CIRCADIAN AND SLEEP-RELATED POLYGENIC SCORES CAN MODULATE CLINICAL RESPONSE TO LITHIUM IN BIPOLAR DISODER

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BACKGROUND

BIPOLAR DISORDER

- Bipolar disorder (BD) is a psychiatric disorder defined by mood episodes of depression and mania[1].
- Disrupted circadian rhythms
- **Evening** chronotype.
- Genetic factors overlapped with **sleep disorders and chronotype**[1].

LITHIUM (LI)

- First-line mood-stabilizing therapy for BD, although **only 30% of the patients are excellent responders**[2].
- Li **lengthens the circadian period** and **increases morningness**. Patients with short circadian period and a morning chronotype can tolerate the lengthening and may predict a positive response[1]. Excellent responder BD patients display a stronger morning chronotype and less circadian disruption compared to non-responders (NRp)[1].
- Li effects on circadian rhythms seem necessary for a good response[1].

We aimed to evaluate the genetic burden of eight sleep-related traits in BD patients in relation to clinical response to Li. Also, a multi-polygenic (MPG) model to assess the predictive power of these traits in determining response to Li is proposed.

METHOD

SAMPLE

121 patients

BD (DSM-IV-TR)[3]

73% BD I

European

Hospital Clínic (Barcelona), Mental Health Services Oviedo

83 RESPONDERS
Reduction 50% of episodes.
♀47.0%

38 NON-RESPONDERS
No reduction of 50% of episodes or required ECT.
♀44.7%

GENOTYPING

- Whole-genome profiles were obtained using **Infinium Global Screening Array-24 v3.0 BeadChip (Illumina).**
- Data QC was done following standard procedures, imputation through Michigan Imputation Server (https://imputationserver.sph.umich.edu), and SNPs with R2<0.7 and MAF<0.005 were excluded, as well as individuals not matching with European ancestry based on 1000 genomes reference. Principal Components (PC) were calculated using Plink1.9.[4]

POLYGENIC SCORES

Polygenic scores (PGS) of 8 sleep traits were calculated with Plink1.9[4] and **PRScs**.

GWAS from Jones et al., (2019)[5]

SNORING · **NAPPING** · **MORNINGNESS** · **DAYTIME DOZING** · **EASE OF GETTING UP** · **SLEEP DURATION** · **INSOMNIA**

GWAS from Jansen et al., (2019)[6]

