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This work was completed at the University of Oxford

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Disclosures

**GMG** holds shares in P1vital and has served in the last 2 years as consultant, advisor or CME speaker for AstraZeneca, Abbvie, Cephalon/Teva, Convergence, Eli Lilly, GSK, Lundbeck, Medscape, Merck, Otsuka, P1Vital, Servier, Sunovion, Takeda.

**BCS** provides clinical support to Sleepio / Big Health Ltd.

**CAE** holds shares in Sleepio/ Big Health Ltd and has served in the last 2 years as consultant, advisor or CME speaker for Boots Pharmaceuticals, UCB, and Novartis.

**All other authors have no conflict of interest.**

Abstract

**Study objectives:** To group participants according to markers of risk for severe mental illness based on subsyndromal symptoms reported in early adulthood and evaluate attributes of sleep across these risk categories.

**Design:** Cross-sectional survey data were used to cluster participants based on dimensional measures of psychiatric symptoms (hallucinations, paranoia, depression, anxiety and (hypo)mania). High, medium and low symptom groups were compared across sleep parameters: insomnia symptoms, nightmares, chronotype and social jet lag.

**Setting:** An online survey of sleep and psychiatric symptomatology (The Oxford Sleep Survey) recruiting from one UK university.

**Participants:** 1403 Oxford University students (undergraduate and post-graduate). There were no inclusion and exclusion criteria. The median age was 21 (IQR = 20-23) and 55.60% were female.

**Measurements & Results:** Insomnia symptoms, nightmares frequency and nightmare related distress increased in a dose response manner with higher reported subsyndromal psychiatric symptoms (low, medium and high). The high-risk group exhibited a later chronotype (mid sleep point for free days) than the medium or low-risk group. The majority (71.7%) of participants in the high-risk group screened positive for insomnia and the median nightmare frequency was two per fortnight (moderately severe pathology).

**Conclusions:** Insomnia, nightmares and circadian phase delay are associated with increased subsyndromal psychiatric symptoms in young people. Each is a treatable sleep disorder and might be a target for early intervention to modify the subsequent progression of psychiatric disorder.
**Key words:** severe mental illness; sleep; insomnia; nightmares; chronotype; social jet lag, cluster analysis

**Introduction**

Sleep disturbance is common: 8-18% of the population report feeling dissatisfied with the quality or quantity of their sleep, whilst 6-10% suffer with insomnia disorder. Sleep and circadian rhythm disorders are also very common in those with established severe mental illness (SMI), including psychosis and bipolar disorder. Disturbed sleep is not simply a result of distressing daytime symptoms. Instead, sleep disruption commonly presents prior to acute psychiatric difficulties. For example, it elevates risk for a manic episode, first episode of psychosis or transition to major depression. Moreover, insomnia in particular predicts the inception of individual symptoms of SMI, including paranoia and hallucinations in general population samples. Thus, sleep disturbance may be an important mediator of severity, onset or relapse of a range of psychiatric disorders.

If correct, the prediction is that interventions to improve sleep quality per se should have an impact on all the associated disorders. Preliminary studies suggest this may be true for psychotic, depressive, anxiety and manic symptoms. If this trans-diagnostic approach works for fully developed psychiatric disorders it might be equally important for pre-morbid risk or prodromal states. Indeed, sleep interventions could be the kind of simple, acceptable approaches most appropriate in young people with poorly differentiated subsyndromal states, predictive of future problems. Accordingly, better understanding of the kind of sleep disruption prevalent at the point at which psychiatric symptoms have begun to emerge will be important to inform clinical interventions targeting sleep.

‘Sleep disturbance’ is an umbrella term which captures many sleep disorders, each of which requires different treatment refinements. There is growing evidence that people diagnosed with a SMI exhibit increased rates of insomnia, circadian disruption and more frequent and distressing nightmares. Whilst there is evidence of altered sleep timings at the early stages of mental illness, to our knowledge, there is no study which has investigated each of these sleep disorders at the point when symptoms of SMI begin to emerge.

