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**Title**

Sleep loss as a trigger of mood episodes in bipolar disorder: individual differences based on diagnostic subtype and gender.

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**Word Count**

3489 words excluding references and figure legends.

## Abstract

**Background:** Sleep loss may trigger mood episodes in people with bipolar disorder (BD) but individual differences could influence vulnerability to this trigger.

**Aims:** To determine whether bipolar subtype (BD-I or BD-II) and gender were associated with vulnerability to the sleep loss trigger.

**Method:** During a semi-structured interview, 3140 individuals (68% female) with BD (66% BD-I) reported whether sleep loss had triggered episodes of high or low mood. DSM-IV diagnosis of bipolar subtype was derived from case note and interview data.

**Results:** Sleep loss triggering episodes of high mood was associated with female gender (OR = 1.43, 95% CI 1.17-1.75,  $P < .001$ ) and BD-I subtype (OR = 2.81, 95% CI 2.26-3.50,  $P < .001$ ). Analyses on sleep loss triggering low mood were not significant following adjustment for confounders.

**Conclusions:** Gender and bipolar subtype may increase vulnerability to high mood following sleep deprivation. This should be considered in situations where patients encounter sleep disruption, such as shift-work and international travel.

### **Declaration of interest**

None.

## Introduction

Numerous lines of evidence suggest that sleep loss, in addition to being a core-symptom and early-warning sign of impending mood episodes,<sup>1</sup> can also trigger relapse, particularly mania.<sup>2-4</sup> However, sleep loss does not appear to be a trigger for all individuals with bipolar disorder, and those who are vulnerable to this trigger may also differ in whether sleep loss triggers mania or depression.<sup>5,6</sup> In addition to aiding our understanding of the underlying mechanisms of bipolar illness, understanding what factors influence the relationship between sleep and mood episodes could (a) help clinicians predict which individuals are most likely to relapse following periods of sleep deprivation (e.g. due to long-haul travel or shift-work), and (b) inform self-management techniques such as 'e-monitoring'.<sup>7</sup> Two factors that may influence vulnerability to relapse following sleep loss are bipolar diagnostic subtype and gender. Bipolar disorder type I (BD-I) and type II (BD-II) are subtypes of bipolar disorder that are distinguished (according to DSM criteria) via the presence of manic (BD-I) or merely hypomanic (BD-II) episodes.<sup>8</sup> Exploring whether there are differential reported effects of sleep disruption on mood in BD-I and BD-II is important, given that they represent two well-defined diagnostic subtypes within bipolar disorder<sup>8</sup> with distinct clinical features and illness course.<sup>9</sup> Gender may also influence vulnerability to mood episodes following sleep loss, as emerging evidence suggests that women are more prone to emotional dysregulation following sleep deprivation<sup>10-12</sup> and more likely than men to experience insomnia.<sup>13</sup> Therefore, within a large, well-characterised sample of individuals with bipolar disorder, the bipolar disorder research network (BDRN) study, we examined rates of mood episodes triggered by sleep loss according to bipolar subtype and gender.

## Method

### *Sample*

Our sample was drawn from the Bipolar Disorder Research Network (BDRN), a research programme which aims to identify the environmental and genetic determinants of bipolar disorders using rich phenotypic data.<sup>14</sup> Participants were recruited from across the United Kingdom, both systematically (via National Health Service (NHS) Community Mental Health Teams) and non-systematically (via advertisements in the media and through patient support organisations, such as Bipolar UK). The study protocol was approved by an NHS Research Ethics Committee (MREC/97/7/01) and by all participating NHS Trusts and Health Boards. All participants provided written informed consent.

### *Inclusion and Exclusion Criteria*

For inclusion into the BDRN research programme, individuals had a lifetime diagnosis of affective disorder, were at least 18 years old and of UK or Irish White ethnicity (due to the focus on genetic determinants of mood disorders). Exclusion criteria included affective disorder secondary to alcohol or substance misuse, medical illness, organic brain disorder or medication. Participants included in the current study had a DSM-IV main lifetime diagnosis of bipolar disorder (BD-I or BD-II) and had been asked at interview about sleep loss triggering mood episodes. A total of 3,140 participants met these criteria.