CHRONOTYPE

- **Logistic regression** for Li response (sex, age, and the first 4 PC as

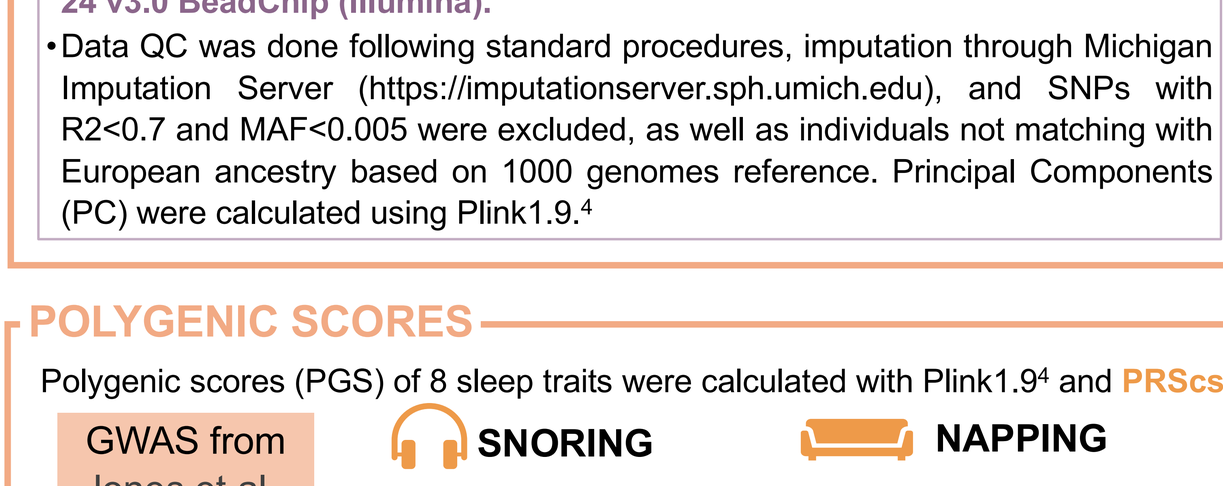
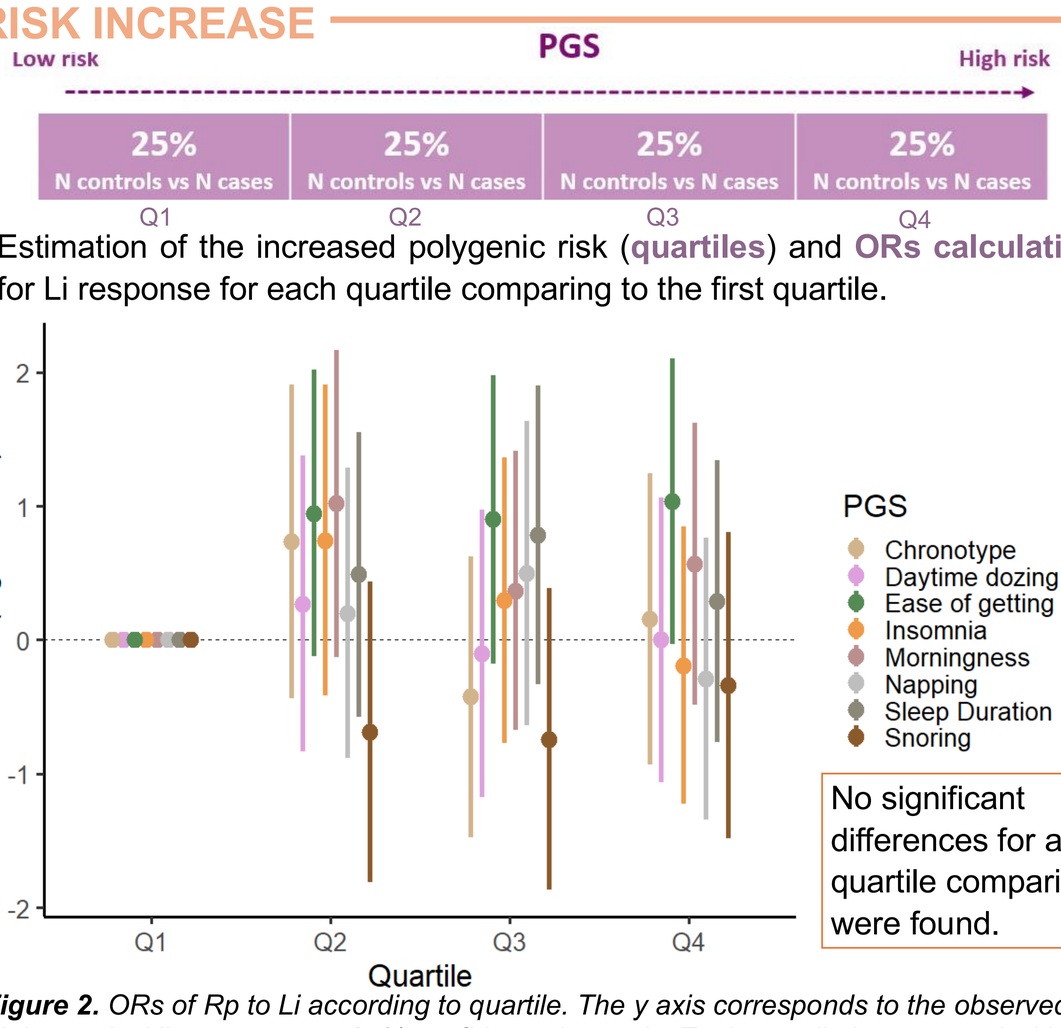


Figure 1. *Percentage of the variance in Rp risk explained by the sleep-traits.*

- **Ease of Getting up** was associated with a **response to Li (Rp)**, explaining **4.18% (p-val=0.036)** of the variance, although it did not survive after FDR's correction.

RISK INCREASE



Estimation of the increased polygenic risk (**quartiles**) and **ORs calculation** for Li response for each quartile comparing to the first quartile.

No significant differences for any quartile comparison were found.

Figure 2. *ORs of Rp to Li according to quartile. The y axis corresponds to the observed OR, and the vertical lines represent 95% confidence intervals. Each quartile is compared with the 1st (baseline).*

MULTI-POLYGENIC MODEL

The sample was split into train and test subsamples, and a MPG model based on obtaining the highest R^2 was trained. An **elastic net regularized regression** was used, which estimated the joint effect of the seven traits on Li response variation, adjusted for age, sex, and the first 4 PC.