Young adulthood corresponds to a developmental stage where the symptoms of SMI (e.g. paranoid thoughts, hallucinatory experiences) can be identified reliably. This age also corresponds to an elevated risk for first incidence of severe mental illnesses such as
schizophrenia\textsuperscript{20} and bipolar disorder \textsuperscript{20,21}. However, at this age most individuals will have the known negative consequences of psychiatric disorder ahead of them and will often display subsyndromal (attenuated) symptoms rather than a diagnosable severe mental illness\textsuperscript{23}. It is this group that is the focus of the current investigation.

The aims of the study were (a) to group participants based on symptom counts as a marker of risk for SMI and (b) to evaluate attributes of sleep across these risk categories. We took a trans-diagnostic approach to risk: we used cluster analysis to group participants based on dimensional measures of hallucinatory experiences, paranoia, mania, depression and anxiety. These measures capture the spectra of symptom severity: many people will endorse low levels of any symptom, whilst few people will endorse high levels.

The hypothesis we investigate is whether those with higher levels of psychiatric symptoms (and by definition at higher risk of further problems) exhibit an elevated rate of insomnia disorder and more frequent and distressing nightmares when compared to those at medium or low levels of symptoms. Exploratory analyses investigated whether chronotype (genetic predisposition of endogenous circadian phase) and social jet lag (misalignment of endogenous circadian phase with social time) differed across groups. We had no directional hypotheses for these latter analyses.

\textbf{Method}

\textit{Setting \& Design}

The Oxford Sleep Survey was a cross-sectional online survey. The survey included 122 questions designed to assess habitual sleep timing and quality and dimensional experiences of psychiatric symptoms. The study was reviewed and approved by the University of Oxford Research Ethics Committee (MSD/IDREC/C1/2012/65).

The survey was advertised to University of Oxford students via an email advert sent to students directly from their university college. In the majority of cases this email was distributed individually to students’ email accounts and in a minority of cases it was included as part of a broader information bulletin.

Twenty two of the 44 University of Oxford colleges were contacted to advertise the study (total student population: 12,220). There were no inclusion or exclusion criteria. All participants provided online informed consent. This resulted in 2055 participants clicking on a hyperlink to the survey and 1686 participants with at least one complete survey section (response rate: 13.80\% of total student population). Data were checked for duplicate responses based on
matching email addresses or IP addresses. No duplicates were found. Data cleaning resulted in 100 participants being omitted from the analyses (8 due to implausible ages, 90 implausible sleep times and 2 inconsistent responses to physical health questions). Only those with complete data for the mental health variables (paranoia, hallucinations, mania, depression and anxiety) were entered into the cluster analysis (N=1403).

**Measures**

*Psychotic like experiences:* Paranoia and hallucinations were measured using sub-scales from the Specific Psychotic Experiences Questionnaire (SPEQ) \(^{24}\). All SPEQ subscales show good to excellent internal consistency (Chronbach’s alpha .77-.93)\(^{24}\). The scales list fifteen paranoid thoughts and nine hallucinatory experiences. Statements are rated on a six point frequency scale from not at all (0) through to daily (5). None of the items measure sleep disturbance. The subscales have been validated as a measure of psychotic experiences in a general population sample of adolescents \(^{24}\).

*Mania:* The Mood Disorder Questionnaire is a validated screening instrument for bipolar disorder \(^{25}\). The questionnaire lists thirteen symptoms of mania. One of the thirteen items marks sleep disturbance: ‘You got much less sleep than usual and found you didn’t really miss it’. This item relates to reduce need for sleep, rather than insomnia, nightmares, chronotype or social jet lag specifically and hence was retained. The current study utilised the dimensional symptom count score (range 0-13) which has good internal consistency (Cronbach’s alpha = 0.84)\(^{25}\).

*Depression and anxiety:* Depression and anxiety were measured using two sub-scales from the Depression, Anxiety and Stress Scales (DASS-21) \(^{26}\). Fourteen items yield the two subscale scores which range from 0 to 42. None of the items measure sleep disturbance. The scales have good psychometric properties for measuring depression and anxiety in a non-clinical population \(^{27}\). The scales have good internal consistency (.82-.88)\(^{27}\).

*Insomnia:* The Sleep Condition Indicator \(^{28}\) is an 8 item screening measure for DSM-5 Insomnia Disorder. Scores range from 0-32 with higher scores indicating better sleep. A clinical cut off of ≤16 has been shown to correctly identify 89% of those with probable insomnia disorder. The measure has good internal consistency (Cronbach’s alpha = 0.86)\(^{28}\).