### *Assessments*

Trained research psychologists or psychiatrists administered all assessments and diagnostic procedures. Lifetime diagnosis was based on information obtained from a semi-structured interview, the Schedules for Clinical Assessment in Neuropsychiatry,<sup>15</sup> and psychiatric case-notes. Further details on derivation of diagnosis within this study are available elsewhere.<sup>14</sup>

Information on whether sleep loss had ever triggered episodes of high mood or depression was derived at interview, where participants were asked about specific past triggers of their mood episodes. Response options, in addition to sleep loss, included physical illness, medication, non-prescription drugs and alcohol. Participants responses were coded 'Yes', 'No', 'Unsure' or 'Not Applicable' for each of the trigger options. The 'Not Applicable' rating was used when individuals had not experienced the relevant mood episode or trigger (e.g., if a person with BD-I had never experienced a depressive episode, then questions relating to triggers of depressive episodes were rated not applicable).

### *Statistical Analysis*

All analyses were performed using SPSS version 20. Initial analyses were calculated using the chi-squared ( $\chi^2$ ) test to investigate associations between i) bipolar subtype (BD-I vs. BD-

ii) and iii) gender (male vs. female), and participant reports of sleep loss triggering episodes of (hypo)mania and major depression. Initial chi-squared tests for independence included all responses to the sleep trigger questions (i.e. 'Yes', 'No' and 'Unsure'). Tests that revealed significant associations were followed by partitioned chi-square tests that examined only 'Yes' and 'No' responses.

For analyses that were significant at the univariate level, we conducted a multivariate logistic regression analysis with bipolar subtype and gender as predictors and whether sleep loss had triggered mood episodes as the outcome. This enabled us to control for age, number of episodes of (hypo)mania or depression (depending on whether the outcome was sleep loss triggering episodes of high or low mood), and method of recruitment (systematic vs. non-systematic). These covariates were chosen due to their potential relationship with the likelihood of reporting sleep loss as a trigger. All tests were two-tailed with a  $P < .05$  criterion for statistical significance.

## Results

A total of 3140 individuals met the inclusion criteria, of which 2075 (66%) had a lifetime diagnosis of BD-I and 1065 (34%) had a diagnosis of BD-II. Of our sample, 68% were female (n=2146), and the mean age at interview was 46.44 years (range 18-86, s.d. 12.40).

### *Prevalence of sleep loss triggering mood episodes in bipolar disorder*

The responses for sleep disruption and the other triggers that were specifically asked about during the interview are given in Table 1. From the table, it can be seen that of those triggers asked, sleep loss was the most commonly reported trigger of mood episodes in individuals with bipolar disorder.

[Insert Table 1 here]

Within the total sample of 3140 individuals, 20% (95% CI 18.6-21.4%, n=627) of participants reported that sleep loss had triggered episodes of mania or hypomania. Of those who had experienced at least one major depressive episode (n=3064), 12% (95% CI 10.6-12.9%, n=359) reported that sleep loss had triggered episodes of depression.

### *Differences between bipolar subtypes*

#### **Episodes of high mood:**

Bipolar diagnosis (BD-I or BD-II) was associated with self-reports of sleep loss triggering episodes of high mood ( $\chi^2(2)=96.189$ ,  $P<.001$ ). As shown in Figure 1A, individuals with a diagnosis of BD-I were more likely than those with BD-II to report that sleep loss had triggered episodes of high mood (24.7% vs. 10.8%). Partitioned chi-square analyses comparing 'Yes' and 'No' responses (n=2952) revealed that BD-I participants were 2.81 times more likely than those with BD-II to report that sleep loss had triggered episodes of high mood ( $\chi^2(1)=90.808$ ,  $P<.001$ , OR=2.81, 95% CI 2.26-3.50).

#### **Episodes of major depression:**

Diagnostic subtype (BD-I or BD-II) was significantly associated with participants' responses on whether sleep loss had triggered episodes of depression (i.e. Yes, No, Unsure) ( $\chi^2(2)=17.050$ ,  $P<.001$ ). As shown in Figure 1B, there was a trend for participants with BD-II to be more likely than those with BD-I to report that sleep loss had triggered episodes of depression (13.6% vs. 10.7%) but this difference did not meet criteria for statistical significance in partitioned chi-square analyses ( $\chi^2(1)=3.716$ ,  $P=.054$ , OR=1.25, 95% CI 0.99-1.57, n=2737).

