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Abstract

BACKGROUND: Women with bipolar disorder are at high risk of affective psychoses following childbirth (i.e. “postpartum psychosis”, PP) and there is a need to identify which factors underlie this increased risk. Vulnerability to mood dysregulation following sleep loss may influence risk of PP, as childbirth is typified by sleep disruption. We investigated whether a history of mood episodes triggered by sleep loss was associated with PP in women with bipolar disorder (BD).

METHODS: Participants were 870 parous women with BD recruited to the Bipolar Disorder Research Network. Lifetime diagnoses of BD and perinatal episodes were identified via interview and case notes. Information on whether mood episodes had been triggered by sleep loss was derived at interview. Rates of PP were compared between women who did or did not report mood episodes following sleep loss.

RESULTS: Women who reported sleep loss triggering episodes of mania were twice as likely to have experienced an episode of PP (OR=2.09, 95% CI = 1.47-2.97, $p < 0.001$) compared to women who did not report this. There was no significant association between depression triggered by sleep loss and PP ($p = 0.526$).

LIMITATIONS: Data were cross-sectional therefore may be subject to recall bias. We also did not have objective data on sleep disruption that had occurred during the postpartum period or prior to mood episodes.

CONCLUSIONS: In clinical practice, a history of mania following sleep loss could be a marker of increased vulnerability to PP, and should be discussed with BD women who are pregnant or planning to conceive.

Key words: sleep; postpartum; psychosis; mania; depression.

Mania triggered by sleep loss and risk of postpartum psychosis in women with bipolar disorder.

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1 Introduction

Women with bipolar disorder are at increased risk of affective psychoses (i.e. including mania, mixed episodes and psychotic depression) in the postpartum period (Jones et al., 2014). These episodes have traditionally been labelled as 'postpartum psychosis' (PP), with the majority of episodes having a sudden onset, typically within the first two postpartum weeks (Brockington et al., 1981a; Heron et al., 2007). In the general population, PP affects approximately 1 in 1000 parous women (Kendell et al., 1987). In contrast, 20-30% of parous women with a history of bipolar disorder have experienced an episode of PP (Di Florio et al., 2013; Jones and Craddock, 2001; Wesseloo et al., 2016). This, combined with other evidence (reviewed in Jones et al., 2010), suggests that PP may be best conceptualised as a bipolar diathesis combined with a vulnerability to a puerperal (i.e. childbirth-related) trigger.

Research to date has primarily focused on how childbirth might trigger episodes of bipolar illness. Proposed triggers include changes in medication, the psychosocial adaptation to parenthood, and obstetric complications, in addition to biological factors such as the dramatic hormonal changes that occur following delivery. To date, the most promising factors implicated in the aetiology of PP include primiparity, dysregulation of immune system function, and genetic factors (see Jones et al., 2014, for a recent review).

However, a plausible but understudied candidate for triggering PP is sleep disruption, which has been associated with the onset of mania (Wehr, 1991) and, of course, is characteristic of the perinatal period. Sleep loss is a commonly reported antecedent of manic episodes (Jackson et al., 2003), a finding corroborated in clinical case-studies, longitudinal studies of sleep and mood within individuals with BD, and experimentally-induced sleep deprivation studies (Bauer et al., 2006; Leibenluft et al., 1996; Wehr, 1991, 1989, Wehr et al., 1987, 1982). This, in combination with findings that sleep deprivation can be a dramatic but short-term treatment for depression (Benedetti, 2012; Benedetti et al., 2001), has led to the hypothesis that acute sleep loss has mania-inducing effects (Wehr, 1991; Wehr et al., 1987; Wu and Bunney, 1990). Examination of the biological mechanisms that may underlie this effect is ongoing, although recent theories propose that sleep loss exerts an antidepressant effect by resetting processes that are a result of abnormal clock genes (Bunney and Bunney, 2013).

