



# Clinical Utility of Polygenic Risk Score in Sleep Disorder

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Recently, polygenic risk scores (PRS) using genome-wide association study (GWAS) data have attracted much attention. The present article aimed to review the literature on the relationship between sleep or sleep disorder and PRS. PRS for restless legs syndrome was a very useful marker for genetic risk and clinical characteristics. In addition, highest snoring-PRS decile had approximately twice the odds of reporting recent snoring and choking during sleep. Another study revealed that PRS for schizophrenia was associated with higher fast spindle amplitude, density, and intensity. In case of depression, REM sleep fragmentation was also associated with PRS for depressive symptoms in adolescents. Regarding bipolar disorder, the relationship between insomnia-PRS and bipolar II disorder and sleep-duration-PRS and bipolar I disorder have also been reported. Insomnia-PRS also predicted an earlier age of first cannabis use and increased the number of symptoms of cannabis use disorder. Given the small effect size in the SNP-based association, PRS is a very useful marker for clinical settings, as well as for diagnosis and treatment. In the future, PRS will be a useful tool for personalized medicine.

**Key Words:** Polygenic risk score; Sleep disorder; Sleep trait

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## INTRODUCTION

Recently, polygenic risk scores (PRS) using genome-wide association study (GWAS) data have attracted much attention. PRS are produced using the odds ratios (ORs; patients vs. normal controls) from an existing GWAS as a discovery sample and applied to a GWAS of an independent target sample [1].

Several studies using PRS have been conducted in patients with schizophrenia and mood disorders. One study examined the use of PRS for schizophrenia (SPR-PRS) to predict treatment response to lithium in patients with bipolar disorder [2]. The results found that patients with higher SPR-PRS responded less to lithium. In another study, SPR-PRS and PRS for bipolar disorder (BD-PRS) were calculated for a normal population with high creativity [3]. The higher the creativity, the higher the SPR and BD-PRS relative to a normal population with lower creativity. Recently, PRS has been in the spotlight for personalized medicine. For example, some investigators described the clinical utility of SPR-PRS, BD-PRS, and PRS for major depressive disorder (MDD-PRS) in a depressed patient. If the patient had high SPR- and BD-PRS, and low MDD-

PRS, atypical antipsychotics can be selected as a first-line treatment. PRS have also been used in sleep research [1]. However, the research is not well known compared to schizophrenia and mood disorders.

The present article aimed to review the literature on the relationship between sleep or sleep disorder and PRS.

## RESTLESS LEGS SYNDROME AND POLYGENIC RISK SCORES

Recently, one restless legs syndrome (RLS) study using PRS was published. PRS was calculated using the GWAS meta-analysis for RLS patients who participated in the UK Biobank [4]. The p-value threshold was set at 0.01 because it had the largest variance. The number of variants included in the RLS-PRS was 600,420. Unlike GWAS results, PRS based on GWAS has greater clinical utility. Although GWAS only provides statistically different variant information between patients and the normal population, PRS allows us to identify the clinical characteristics of each individual or group. In the study, the higher the PRS in the target sam-

ple, the lower the educational attainment, and the lower the cognitive function [4]. PRS also showed positive correlations between neuroticism and all body fat, as well as percentage fat in the trunk, legs, and arms, and waist-to-hip ratio [4]. These results are consistent with a study that reported an association between high RLS-PRS and an unhealthy lifestyle [5]. The results from this study were also consistent with an epidemiological study that identified specific characteristics associated with patients with RLS including normal weight, high activity, non-smoking status, and low alcohol intake [6].

When calculating PRS, one can analyze a large number of variants using the p-value threshold of the GWAS data. However, only a small number of target variants can be selected. For example, in one study, PRSs based on 20 association variants in the GWAS data were calculated, and according to these PRSs, the target sample was divided into several groups [7]. The OR for RLS risk of individuals in the highest risk group (PRS 99.5% quantile) was 17.6 [7]. When the 25% quantile and the 75% quantile groups were compared, the OR for RLS risk was 59. As demonstrated, RLS-PRS is a very useful marker for genetic risk and clinical characteristics.

## OBSTRUCTIVE SLEEP APNEA AND POLYGENIC RISK SCORES

A recent study investigated PRS using GWAS data from the UK Biobank to predict recent snoring and obstructive sleep apnea (OSA) in an Australian sample [8]. Snoring PRS was significantly associated with recent snoring. Participants in the highest snoring-PRS decile had approximately twice the odds of reporting recent snoring and choking or struggling to breathe during sleep compared with those in the lowest decile. These findings suggest that PRS is a very useful marker for predicting OSA.