[Insert Figure 1 here]

## Gender differences

### **Episodes of high mood:**

As shown in Figure 2A, we found an association between gender and reports of sleep loss triggering episodes of (hypo)mania ( $\chi^2(2)=12.739$ ,  $P=.002$ ), with women being more likely than men to report that sleep loss had triggered episodes of high mood (21.7% vs. 16.3%). A partitioned chi-square analysis comparing only 'Yes' and 'No' responses ( $n=2952$ ) showed that this difference was statistically significant ( $\chi^2(1)=12.668$ ,  $P<.001$ ) with the odds of women reporting manic or hypomanic episodes triggered by sleep loss being 1.43 times greater than men (OR=1.43, 95% CI 1.17-1.75).

### **Episodes of major depression:**

Gender was significantly associated with self-reports of episodes of depression triggered by sleep loss ( $\chi^2(2)=7.297$ ,  $P=.026$ ). A partitioned chi-square analysis comparing only 'Yes' and 'No' responses ( $n=2737$ ) showed that this difference was statistically significant ( $\chi^2(1)=6.133$ ,  $P=.013$ ) with women being more likely than men (12.7% vs. 9.5%, respectively, see Figure 2B) to report that sleep loss had triggered episodes of depression (OR=1.37, 95% CI 1.07-1.77).

### *Multivariate binary logistic regression models*

When adjusting for potential confounders, a multivariate logistic regression with (hypo)mania triggered by sleep loss as the outcome and including both bipolar diagnosis and gender as predictors found that the associations with (hypo)mania triggered by sleep loss remained significant for bipolar I diagnosis (OR=2.81, 95% CI 2.23-3.53,  $P<.001$ ) and female gender (OR=1.30, 95% CI 1.05-1.61,  $P=.015$ ). The association between female gender and episodes of depression triggered by sleep loss was not significant when controlling for potential confounders (OR=1.29, 95% CI 0.99-1.68,  $P=.06$ ).

[Insert Figure 2 here]

## Discussion

Sleep loss has been proposed as a potential trigger of mood episodes (particularly high mood) in individuals with bipolar disorder.<sup>2</sup> Despite support from experimental research in animals<sup>4</sup> and in healthy human populations,<sup>16,17</sup> longitudinal studies of clinical populations have not always found that reduced sleep predicts subsequent mania in all individuals with a bipolar diagnosis.<sup>5,6</sup> It is possible, therefore, that some individuals with BD have increased vulnerability to experiencing high mood following sleep disruption whereas others may be unaffected or become depressed. If so, this would concord with research in healthy populations which finds individual differences in vulnerability to the neurocognitive effects of sleep loss.<sup>18,19</sup>

Our main finding was that individuals with bipolar disorder seem to differ in their tendency for sleep loss to trigger mood episodes depending on their gender and bipolar subtype. Specifically, we found that participants who were female or had a diagnosis of BD-I were more likely to report that sleep loss had triggered episodes of high mood than male participants or those with a BD-II diagnosis. In contrast, women and individuals with a BD-II diagnosis were more likely to report sleep loss triggering episodes of depression than men or those with a BD-I diagnosis. However, these differences did not meet criteria for statistical significance.

### *Bipolar subtype*

In our sample, individuals with BD-I were significantly more likely than those with BD-II to report that sleep loss had triggered episodes of high mood, with 1 in 4 individuals with BD-I reporting this compared to around 1 in 10 individuals with BD-II. To our knowledge, this is currently the largest study to date reporting on the prevalence of sleep loss as a trigger in individual with bipolar disorder. Research to date has primarily focused on early symptoms of mood episodes<sup>1</sup> or has explored the proportion of individuals with bipolar disorder who become manic or hypomanic following sleep deprivation therapy for depression. The proportion of individuals who become manic or hypomanic in these contexts has been reported to range from 4.85% to 29%.<sup>20</sup>

Differences between bipolar subtypes in the tendency for sleep loss to trigger high mood may reflect clinical and underlying neuroanatomical (and associated functional) differences between BD-I and BD-II that have been highlighted elsewhere.<sup>9,21,22</sup> One of the proposed mechanisms by which sleep loss affects emotion regulation is by disrupting emotion regulation systems in the brain (e.g. prefrontal and limbic areas)<sup>16</sup> and recent neuroimaging studies have found that these same neurological systems vary between individuals with BD-I and BD-II, and correspond with behavioural differences in emotion regulation.<sup>23</sup>

Alternatively, it is possible that fewer participants with BD-II reported sleep loss triggering high mood because they were generally less able to identify triggers of their episodes. However, analysis of the 'unsure' responses for this question revealed that 4.7% of participants with a BD-II diagnosis responded 'unsure' compared to 6.7% of those with BD-I ( $P=.029$ ).