*Nightmares:* A retrospective Dream Log was adapted from Levin and Fireman \(^{30}\). Participants were asked to indicate how many nightmares they estimated experiencing over the last two
weeks prior to completing the survey (14 nights). If the participant had experienced at least one nightmare, they were asked to pick their worst nightmare and rate it on a seven-point likert scale for distress. Retrospective nightmare logs measuring up to one month in the past are known to yield similar results to prospective measures in a sample of undergraduate students.¹¹

Chronotype: Chronotype was derived from the Munich Chronotype Questionnaire (MCTQ)³², which consists of six questions concerning self-reported, habitual sleep timings. The primary outcome of the MCTQ is the Mid-Sleep point on Free days (MSF). This parameter is calculated as the midpoint between sleep start and sleep end. The MSF is corrected for oversleep on free days (MSFsc): oversleep occurs as a result of sleep debt due to sleep deprivation on work days. The equation for calculating MSFsc is: MSFsc = MSF – (0.5*(SDf – (((nWD*SDw)+((7-nWD)*SDf))/7))) where SDf = the Sleep Duration on free days, SDw = the Sleep Duration on work days and nWD = the number of Work Days. Work days were defined as “days with commitments e.g. work, lecture or sport practise” and students were informed that “work days include any days where you have a schedule that causes you to get up or go to bed at a certain time and can include the weekend”. The MSF is strongly correlated to Horne-Östberg’s Morningness-Eveningness Questionnaire score³³ (r=-0.73)³⁴, demonstrating convergent validity.

Social Jet Lag (SJL) is defined as the discrepancy between the endogenous circadian phase for sleep and the actual sleep period that is influenced by social and work commitments. SJL is calculated as the difference between the endogenously driven sleep period and that imposed by external commitments i.e. the free day sleep period and that of work days. The mid-sleep points on work and free days from the MCTQ were used as correlates of chronotype. The equation for calculating SJL is: SJL = MSF – MSW. Where MSW = Mid Sleep point on Work days.

Analyses

Statistical analysis: SPSS 19³⁵ was used. All mental health symptom counts and nightmare frequency variables were positively skewed and the SCI (insomnia) score was negatively skewed. Medians and interquartile range (IQR) and non-parametric statistics are therefore reported throughout. We used the Spearman correlation coefficient to quantify the extent of statistical association strength between variables. There is no formal statistical definition of what constitutes a statistically strong relationship, since this depends on the application. Here, we used the empirical guideline that in medical applications we consider relationships to be statistically strong if the magnitude of the correlation coefficient is larger than 0.3.³⁶,³⁷ Given the exploratory nature of the study, a conservative alpha level of <0.01 was used.
Cluster analysis: Each of the five mental health characteristics was normalized (linearly scaled to have a minimum value of 0 and a maximum value of 1) to ensure that there is no single symptom dominated the clustering. This is a standard approach in general distance-based algorithmic approaches in machine learning.

We used two approaches to cluster the data: the standard k-means clustering, and hierarchical clustering. Henceforth, we focus on the hierarchical clustering results, and defer direct comparison of the results of the two clustering methods for the supplementary material. Hierarchical clustering is a robust method for grouping data based on the similarity of their characteristics (in this study, the five measures discussed in the preceding section). Unlike k-means, hierarchical clustering does not require pre-specifying the number of clusters in the data, and does not require an initial arbitrary starting configuration assignment.

Hierarchical clustering can be thought of as a tree where at each level the data is recursively split into new clusters, so that the between group dissimilarity is maximized (the concept of dissimilarity refers to the metric used to assess whether samples have similar properties). Ultimately, this process results in a concise graphical representation of all data samples called a dendrogram. Part of the popularity of hierarchical methods has been attributed to this property, where it is possible to visualize how samples group together at each level. The number of clusters was decided by determining a cut-off horizontally to partition the data. In this study, the similarity of the samples was determined using Ward's linkage with Euclidean distance, as has been similarly used in another recent study. The number of clusters was selected by visual inspection of the computed dendrogram.