To date, few studies have examined the association between perinatal sleep loss and PP (Lewis et al., 2016). A retrospective study of parous women found that those who developed PP had significantly longer

labours and were more likely to give birth during the night (Sharma et al., 2004), suggesting that women with PP experienced greater sleep disruption in the perinatal period. Furthermore, a case study of 3 women with a history of PP found that they became manic or hypomanic following experimentally-induced sleep deprivation (Strouse et al., 1992). Conversely, one of the few prospective studies on PP and perinatal sleep comparing the sleep of pregnant women with a history of BD or PP (i.e. a group at high risk of PP) to pregnant healthy controls found no significant differences in sleep/wake patterns during pregnancy between these groups (Bilszta et al., 2010). However, due to insufficient sample size, the authors were unable to compare the sleep of women who relapsed following childbirth to those who remained well. Thus it remains unclear whether women who develop PP experience greater sleep disturbance prior to episode onset. However, an alternative explanation is that women who develop PP are more sensitive than average to the sleep disturbances that typify the perinatal period. This hypothesis is plausible for two reasons. First, research examining responses to sleep deprivation finds that there is considerable variation within healthy populations, with some individuals showing more pronounced neurobehavioural sequelae than others (Rupp et al., 2012) and emerging evidence suggests that this might be moderated by genetic factors (Groeger et al., 2008; Kuna et al., 2012). Second, although it is thought that individuals with psychiatric disorders are more vulnerable to the negative effects of sleep disturbance than healthy populations, there is evidence of variation in response to sleep deprivation within the BD population. For example, Benedetti and colleagues have found that an antidepressant response to sleep deprivation in individuals with BD is associated with genetic factors (Benedetti et al., 2012; Benedetti and Smeraldi, 2009). This variation within the BD population in how individuals respond to sleep loss may extend to women in the perinatal period, with some women with BD being more sensitive to perinatal sleep disturbance and therefore potentially more susceptible to PP.

In light of the above literature, and given that episodes of PP typically have a manic presentation (Brockington et al., 1981b), we hypothesised that women with BD who report episodes of mania being triggered by sleep loss would be more likely to experience PP than those who do not report sleep loss as a trigger for manic episodes. This paper explores this hypothesis in parous women (i.e. women who have given birth) who were recruited to the Bipolar Disorder Research Network (BDRN, bdrn.org).

2 Methods

2.1 Recruitment

Data were analysed from an ongoing large clinical and molecular genetic research programme of mood disorders, the Bipolar Disorder Research Network (BDRN). Participants are recruited systematically and non-systematically from a variety of settings including UK community mental health teams, media and patient support organizations (such as Bipolar UK). Recruitment methods and further information about BDRN has been reported elsewhere (Di Florio et al., 2013). The research programme has UK National Health Service (NHS) Research Ethics Committee approval and local Research and Development approval in all participating NHS Trusts/Health Boards. All participants included in the study reported here met DSM-IV criteria for bipolar disorder, were ≥ 18 years of age and provided written informed consent. Exclusion criteria were affective illness experienced only in relation to alcohol, substance dependence, physical illness or medication. The participants included in the current analysis were recruited between November 2007 and July 2013, as this was the period in which questions on triggers of mood episodes (described below) were added to the main interview.

2.2 Assessments

Research psychologists or psychiatrists administered all assessments and diagnostic procedures. Evidence suggests that risk of PP is greatest for women with bipolar I disorder (BD-I) (Di Florio et al., 2013), thus we limited the current analyses to women with a lifetime DSM-IV diagnosis of BD-I. Best estimate lifetime diagnoses according to DSM-IV were based on psychiatric history ascertained via a semi-structured interview, the Schedules for Clinical Assessment in Neuropsychiatry (Wing et al., 1990) and available psychiatric case-notes. Interview and case note data were also combined to determine key clinical variables such as occurrence of psychiatric episodes in the perinatal period. In cases where there was doubt, diagnostic and clinical ratings were made by at least two members of the research team blind to each other's rating and consensus was reached via discussion where necessary. The inter-rater reliability for DSM-IV diagnoses, for both lifetime and perinatal episodes, was high ($\kappa = 0.85$ and 0.92 respectively).