### *Gender*

Our results also suggest that women may be more susceptible than men to mood dysregulation following sleep loss, with women being significantly more likely than men to report that sleep loss had triggered episodes of high mood. Our findings may have been due to women being more likely to over-report triggers or generally being better at identifying triggers of mood episodes than men. However, when we examined responses for other triggers that participants were asked at interview (i.e. medication, antidepressants, alcohol or non-prescription drugs) we found that women did not consistently endorse triggers more than men (results available from first author). In addition, our analyses of 'unsure' responses found that men were not significantly more likely than women to respond 'unsure' when asked about triggers of high mood (5.8% vs. 6.1%, respectively,  $P=.807$ ) or depressive episodes (11.6% vs. 10.3%, respectively,  $P=.274$ ).

Our findings are in agreement with previous research that has also found women to be at greater risk than men of mood disturbances following sleep loss<sup>11,12</sup> and may partly explain why women with BD are at high risk of experiencing mania following childbirth<sup>24</sup> (a life event associated with sleep deprivation). Furthermore, there is evidence that women with BD-I are more likely to become manic following childbirth compared to those with BD-II,<sup>25</sup> which is concordant with our results for BD subtype.

These gender differences provide interesting avenues to explore underlying mechanisms by which gender and sleep may interact to influence bipolar disorder phenotypes. For example, it has been suggested that ovarian hormones may interact with the circadian system to influence the sleep-wake cycle and responses to sleep deprivation.<sup>26</sup>

### *Episodes of depression triggered by sleep loss*

It is possible that the association between sleep loss and mania has been attenuated in some studies by the inadvertent inclusion of individuals who, following sleep loss, are more likely to experience shifts in mood towards the opposite polarity (i.e. depression). Therefore, we examined whether bipolar subtype and/or gender were associated with an increased likelihood of reporting episodes of depression triggered by sleep loss.

First, we found some evidence that individuals with BD-II were more likely than those with BD-I to report that sleep loss had triggered episodes of depression (14% vs. 11%, respectively) but this difference did not meet criteria for statistical significance ( $P=.054$ ). Of note is that fewer participants reported sleep loss triggering episodes of depression ( $n=359$ ,

11%) compared to high mood (n=627, 20%) and more participants responded 'unsure' when asked whether sleep loss had triggered episodes of depression (10.7%) compared to episodes of (hypo)mania (6.0%). The reasons for this are unclear, however, Jackson *et al*<sup>1</sup> reported that individuals with bipolar disorder found it easier to identify early symptoms of mania than depression. Therefore, if the onset of depressive episodes is less noticeable than manic episodes, it may be more difficult for individuals to identify triggers.

Second, we found that women were more likely than men to report that sleep loss had triggered episodes of depression. This concurred with previous research finding that women are more likely than men to experience depressed mood following sleep loss.<sup>11,12</sup> Our findings may be due to women being at a greater risk of experiencing insomnia, which has been associated with subsequent depressive episodes.<sup>27</sup> However, the association between gender and sleep loss triggering depression did not remain significant when controlling for potential confounding factors. This may be because rates of insomnia have been found to increase with age in both sexes<sup>27</sup> and our sample included a wide age-range (median = 46 years, range = 18-86).

#### *Strengths and limitations*

The strengths of this study are that it is the first to examine sleep loss as a trigger of both manic and depressive episodes in a large sample of individuals with bipolar disorder. In contrast to previous studies, our large sample allowed us to examine whether bipolar subtype and gender affect vulnerability to sleep loss. A further strength is that participant diagnoses were derived from rich clinical data.

However, our study is limited by (i) the retrospective and subjective nature of our data, and therefore (ii) the inability to disentangle whether sleep loss was a trigger or prodrome of mood episodes.

