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REVIEW

The Relationship Between Genetic Risk for Insomnia and Psychiatric Disorders

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Abstract

Purpose of Review Insomnia has a bi-directional relationship with both psychiatric and addictive disorders, and recent twin studies have shown an overlap in the genetic risk between insomnia and these conditions. Given the multiple single nucleotide polymorphisms (SNPs) identified with small effect sizes in prior genome-wide association studies (GWAS), a polygenic risk score (PRS) estimates the disorder's overall genetic risk using these SNPs. This narrative review evaluates the emerging data on the relationship between the genetic risk for insomnia and these disorders.

Recent Findings The studies show that PRS of insomnia is positively associated with sleep disturbance symptoms, alcohol use disorder, marijuana use, and obsessive-compulsive disorder.

Summary This emerging evidence shows a shared genetic risk between insomnia and these disorders. Future studies should compute insomnia PRS with larger sample sizes, elaborate on how the PRS interacts with other risk factors for disease, and identify underlying subtypes of these disorders.

Keywords Difficulty initiating and maintaining sleep · Polygenic risk score · Mental disorders · Insomnia · Genetics

Introduction

Insomnia is a disorder of sleep continuity consisting of difficulty falling asleep, staying asleep, early morning awakening, and impaired daytime functioning. The prevalence of insomnia disorder is estimated to be about 10–15% [1]. Insomnia can present as a primary disorder or as a symptom of other conditions, such as major depressive disorder (MDD), post-traumatic stress disorder (PTSD), or alcohol use disorder (AUD) [2]. It has long been presumed that insomnia is a consequence of psychiatric disorders, where the severity of insomnia is a direct consequence of the severity of depression, anxiety, or other symptoms. However, the current consensus is that insomnia independently confers a risk for psychiatric disorders like depression, as individuals with chronic insomnia are 2–6 times more likely to have a new onset or recurrent episodes of depression (within 6 months to 3 years) when compared to those without chronic insomnia [3]. A worsening of insomnia may serve as a prodromal feature of several psychiatric disorders [4]; further, individuals with co-occurring insomnia and a psychiatric disorder have lower treatment responsiveness compared to those without insomnia [5]. Thus, insomnia has a bidirectional relationship with many psychiatric disorders.

There is a growing interest in determining whether these phenotypic associations between insomnia and psychiatric or addictive disorders are also seen at the genetic level. Heritability is the amount of variation in the phenotypic trait that can be explained by the genetic variation between individuals in the population. Several twin and family studies in adults have demonstrated moderate heritability of insomnia, with a recent meta-analysis finding an overall heritability of 40% [6]. Recent single nucleotide polymorphism (SNP)-based estimates of heritability have been shown at 7–17% for insomnia [7••, 8•] and 6–16% for AUD [9, 10] among individuals of European descent. Further, twin studies have shown that the genetic factors related to insomnia risk overlap substantially with those for psychiatric disorders [11],

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suggesting the existence of pleiotropy (a phenomenon when one gene influences two or more unrelated phenotypic traits) and the low probability of finding genetic variants that only impact sleep. Insomnia, psychiatric disorders such as major depressive disorders and schizophrenia, and addictive disorders such as alcohol or opioid use disorder and lifetime cannabis use have also been shown to have a genetic basis that involves multiple genes. Thus, genetic factors influence variability in insomnia- and psychiatric or addiction-related traits and involve multiple genes with small effect sizes.

Many genome-wide association studies (GWAS) have been conducted for insomnia-related phenotypes [12, 13]. Initial studies using relatively small datasets ($N \leq 10{,}000$) failed to find any genome-wide significant associations with insomnia symptoms [14, 15] but described suggestive associations with *ROR1*, *PLCB1*, *CEP152*, and *SATB2* genes. Over the years, the size of insomnia GWAS efforts has grown exponentially with the release of the entire dataset from the United Kingdom Biobank and the availability of other datasets. These recent studies identified numerous genome-wide associations using larger cohorts [16]. A recently published study involving 1.3 million individuals from the UK Biobank and 23andMe replicated many of these associations [17]. This study identified 202 genome-wide significant loci for insomnia. Another study recently conducted using a sample size of 2.3 million individuals has identified 554 risk loci, among which 364 are novel loci [18]). These recently identified loci have shown enrichment in specific brain regions previously implicated with sleep regulation, such as the frontal cortex, cingulate cortex, hypothalamus, and medial temporal lobe. Thus, the availability of larger datasets has uncovered additional genetic risk loci for insomnia and shed light on the underlying brain regions and the associated molecular mechanisms.