Data collected on all the pregnancies of each parous woman were used to make lifetime ratings of postpartum episodes. PP was defined as a lifetime DSM-IV manic, mixed, psychotic depression or other psychotic episode occurring within 6 weeks of delivery. Postpartum depression (PD) was defined as a lifetime DSM-IV episode of non-psychotic depression with onset within 6 weeks of delivery, with no lifetime episodes of PP. The temporal association of episodes to childbirth was chosen as 6 weeks based on previous research indicating that the majority of postpartum episodes occur within this time-frame and to include both DSM-IV and ICD-10 definitions of the postpartum period (Di Florio et al., 2013). Women were assigned to PP or PD categories in a hierarchical manner so that in instances where women had experienced both PP and PD, they were assigned to the PP group.

Information on triggers of past manic and depressive episodes was derived at interview, where participants were asked about triggers of their episodes of mania and depression, which included specific questions about sleep loss, physical illness, non-prescription drug use, medication and alcohol. Interviewers made it clear to participants that (1) questions referred to triggers rather than early warning signs, and (2) for an event to qualify as a trigger it had to have occurred during a euthymic period. If participants could not distinguish whether sleep loss (or any other trigger) had acted as early warning sign or trigger, their responses were rated as 'unsure'.

For our analyses, we focused on whether women had reported that sleep loss had triggered manic or depressive episodes. Responses were used to group women into (i) those who reported that their episodes of mania were triggered by sleep loss versus those who did not (i.e. "sleep loss triggering mania") and (ii) those who reported that their episodes of depression were triggered by sleep loss versus those who did not (i.e. "sleep loss triggering depression"). As data were retrospective, it is possible that women who reported sleep loss as a trigger of mood episodes were referring solely to episodes that had occurred in the postpartum period. To reduce the likelihood of this, we excluded women who had only experienced mood episodes in relation to childbirth.

2.3 *Statistical analysis*

All analyses were conducted using SPSS version 20. In primary analyses, we used chi-square tests to examine associations between sleep loss triggering mania and lifetime PP. Specifically, we compared the rates of PP in women who did or did not report that sleep loss had triggered episodes of mania. Significant associations were followed with multivariate logistic regression analyses that examined the association between sleep loss triggering mania (predictor) and lifetime PP (outcome) whilst controlling for number of deliveries, age, marital status, number of manic episodes experienced and method of recruitment.

3 Results

3.1 *Sample characteristics and perinatal episodes*

Within the BDRN cohort, 870 women met the inclusion criteria for this study. Within the sample, 23.5% of women had experienced a lifetime episode of postpartum psychosis ($n = 204$) and a further 21.2% ($n = 184$), while not experiencing PP, had experienced non-psychotic depression within 6 weeks of delivery. The remaining women who did not meet criteria for PP or PD within 6 weeks of delivery, had experienced (i) no perinatal episodes despite giving birth ($n = 207$, 23.8%) or (ii) while not meeting our criteria for PP or PD, had experienced an affective episode in pregnancy or later in the postpartum period, or there were insufficient data to reach a conclusion on perinatal episodes ($n = 275$, 31.6%). Demographic and clinical information on the sample is presented in Table 1.

3.2 *Mania triggered by sleep loss and postpartum psychosis*

Within our sample of 870 women, 25.3% ($n = 220$) reported that sleep loss had triggered mania, 68.4% reported that sleep loss had not triggered mania ($n = 595$), and 6.3% of women reported that they were unsure whether sleep loss had triggered mania ($n = 55$). Subsequent analyses were conducted on women who had responded "Yes" or "No" to the sleep trigger question and had information on puerperal episodes, resulting in a sample of 732 for analysis. Figure 1 shows the proportion of perinatal episodes within this sample, split according to whether women had or had not reported sleep loss triggering mania. We found that women who reported sleep loss triggering mania were significantly more likely to experience PP than those who did not report this ($\chi^2(1)=17.191$, $p < 0.001$, 36.8% vs. 21.8%, respectively). Compared to women without a manic response to sleep loss, women who reported sleep loss triggering episodes of mania had more than twice the odds of experiencing a lifetime episode of PP (OR=2.09, 95% CI = 1.47-2.97). The association remained significant when controlling for number of episodes of mania, age at interview, number of deliveries, marital status and method of recruitment (OR=2.09, 95% CI=1.43-3.04, $p < 0.001$).

