This is an Open Access document downloaded from ORCA, Cardiff University's institutional repository:https://orca.cardiff.ac.uk/id/eprint/126847/

This is the author’s version of a work that was submitted to / accepted for publication.

Citation for final published version:


Please note:
Changes made as a result of publishing processes such as copy-editing, formatting and page numbers may not be reflected in this version. For the definitive version of this publication, please refer to the published source. You are advised to consult the publisher’s version if you wish to cite this paper.

This version is being made available in accordance with publisher policies. See http://orca.cf.ac.uk/policies.html for usage policies. Copyright and moral rights for publications made available in ORCA are retained by the copyright holders.
Comparison of Genetic Liability for Sleep Traits Among Individuals With Bipolar Disorder I or II and Control Participants

Katie J. S. Lewis, PhD; Alexander Richards, PhD; Robert Karlsson, PhD; Ganna Leonenko, PhD; Samuel E. Jones, PhD; Hannah J. Jones, PhD; Katherine Gordon-Smith, PhD; Liz Forty, PhD; Valentina Escott-Price, PhD; Michael J. Owen, FRCPsych, PhD; Michael N. Weedon, PhD; Lisa Jones, PhD; Nick Craddock, FRCPsych, PhD; Samuel E. Jones, PhD; Hannah J. Jones, PhD; Katherine Gordon-Smith, PhD; Liz Forty, PhD; Valentina Escott-Price, PhD; Michael J. Owen, FRCPsych, PhD; Michael N. Weedon, PhD; Lisa Jones, PhD; Nick Craddock, FRCPsych, PhD; Arianna Di Florio, MD, PhD; Michael C. O’Donovan, FRCPsych, PhD

IMPORTANCE Insomnia, hypersomnia, and an evening chronotype are common in individuals with bipolar disorder (BD), but whether this reflects shared genetic liability is unclear. Stratifying by BD subtypes could elucidate this association and inform sleep and BD research.

OBJECTIVE To assess whether polygenic risk scores (PRSs) for sleep traits are associated with BD subtypes I and II.

DESIGN, SETTING, AND PARTICIPANTS This case-control study was conducted in the United Kingdom and Sweden with participants with BD and control participants. Multinomial regression was used to assess whether PRSs for insomnia, daytime sleepiness, sleep duration, and chronotype are associated with BD subtypes compared with control participants. Affected individuals were recruited from the Bipolar Disorder Research Network. Control participants were recruited from the 1958 British Birth Cohort and the UK Blood Service. Analyses were repeated in an independent Swedish sample from August 2018 to July 2019. All participants were of European ancestry.

EXPOSURES Standardized PRSs derived using alleles from genome-wide association studies of insomnia, sleep duration, daytime sleepiness, and chronotype. These were adjusted for the first 10 population principal components, genotyping platforms, and sex.

MAIN OUTCOMES AND MEASURES Association of PRSs with BD subtypes, determined by semistructured psychiatric interview and case notes.

RESULTS The main analysis included 4672 participants with BD (3132 female participants [67.0%]; 3404 with BD-I [72.9%]) and 5714 control participants (2812 female participants [49.2%]). Insomnia PRS was associated with increased risk of BD-II (relative risk [RR], 1.14 [95% CI, 1.07-1.21]; P = 8.26 × 10\(^{-5}\)) but not BD-I (RR, 0.98 [95% CI, 0.94-1.03]; P = .409) relative to control participants. Sleep-duration PRS was associated with BD-I (RR, 1.10 [95% CI, 1.06-1.15]; P = 1.13 × 10\(^{-5}\)) but not BD-II (RR, 0.99 [95% CI, 0.93-1.06]; P = .818). Associations between (1) insomnia PRS and BD-II and (2) sleep-duration PRS and BD-I were replicated in the Swedish sample of 4366 individuals with BD (2697 female participants [61.8%]; 2627 with BD-I [60.2%]) and 6091 control participants (3767 female participants [61.8%]). Chronotype and daytime-sleepiness PRS were not associated with BD subtypes.