Although GWAS studies have identified many risk loci for insomnia, the increased risk associated with these individual variants is small. A polygenic risk score (PRS) may provide a practical solution in evaluating the genetic risk factors associated with complex traits like insomnia. A PRS summarizes the estimated effect of many genetic risk variants on an individual's phenotype and is computed as the sum of the genetic variants associated with the trait, weighted by the risk allele effect sizes [19]. Thus, it reflects an individual's estimated genetic predisposition for a trait. PRS is a robust tool to validate genetic links to disease, dissect pleiotropic associations across traits such as that between insomnia and psychiatric disorders, and provide a quantitative measure of an aggregated genetic burden or genetic risk factor for illness in a person. PRS are increasingly being used on a clinical basis to provide a measure of disease risk and the progression of disease and to ascertain the response to treatment in cardiovascular medicine and other medical specialties where it may be harnessed within screening programs, preventive treatment, and counseling for lifestyle modifications to prevent the occurrence of disease [20]; see Fig. 1 for an explanatory cartoon on PRS.

PRS has only recently been evaluated in the context of psychiatric disorders. The goal of this narrative review was to evaluate the emerging data that describes the relationship between the genetic risk for insomnia and

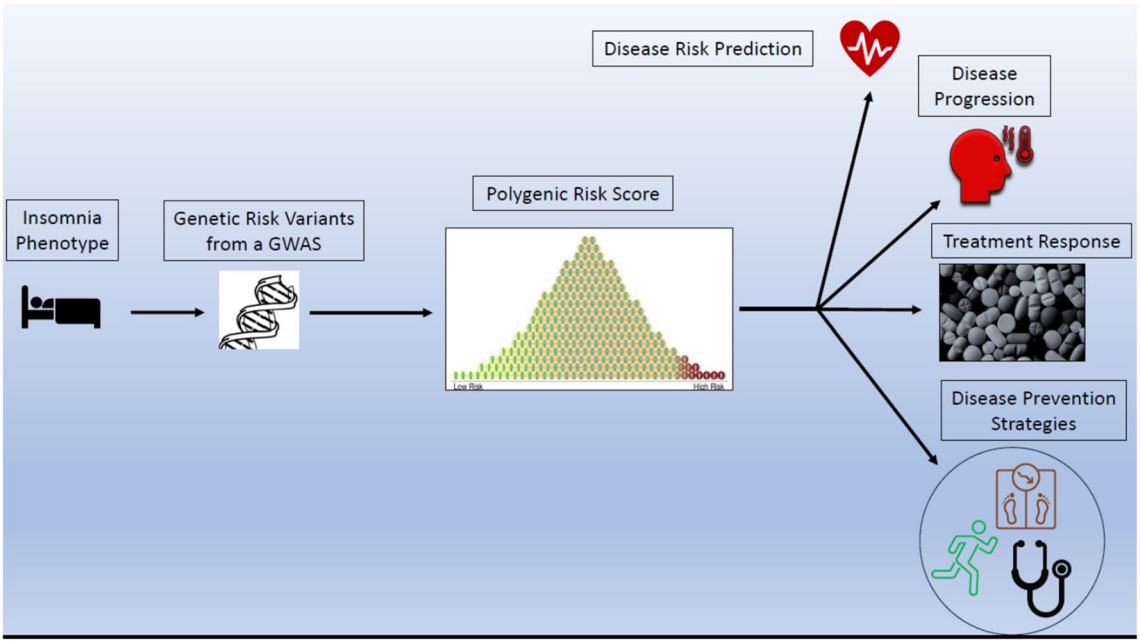

Fig. 1 Polygenic risk score and its clinical utilities

psychiatric disorders. The existence of such relationships will enhance our understanding of the role that genetic risk plays in these established epidemiological relationships between insomnia and psychiatric or addictive disorders. An appreciation of the role of PRS in these disorders will help us enhance precision medicine, e.g., by categorizing different psychiatric disorders subtypes or by treatment response.