In addition, the association between mania triggered by sleep loss and PP remained significant when separating women according to whether the first episode experienced was in relation to childbirth ($n = 164/870$) ($\chi^2(1)= 8.955$, $p = 0.011$, OR=2.91, 95% CI=1.31 - 6.48) or unrelated to childbirth ($n = 643/870$) ($\chi^2(1)= 17.230$, $p < .001$, OR=2.45, 95% CI=1.58 - 3.79).

3.3 *Specificity of findings*

To examine the specificity of our findings for the trigger, namely mania triggered by sleep loss, and the outcome, namely episodes of PP, we conducted follow-up analyses examining (i) the association between reporting a depressive response to sleep loss (i.e. sleep loss triggering episodes of depression) and PP, and (ii) the association between depression or mania triggered by sleep loss and PD.

3.3.1 *Depression triggered by sleep loss and postpartum psychosis*

Some women in our sample had not experienced depressive episodes, and therefore responded “not applicable” to whether sleep loss had triggered episodes of depression. The following analyses were conducted on the 669 women in the sample who had responded “Yes” or “No” to the sleep trigger question. As shown in Figure 2, in contrast to the findings for sleep loss triggering high mood, women who reported that sleep loss had triggered episodes of depression did not demonstrate higher rates of PP than women who did not report this (22.8% vs. 26.1%, respectively, $\chi^2(1) = 0.401$, $p = 0.526$).

3.3.2 *Mood episodes triggered by sleep loss and postpartum depression*

Compared to the rest of the women in the sample (i.e. those who had experienced no perinatal episodes or perinatal episodes that did not meet our criteria for postpartum depression), women who experienced postpartum depression within 6 weeks of delivery were not more likely to report sleep loss triggering episodes of depression (25.3% vs. 25.6%, respectively, $\chi^2(1) = 0.004$, $p = 0.948$) or sleep loss triggering episodes of mania (25.7% vs. 20.9%, respectively, $\chi^2(1) = 1.797$, $p = 0.180$).

3.4 *Analyses to address potential recall bias*

We conducted further analyses to address the likelihood that reporting sleep loss as a trigger of mania was due to recall bias (i.e. due to women assuming that their postpartum episodes were caused by sleep loss they may have experienced in the perinatal period).

3.4.1 *Episodes of mania “usually” triggered by sleep loss*

First, we repeated the analyses on a sample of women who had said that sleep loss “usually” triggered episodes of mania. This question was only asked to women who had experienced at least 3 episodes of mania ($n = 547$), reducing the likelihood that they were referring primarily to episodes that had occurred in the

postpartum period. Among these women, those who reported that sleep loss had “usually” triggered episodes of high mood were more likely to experience PP than women who did not report this ($\chi^2(1)=7.157$, $p = 0.001$, $OR=2.00$, $95\% CI=1.20-3.36$). This association remained significant when controlling for number of episodes of mania, age at interview, number of deliveries, marital status and method of recruitment ($OR=1.99$, $95\% CI=1.16-3.41$, $p = 0.012$).

3.4.2 *Parous vs. nulliparous women*

We compared the rates of reporting sleep loss triggering mania in parous and non-parous (nulliparous) women. If experiencing childbirth leads to an increased tendency to report that sleep loss triggers mood episodes, then we would expect parous women to be more likely to report this than nulliparous women (i.e. women who have not given birth). Parous women did not have higher rates of sleep loss triggering mania than nulliparous women – in fact, the opposite was true – with 30.7% of the non-parous BD-I women in the BDRN sample ($n = 158/515$) reporting that sleep loss had triggered episodes of mania compared to 25.3% of parous women ($n = 220/870$) ($\chi^2(1)=4.495$, $p = 0.034$, $OR=0.77$, $95\% CI=0.60-0.98$).

