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ORIGINAL ARTICLE

Insomnia disorder with objective short sleep duration (ISS) phenotype and cognitive performance: a systematic review and meta-analysis

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Abstract

Objective Insomnia disorder with objective short sleep duration (ISS) has been considered as a biologically severe subtype. The aim of this meta-analysis was to reveal the association of the ISS phenotype and cognitive performance.

Methods We searched PubMed, EMBASE, and the Cochrane Library for studies that observed an association of cognitive performance and insomnia with objective short sleep duration (ISS) phenotype. The "metafor" and "MAd" packages in R software (version 4.2.0) were used to calculate the unbiased standardized mean difference (Hedge's g), which was adjusted so that a negative value indicated worse cognitive performance.

Results The pooled analysis with 1339 participants revealed that the ISS phenotype was associated with overall cognitive impairments (Hedges' $g = -0.56$ [$-0.89, -0.23$]), as well as specific cognitive domains including attention (Hedges' $g = -0.86$ [$-1.25, -0.47$]), memory (Hedges' $g = -0.47$ [$-0.82, -0.12$]), and executive function (Hedges' $g = -0.39$ [$-0.76, -0.02$]). However, cognitive performance was not significantly different between insomnia disorder with objective normal sleep duration (INS) and good sleepers ($p > .05$).

Conclusion Insomnia disorder with the ISS phenotype, but not the INS phenotype, was associated with cognitive impairments, suggesting the possible utility of treating the ISS phenotype to improve cognitive performance.

Keywords Insomnia with objective short sleep duration · Insomnia disorder · ISS phenotype · Cognitive performance

Introduction

Insomnia disorder is defined as difficulty initiating sleep, maintaining sleep, or early-morning awakening, and the predominant complaints at least 3 nights per week for at least 3 months with associated daytime impairment [1, 2]. Approximately, 30% of the general population experience insomnia symptoms, and 10% experience chronic disorder [3]. Sleep is inherently a multidimensional biobehavioral process. To understand insomnia disorder using a multidimensional clinical approach, the insomnia with objective short sleep duration (ISS) phenotype is developed by relying on both self-reported and objectively measured domains [4]. A proposed hallmark of the ISS phenotype is physiologic hyperarousal, reflecting 24-h activation of the stress system, and has been considered as a biologically severe subtype of insomnia disorder [5].

Although a causal link of the ISS phenotype with physical health has been suggested, a potential causal link with the cognitive impairment remains elusive [6]. Mild cognitive impairment (MCI) is considered a precursor of Alzheimer's disease (AD). Increasing evidences suggest that insomnia disorder makes individuals be vulnerable to developing MCI and progress into AD [7]. In this case, if we can confirm a causal link of the ISS phenotype with cognitive impairment, an opportunity of early intervention for insomnia disorder may be provided to prevent the progression to AD.

Therefore, we performed a meta-analysis to identify the association between insomnia disorder with the ISS phenotype and cognitive performance.

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Methods

This meta-analysis was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) protocol [8].

We searched PubMed, EMBASE, and the Cochrane Library for studies that observed an association of cognitive performance and insomnia with objective short sleep duration (ISS) phenotype through Aug. 31, 2022 by using combination of "insomnia" AND "cognitive" or "cognition" or "neuropsychology."

Inclusion and exclusion criteria

The PICOS principle were following (1) patients with insomnia disorder diagnosed with DSM (Diagnostic and Statistical Manual of Mental Disorders) or ICD (International Classification of Diseases) criteria, excluding comorbidity insomnia and obstructive sleep apnea; (2) the ISS phenotype defined as less than 6 h of total sleep using polysomnography (PSG); (3) comparisons with good sleepers or insomnia with objective normal sleep duration (INS) phenotype (more than 6h total sleep); and (4) available cognitive performance measures, including a battery of standardized neuropsychological tests commonly used in clinical practice to assess a wide range of cognitive domains before the sleep recording. The classification of cognitive domains used the previous definition [9].

Data extraction and quality assessment

Two independent raters (D.R. and Z.G.) abstracted data using a standardized form, and discrepancies were resolved by discussion. To facilitate comparison and continuity, cognitive domains were classified according to the previous criteria [9, 10].

The included studies were assessed using the Newcastle-Ottawa Scale (NOS) for non-randomized studies. A study is judged by the NOS on three broad perspectives: the selection of the study groups, the comparability of the groups, and the ascertainment of either the exposure or outcome of interest for case-control studies [8].