Methods

We conducted a literature search using the following steps. In step 1, we formulated the search terms to cover the topic of PRS of insomnia. In step 2, we conducted a literature search using the PubMed database. We conducted this literature search using the terms "polygenic risk score" AND "insomnia." To maximize the retrieval of original research studies, we selected all the available literature till October 22, 2023. The studies were limited to human subjects, in the English language, and original research studies. We identified 22 studies, among which 10 were rejected as they did not involve PRS analysis or they used PRS of traits other than insomnia (Fig. 2). We excluded four of the remaining 12 articles, as they involved the association of PRS of insomnia with non-psychiatric disorders, sleep duration PRS, or a corrigendum to one of the articles selected for review. We discuss the final 8 articles selected for review.

Results

The list of articles reviewed is presented in Table 1, along with a summary of their main findings.

Summary of Findings in Insomnia Disorder

Although the GWAS used to calculate PRS for insomnia were conducted in datasets comprised of middle-aged to elderly adults primarily of European ancestry, these scores have been associated with insomnia-related symptoms in children, adolescents, and young adults. Across childhood and adolescence, higher insomnia PRS was associated with more parent-reported sleep problems. This study was conducted in children and adolescents of European ancestry; however, an additional study in adolescents of non-European ancestral backgrounds also observed a relationship between higher insomnia PRS and increased risk for sleep onset and maintenance disorders [22]. Further, a relationship was observed between higher insomnia PRS and reduced delta and theta power measured using electro-encephalographic data across different sleep stages in young adults [23]. This same study by Koshmanova et al. also found that increased genetic risk for insomnia was associated with a decreased likelihood of falling asleep during the day as measured by the multiple sleep latency test [24].

Summary of Findings in Psychoactive Substance Use Disorders and Psychiatric Disorders

Several genetic studies interrogating pleiotropic effects of insomnia genetic risk factors have observed relationships between PRS for insomnia and expression of many conditions that are often co-occurring. Studies have found links between genetic risk for insomnia and expression of substance use disorders and other mental health conditions. For example, a recent study tested if the increased genetic risk for insomnia was associated with lifetime diagnosis of Alcohol Use Disorder (AUD) or past-year Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) scale scores [25•]. Higher genetic risk for insomnia was associated with an increased risk for having an AUD diagnosis but lower AUDIT-C scores

