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Short communication

Short communication: Self-reported sleep-wake disturbances preceding onset of full-threshold mood and/or psychotic syndromes in community residing adolescents and young adults

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ABSTRACT

Background: Insomnia may predict onset of mental disorders in adults. However, it is unclear whether the same directional relationship exists during the peak age range for the onset of major mental disorders and/or whether other types of sleep-wake disturbance, such as hypersomnia, show similar associations.

Methods: Longitudinal follow-up of >1800 community residing twins and non-twin siblings (mean age ~26; 57% female). Adjusted relative risk ratios and 95% confidence intervals (Adj RR and 95% CI) were estimated for onset of depression, hypomania and psychosis in individuals with prior self-reported exposure to Insomnia and/or Hypersomnia or proxies for insomnia disorder (Insomnia and Daytime Impairment) and atypical symptom profile (Hypersomnia and Anergia).

Results: Risk of onset differed somewhat according to type of syndrome and the nature of sleep-wake disturbance (e.g. Insomnia alone increased risk of first onset of psychosis). Overall, the risk for onset of any syndrome was best identified using composite measures (Adj RR were ~1.5–2.5) such as Insomnia and Hypersomnia, Insomnia and Daytime Impairment, or Hypersomnia and Anergia, rather than singular items describing night-time disruption only.

Conclusions: The magnitude of risk of onset of major mental health problems and the availability of effective, low-cost, individual and population-based interventions for sleep-wake disturbances, suggest that it is justifiable to introduce screening for and strategies to overcome sleep problems in youth.

1. Introduction

Three decades ago, Ford and Kamerow's (1989) epidemiological catchment area study demonstrated that the odds of onset of a mental disorder was increased in individuals with a history of insomnia or hypersomnia. The study was noteworthy as it reported trans-diagnostic findings and it demonstrated that unadjusted odds ratios (OR) are much higher than OR adjusted for key moderators or confounders (e.g. age, sex). Recent studies have largely focused one sleep problem or one diagnosis in samples aged 30–40 years and/or examined all new episodes (conflating first onset with recurrence). Despite these limitations, most evidence confirms that onset of major mental disorders is increased by the presence of sleep, circadian or sleep-wake cycle disruptions.

Fewer studies have been undertaken of any associations between sleep disturbances and onset of mental disorders in adolescents, and young adults (e.g., Lovato and Gradisar, 2014; Reeve et al., 2015). This is potentially important as three of the four most globally burdensome conditions in young people are depressive, bipolar, and psychotic disorders (Gore et al., 2011) and clinical research increasingly highlights the need to incorporate primary and early secondary prevention into youth mental health services. Interest in targeting sleep-wake patterns arises for several key reasons e.g. (a) it is established that sleep difficulties during childhood and adolescence may lead to multiple adverse outcomes and impaired functioning downstream (Lovato and Gradisar, 2014; Kolla et al., 2019); (b) sleep difficulties are common elements of subthreshold and clinical high-risk syndromes that precede onset of major mental disorders (Jackson et al., 2003; Shankman et al., 2009); and (c) many interventions are available that can modify sleep patterns in post-pubertal children, adolescents and young adults

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(Eaton et al., 1995; Kolla et al., 2019).

To take this research forward, it is necessary to address some knowledge gaps. For example, we know that insomnia is predictive of some mental disorders in adults (Hertenstein et al., 2019), but it is unclear whether the same directional relationship exists during the peak age range for the onset of major mental disorders (i.e. post-puberty up to ~30 years). Additionally, we have limited data on other sleep-wake disturbances and first onset of mental disorders. This is relevant as it is increasingly clear that several sleep profiles occur more frequently in adolescence and early adulthood, e.g. initial insomnia may co-occur with hypersomnia (giving rise to a delayed sleep phase syndrome; Steinan et al., 2016), insomnia and hypersomnia can occur sequentially in the same individual (Kolla et al., 2019), and symptoms similar to atypical depression (hypersomnia and anergia) can be associated with early transition from depression to bipolar disorders (Shankman et al., 2009). Also, studies of subthreshold or clinical high risk syndromes suggest that sleep disturbances (variously defined) are a common risk factor for transition to full-threshold disorders, but currently we do not know if the magnitude of any associations differ according to the type of sleep-wake problem or the mental disorder being studied. Critically, studies of specific disorders have largely ignored the problem that youth typically present with comorbid rather than singular disorders (Krueger and Markon, 2006). Lack of awareness of this has meant that many analyses fail to consider the complexity of clinical presentations in this age group (Scott et al., 2020).