First, the retrospective nature of our data means it is possible that participants over- or underestimated the role of sleep loss in triggering mood episodes. However, there is some evidence that there is a moderate correlation between objective and subjective measures of sleep in remitted patients with BD.<sup>28</sup> Other studies have examined this relationship using experimental methods (i.e. sleep deprivation protocols) in which sleep duration and mood is ascertained via nurse or psychiatrist observations.<sup>3,29,30</sup> These studies provide the most convincing evidence that sleep loss can trigger relapse. However, the labour-intensive nature of such studies means that the sample sizes are several orders of magnitude lower than that of our sample, (ranging from single case studies<sup>29</sup> to 143 patients<sup>30</sup>). The less-intensive nature of our self-report measure allowed us to collect this information in a large sample of individuals and therefore ensured that we could compare the responses of men and women,

as well as bipolar subtypes. In addition, the simplicity of our measure allows for easier application to clinical practice.

Second, the bidirectional relationship between sleep and mood<sup>2,10,16</sup> could have made it difficult for participants to judge whether sleep loss had been a trigger or prodrome of episodes (although participants had the option to respond 'unsure'). However, in addition to the studies mentioned above, multiple experimental studies have provided supporting evidence that sleep deprivation can perturb emotion regulation (for reviews, see Kahn *et al*,<sup>16</sup> and Harvey *et al*,<sup>31</sup>) and can be a risk factor for the development of BD in high-risk children.<sup>32</sup> In addition, if sleep disruption is a prodrome rather than a trigger, it could nevertheless be a clinically useful warning-sign of incipient mood episodes, therefore distinguishing the characteristics of those individuals with BD who describe a close relationship between changes in sleep and the onset of a mood episode could aid illness management.

#### *Future research*

The results of the present study should inform future research investigating associations between sleep and mood in bipolar disorder, as samples containing a mix of genders and bipolar subtypes might obfuscate associations between sleep and mood. However, our results need to be validated in longitudinal studies using objective measures of sleep such as actigraphy, as we did not have objective data on whether participants experienced sleep loss prior to mood episodes, or on the type of sleep loss that they experienced (e.g. total or partial sleep deprivation). Such research may also inform the rapidly expanding field of 'Digital Psychiatry' that aims to use technology such as smartphone applications to improve patient care.<sup>33</sup>

It is unclear why some individuals become depressed following sleep deprivation and others become manic. It is possible that other triggers associated with relapse in bipolar disorder (e.g. stressful or exciting life events, medication use or interpersonal conflict) may have coincided with the sleep loss that our participants reported. However, vulnerability to the negative cognitive and emotional effects of sleep loss has been studied more extensively in healthy populations, which provides further support that differential vulnerability to sleep loss is trait-like and potentially genetic (see Banks & Dinges<sup>19</sup> for a review). Some studies have explored this in participants with bipolar disorder, however to date this has been limited to candidate gene studies (e.g. <sup>34</sup>). Future research could potentially use manic or depressive responses to sleep loss as a sub-phenotype for genome-wide analyses or examine whether individuals at high familial risk of BD are more prone to mood dysregulation following sleep loss.

Another intriguing avenue for further research is the relationship between sleep and pharmacology. For example, lithium is known to affect circadian rhythms,<sup>35</sup> and there is preliminary evidence that patients with specific variants in genes that encode enzymes targeted by lithium are more likely to experience mood elevation following sleep deprivation.<sup>36</sup>