4 Discussion

We examined rates of lifetime postpartum mood episodes in parous women with BD-I according to self-report of sleep loss triggering episodes of mania or depression. Women who reported that sleep loss had triggered episodes of mania were more than twice as likely to have experienced PP. This effect remained significant when controlling for potential confounders.

The association between sleep loss and postpartum episodes was specific to i) a vulnerability to sleep disturbance triggering mania rather than depression, and ii) experiencing PP rather than PD. This suggests that a vulnerability to the mania-inducing qualities of sleep loss increases the risk of experiencing PP, and is consistent with previous research suggesting that PP is frequently a manifestation of manic or mixed episodes triggered by childbirth (Brockington, 1996; Jones et al., 2001). Importantly, our results suggest that women with BD-I who report manic episodes triggered by sleep loss could be more vulnerable to developing PP, although this needs further investigation in prospective studies.

In contrast, we found that a lifetime history of depressive episodes being triggered by sleep loss was not associated with an increased rate of PD in our sample. Other research has found an association between perinatal sleep loss and PD (Khazaie et al., 2013; Skouteris et al., 2009), therefore it is perhaps surprising to find no significant lifetime associations between PD and depression triggered by sleep loss. It is worth noting, however, that fewer women in our sample reported depressive episodes triggered by sleep loss ($n = 93$) compared to mania triggered by sleep loss ($n = 220$), which will impact on power to detect a difference between the groups. In addition, it is possible that the mechanisms involved in triggering PD in BD women are different to women with unipolar depression. Finally, PD may be more likely to develop after exposure to chronic rather than acute sleep loss, which may not have time to have its impact within the 6 weeks specified in the current study. In fact, previous studies examining the association between sleep and PD have used a broader onset criterion (Dørheim et al., 2014; Montgomery-Downs et al., 2010; Okun et al., 2011). However, even if we expand our definition of PD to include episodes that occurred within 6 months of birth, we still find that a depressive response to sleep loss is not associated with an increased rate of PD ($\chi^2(1) = 0.006$, $p = 0.937$).

4.1 *Strengths and limitations*

An advantage of the present study is the large sample of parous women with BD and detailed clinical phenotype data. However, a major limitation is that the data on sleep loss triggering mood episodes were collected retrospectively at interview. Despite interviewers' efforts to ensure that participants referred to triggers rather than early warning signs, it may still be difficult for participants to differentiate between sleep loss as an early symptoms vs. sleep loss as a trigger. In addition, it is possible that women with a history of PP over-reported that sleep loss had triggered mania due to attributing their postpartum episode(s) to sleep disruption that is typical in the perinatal period.

We attempted to address these issues in the following manner. First, we excluded women from our analyses if they had experienced manic episodes solely in relation to childbirth. Furthermore, secondary analyses provided support that this was not the major driver of the association we observed. First, if this were the case, we may also expect women with PD to over-report a depressive response to sleep loss. However, in our study, women who reported that sleep loss had triggered episodes of depression were no more likely to experience PD than those who did not report sleep loss triggering depression. Second, we performed additional analyses on a subsample of women who reported their manic episodes had *usually* been triggered by sleep loss, as opposed to on a single occasion, with the requirement that women had experienced at least three episodes of mania. This increased the likelihood that we selected a group of women with an underlying susceptibility to sleep loss triggering non-puerperal episodes of mania rather than those that occurred primarily in relation to PP. In this subsample, the association between reports of sleep loss triggering mania and PP remained, even when controlling for potential confounders. Finally, if childbirth increases the likelihood of reporting that sleep loss triggers mood episodes, then we would expect parous women to report this more frequently than nulliparous women. However, we found that nulliparous women actually had higher rates of reporting sleep loss triggering mania than parous women.

An additional complication of using retrospective data is that we have to rely on participants' interpretation of causality. For example, sleep loss may be involved in the genesis of mania as (1) the sole trigger of mood episodes, (2) a corollary of another trigger (e.g. medication changes or the use of stimulants), or (3) a factor that increases the risk of relapse in the context of other triggers. This further emphasises the need for prospective, longitudinal studies in this area that take into consideration these factors.