## SLEEP TRAIT AND POLYGENIC RISK SCORES

In a study using UK Biobank data, PRS based on 78 SNPs related to long sleep duration were calculated [9]. Each participant's PRS was produced by summing the OR of risk alleles at each genetic variant which were weighted by the respective allelic effect sizes on longer sleep duration. Phenotypic variance in sleep duration showed a 1.4% variance. After adjusting for age, sex, and principal components, PRS was associated with obesity, congestive hypertension, heart failure, insomnia, and RLS. The PRS based on a focused set of variants with self-reported sleep duration in the Biobank confirmed the clinical utility of this score as a biological marker to predict sleep duration.

In another study, SPR-PRS was associated with higher fast spindle amplitude, density, and intensity [10]. PRS was calculated using ORs and p-values from data of the Psychiatric Genomics Consortium (PGC) GWAS dataset, which included 38,131 schizophrenia cases and 114,674 controls. A positive association between the genetic variants of schizophrenia and sleep spindle activity among

healthy adolescents supported the hypothesis that sleep spindles and schizophrenia share similar genetic pathways. These findings were not consistent with the traditional hypothesis that patients with schizophrenia are associated with lower sleep spindle activity than normal controls [11,12]. This study indicated that altered sleep spindle activity may serve as a biological marker of schizophrenia and raised a new assumption that contradicted existing research evidence.

Some investigators have revealed that REM sleep fragmentation is associated with PRS for depressive symptoms in adolescents [13]. PRS was calculated using data from the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium GWAS for three dimensions of depressive symptoms [14]. The dimensions were three sub-items from the Center for Epidemiologic Studies Depression Scale (CES-D): negative emotion, lack of positive emotion, and somatic complaints. The p-value threshold was set at 0.01. The number of SNPs included in the PRS was 5,563, 5,575, 5,823, and 5,587 variants for positive affect, negative affect, and somatic and total scores, respectively. Depressive symptoms and PRS for somatic complaints were independently associated with more fragmented REM sleep. These findings suggested that REM fragmentation may be a distinct mechanism that lowers the quality of sleep and was associated with PRS for depressive symptoms.

The relationship between insomnia-PRS and bipolar II disorder (BIID) and sleep-duration-PRS and bipolar I disorder (BID) have also been reported. PRS was calculated using data on insomnia, sleep duration, daytime sleepiness from GWAS data in the UK Biobank [15]. Insomnia-PRS was associated with an increased relative risk of BIID compared to normal controls and BID. Sleep-duration PRS was also associated with an increased relative risk of BID compared with BIID. Daytime-sleepiness-PRS was associated with both BID and BIID. In contrast, the relative risk between BD subtypes for daytime-sleepiness-PRS did not differ significantly, unlike insomnia-PRS and sleep-duration PRS. In addition, "morningness"-PRS was associated with a reduced relative risk of BID and BIID compared with normal controls. This study suggests that the genetic liability of sleep traits of BID and BIID, as well as that of BD and normal controls differ from each other.

One study examined the predictive response of PRS to therapeutic sleep deprivation (SD) [16]. PRS was produced using GWAS data from the PGC. The PRS was significantly higher in non-responders to SD than in normal controls and higher PRS in non-responders than in responders to SD, although the differences were not statistically significant. These findings suggest that by applying the therapeutic SD based on genetic liability, such as PRS, a better understanding of the mechanisms of depression may be gained.

## SLEEP DISORDER, COMORBIDITY, AND POLYGENIC RISK SCORES

Some investigators have revealed the relationship between PRS

based on sleep-related GWAS and cannabis use in a target sample [17]. Insomnia-PRS predicted an earlier age of first cannabis use and increased the number of symptoms of cannabis use disorder. However, the short sleep duration and “eveningness” chronotype PRS did not significantly predict any of the cannabis variables in the target sample.

Another PRS study has suggested that narcolepsy is genetically associated with attention-deficit/hyperactivity disorder (ADHD) [18]. The discovery sample for narcolepsy consisted of 1,562 normal controls and 409 patients with narcolepsy. The narcolepsy-PRS was significantly associated with hyperactivity, inattention, and total scores on the attention deficit hyperactivity disorder rating scale. However, essential hypersomnia-PRS was not significantly associated with either domain of ADHD traits. The results indicated that there may be a shared genetic background in ADHD and narcolepsy. These findings suggest a shared genetic background in ADHD and narcolepsy.

## CONCLUSIONS

Given the small effect size in the SNP-based association, PRS is a very useful marker for clinical settings, as well as for diagnosis and treatment. In the future, PRS will be a useful tool for personalized medicine.

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## Conflicts of Interest

The author has no potential conflicts of interest to disclose.

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