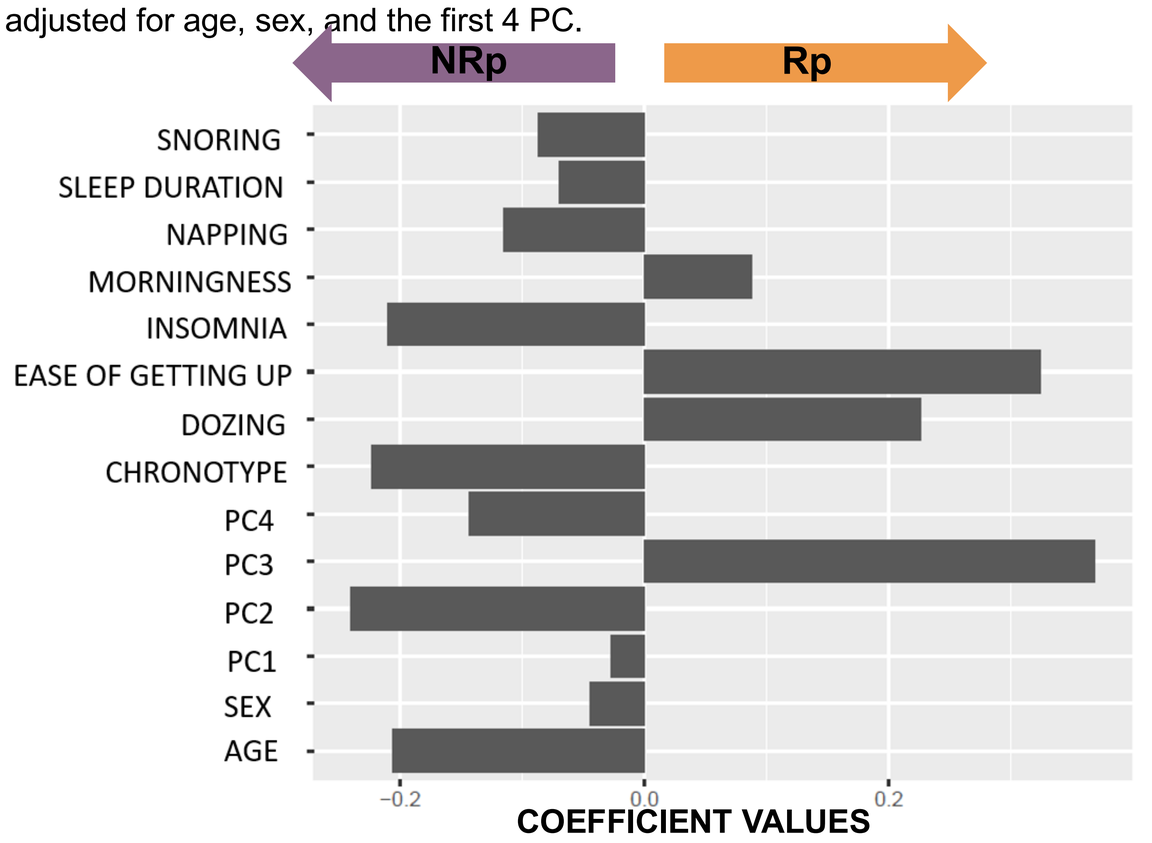


Figure 3. *Coefficient values for each trait in the elastic net regression model with the highest R^2*

The model that explained the highest proportion of variance in MPG was the **RIDGE regression (α=0)**, achieving an R^2 of 0.059. This represents an **improvement of 0.017 (over 40%)** compared to the best single-score model, 'Ease of getting up' (R^2=0.042).

DISCUSSION

- A trend for significance suggesting a **higher genetic load for ease of getting up in BD patients who respond to Li** treatment was found. This could be related with Li's action in mitigating the difficulty of getting out of bed[8]. The other PGS followed the expected direction when comparing Rp and no-Rp, although the results were not significant.
- Our **multi-polygenic scores model** using an elastic net regression **selected all the traits**, showing the importance of the sleep-related phenotypes to the response to Li. It also **increased the proportion of variance explained** and proportioned a new method to potentially predict the outcome of the response to Li.
- Our results point to the importance of considering the sleep patterns when studying the response to Li in BD, and further studies with a larger sample size are needed.

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1. Rohr, K. E., & McCarthy, M. J. (2022). *Neuroscience Letters*, *786*, 136772. **2**. Riedinger et al., (2023). *Human Psychopharmacology*, 38(5), e2881. **3**. *American Psychiatric Association* (2000). **4**. Chang et al., (2015). *GigaScience*, 4 .**5**. Jones et al., (2019) (2019*). Nature communications*, 10(1), 343**. 6.** Jansen et al,. (2019). *Nature Genetics*, 51(3), 394–403. **7.** Walz et al., (2013). *Acta Neuropsychiatrica*, 25(2), 101–104. **8.** Lopez et al., (2017). *Sleep Medicine Clinics*, 12(3), 395–405.