We also did not objectively measure sleep loss and therefore cannot determine what level of sleep disruption women experienced around childbirth or at any other time. In addition to obtaining more detailed subjective measures of sleep, future prospective studies of pregnant women with BD should include objective measures of sleep such as actigraphy. Such prospective designs will be instrumental in establishing whether a history of sleep disruption triggering episodes of mood disorder is a clinically useful predictor of developing severe postpartum episodes.

4.2 *Vulnerability to the mania-inducing qualities of sleep loss*

Further research on individual differences in vulnerability to sleep disturbance may provide markers of increased sensitivity to sleep loss in bipolar disorder, thus allowing clinicians to predict vulnerable individuals prior to significant exposures to sleep loss. A particularly promising area of interest is whether genetic variation (for example in circadian rhythm genes) predicts an individual's response to acute sleep loss (Benedetti et al., 2008; Benedetti and Terman, 2013; Bunney and Bunney, 2013). It will be of particular interest to determine whether genetic factors for vulnerability to mania following sleep loss overlap with those that predict episodes of PP in women with bipolar disorder.

4.3 *Clinical implications*

If our findings are replicated in prospective studies, a history of manic episodes triggered by sleep loss could be a potential screening question to identify pregnant women with bipolar disorder at heightened risk of PP. This will help to individualise the risk of severe postpartum episodes in women with BD and potentially help with difficult decisions regarding the use of medication during the perinatal period. Furthermore, it may identify women for whom obstetric management may need to pay particular attention to sleep disruption in labour and for whom specific measures to protect sleep in the postpartum period may be indicated.

5 Conclusions

In summary, our results suggest that individual differences in vulnerability to mood dysregulation following sleep loss in bipolar disorder may be a promising marker for identifying women at heightened risk of PP.

Further study in prospective samples is required in order to confirm these findings, which may have important implications for understanding the aetiology of PP and of mood disorders more generally.

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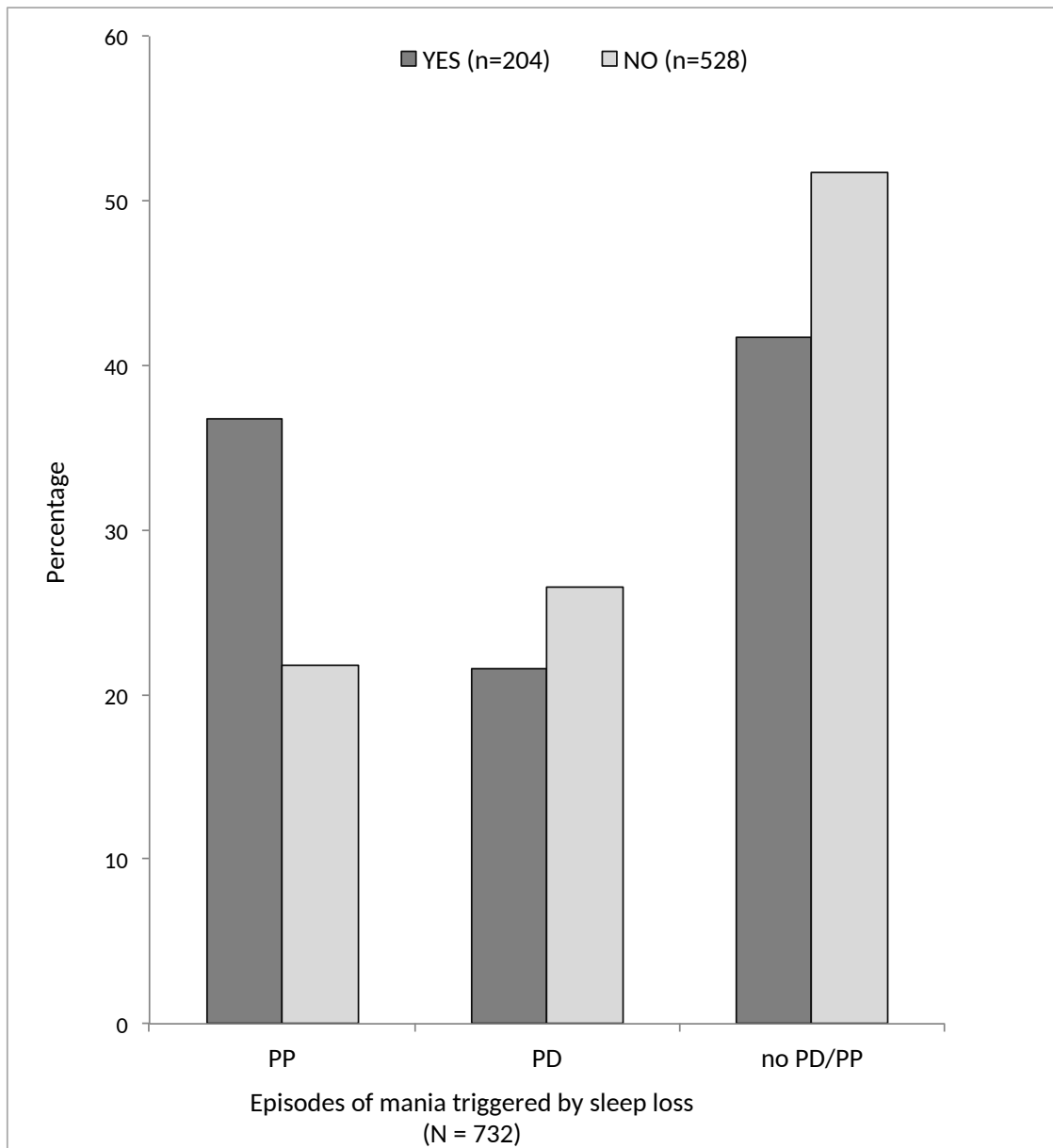