Visualisation: The clustering analysis will assign each of the 1403 participants into one of the possible groups (clusters). However, it is difficult to intuitively understand how the five mental health characteristics contribute towards the clustering results. One way to visualize the clustering findings is to project these five characteristics down to a lower dimensional space (transformed characteristics) which can be graphically represented in a two dimensional plot. There are a number of different methods available to project data, but essentially all different algorithms attempt to preserve the high-dimensional similarities of the samples in a more compact setting. Here, we used a dimensionality reduction method called t-SNE to project the five characteristics into a two dimensional space. t-SNE is a state of the art dimensionality
reduction algorithm, which is particularly popular for visualizing high dimensional (in this case five dimensional) data.

**Results**

The total sample comprised 780 females (55.6%), 612 males (43.6%), 11 declined to answer, 0.8%. The median age was 21 (IQR = 20-23). Of the total sample 104, (7.4%) were in receipt of mental health treatment, 1299 (92.6%) were not. With regards to diagnosis, 233 (16.6%) self-reported a psychiatric diagnosis, 1170 (83.4%) reported no psychiatric diagnosis.

*Cluster solutions*

Following visual inspection of the dendrogram, we decided to use five clusters. Hierarchical clustering revealed a group with elevated scores on all five mental health variables (‘high risk’), a group with low scores on all five mental health variables (‘low risk’) and three groups with symptom count scores falling in between these high and low risk groups, but with mixed profiles (see table 1). Group two was particularly characterised by elevated (hypo)manic symptoms in addition to other symptoms of depression, anxiety, hallucinations and paranoia. Group three was particularly characterised by elevated depression scores, in addition to symptoms of paranoia, anxiety, depression and (hypo)mania. Group four exhibited mild elevation (compared to the low risk group) on all symptoms excluding hallucinations.

**Table 1. Symptom count scores according to hierarchical cluster analysis with ward linkage (median and interquartile range).**

<table>
<thead>
<tr>
<th></th>
<th>Group 1* (N=46)</th>
<th>Group 2 (N=144)</th>
<th>Group 3 (N=276)</th>
<th>Group 4 (N=396)</th>
<th>Group 5** (N=541)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M IQR</td>
<td>M IQR</td>
<td>M IQR</td>
<td>M IQR</td>
<td>M IQR</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>5 1-10</td>
<td>3 0-7</td>
<td>0 0-2</td>
<td>0 0-2</td>
<td>0 0-1</td>
</tr>
<tr>
<td>Paranoia</td>
<td>38 29-46</td>
<td>18 12-27</td>
<td>12 5-19</td>
<td>8 3-12</td>
<td>3 1-7</td>
</tr>
<tr>
<td>Anxiety</td>
<td>22 16-26</td>
<td>11 6-16</td>
<td>10 6-14</td>
<td>4 2-8</td>
<td>2 0-4</td>
</tr>
<tr>
<td>Depression</td>
<td>28 20-36</td>
<td>14 10-18</td>
<td>20 16-26</td>
<td>6 2-8</td>
<td>4 2-8</td>
</tr>
<tr>
<td>(Hypo)mania</td>
<td>10 8-12</td>
<td>9 8-10</td>
<td>3 2-5</td>
<td>6 5-8</td>
<td>1 0-2</td>
</tr>
</tbody>
</table>

*=high risk group, **=low risk group. M =median, IQR = interquartile range. All other groups combined to form medium risk group. Minimum possible score on all scales = 0. Maximum scores for individual scales: paranoia = 75, hallucinations = 45, anxiety = 42, depression = 42 and (hypo)mania = 13.

Given the mixed profiles of the middle groups and lack of clear clinical differentiation we combined these clusters into an overall ‘medium risk’ group. The median and inter-quartile
range for symptoms within each of these three clusters is in table 2. K-means clustering provided a similarly distinct high and low-risk groups and three medium-risk groups. This analysis is included in the supplementary material.

Of the three groups, 46 (3.3%) participants fell into the high-risk group, 816 (58.2%) fell into the medium-risk group and 541 (38.6%) fell into the low-risk group. The median age was 20 (IQR = 19-22) for the high-risk group, and 21 for both the medium-risk group (IQR = 20-23) and low-risk group (IQR = 20-24). The percentage of males in the high-risk group was 51.1%, the medium-risk group was 45.0% and the low-risk group was 41.8%.

