	16.05 (2.75)	<0.001	NA
Female, n (%)	52 (52.53)	38 (46.91)	0.45	NA
Pre/early puberty, n (%)	53 (53.54)	25 (31.25)	0.003	NA
Sleep and circadian rhythm disorders, n (%)				
Any sleep and circadian rhythm disorders	23 (23.23)	19 (24.46)	1.01 (0.50 to 2.07)	1.07 (0.43 to 2.67)
Delayed sleep phase disorder	2 (2.02)	10 (12.50)	6.93 (1.44 to 33.42)	3.25 (0.47 to 22.70)
Advanced sleep phase disorder	1 (1.01)	0 (0.00)	0.37†	NA
Insomnia	11 (11.11)	8 (9.88)	0.88 (0.31 to 2.46)	0.77 (0.16 to 3.59)
Restless legs syndrome	3 (3.03)	2 (2.47)	0.81 (0.13 to 4.89)	0.60 (0.02 to 18.64)
Nightmare	13 (13.13)	3 (3.80)	0.26 (0.07 to 0.94)	0.41 (0.07 to 2.40)
Sleep and circadian rhythm symptoms, n (%)				
Any sleep and circadian rhythm symptoms	32 (32.32)	27 (33.33)	1.05 (0.56 to 1.95)	1.30 (0.61 to 2.80)
Delayed sleep phase symptoms	5 (5.05)	16 (20.00)	4.70 (1.63 to 13.56)	**3.83 (1.11 to 13.16)**
Advanced sleep phase symptoms	1 (1.01)	0 (0.00)	0.37†	NA
Insomnia symptoms	19 (19.19)	12 (14.81)	0.73 (0.32 to 1.66)	0.86 (0.29 to 2.55)
Restless legs syndrome symptoms	4 (4.04)	2 (2.47)	0.60 (0.11 to 3.32)	0.53 (0.02 to 12.24)
Nightmare symptoms	19 (19.19)	4 (5.06)	0.23 (0.07 to 0.68)	0.37 (0.09 to 1.57)

Because missing data were not imputed, the denominators used to calculate the percentages in this table are the valid data. Significant adjusted OR value (with its 95% CI) is highlighted in bold.
*Adjustment for age at the recruitment, sex and region.
†Mann-Whitney U test was applied.
NA, not applicable.

diagnostic assessments used in this study, K-SADSPL and DISP could still be regarded as the most appropriate diagnostic assessments in this study. K-SADSPL is commonly applied to determine the lifetime profiles of mental problems in the offspring aged between 6 and 18 years, but the study has extended the use of the instrument to late adolescent/early adult subjects aged between 18 and 21 years. In order to better understand lifetime diagnosis, other international bipolar offspring studies in Canada, the Netherlands and Australia have used similar K-SADS instruments for this group of older adolescents/young adults. Additionally, we have adapted the items of DISP according to ICSD-3 criteria to meet the diagnostic criteria of sleep and circadian disorders among children and adolescents. Moreover, as some