CONCLUSIONS AND RELEVANCE Per this analysis, BD subtypes differ in genetic liability to insomnia and hypersomnia, providing further evidence that the distinction between BD-I and BD-II has genetic validity. This distinction will be crucial in selecting participants for future research on the role of sleep disturbance in BD.
Bipolar disorder (BD) and sleep have often been linked. First, reduced sleep duration, a symptom of manic episodes, has been implicated as a prodrome and trigger of mania. Second, insomnia (difficulty initiating and maintaining sleep) and hypersomnia (prolonged sleep duration or excessive daytime sleepiness) are commonly reported symptoms of bipolar depression and hypersomnia (prolonged sleep duration or excessive daytime sleepiness) are commonly reported symptoms of bipolar depression and are associated with significant distress and impairment. Third, there is evidence that individuals with BD display greater evening preference for sleep (ie, an evening chronotype) than healthy control participants. At present, sleep interventions for individuals with BD primarily focus on reducing insomnia and stabilizing circadian rhythms. Understanding the association between sleep and BD is important and could inform clinical interventions.

Recent genome-wide association studies (GWAS) provide an opportunity to examine the association between sleep and BD at the genomic level. Using summary-level data, some studies have demonstrated a positive genetic correlation between BD and sleep duration. Other studies, however, have found no significant genetic correlations between BD, chronotype, and insomnia. These analyses have used summary-level data and therefore may have been limited by a lack of individual bipolar phenotypic and genotypic data. In particular, associations between BD subtypes (ie, type 1 [BD-I] and type 2 [BD-II]) and sleep traits have been neglected, despite evidence of heterogeneity between BD subtypes in genetics, illness course, clinical features, and etiologies. There is also evidence that individuals with BD subtypes differ in sensitivity to sleep loss and rates of hypersomnia and insomnia during depressive episodes.

We therefore aimed to determine whether genetic liability for insomnia, hypersomnia, and chronotype differs in BD-I and BD-II. Given a lack of evidence on whether these sleep traits differ between individuals with BD-I or BD-II in the interepisode period, we had no prior hypothesis about which sleep traits, if any, would be associated with BD subtypes.

To test the associations between sleep and BD phenotypes, we adopted the polygenic risk score (PRS) method to estimate the burden of risk alleles associated with 4 sleep-associated phenotypes (insomnia, sleep duration, excessive daytime sleepiness, and chronotype) in people with BD-I or BD-II and control participants. In secondary analyses, we conducted a 2-sample mendelian randomization (MR) study to test whether the data were consistent with a causal association between sleep and BD phenotypes.

**Method**

**Sample Recruitment**

**Individuals With BD**

Participants with BD were recruited within the United Kingdom by the Bipolar Disorder Research Network (bdrn.org). All participants reported their race as white. Participants were excluded if they had affective illness experienced solely in response to alcohol or substance misuse or secondary to medical illness or medication use.

Participants provided written informed consent. The study had ethical approval from the West Midlands Multi-Centre Research Ethics Committee, in addition to local research and development approval by UK National Health Service Trusts and Health Boards.

**Control Participants**

Control participants aged 18 years or older were recruited via the UK Blood Service and the 1958 Birth Cohort. Characteristics and recruitment of this sample has been described previously. All control participants reported their race as white.

**Measures**

Individuals with BD were assessed using the Schedules for Clinical Assessment in Neuropsychiatry interview, administered by trained research psychologists or psychiatrists in the research team (A.D.F., L.F., K.G.-S., L.J., N.C., and I.J.). Information from this interview was combined with clinical case note data to make lifetime best-estimate DSM-IV diagnoses. Measures taken to increase reliability of distinguishing BD subtypes are outlined in eAppendix 1 in the Supplement. Interrater reliability for differentiating between a best-estimate lifetime DSM-IV diagnosis of BD-I and BD-II was found to be good (κ, 0.85).