In order to get a visual illustration of the findings of the cluster analysis, we used the t-SNE algorithm to obtain a two-dimensional representation of the five symptom counts, and assigned a different colour to each of the three groups. The results appear in figure 1, and are intuitively appealing: it seems that the participants are very well separated overall. For example, there is no overlap between the high and low risk groups on the Y axis. For most nonlinear dimensionality reduction techniques (such as t-SNE) it is not straightforward to describe what the projected dimensions represent, since they are nonlinear combinations of the original characteristics. Here, we attempt to have some tentative insight into this link by associating the original characteristics to the projected dimensions obtained with t-SNE. Specifically, we have computed the Spearman correlation coefficients between each of the five original characteristics and each of the two projected dimensions in order to quantify these relationships. The first projected dimension (t-SNE variable1) is statistically very strongly correlated with (hypo)mania (R=0.79), and moderately with depression (R=-0.19), hallucinations (R=0.13) and paranoia (R=0.11) but not with anxiety (R=.05). The second projected dimension (t-SNE variable2) is statistically strongly correlated with all the original characteristics: hallucinations (R=-0.35), paranoia (R=-0.57), anxiety (R=-0.56), depression (-0.70) and (hypo)mania (R=-0.79).

Table 2. Mental health symptoms as a function of hierarchical cluster analysis risk category (total N=1403)

<table>
<thead>
<tr>
<th></th>
<th>High risk (N=46)</th>
<th>Medium risk (N=816)</th>
<th>Low risk (N=541)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>IQR</td>
<td>Median</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>5</td>
<td>1-10</td>
<td>0</td>
</tr>
<tr>
<td>Paranoia</td>
<td>38</td>
<td>29-46</td>
<td>10</td>
</tr>
<tr>
<td>Anxiety</td>
<td>22</td>
<td>16-26</td>
<td>6</td>
</tr>
<tr>
<td>Depression</td>
<td>28</td>
<td>20-36</td>
<td>12</td>
</tr>
<tr>
<td>(Hypo)mania</td>
<td>10</td>
<td>8-12</td>
<td>6</td>
</tr>
</tbody>
</table>

Minimum possible score on all scales = 0. Maximum scores for each scale: hallucinations = 45, paranoia = 75, anxiety = 42, depression = 42 and (hypo)mania = 13.
The face validity of the risk groups is confirmed by self-reported mental health, receipt of treatment, self-reported diagnoses and family history of psychiatric difficulties (see table 3). Across high, medium and low-risk groups, ‘very poor’ mental health was rated by 10.9%, 0.9% and 0.4% respectively, ‘poor’ was rated 50.0%, 13.7% and 2.0% respectively, ‘average’ by 37.0%, 35.9% and 15.7% respectively, ‘good’ by 2.2%, 31.9% and 44.4% respectively and ‘very good’ by 0.0%, 17.6% and 37.5% respectively. Across groups, 92.4% of the low risk group, 79.4% of the medium-risk group and 47.8% of the high-risk group reported having no mental health diagnosis. There was one participant reporting a psychotic illness (in the medium-risk group). With regards to receipt of treatment, 23.9% of the high-risk group, 9.8% of the medium-risk group and 2.4% of the low-risk group reported receiving treatment for mental health difficulties.
Table 3. Mental health diagnoses and family history within each risk group (high, medium and low)

<table>
<thead>
<tr>
<th></th>
<th>High risk</th>
<th>Medium risk</th>
<th>Low risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Percentage of group with diagnosis (%)</td>
<td>Percentage of group with family history (%)</td>
<td>Percentage of group with diagnosis (%)</td>
</tr>
<tr>
<td>Mood disorder</td>
<td>37.0</td>
<td>45.7</td>
<td>10.2</td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td>23.9</td>
<td>23.9</td>
<td>7.6</td>
</tr>
<tr>
<td>Psychotic disorder</td>
<td>0.0</td>
<td>6.5</td>
<td>0.1</td>
</tr>
<tr>
<td>Eating disorder</td>
<td>15.2</td>
<td>10.9</td>
<td>3.1</td>
</tr>
<tr>
<td>Neurodevelopmental disorder</td>
<td>4.3</td>
<td>10.9</td>
<td>2.0</td>
</tr>
<tr>
<td>‘Other’</td>
<td>2.2</td>
<td>2.2</td>
<td>2.7</td>
</tr>
<tr>
<td>‘Unsure’</td>
<td>8.7</td>
<td>1.3</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Sleep profiles across risk group