As a preliminary investigation, this brief report uses data from an ongoing community cohort study of adolescents and young adults to explore whether:

(i) prior exposure to sleep-wake problems increases risk of onset of any major syndrome and
(ii) whether the magnitude of any observed effects shows any specificity according to the exposure (sleep-wake disturbance) or outcome (depression, hypo/mania or psychosis).

2. Methodology

This study was undertaken as part of the Brisbane Longitudinal Twin Study (BLTS) with ethical approval from the Human Research Ethics Committee at the Queensland Institute of Medical Research (QIMR reference numbers: EC00278 and P1212). Details of the BLTS, including self-ratings of mental health symptoms and criteria for identifying mental disorders are published elsewhere (e.g. Couvy-Duchesne et al., 2018; Mitchell et al., 2019; Scott et al., 2020). To briefly summarize, the BLTS is a community-based study of twins and their non-twin siblings aged ≥12, and participants were recruited continuously between 1992 and 2015 and have been interviewed in waves every three or so years. Written informed consent was obtained from potential participants (if aged ≥18) or a parent (if aged <18). Individuals were excluded if parental report indicated a history of head injuries, neurological or pre-existing psychiatric conditions, substance misuse and/or taking medications with significant central nervous system effects. Follow-ups (waves) have increased the assessments of mental health (see Scott et al., 2018), with those undertaken between 2009 and 2016 including several reliable and valid self-report questionnaires and the Composite International Diagnostic Interview (CIDI; Kessler et al., 2004). Individuals who miss one follow-up can be interviewed at the next wave.

De-identified data were extracted from the BLTS dataset only for individuals who had completed a self-report mental health rating between 2009 and 2016 and participated in a CIDI assessment at the 19Up follow-up. A priori, we identified that the analyses required the following data:

(a) Demographics, twin status, and Body Mass Index (BMI) in kg/m^2
(b) Sleep-Wake Self-Report – we identified four items (recording the presence of Insomnia, Hypersomnia, Daytime Impairment and/or Anergia for ≥2 consecutive weeks), that were recorded in self-ratings of mental health. For this study, sleep disturbances were categorized as Insomnia, Hypersomnia or Insomnia and Hypersomnia. Sleep-wake difficulties were identified by a proxy for insomnia disorder (Insomnia and Daytime Impairment for ≥2 weeks) and for atypical symptom profile (Hypersomnia and Anergia for ≥2 weeks).
(c) CIDI Syndromes – we focused on three syndromes: depression, hypo/mania and/or psychosis (see Scott et al., 2020). We chose to report hypo/mania rather than bipolar disorders as we wanted to test whether there were differences in associations of depression and hypo/mania.

Statistical analyses: we estimated Relative Risk with 95% confidence intervals (RR and 95% CI) for any association between exposures (prior self-reported sleep-wake disturbances) and outcomes of interest (first onset of depression, hypo/mania or psychosis). We adjusted the RR for age, sex, twin status, BMI, and comorbid CIDI syndromes.

3. Results

Table 1 outlines the key characteristics of the 1838 participants eligible for inclusion in the planned analyses. At follow-up, 31% of participants met BLTS study criteria for ≥1 CIDI syndrome with a median age at onset of about 20 years (IQR: 18–23). Rates of prior self-reported sleep-wake difficulties ranged from 6% for co-occurring Insomnia and Daytime Impairment to 21% for Insomnia only. The median time gap between sleep ratings and CIDI onset varied per individual (depending on timing of each assessment) but was about 2 years (IQR (1–3.5).

As shown in Table 2, risk for onset of any CIDI syndrome was best identified using composite measures (RR were ~1.5–2.5 for Insomnia and Hypersomnia, Insomnia and Daytime Impairment, or Hypersomnia and Anergia) rather than singular sleep items. Notable findings were that Insomnia alone was associated with a reduced risk of depression onset whereas the composite of Insomnia and Hypersomnia or of Insomnia and Daytime Impairment (and Hypersomnia and Anergia) were

Table 1.
Key characteristics of study cohort.