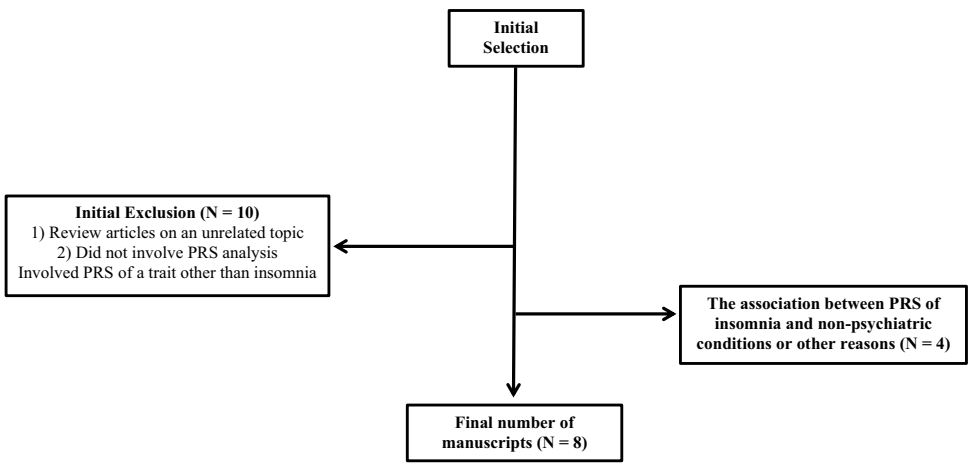

Fig. 2 Manuscript selection process for the current review

Table 1 Insomnia PRS and its association with a range of disorders

Study	Insomnia GWAS summary statistics	Target dataset	Main findings
Other sleep disorders			
Koshmanova et al. (2022)	Insomnia GWAS from 23andMe ($N = 944,477$) [7••]	Healthy, young individuals of European ancestry ($N = 456$)	1. Insomnia PRS was negatively associated with EEG delta and theta power during REM and NREM 2. Insomnia PRS was negatively associated with MSLT daytime likelihood of falling asleep (among men only)
Ma et al. (2021)	Insomnia GWAS from the UK Biobank ($N = 386,533$) [21]	Adolescents of diverse ancestries participants of the Adolescent Brain Cognitive Development (ABCD) study ($N = 9737$)	Insomnia PRS was positively associated with disorders of initiating and maintaining sleep (among those of European ancestry only)
Kocevska et al. (2023)	Insomnia GWAS from the UK Biobank ($N = 386,533$) [21]	Children of European ancestry part of The Generation R Study ($N = 2063$)	Insomnia PRS was positively associated with sleep problems at age 6, among those that experienced prenatal life events
Substance use			
Chakravorty et al. (2023)	Insomnia GWAS from the UK Biobank ($N = 453,379$) [8•]	European ancestry U.S. Veterans with data on alcohol consumption and alcohol use disorder diagnosis ($N = 209,020$)	1. Insomnia PRS was positively associated with AUD and inversely associated with alcohol consumption scores on the AUDIT-C
Winiger et al. (2021)	Insomnia GWAS from the UK Biobank ($N = 453,379$)	European-ancestry individuals in a mixed sample ($N = 491$) from the Center on Antisocial Drug Dependence and the Genetics of Antisocial Drug Dependence datasets	Insomnia PRS was negatively associated with an age of first cannabis use and positively with the lifetime cannabis use disorder symptom count
Mental health			
Beupre et al. (2021)	Insomnia GWAS from the UK Biobank ($N = 386,533$) [21]	European ancestry participants with diagnosis of MDD part of the PGC-MDD Working Group ($N = 6698$)	Insomnia PRS (using a thresholding approach) was associated with insomnia; < 1% of variance was explained by the included SNPs
Forthman et al. (2023)	Insomnia GWAS from the UK Biobank ($N = 386,078$) [18]	Participants of the Tulsa 1000 Study with mood/anxiety, substance, or eating disorders and healthy controls ($N = 480$). Mostly European ancestry, but inclusive of all geographic ancestries	No significant associations between insomnia PRS and severity of repetitive negative thinking
Strom et al. (2021)	Insomnia GWAS from the UK Biobank ($N = 386,533$) [21]	European ancestry participants of the Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH) with diagnosis of OCD and comorbid conditions ($N = 2678$)	Insomnia PRS was positively associated with OCD comorbid with MDD, ADHD, and multi-comorbid OCD, but not with ASD

signifying lower risky drinking patterns. Conversely, individuals with higher PRS for sleep duration abnormalities were more likely to have higher AUDIT-C scores. Another study identified genetic correlations between the risk for insomnia–as well as other sleep-related traits—and risk for cannabis use. This study calculated a more comprehensive PRS for sleep deficits by combining results from GWAS of insomnia with those investigating sleep duration and chronotype [26]. Notably, associations were observed between increased genetic risk for diagnosis of cannabis use disorder and higher genetic risk for both insomnia and short sleep duration. In addition, insomnia PRS predicted an earlier age of first cannabis use and increased number of lifetime cannabis use disorder symptoms.

Additional studies have tested for relationships between sleep-related PRS and risk for expression of other mental health conditions including disorders influenced by repetitive negative thinking (e.g., substance use, mood/anxiety, and eating disorders), major depressive disorder, attention deficit hyperactivity disorder, obsessive compulsive disorder, and autism spectrum disorder. Although insomnia PRS was observed to be related to expression of substance use disorders in the studies detailed above, a study assessing the relationship with repetitive negative thinking—which can exacerbate substance use—did not observe significant results [27]. Although not directly related to risk for the mental health condition, one study demonstrated that insomnia PRS was associated with evidence of insomnia in individuals diagnosed with major depressive disorder [28]. In yet another study, genetic risk for insomnia was correlated with genetic risk for major depressive disorder comorbid with obsessive compulsive disorder. Notably, insomnia PRS demonstrated the strongest relationship with genetic risk for obsessive compulsive disorder with attention deficit hyperactivity disorder [29].