Statistical analysis

The "metafor" and "MAd" packages in R software (version 4.2.0) were used to calculate the unbiased standardized mean difference (Hedge's g), which was adjusted so that a negative value indicated worse cognitive performance.

Given that multiple measures within the same cognitive domain were often used, we firstly implemented the "BHHR" method in the "MAd" package to aggregate dependent effect sizes into only a single effect size [11, 12]. The aggregation of dependent effect sizes contributed only one effect size for each cognitive domain from each independent sample. Secondly, we further aggregated effect sizes across cognitive domains, so that each independent sample only contributed one effect size. Lastly, we conducted an omnibus meta-analysis to examine the overall effect of the ISS phenotype on cognitive performance across all cognitive domains and studies.

Results

We identified five studies [13–17] to make omnibus meta-analysis (Fig. 1) with 1339 participants, including 241 patients with the ISS phenotype, 235 patients with the INS phenotype, and 863 good sleepers (Table 1). The quality scores of the single included studies ranged from five to eight stars, with a mean quality score of 7.2 and a standard deviation of 0.84.

Compared to patients with the INS phenotype, the overall cognitive performance was significantly impaired in patients with the ISS phenotype (Hedges' $g = -0.56$, 95% CI [− 0.89, − 0.23]), as well as in cognitive domains of attention (Hedges' $g = -0.86$, 95% CI [− 1.25, − 0.47]), memory (Hedges' $g = -0.47$, 95% CI [− 0.82, − 0.12]), and executive function (Hedges' $g = -0.39$, 95% CI [− 0.76, − 0.02]) (Fig. 2). The heterogeneity statistic was not significant in omnibus meta-analyses with standardized mean difference (SMD) as effect size (Fig. S1 and S2).

The cognitive performance was not significantly different between patients with the INS phenotype and good sleepers, in terms of overall cognitive performance, general cognitive function, attention, memory, and executive function (Fig. 2). The heterogeneity statistic was not significant in most omnibus meta-analyses with standardized mean difference (SMD) as effect size (Fig. S1 and S2).

Publication bias with funnel plot analysis indicated that there was no significant asymmetry ($p = .24$). We did not conduct a meta-regression analysis to reveal potential moderating effects of age, gender, body mass index (BMI), or education in the omnibus meta-analysis because of limited original data.

Discussion

The current meta-analysis indicated that insomnia with objective short sleep duration (ISS) phenotype significantly impaired overall cognitive performance, as well as specific cognitive domains including attention, memory, and executive function. However, insomnia with objective normal