#### *Implications for clinical practice*

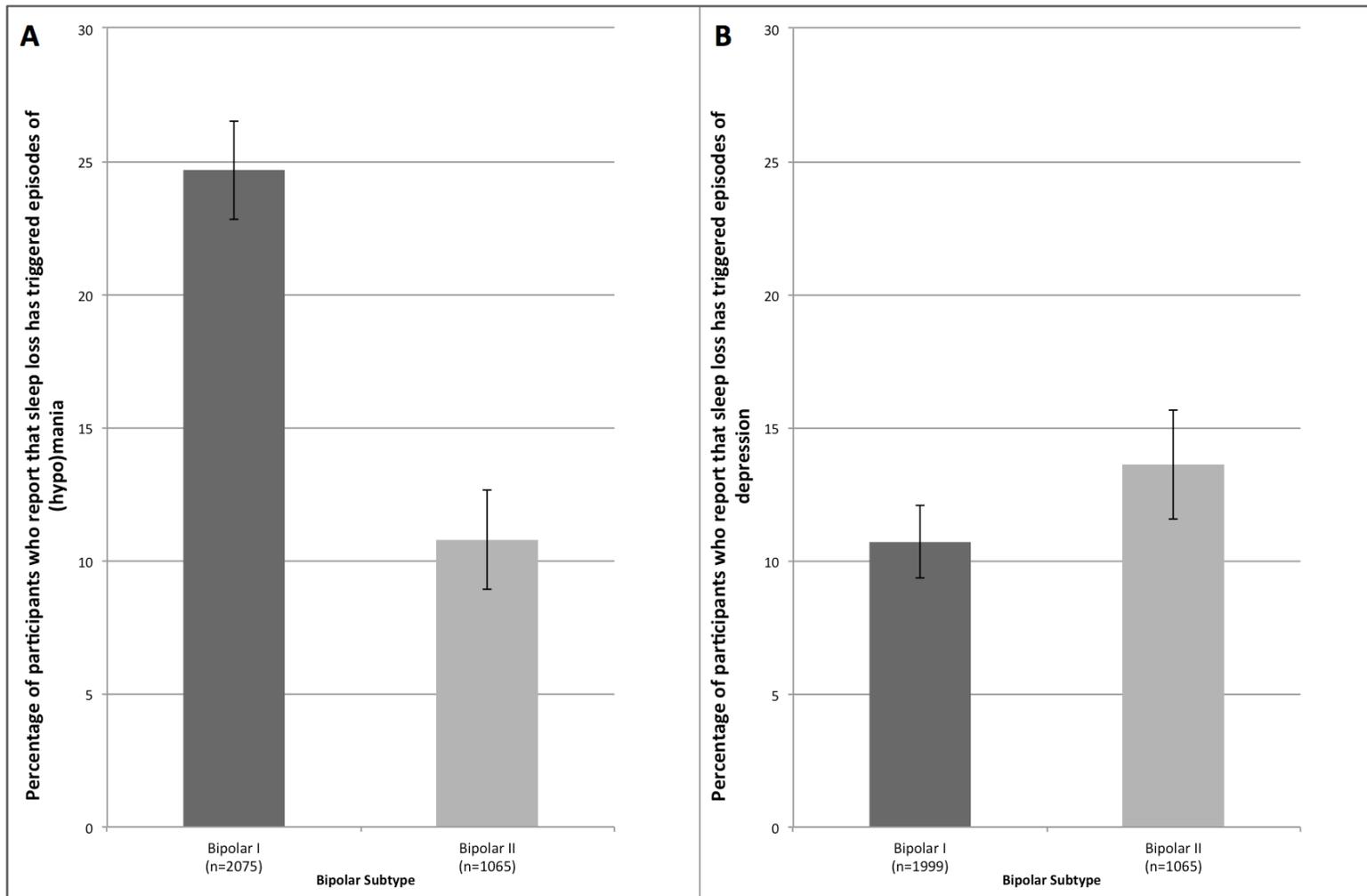
The findings of this study can inform self-management for bipolar disorder, particularly in light of recent attempts to engage patients with electronic self-monitoring tools, which aim to alert the individual of impending mood episodes based on fluctuations in behaviours such as sleep (e.g.<sup>7</sup>). Adjusting these estimates based on individual differences that are likely to affect the relationship between sleep and mood will improve the accuracy of such tools.

Furthermore, our study suggests that up to 1 in 4 individuals with BD may be at risk of an episode of high mood following sleep loss, with women and those with a bipolar I diagnosis particularly at risk. Clinicians should therefore discuss the importance of this trigger with patients, including encouraging a regular sleep pattern and considering the potential impact of specific situations such as shift work and long-haul travel.