Figure 1. Proportion of women with perinatal episodes split by manic response to sleep loss.

Abbreviations: PP, Postpartum Psychosis; PD, Postpartum Depression; no PD/PP, includes: no perinatal episode, any other psychiatric illness occurring in the perinatal period up to 6 months postpartum, or onset of PP or PD outside of 6 weeks of delivery.

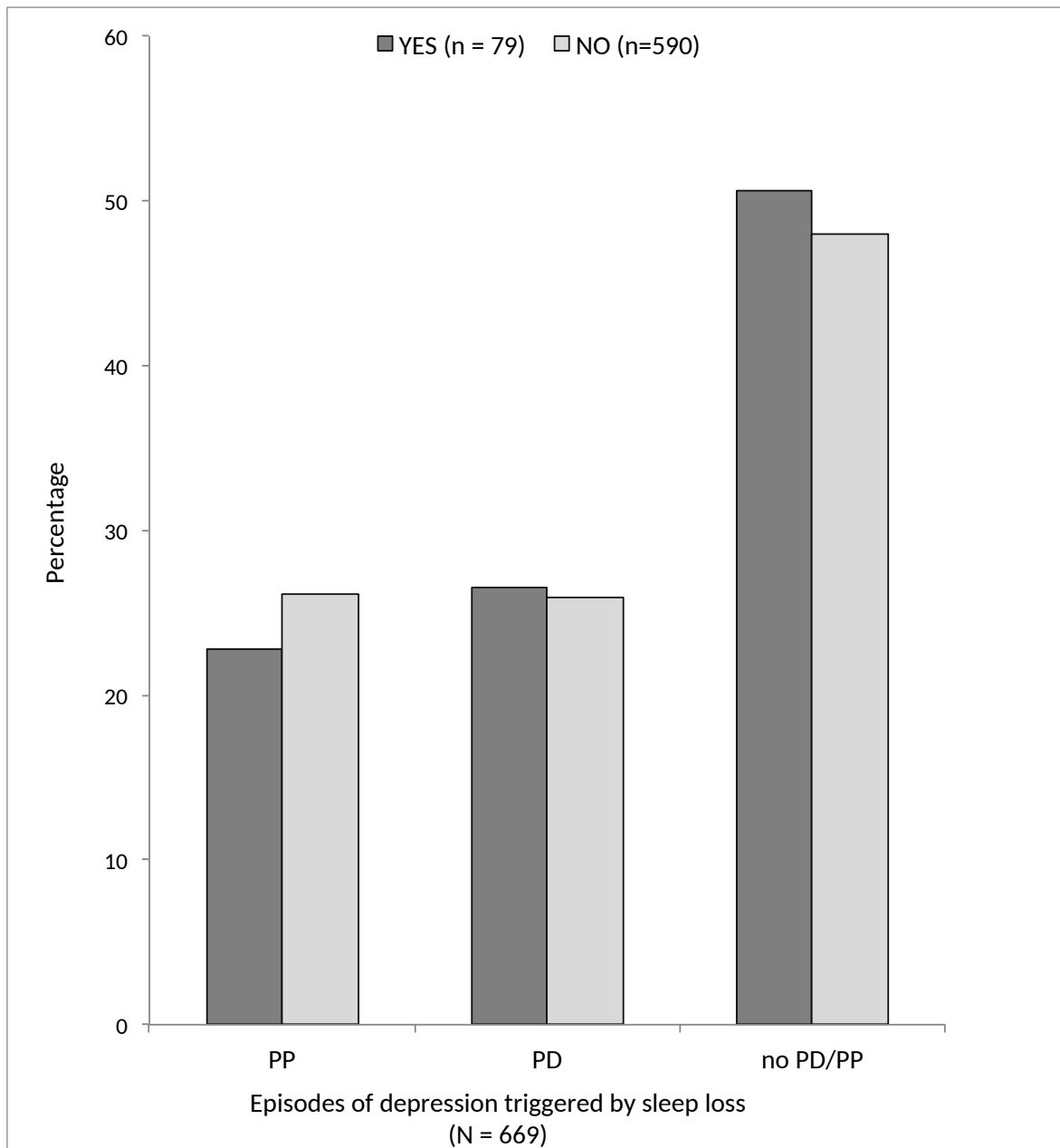


Figure 2. Proportion of women with perinatal episodes split by depressive response to sleep loss.

Abbreviations: PP, Postpartum Psychosis; PD, Postpartum Depression; no PD/PP, includes: no perinatal episode, any other psychiatric illness occurring in the perinatal period up to 6 months postpartum, or onset of PP or PD outside of 6 weeks of delivery.

Table 1: Sample Clinical and Demographic Information

Demographic/clinical characteristics (n=870)	
Age at interview in years, median (range)	49 (21-80)
Number of deliveries, median (range)	2 (1-8)
Number of episodes of mania	
Mode	20
Median	7
Range	1-100
Number of episodes of depression	
Mode	20
Median	10
Range	0-100
Age at illness onset, mean (SD)	22.53 (8.93)
Systematic recruitment, n (%)	261 (30.0)
Highest educational achievement, n (%)*	
No secondary education qualifications	93 (10.7)
CSE/O-level/GCSE	215 (24.7)
A-level/AS-level	184 (21.1)
Degree	218 (25.1)
Postgraduate degree	96 (11.0)
Unknown	64 (7.4)
Highest occupational attainment, n (%)	
Professional	385 (44.3)
Non-Professional	416 (47.8)
Never worked	15 (1.7)
Unknown	54 (6.2)

* Grades of UK secondary education are specified as GCSE, General Certificate of Secondary Education; O-level, ordinary level; A-level, advanced level; AS-level, advanced subsidiary level.

Declaration of interests

Conflicts of interest: none.

Contributors

Study concept and design: LJ, NC, IJ

Acquisition, analysis, or interpretation of data: All authors

Drafting of the manuscript: KJSL, IJ, NC, LF

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

Statistical analysis: KJSL

Obtained funding: LJ, NC, IJ

All authors reviewed and approved the final version of the manuscript.

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