Characteristic	*N* = 1838
Mean Age in years (± Standard Deviation)	26.4 ± 4.2
	Number (%)
Females	1056 (57%)
Educational Level: Junior or Senior School only	307 (18%)
Full-Time Employment	1108 (60%)
Civil Status: Single	1026 (56%)
Zygosity*	
Monozygotic Twins: Females/Males	331 (18%)/246 (13%)
Dizygotic Twins: Same Sex/Both Sexes	345 (19%)/346 (19%)
Non-Twin Siblings	570 (31%)
Mean BMI in kg/m^2 (± Standard Deviation)	23.83 ± 5.06
	Number (%)
Self-Reported Sleep-Wake Disturbances:	
Insomnia	386 (21%)
Hypersomnia	278 (15%)
Insomnia and Hypersomnia	226 (12%)
Insomnia and Daytime Impairment	110 (6%)
Hypersomnia and Anergia	147 (8%)
1st Onset of CIDI syndrome(s) during follow-up:	
Depression	485 (26%)
Hypo/Mania	150 (8%)
Psychosis	84 (5%)
>1 CIDI diagnosis	303 (16%)

% reported to the nearest whole number.
BMI: Body Mass Index; CIDI: Composite International Diagnostic Interview.
* Odd numbers indicate only one co-twin was assessed.

Table 2.
Relative risk (RR and 95% CI)* of first onset of any syndrome and for depression, hypo/mania or psychosis according to exposure to different types of sleep-wake disturbance.

Exposure	Outcome: Adjusted RR (95% CI)*			
	≥1 CIDI syndrome	Depression	Hypo/Mania	Psychosis
Insomnia only	1.11 (.60, 2.05)	***.73 (.53, .94)***	.56 (.13, 2.53)	***2.78 (1.24, 5.98)***
Hypersomnia only	.89 (.62, 1.27)	.99 (.69, 1.43)	1.33 (.42, 2.02)	.63 (.27, 1.51)
Insomnia and Hypersomnia	***1.79 (1.35, 2.37***	***1.66 (1.25, 2.21)***	1.55 (.99, 2.48)	1.46 (.91, 2.32)
Insomnia and Daytime Impairment	***2.62 (1.78, 3.87)***	***2.51 (1.39, 4.56)***	***2.34 (1.12, 4.94)***	1.31 (.60, 2.83)
Hypersomnia and Anergia	***1.86 (1.34, 2.60)***	***1.53 (1.06, 2.22)***	***1.49 (1.00, 2.44)***	1.32 (.75, 2.31)

Bold type indicates the Adjusted RR and 95% CI are statistically significant.

* All analyses adjusted for age, sex, Body Mass Index, zygosity (Monozygotic: Dizygotic: Non-Twin Sibling) and presence of comorbid CIDI syndrome (e.g. analysis of ≥1 CIDI syndrome was adjusted for number of comorbidities; analysis of a specific syndrome was adjusted for the other syndromes e.g. Depression adjusted for presence of Psychosis and/or Hypo/Mania).

associated with increased risk. In contrast, risk of hypo/mania was increased for composite measures of sleep-wake disturbances. Interestingly, risk of onset of psychosis was strongly associated with Insomnia but not with other sleep-wake disturbances.

4. Conclusions

This brief report examines sleep-wake disturbances associated with first onset of major psychiatric syndromes which have peak ages at onset during adolescence and early adulthood. The risk of any CIDI syndrome and then specifically for depression, hypo/mania and psychosis was analysed for five different exposures that were chosen as previous research indicates that they may be associated with one or more of the CIDI syndromes selected. Importantly, as sleep-wake disturbances were measured prior to individuals developing a full-threshold mood or psychotic syndrome, self-reported patterns were unlikely to confounded by prescriptions of antidepressants, atypical antipsychotics or mood stabilizers. This is particularly interesting as the strongest association we identified for a specific syndrome was for insomnia and future onset of psychosis. The finding is notable as it supports evidence regarding the nature of sleep disturbances in individuals with clinical high risk syndromes (Reeve et al., 2015), and contrasts markedly with sleep profiles reported in adults treated for established psychotic disorders (e.g. prolonged sleep; daytime impairment) (Meyer et al., 2020). Also noteworthy was the finding that increased risk of onset of depression was best identified by the composite measures we employed. The finding that insomnia alone was associated with a lower risk of depression was unexpected, although perhaps explained by our use of mutually exclusive categories for Insomnia and/or Hypersomnia (thus reducing the number of cases classified with Insomnia only). However, we note that several studies report that associations between insomnia and depression are markedly attenuated after controlling for confounders such as anxiety (Alvaro et al., 2013). Hypersomnia alone did not show a strong association with hypo/mania, but Hypersomnia and Anergia showed a significant association. The magnitude of other findings that showed trends towards statistical significance may have been attenuated by including multiple covariates in analyses especially comorbidities.