Risk groups were compared on sleep variables using the Kruskal-Wallis test statistic (Table 4). Insomnia, nightmare frequency, nightmare distress and MSFsc showed significant group differences whereas social jet lag did not. Mann-Whitney U tests were used to assess pairwise comparisons between risk groups. The high-risk group exhibited more insomnia symptoms ($z=-6.69$, $p<.001$), nightmare frequency ($z=-5.26$, $p<.001$) and higher nightmare related distress ($z=-4.14$, $<.001$) than the medium-risk group. The high-risk group had a descriptively later MSFsc than the medium-risk group, but this was not statistically significant ($z=-.97$, $p=0.33$). The medium-risk group reported higher levels of insomnia ($z=-10.16$, $<.001$), nightmare frequency ($z=-5.79$, $<.001$) and had a later MSFsc ($z=-2.67$, $p=0.008$) than the low-risk group. Nightmare related distress was not significantly different across medium and low-risk groups ($z=-0.86$, $p=0.39$).

Table 4. Sleep profiles by risk group

<table>
<thead>
<tr>
<th></th>
<th>High risk</th>
<th>Medium risk</th>
<th>Low risk</th>
<th>Kruskal-Wallis statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>IQR</td>
<td>Median</td>
<td>IQR</td>
</tr>
<tr>
<td>Insomnia (SCI total)</td>
<td>11.50</td>
<td>7.00-17.00</td>
<td>21.00</td>
<td>15.00-26.00</td>
</tr>
<tr>
<td>Nightmare frequency (/fortnight)</td>
<td>2</td>
<td>1-4</td>
<td>0</td>
<td>0-2</td>
</tr>
<tr>
<td>Nightmare distress (1-7)</td>
<td>5</td>
<td>4-6</td>
<td>4</td>
<td>3-5</td>
</tr>
<tr>
<td>Chronotype (MSFsc, local time)</td>
<td>4.87</td>
<td>3.96-6.36</td>
<td>4.64</td>
<td>3.63-5.75</td>
</tr>
<tr>
<td>Social Jet Lag (hours)</td>
<td>1.00</td>
<td>0.38-2.00</td>
<td>1.13</td>
<td>0.53-1.75</td>
</tr>
</tbody>
</table>
The SCI has a validated clinical cut-off for probable Insomnia Disorder (total score ≤16; lower total score indicates poorer sleep)\textsuperscript{28}. In the high-risk group 71.7\% scored below the clinical cut-off for probable Insomnia Disorder, in the medium-risk group 27.6\% fell below the cut-off and 12.2\% of the low risk group fell below the cut-off. Exploratory analysis revealed that the scores for each of the eight items on the SCI (i.e. each of the diagnostic criteria for DSM-5 Insomnia Disorder) were statistically significantly different across risk groups, $X^2(2) = 24.35$ to 165.10, all $p<0.001$. The percentage of participants in each group achieving a DSM-5 score for each individual symptom is shown in figure 2.

**Figure 2.** Percentage of participants meeting DSM-5 criteria for each SCI insomnia symptom, as a function of risk grouping (high, medium or low).

The individual associations between the five subsyndromal symptoms and the five sleep characteristics are shown in table 5.
Table 5. Spearman’s correlation co-efficients between the subsyndomal psychiatric symptoms and sleep characteristics (N=1403).

<table>
<thead>
<tr>
<th></th>
<th>Insomnia (SCI)</th>
<th>Nightmare frequency</th>
<th>Nightmare distress</th>
<th>Chronotype (MSFsc)</th>
<th>Social Jet Lag (SJL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hallucinations</td>
<td>-0.14**</td>
<td>0.20**</td>
<td>0.21**</td>
<td>0.03</td>
<td>0.07</td>
</tr>
<tr>
<td>Paranoia</td>
<td>-0.25**</td>
<td>0.20**</td>
<td>0.18**</td>
<td>0.06</td>
<td>-0.01</td>
</tr>
<tr>
<td>Anxiety</td>
<td>-0.42**</td>
<td>0.28**</td>
<td>0.19**</td>
<td>0.01</td>
<td>-0.03</td>
</tr>
<tr>
<td>Depression</td>
<td>-0.50**</td>
<td>0.26**</td>
<td>0.17**</td>
<td>0.07*</td>
<td>0.02</td>
</tr>
<tr>
<td>(Hypo)mania</td>
<td>-0.20**</td>
<td>0.16**</td>
<td>0.09</td>
<td>0.11**</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*p<.01,  **p<.001