**Discovery Data Sets for Sleep Traits**

The discovery data sets were GWAS summary statistics for insomnia, sleep duration, daytime sleepiness, and chronotype conducted in participants recruited to the UK Biobank. Sleep phenotypes were assessed using touchscreen questions. To assess insomnia symptoms, participants were asked, “Do you have trouble falling asleep at night, or do you wake up in the middle of the night?” with the possible responses “never/rarely,” “sometimes,” “usually,” and “prefer not to answer.” The insomnia GWAS was conducted in 236,163 participants who answered “usually” (affected individuals) or “never/rarely” (control participants). We chose to

---

**Key Points**

**Question**

Does genetic liability to insomnia, hypersomnia, and chronotype differentiate subtypes of bipolar disorder?

**Findings**

In this case-control study of 4672 participants with bipolar disorder and 5714 control participants, individuals with bipolar disorder I had significantly greater genetic liability to longer sleep duration, whereas individuals with bipolar disorder II had significantly greater genetic liability to insomnia; these findings were replicated in an independent sample. Individuals with bipolar subtypes did not differ in genetic liability to morning or evening chronotype.

**Meaning**

Associations between polygenic liability to insomnia and hypersomnia and clinical strata within bipolar disorder are shown in this study for the first time, to our knowledge.
Comparison of Genetic Liability for Sleep Traits in Individuals With Bipolar Disorder and Controls

Original Investigation  Research

Polygenic Risk Scores
Full details on genotyping, quality control, and imputation are in eAppendix I and the eFigure in the Supplement. We generated polygenic risk scores (PRSs) using PLINK version 1.9.44 in PRSice.45 Imputed genotypes were clumped for linkage disequilibrium (window, 500 kb; \( r^2 = 0.20 \)), and single-nucleotide polymorphisms most significantly associated with sleep traits were retained. Clumping resulted in retaining 92 085, 92 096, and 91 950 single-nucleotide polymorphisms for daytime sleepiness, sleep duration, and insomnia, respectively. After clumping, PRSs for sleep traits were generated using PRSice\(^ {45} \) at \( P \) value thresholds (\( P_\text{v} \)) \( P < 1.00 \), \( P \leq .50 \), \( P \leq .20 \), \( P \leq .10 \), \( P \leq .05 \), \( P \leq .01 \), and \( P \leq .001 \) and converted to \( z \) scores. This range of \( P \) value thresholds was chosen in the absence of an independent sample that indicated each of the respective sleep phenotypes.

Results
Sample Description
Among the individuals with BD, 3132 were female (67.0%), with a median age of 46 (range, 18-89) years. A total of 3404 participants met criteria for BD-I, and 1268 met criteria for BD-II. Among control participants, 2812 of 5714 (49.2%) were female. The Swedish sample consisted of 6091 control participants to participants with BD-I or BD-II, and then by using logistic regressions that corrected for age, sex, and 10 population principal components. Results are reported at the \( P \) value thresholds that showed the most significant results with a false-discovery rate correction applied (using the Benjamini and Hochberg\(^ {46} \) approach).

MR Analyses
In cases in which we observed significant associations between sleep phenotype PRSs and BD subtypes, we conducted follow-up 2-sample MR studies to test whether sleep phenotypes (exposures) were potentially causally related to BD subtypes (the outcome). Mendelian randomization is a causal inference method that uses genetic variants as instrumental variables for an exposure of interest. It relies on 3 assumptions: (1) genetic variants must be strongly associated with the exposure, (2) genetic variants should not be associated with confounders of the exposure-outcome relationship, and (3) genetic variants should only be associated with the outcome through the exposure in question.\(^ {47} \) We used genome-wide significant single-nucleotide polymorphisms as genetic instruments for the sleep phenotypes. Instrument-exposure effects were taken from the sleep-trait GWAS summary statistics, and instrument-outcome effects were taken from BD-I and BD-II GWAS summary statistics.\(^ {48} \) Four MR methods were used to assess relationships between sleep phenotypes and BD subtypes: the inverse variance weighted,\(^ {49} \) weighted median,\(^ {50} \) and MR Egger\(^ {49} \) regression methods. To test for evidence of pleiotropy, we examined the intercept of MR Egger regressions\(^ {48} \) and the Cochran \( Q \) and \( R \)\^{\text{25}}\text{31} \) statistics. Data pruning, harmonization, and analyses were conducted in R version 3.33 using the “TwoSampleMR\(^ {54} \) package.