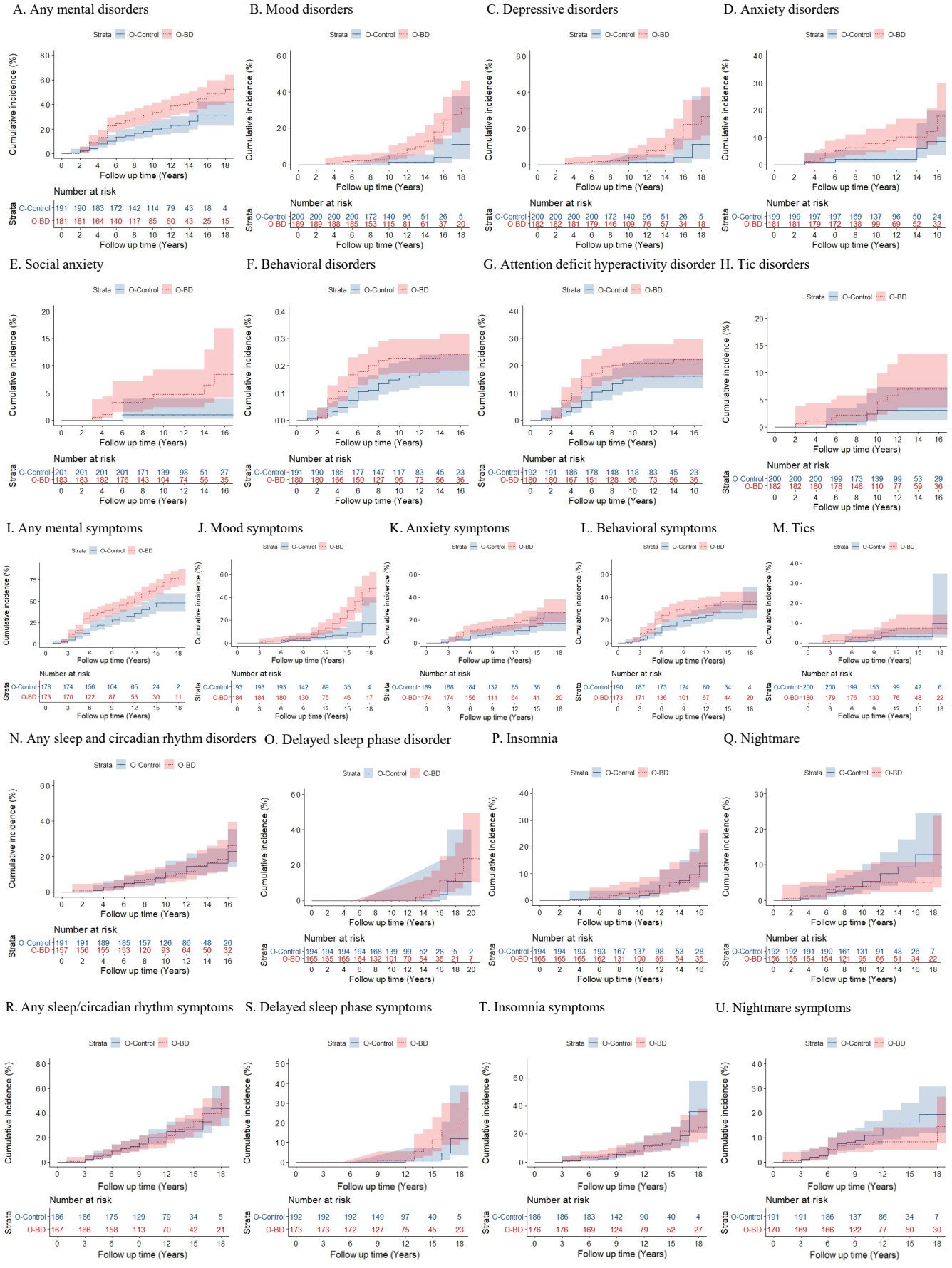

Figure 2 Probability of psychopathologies (A to M) and sleep/circadian rhythm dysfunction (N to U) among the offspring of parents with (O-BD) and without bipolar disorder (O-control).

offspring have not yet reached the typical onset age for the conditions studied, follow-up of this cohort will be essential to collecting information on the full trajectory of risk of psychopathologies and sleep/circadian rhythm dysfunction with regard to the emergence of bipolar disorder. Finally, there were missing data in the current study. The most common missing data included items related to suicide (3.56%) and nightmares (2.68%). As the proportion of missing data was relatively small (less than 5%), it was deemed that it would not lead to significant bias, and the statistical significance of the main analysis remained the same even after multiple imputations.

Implications

The findings of the current study have several important clinical implications for further understanding bipolar disorder. First, the study identified several clinical markers in the high-risk population, especially delayed sleep phase symptoms, which were first reported as the early core manifestation and marker of bipolar disorder. Second, the findings enhanced the understanding of the preclinical staging model of bipolar disorder. Hence, different early clinical intervention and prevention strategies could be developed according to the ages and stages of the high-risk offspring of bipolar disorder. Third, the strong familial association of bipolar disorder and circadian rhythm dysfunction in offspring may provide evidence for the novel prevention of bipolar disorder. Thus, family education and family-based therapy should be prioritised to reduce the risk of bipolar disorder, and our study further highlights the importance of chronotherapeutic management among high-risk offspring.[11] In conclusion, the identification of novel prodromal markers and preclinical stages of bipolar offspring emphasises the importance of identification and age-specific precision prevention of bipolar disorder.

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Contributors YKW and JZ were involved in the conceptualisation and design of the study. BL, HF, JW, JC, WS, CJ, KZ, QW and JCCT recruited the participants. BL, HF and LY conducted the data analysis. BL wrote the first draft of this paper. NYC, YL, JWYC, JP, BZ, TL, KRM, JZ and YKW reviewed and edited the manuscript. YKW was responsible for validation and supervision as the guarantor.

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Patient consent for publication Consent obtained from parent(s)/guardian(s).

Ethics approval This study involves human participants and was approved by the Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee (Joint CUHK-NTEC CREC, ref no: 2015.699), and each study site, including Shatin Hospital in Hong Kong, and Shenzhen Nanshan Center for Chronic Disease Control, Shenzhen Longgang Center for Chronic Disease Control and Shenzhen Bao'an People's Hospital in Mainland China. The participants gave informed consent to participate in the study before taking part.

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