Our study advances the research field in five important ways. First, we examine associations longitudinally between exposures and outcomes, reducing the need to extrapolate from pooled findings from cross-sectional analyses (Lovato and Gradisar, 2014). Second, we explore a range of exposures in a trans-diagnostic cohort, which enhances discussion of shared and specific features of prodromes and risk syndromes (Eaton et al., 1995). Third, our approach highlights the importance of appreciating that comorbidity is the rule rather than the exception in youth, which is frequently ignored in disorder-specific research (Krueger and Markon, 2006). Fourth, we focus on adolescents and young adults specifically because this is the peak age range for onset of major mood and psychotic disorders and offers prospects for considering preventative interventions (Gore et al., 2011). Fifth, analyses were adjusted to account for the fact that age, sex and BMI moderate sleep-wake patterns and that sleep profiles show varying degrees of heritability (Madrid-Valero et al., 2020).

The study has several limitations. For example, it was an opportunistic analysis of existing data, rather than a study planned specifically to address the issues reported and, for instance, data were not available on comorbid physical health conditions. Although the cohort was large, future BLTS waves will include >2500 individuals and use assessments that measure in a more nuanced way the severity of any sleep-wake symptoms and quality of sleep (Mitchell et al., 2019). A larger sample size will reduce the risk of type 1 and type 2 statistical errors and allow more sophisticated approaches to analyses (e.g. for twin status/familial clustering). Also, use of reliable and valid tools will avoid reliance on single item ratings or proxy measures of potentially important exposures such as delayed sleep phase (Robillard et al., 2013; Steinan et al., 2016).

In summary, we found that the symptom of insomnia was prevalent in community-residing youth, and that this symptom was associated with a nearly 3-fold increase in risk of onset of psychosis. For mood syndromes, risk of onset was increased 1.5–2.5-fold in individuals who showed both sleep and daytime disturbances. We conclude that whilst the increased risk is modest for new onset mental disorder, it is sufficient to recommend screening for sleep disruptions. This is especially true given that effective interventions already exist for insomnia (with or without daytime disturbance) such as CBT-I (which can be delivered digitally with minimal resource use) and because prevention of a major mental disorder is socially, clinically and economically justifiable (Eaton et al., 1995; Gore et al., 2011). If our findings are replicated, then it is reasonable to consider further research on the impact of a range of interventions that modify post-pubertal sleep profiles on rates of major mental disorders. Approaches might use targeted individual therapies but could encompass population-based strategies, such as changing in school start times to minimise the risk of sleep deprivation in adolescents (Kolla et al., 2019).

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Author contribution

JS and IH were involved in the conception and design of the current study and JS undertook the planned analyses. All authors were involved in interpretation of the analyses. JS wrote the first draft of the manuscript. All authors contributed to and approved the final manuscript.

Data availability statement

Data are still being collected in the main cohort study and not all data are yet available for release. However, the dataset analysed during the current study is available from the corresponding author on reasonable request (if permission is obtained from grant holders and grant givers) and the applicant has obtained ethics approval from QIMR.

Declarations of Competing Interest

JS is a visiting professor at the Brain and Mind Centre and at Diderot University (Paris), the Norwegian University of Science and Technology (Trondheim) and is a "Science without Borders" fellow (Brazil). She has received grant funding from the UK Medical Research Council and from the UK NIHR Research for Patient Benefit programme; she declares no financial or other conflict of interests in relation to the topics addressed in this article.

IBH was a Commissioner in Australia's National Mental Health Commission from 2012 to 2018. He is the Co-Director, Health and Policy at the Brain and Mind Centre (BMC) University of Sydney. IBH has previously led community-based and pharmaceutical industry supported (Wyeth, Eli Lily, Servier, Pfizer, AstraZeneca) projects focused on the identification and better management of anxiety and depression. He is a Board Member of Psychosis Australia Trust and a member of Veterans Mental Health Clinical Reference group. He is the Chief Scientific Advisor to, and an equity shareholder in, InnoWell. InnoWell has been formed by the University of Sydney and PwC to administer the $30M Australian Government Funded Project Synergy. Project Synergy is a 3-year program for the transformation of mental health services using innovative technologies.

Other authors declare no conflicts.

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