Discussion

Hierarchical clustering created a clinically useful grouping of the student cohort on the basis of five dimensional symptoms (paranoia, hallucinations, depression, anxiety and mania). In the high-risk group all symptoms were elevated, suggestive of an elevated risk for the development of a SMI. In the low-risk group all risks were low, and the medium group fell directly between these two extreme groups. Face validity was confirmed by the participants’ own global ratings of current mental health in the three clusters. Insomnia, nightmare frequency and nightmare distress increase in a dose response fashion across the low, medium and high risk groups. There was evidence of a circadian phase delay in the high and medium risk groups, compared to the low risk group, as assessed by mid sleep point on free days. Analysis of single insomnia symptoms (e.g. time to fall asleep, wake after sleep onset) suggest that all symptoms measured by the SCI contribute to higher levels of insomnia in the high risk group (figure 2). There is not a dominant insomnia symptom. Social jet lag (the degree of misalignment between endogenous circadian phase and habitual sleep time) was not statistically different across groups.

The high-risk group was characterised by elevated levels of paranoid thoughts, hallucinatory experiences, manic symptoms and affective symptoms. The majority (60.9%) of the high-risk group rated their mental health as poor or very poor. There was an elevated family history of psychotic illness, and much higher rates of current depression or anxiety diagnoses compared to the medium and low-risk groups. None of the groups self-reported a diagnosed psychotic illness, and the constellation of symptoms and risk factors was not very specific for schizophrenia on the one hand or bipolar disorder on the other. This lack of diagnostic specificity confirms what has been described in young clinic samples. However, such groups are likely to be at high risk for a SMI. They represent a group in which proof of concept studies for
treatments to prevent the onset and progression of mental illness could be informative. The medium-risk group confirms the existence of a gradient between high and low risk participants.

The majority (71.7%) of the high-risk group screened positive for probable insomnia disorder. This was higher than the 12.2% in the low-risk group and markedly higher than the prevalence of insomnia in the general population (6-10%)\(^1\). In addition to high rates of insomnia, those in the high-risk group had a median nightmare frequency of one per week, reflective of moderately severe pathology\(^2\), furthermore, these nightmares were more distressing than those experienced by the medium or low-risk groups. Analysis of the relationship between individual subsyndromal psychiatric symptoms and the sleep characteristics revealed statistically strong associations between insomnia and both depression and anxiety. However weak relationships were also found for each of the five subsyndromal psychiatric symptoms with insomnia and nightmares (see Table 5). Weak associations were found between chronotype and both depression and (hypo) mania. It is likely that whilst each of these relationships is weak, there is a cumulative effect, such that those at high risk for SMI, presenting with multiple subsyndromal symptoms, have poorer sleep compared to those individuals with just one subsyndromal symptom.

