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Integrating Sleep-Related Breathing Disorders and Epigenetics into the Genetic Landscape of Sleep Disturbances in Psychotic Disorders

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Integrating Sleep-Related Breathing Disorders and Epigenetics into the Genetic Landscape of Sleep Disturbances in Psychotic Disorders

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Recent advances in psychiatric genetics have underscored the role of polygenic scores (PGSs) in shaping sleep phenotypes in individuals with psychotic disorders. The study by Cederlöf et al. [1] makes an important contribution by leveraging genome-wide association data to disentangle the complex interplay between genetic liability for insomnia, sleep duration, chronotype, and schizophrenia. Their findings offer compelling insights into how distinct genetic risks manifest in both subjective experiences and cognitive performance. Yet, the genetic landscape of sleep in psychosis is even more nuanced than the current framework suggests. Several biologically and clinically relevant dimensions—namely sleep-related breathing disorders (SRBDs), the COMISA phenotype (comorbid insomnia and sleep apnea), and the dynamic influence of epigenetic regulation—warrant deeper integration into this conversation.

Obstructive sleep apnea (OSA), the most prevalent SRBD, is significantly underrecognized in psychotic populations despite high clinical relevance. Individuals with schizophrenia are at increased risk for OSA due to overlapping predisposing factors, including antipsychotic-induced weight gain, sedative use, metabolic syndrome, and lifestyle-related variables [2,3]. The consequences of untreated OSA—fragmented sleep, intermittent hypoxia, and excessive daytime sleepiness—may mimic, mask, or exacerbate core psychiatric symptoms, such as cognitive impairment and mood instability [4]. Importantly, studies have shown that treatment with continuous positive airway pressure (CPAP) improves psychiatric outcomes, including mood and attention, in individuals with psychotic disorders [5]. Despite this, genetic models of sleep in psychosis rarely incorporate SRBDs or the emerging polygenic scores for OSA recently developed from population-based cohorts [6]. Their absence may obscure an important dimension of biological vulnerability.

The intersection of insomnia and OSA—referred to as COMISA—represents a distinct and consequential phenotype. Epidemiological data suggest that COMISA is more prevalent than either disorder alone and associated with more

severe clinical outcomes, including greater psychiatric symptom burden, metabolic dysregulation, and treatment resistance [7]. The co-occurrence of insomnia and OSA creates a synergistic burden through the convergence of hyperarousal, sleep fragmentation, oxidative stress, and HPA axis dysregulation. These mechanisms overlap with known neurobiological signatures of psychosis, including circadian misalignment, impaired slow-wave sleep, and abnormal synaptic plasticity. Importantly, COMISA complicates therapeutic response, as isolated treatments such as CBT-I or CPAP often fail unless the dual pathology is addressed comprehensively. It is plausible that COMISA constitutes not just a clinical entity but a genetic and epigenetic endophenotype of psychosis, deserving focused investigation. The lack of consideration of COMISA in Cederlöf et al.'s study may therefore limit the scope of their otherwise valuable findings.

While PGSs illuminate inherited predispositions, they do not capture the environmentally responsive layer of gene regulation provided by epigenetics. Mechanisms such as DNA methylation, histone acetylation, and non-coding RNAs mediate the interface between genotype and environment, dynamically shaping gene expression in response to stressors including sleep loss [9], hypoxia [10], psychosocial stress [11], and pharmacological exposure [12]. Epigenetic abnormalities have been widely observed in schizophrenia, affecting genes involved in synaptic signaling, neurodevelopment, and circadian regulation [13]. Sleep disorders such as OSA and insomnia exert measurable epigenetic effects. Sleep fragmentation in OSA alters methylation in genes related to inflammation and neuronal excitability [14], while intermittent hypoxia induces region-specific histone modifications in brain regions central to cognition and psychosis, including the hippocampus and prefrontal cortex [16]. Likewise, chronic insomnia, through sustained activation of stress-related systems, may reinforce maladaptive methylation patterns [15].

This growing body of evidence supports a shift from single-layer genetic analysis toward a comprehensive multi-omic framework that integrates genomics, epigenomics, transcriptomics, and high-resolution phenotypic data. Objective sleep metrics—polysomnography, actigraphy, respiratory parameters, and circadian phase markers—are essential to adequately capture the complexity of sleep phenotypes in psychosis. Reliance on self-report measures, though convenient, may compromise accuracy, particularly in populations where

cognitive and metacognitive deficits are common. Future studies should consider incorporating composite PGSs for OSA, COMISA, and chronobiological misalignment to refine predictive models.

These insights are not merely theoretical. They have substantial implications for clinical care. Patients with high genetic liability for insomnia but no SRBDs may benefit most from behavioral therapies like CBT-I. Conversely, individuals with overlapping risk for both insomnia and OSA—particularly those with COMISA—require a dual-pronged approach, combining behavioral, mechanical, and possibly pharmacological treatments. COMISA in psychosis may signify a subgroup with elevated risk for cognitive decline, functional deterioration, and treatment non-response, thereby meriting targeted early intervention. Moreover, recognition of the epigenetic plasticity of sleep-related pathways introduces new possibilities for preemptive and therapeutic modulation, as epigenetic changes induced by sleep disruption are reversible with adequate intervention. CBT-I, for example, has been shown to normalize stress-related gene methylation, while CPAP use may reverse hypoxia-induced epigenetic marks.

In summary, while the study by Cederlöf et al. marks an important advance in understanding sleep-related polygenic influences in psychosis, we argue for a broader conceptualization that incorporates sleep-related breathing disorders, the COMISA phenotype, and the critical role of epigenetic regulation. A deeper integration of these dimensions may allow for more accurate stratification of sleep phenotypes, refinement of risk prediction models, and ultimately, the development of targeted interventions that improve outcomes for individuals with psychotic disorders.

Conflict of Interest: None

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Response to Reviewers

We thank the editor for the opportunity to revise our Letter to the Editor entitled “Integrating Sleep-Related Breathing Disorders and Epigenetics into the Genetic Landscape of Sleep Disturbances in Psychotic Disorders.”

In response to the editorial recommendation, we have made the following change:

Comment: Please reduce the word count to 900 words or fewer, and remove all subheadings.

Response: As requested, we have revised the manuscript to meet the word count limit (now ~895 words) and removed all subheadings. The text has been edited for conciseness while retaining its conceptual and scientific clarity.

No other reviewer comments were issued. The revised version now adheres to the format and editorial standards of Psychological Medicine.

We remain grateful for your consideration and look forward to your response.