Replication Sample
We sought to replicate the study findings using Swedish individuals with BD (\( n = 4366 \)) and control participants (\( n = 6091 \)) recruited via the St Göran Bipolar project\(^ {55} \) and the Swedish National Quality Register for Bipolar Affective Disorder (Bipolär).\(^ {56,57} \) Full details of the samples, genotyping, quality control, and imputation are in eAppendix 2 in the Supplement.
Correlations Between PRSs for Sleep Traits Across all PRS P value thresholds, insomnia PRSs were negatively associated with sleep-duration PRSs (r range, −0.17 to −0.30; P <1×10^{-4}) and positively associated with daytime-sleepiness PRSs (r range, 0.04-0.10; P = .007 to P<1×10^{-4}). Sleep-duration PRSs were negatively associated with daytime-sleepiness PRSs (r range, −0.03 to −0.00), but these associations were not significant across all thresholds (range, P = .028-.916). Morningness PRSs were not significantly associated with PRS for insomnia, sleep duration, or daytime sleepiness.

PRSs for Sleep Traits: Case-Control Analyses Logistic regression comparing individuals with BD with control participants revealed that, across all PRS P value thresholds, case status was significantly associated with PRSs for sleep duration (odds ratio [OR], 1.07 [95% CI, 1.03-1.12]; P = 5.52×10^{-5}; P = 5.52 × 10^{-4} with adjustment for false-discovery rate [PRS P_T < 1.00]) and daytime sleepiness (OR, 1.07 [95% CI, 1.09-1.15]; P = 2.31 × 10^{-5}; P = 1.05 × 10^{-5} with adjustment for false-discovery rate [PRS P_T < .001]) and negatively associated with morning chronotype (OR, 0.91 [95% CI, 0.88-0.95]; P = 1.86 × 10^{-5}; P = 6.26 × 10^{-5} with adjustment for false-discovery rate [PRS P_T < .05]) but not significantly associated with insomnia (OR, 0.98 [95% CI, 0.94-1.02]; P = .39 [PRS P_T < 1.00]; eTables 2-5 in the Supplement).

PRS for Sleep Traits by BD Subtypes Results at the most significant PRS P value thresholds (with corrected P values) are summarized. Results at other PRS P value thresholds (P_T) are provided in eAppendix 1 and eTables 18 and 19 in the Supplement.

Insomnia PRS Multinomial regressions comparing individuals with BD subtypes to control participants revealed that insomnia PRS was significantly associated with a decreased risk of BD-I at a PRS P_T of P < 1.00 and P ≤ .50, but significant associations were not seen at other P value thresholds (eTable 6 in the Supplement). At all P value thresholds, insomnia PRS was significantly associated with BD-II (relative risk [RR], 1.14 [95% CI, 1.07-1.21]; P = 8.26 × 10^{-5}, P = .001 with false-discovery rate adjustment [PRS P_T < .001]). Results at all P_T are shown in the Figure, A. In direct tests, insomnia PRS was significantly associated with BD-II compared with BD-I (RR, 1.16 [95% CI, 1.08-1.24]; P = 1.39 × 10^{-5}; P = 1.95 × 10^{-4} with false-discovery rate adjustment [PRS P_T < 1.00]).

Figure. Relative Risk Ratios for Individuals With Bipolar Subtypes vs Control Participants

Relative risk of insomnia (A), sleep duration (B), daytime sleepiness (C), and morningness (D) for patients with bipolar subtypes compared with control participants, as anticipated based on polygenic risk scores. Error bars indicate 95% CIs.
Bipolar disorder is heterogeneous in symptom presentation and most likely in the mechanisms that underlie these presentations. Genetics can help refine diagnostic groups that share similar etiologies.28 In this study, we provide what is to our knowledge the first evidence that genetic liability to insomnia and longer sleep duration differs according to BD subtype.