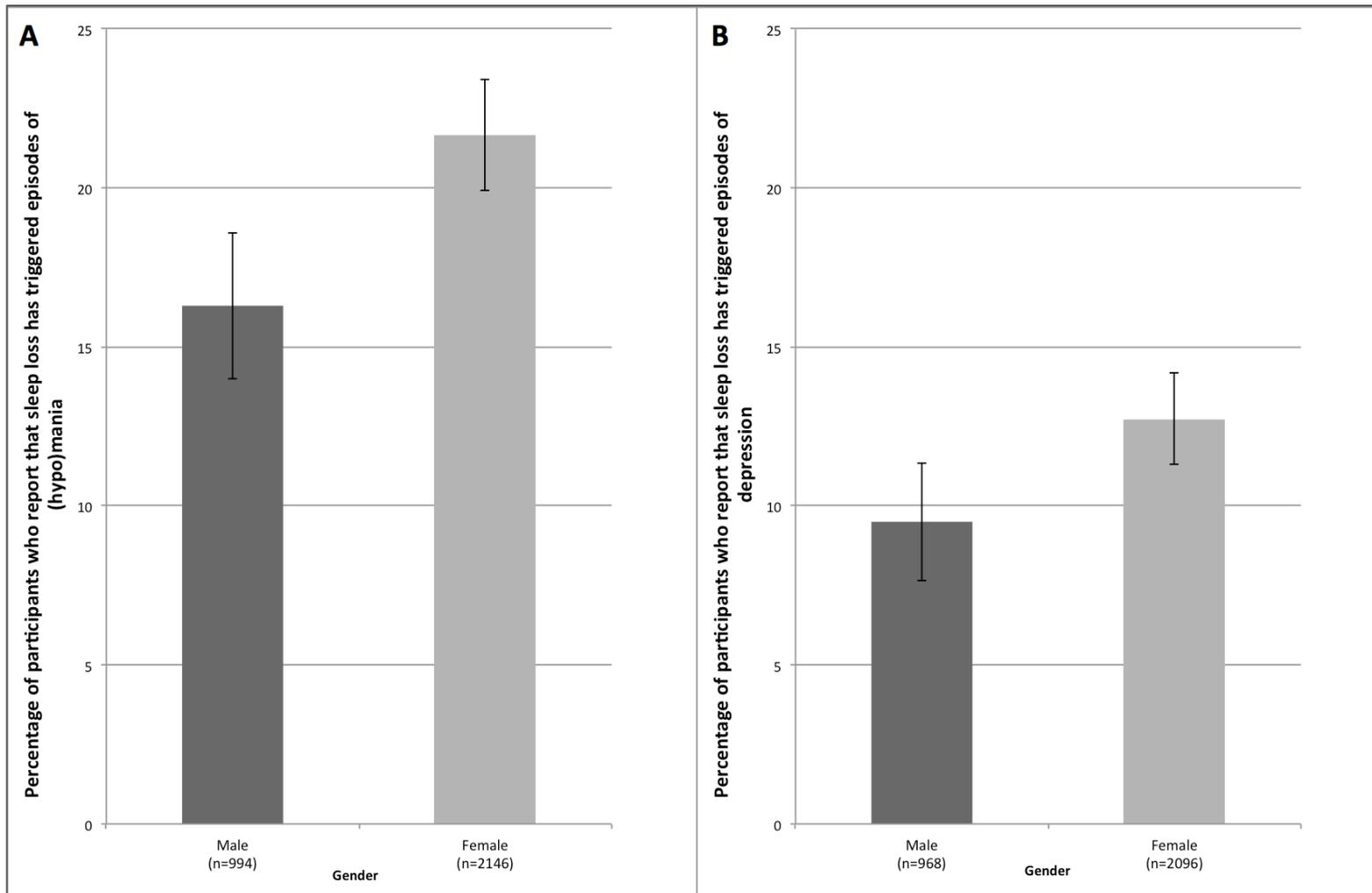
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**Figure 1.** Percentage of individuals with bipolar disorder who report that sleep loss has triggered episodes of (hypo)mania (Panel A) or depression (Panel B) split by bipolar subtype. Error bars represent confidence intervals for point estimates.



**Figure 2.** Percentage of individuals with bipolar disorder who report that sleep loss has triggered episodes of (hypo)mania (Panel A) or depression (Panel B) split by gender. Error bars represent confidence intervals for point estim

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## Funding

This work was supported by grants from the Wellcome Trust (078901) and the Stanley Medical Research Institute (6045240-5500000100).

## Acknowledgements

The authors would like to thank all members of the Bipolar Disorder Research Network, and especially the participants who have kindly given their time to take part in our research.

## Author contributions

Professor Ian Jones had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors reviewed and approved the final version of the manuscript.

*Study concept and design:* LJ, NC, IJ

*Acquisition, analysis, or interpretation of data:* All authors

*Drafting of the manuscript:* KSL, IJ, NC, LF

*Critical revision of the manuscript for important intellectual content:* All authors

*Statistical analysis:* KSL, IJ

*Obtained funding:* LJ, NC, IJ

*Study supervision:* LF, KGS, LJ, NC, IJ