Both Insomnia Disorder and Nightmare Disorder are DSM-5 diagnosable and treatable conditions, which commonly co-occur\(^43\). Cognitive Behavioural Therapy (CBT) is the recommended first line treatment for persistent insomnia and produces moderate to large improvements in sleep onset latency and sleep quality\(^44,45\). Meta-analyses report that Imagery Rehearsal Training (IRT) results in large reductions in nightmare frequency relative to control\(^47,48\) and are recommended, alongside pharmacological options (Prazosin)\(^49,50\). Although chronotype was found to be later for the high and medium risk groups compared to the low risk group, it should be noted that the median differences in sleep timings between the groups are relatively small (16 minutes between the low and medium risk groups and 29 minutes between the low and high risk groups). Nevertheless, chronotype and sleep preferences might be an important consideration in implementing these treatments. Whilst this high-risk group presents with less clearly defined subsyndromal symptoms, they clearly present with sleep disorders in need of treatment. The impact of sleep treatments on secondary psychiatric symptoms and the development of severe mental illness in young people is an important area of research that is already underway. We are conducting a large randomised controlled trial (n>2,000) of CBT for insomnia to investigate the impact on psychiatric symptoms, at an age when these begin to emerge (university students)\(^51\).
Although the findings are compelling, there are limitations to the current study. The sample was homogenous, since all participants were University of Oxford students, which might limit generalisability of the results; moreover the overall response rate is modest and students with sleep problems may have been more likely to complete the survey. Against this, the rates and distribution of hypomanic symptoms and distribution of depression scores were comparable to a previous survey of the student population without a sleep emphasis. Whilst self-report questionnaires facilitate the collection of a large sample size, they limit the depth of assessments. Retrospective accounts of sleep times lose some reliability compared to prospective sleep diaries and future studies should aim to include these as well as objective measures of sleep such as actigraphy. Furthermore this study is limited in its assessment of the variable nature of sleep patterns. Steps were taken to minimise the possible contributors to sleep variability: all students were assessed on work and free days during term time; the definition of work days was clarified for a student population i.e. highlighting that work days can be at the weekend; and the survey was completed in the second academic term when there are fewer exams. In terms of mental health status, a future study would benefit from a comprehensive interview to assess risk of psychiatric difficulties (e.g. the Comprehensive Assessment of At-Risk Mental States interview). Alternatively, following the current groups longitudinally could add validity to their group status (high, medium or low risk for SMI). Lastly, some of the high-risk sample self-reported a psychiatric diagnosis, but were unsure what it was (8.7%). A more thorough diagnostic interview, or report from the participant’s diagnosing care team would be important in future studies to validate the sample as high-risk (rather than those already with a diagnosis).

In conclusion, increased rates of insomnia, nightmares and to a lesser extent circadian phase delay are associated with psychiatric symptoms and poor mental health in a young population. Each of these sleep disturbances is treatable. The clinical challenge is to demonstrate that treatment has an impact on the development and course of severe psychiatric symptomatology in young people.

References:


37. SPSS Inc. SPSS Statistics for Windows. 2010.


Supplementary materials:

Supplementary method

Clustering methods belong to the category of unsupervised machine learning algorithms. It is difficult to quantify how well they perform in real-world problems where there is no ground truth. One approach to have confidence in clustering findings is experimenting with an independent clustering method and comparing the clustering results. Here, we used the standard k-means clustering (Suppl. table 5) to compare the groups determined by hierarchical clustering (Table 4). To ensure comparison is possible we set the number of the k-means clusters to be five. Although not the same samples were assigned identically to clusters between the two methods (as expected), the general properties of each of the five clusters were similar. That is, summarizing each of the five clusters in terms of the five raw characteristics for both methods led to similar findings. This is solid evidence that the clustering results reported in this study are not only clinically interpretable, but are also a valid, robust representation of the studied cohort.

Supplementary table 5. Symptom count scores according to hierarchical and k-means cluster analysis methods (median and interquartile range).

<table>
<thead>
<tr>
<th></th>
<th>Hierarchical cluster analysis with ward linkage</th>
<th>K-means cluster analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1* (N=46)</td>
<td>Group 2 (N=144)</td>
</tr>
<tr>
<td></td>
<td>Group 3 (N=276)</td>
<td>Group 4 (N=396)</td>
</tr>
<tr>
<td></td>
<td>Group 5** (N=541)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>IQR</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>5</td>
<td>1-10</td>
</tr>
<tr>
<td>Paranoia</td>
<td>38</td>
<td>29-46</td>
</tr>
<tr>
<td>Anxiety</td>
<td>22</td>
<td>16-26</td>
</tr>
<tr>
<td>Depression</td>
<td>28</td>
<td>20-36</td>
</tr>
<tr>
<td>(Hypomania)</td>
<td>10</td>
<td>8-12</td>
</tr>
</tbody>
</table>

Group 1* and Group 5** = high risk group, Group 2 and Group 4 = low risk group. M = median, IQR = interquartile range. Minimum scores for each scale were 0. Maximum scores for each scale: hallucinations = 45, paranoia = 75, anxiety = 42, depression = 42 and (hypo)mania = 13.