Genetic liability to insomnia as indexed by PRS was associated with increased relative risk of BD-II compared with control participants and those with BD-I. The stronger association between insomnia PRS and BD-II may explain nonsignificant genetic correlations between BD and insomnia in previous research,26,28 because individuals with BD-II are usually underrepresented in BD GWAS (eg, only 11% in a recent study59). Future research should explore possible reasons for this association.

Hyposomnia in BD populations has remained relatively underresearched, but researchers have recently called for increased efforts to understand its underlying biology and role in BD.36,60 This is because of its high prevalence and recurrence across bipolar depressive episodes7,37 in addition to high

### Table. Results of 2-Sample Mendelian Randomization Studies

<table>
<thead>
<tr>
<th>Mendelian Randomization Method</th>
<th>Insomnia in Bipolar Disorder II*</th>
<th>Sleep Duration in Bipolar Disorder I*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inverse variance weighteda</td>
<td>log(Odds Ratio) or Q Statistic</td>
<td>SE or df</td>
</tr>
<tr>
<td>OR, 1.14 [95% CI, 1.07-1.22]; P = 6.81 × 10⁻⁵ [PRS P &lt; .001]; eTables 10-11 in the Supplement.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weighted medianb</td>
<td>log(Odds Ratio) or Q Statistic</td>
<td>SE or df</td>
</tr>
<tr>
<td>OR, 1.06 [95% CI, 1.00-1.12]; P = 1.11 × 10⁻⁴ [PRS P &lt; .001]; eTables 10-11 in the Supplement.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weighted modec</td>
<td>log(Odds Ratio) or Q Statistic</td>
<td>SE or df</td>
</tr>
<tr>
<td>OR, 1.10 [95% CI, 1.06-1.15]; P = 1.07 × 10⁻⁴ with false-discovery rate adjustment [PRS P &lt; 1.00]; eTable 7 in the Supplement.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MR Eggerd</td>
<td>log(Odds Ratio) or Q Statistic</td>
<td>SE or df</td>
</tr>
<tr>
<td>OR, 1.06 [95% CI, 1.00-1.12]; P = 1.07 × 10⁻⁴; Cochran Q = 54.03; P = .027; sleep duration: Rücker Q = 126.92; P = 8.33 × 10⁻⁸; Cochran Q = 128.91; P = 7.18 × 10⁻⁸; Table, possibly because of horizontal pleiotropy.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rücker Qd</td>
<td>log(Odds Ratio) or Q Statistic</td>
<td>SE or df</td>
</tr>
<tr>
<td>OR, 1.10 [95% CI, 1.06-1.15]; P = 1.07 × 10⁻⁴; Cochran Q = 54.03; P = .027; sleep duration: Rücker Q = 126.92; P = 8.33 × 10⁻⁸; Cochran Q = 128.91; P = 7.18 × 10⁻⁸; Table, possibly because of horizontal pleiotropy.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cochran Qd</td>
<td>log(Odds Ratio) or Q Statistic</td>
<td>SE or df</td>
</tr>
<tr>
<td>OR, 1.10 [95% CI, 1.06-1.15]; P = 1.07 × 10⁻⁴; Cochran Q = 54.03; P = .027; sleep duration: Rücker Q = 126.92; P = 8.33 × 10⁻⁸; Cochran Q = 128.91; P = 7.18 × 10⁻⁸; Table, possibly because of horizontal pleiotropy.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Discussion

Bipolar disorder is heterogeneous in symptom presentation and most likely in the mechanisms that underlie these presentations. Genetics can help refine diagnostic groups that share similar etiologies.28 In this study, we provide what is to our knowledge the first evidence that genetic liability to insomnia and longer sleep duration differs according to BD subtype.