Conclusions and Future Directions

While the number of studies that have utilized insomnia PRS is small, the summary of findings is consistent. First, individuals with a greater genetic risk for insomnia are more likely to experience disturbed sleep. Second, a greater genetic risk for insomnia is associated with a higher likelihood of experiencing mental health disorders, including substance use, mood, and anxiety disorders. This pattern of results suggests that the phenotypic relationships among these disorders are partly due to shared underlying genetic risk. Given that the PRS was generated in separate cohorts from those in these studies, the results also support the validity of the PRS itself.

The relationship between genetic risk for insomnia and self-reported sleep problems is consistent with the behavioral model of insomnia [30]. According to this model, insomnia results from Predisposing, Precipitating, and Perpetuating factors. There has been considerable investigation of the latter two factors, but less work has sought to identify Predisposing factors that increase vulnerability to insomnia. Genetic risk has long been proposed as a critical Predisposing factor, and these studies support this view. Notably, these studies were primarily conducted in children/youth. It has been suggested that cases of insomnia highly related to genetic factors would be expected to appear earlier in life, and previous editions of diagnostic criteria include a subtype labeled Childhood-Onset Insomnia [31]. Few studies were ever conducted on this subtype, and it was abandoned, but these findings suggest that it should be reconsidered. The association between insomnia PRS and specific sleep electroencephalographic features is also intriguing and warrants further follow-up.

The associations between genetic risk for insomnia and mental health disorders suggest the presence of pleiotropy, in which genetic variants contribute to risk for multiple disorders. Research on the genetics of insomnia has long suggested substantial overlap with other diagnoses. For example, analyses of twin pairs found support for common genetic factors that increased the risk for depression, anxiety, and insomnia but no evidence of disorder-specific effects [11]. Most genetic studies are disorder-specific, but these results indicate that new approaches are needed considering the substantial cross-disorder genetic overlap. The insomnia PRS may also have the potential to identify individuals at risk for developing insomnia as well as other mental health disorders.

Given the bidirectional relationship between insomnia and psychiatric or addictive disorders and the close relationships between psychiatric and addictive disorders, genetic moderation analyses may be another area where PRS may give us a unique perspective. One such example is a recent study available as a preprint where the authors evaluated the role of adverse childhood events (ACE, such as childhood sexual, physical, or emotional abuse), PRS of mood/anxiety disorders, or PRS of substance use disorders (SUD) in the development of mood/anxiety disorders or substance dependence [32]. ACEs had a positive direct effect on mood/anxiety disorders and substance dependence. Further, the SUD PRS moderated the relationship between ACE and the substance dependence outcome, where there was a smaller effect of ACEs on substance dependence for those with a higher SUD PRS. This finding suggests that exposure to ACEs contributes more to SUD risk in individuals who are not highly genetically predisposed to develop an SUD. The PRS of insomnia may not only help us improve our understanding of the relationships between insomnia and psychiatric or addictive disorders but also whether a genetic risk of insomnia moderates the risk between psychiatric disorders and substance dependence.

There are several limitations of these findings, most notably the small number of studies that have utilized insomnia PRS. The PRS is also mostly based on individuals of European ancestry, so there is a need to generate PRS in other populations to determine the extent to which they are

generalizable or population-specific. Finally, unlike monogenic disorders caused by high penetrance mutations, in complex disorders, the discriminative ability of PRS is compromised by the multifactorial contributors to the disease, the imperfect measurement of the full genetic signal, and the potentially incorrect measurement.

In summary, insomnia PRS helps to investigate the relationships between genetic risk for insomnia and both sleep and mental health phenotypes. Studies thus far indicate that genetic relationships parallel the phenotypic relationships between insomnia and mental health disorders. The use of PRS may help with screening for individuals at risk for developing psychiatric or addictive disorders in response to stress and complications of risky alcohol consumption or help personalize treatment for insomnia comorbid with psychiatric disorders and stratify risks from treatment [20]. PRS also provides us a unique opportunity to assess the pleiotropic effects of genetic risk variants on two commonly comorbid traits, i.e., insomnia and psychiatric or addictive disorders. Finally, PRS of insomnia may improve our understanding of whether it plays a moderating effect between psychiatric and addictive disorders where insomnia commonly co-exist.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

Human and Animal Rights and Informed Consent No animal or human subjects by the authors were used in this study.

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- • Of importance
- •• Of major importance

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