Genetic liability to insomnia as indexed by PRS was associated with increased relative risk of BD-II compared with control participants and those with BD-I. The stronger association between insomnia PRS and BD-II may explain nonsignificant genetic correlations between BD and insomnia in previous research,26,28 because individuals with BD-II are usually underrepresented in BD GWAS (eg, only 11% in a recent study59). Future research should explore possible reasons for this association.

Hyposomnia in BD populations has remained relatively underresearched, but researchers have recently called for increased efforts to understand its underlying biology and role in BD.36,60 This is because of its high prevalence and recurrence across bipolar depressive episodes7,37 in addition to high

---

*a 37 Single-nucleotide polymorphisms.
*b 56 Single-nucleotide polymorphisms.
*c 47 Single-nucleotide polymorphisms.
*d Log(odds ratio) and SEs are presented.
*e Tomes and df are presented.
interepisode prevalence and association with relapse. We used sleep-duration and daytime-sleepiness PRS as proxies for genetic liability to hypersomnia. Sleep-duration PRS was associated with increased relative risk of BD-I but not BD-II and was significantly more strongly associated with BD-I than BD-II in a direct comparison. In contrast, daytime-sleepiness PRS was not significantly associated with BD subtypes. Daytime-sleepiness PRS may be a proxy for insomnia, in that daytime sleepiness can be induced by insomnia, and we observed significant positive correlations between insomnia and daytime-sleepiness PRS. These results support existing research on the significant positive correlations between insomnia and daytime-sleepiness PRS. These results suggest that clinical trials of sleep interventions should stratify participants by clinical subtype and genetic liability to insomnia or hypersomnia. Future work should explore which factors drive the differences in genetic liability for insomnia/sleep duration between BD subtypes.

Implications
Clinical and biological heterogeneity, combined with a classification that is not grounded in biology, are obstacles to advancing BD research. We provide some evidence of heterogeneity in the genetic instruments, thereby violating the third assumption of MR and potentially biasing the results. Therefore, while insomnia and sleep duration can be useful clinical stratifiers, there is currently insufficient evidence to support a causal inference. Further research is needed to elucidate the biological mechanisms underpinning the genetic association between BD-I and longer sleep duration.

Limitations
This study has several limitations. First, potential recruitment bias in our BD sample may have reduced its representativeness and influenced the results. Second, we were unable to adjust for additional variables (eg, age, education), because these were unavailable for control participants. Third, the index of hypersomnia is imprecise because the available GWAS summary statistics measured sleep duration as total hours slept; previous work suggests that hypersomnia is better characterized by total time in bed. Fourth, there is evidence that 5% to 17% of patients with BD-II convert to BD-I, which could have resulted in some individuals with BD-II being misclassified in this sample. However, this would have reduced power to observe differences between the 2 subtypes rather than resulted in positive results we observe for insomnia and sleep duration. Finally, variants associated with insomnia or hypersomnia at ages 40 to 69 years (the age of the UK Biobank sample) may differ from those associated in childhood or early adulthood. This may have increased our type-2 error rate, because most patients with BD experience the first onset of impairing symptoms in adolescence or early adulthood. Genetic risk for hypersomnia or insomnia that manifests during or prior to early adulthood may be more strongly associated with BD than those associated with midlife insomnia. These results should be replicated using future sleep trait GWAS in younger samples of sufficient size for PRS analysis.

Conclusions
To our knowledge, this is the first study to explore whether genetic liability for sleep traits is associated with clinical strata of individuals with BD. Future work should explore potential mechanisms underlying differences between the BD subtypes in genetic liability for sleep traits.
Additional Contributions: We are grateful to all participants in the Bipolar Disorder Research Network and the Swedish Bipolar Collection, as well as all control participants who gave their time to this research. We are also grateful to Antonio Padiñas, PhD, Cardiff University, for helpful comments on the manuscript. He was not compensated for his contribution.

REFERENCES


29. Jones SE, Tyrrell J, Wood AR, et al. Genome-wide association analyses in 128,266 individuals identifies new morningness and sleep...