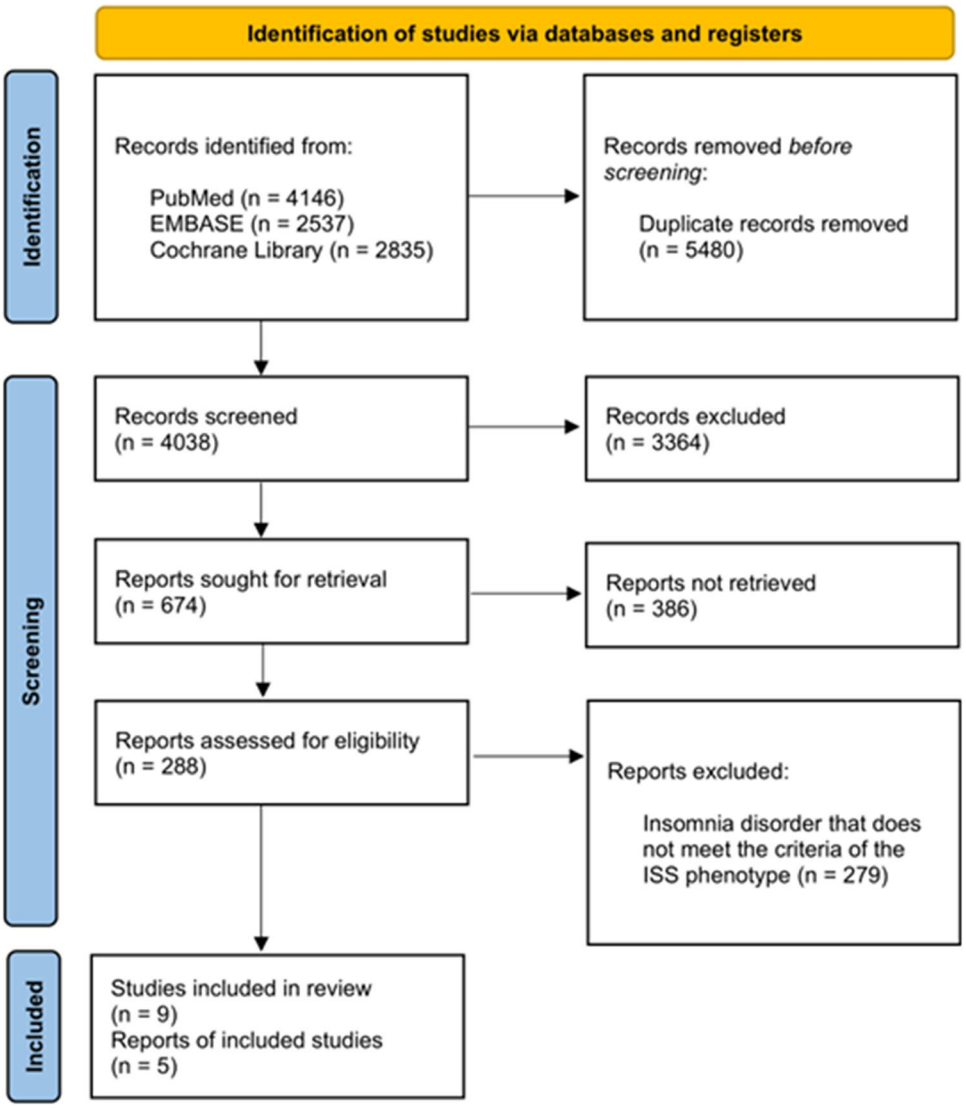

Fig. 1 Flow chart of study selection strategy

sleep duration (INS) phenotype did not show a significant effect on poorer cognitive performance.

It is very meaningful to reveal the relationship of insomnia with poorer cognitive performance due to the negative effects of cognitive impairment, such as lower quality of life, increased costs of care, increased accidents, and morbidity [18–20]. A better understanding of the relationship between insomnia and cognitive performance may inform potential interventions to improve cost-effectiveness of impaired cognition on health. Previous meta-analysis studies have found that insomnia is associated with deficits in objective and subjective cognitive performance, highlighting the utility of treating insomnia disorder to potentially improve cognitive outcomes [9, 10, 21].

However, insomnia disorder is multidimensional; specific phenotype may have specific etiology, pathophysiology, clinical features, natural course, downstream consequences, and intervention procedures [22, 23]. Insomnia with objective short sleep duration (ISS) phenotype as a disorder of physiologic hyperarousal emphasizes the clinical importance of considering the quality and duration of sleep, as well as its perceived and objective aspects [4]. Different from previous meta-analysis studies on the association of insomnia disorder with cognitive performance, we divided insomnia disorder into the ISS subtype and the INS subtype. Our findings indicated that cognitive impairments were associated with the ISS phenotype, but the INS phenotype did not impair cognitive performance. This result is also proved by a previous study that the risk of cognitive disorder is significantly elevated when the nocturnal sleep duration is shortened [21].

Specifically, we found that the ISS phenotype was associated with large (Hedges' $g = -0.86$) deficits in attention. Attention is traditionally measured using reaction time, which is a sensitive measure of cognitive performance. Wang et al. found that reaction time was significantly increased after sleep deprivation, and the increased reaction time was

Table 1 Characteristics of included studies

Study	Sample size (ISS/INS/GS)	Age (years) (ISS/INS/GS)	Female (%) (ISS/INS/GS)	BMI (kg/m^2) (ISS/INS/GS)	Education (years) (ISS/INS/GS)	Cognitive domains	NOS
Fernandez 2021 [13]	98/74/452	N/A	N/A	N/A	N/A	MMSE, SDMT, TMT, BVRT, TWFT	6
Fernandez 2010 [14]	51/65/343	55.9/44.5/47.3	74.5/78.5/58.0	29.8/31.8/29.4	12.4/13.4/13.4	MMSE, SDMT, TMT, BVRT, TWFT	7
Fan 2019 [15]	30/27/29	48.2/44.9/46.0	53.3/66.7/62.1	23.5/22.5/23.1	11.9/12.5/11.3	TMT, BACS-SC, HVLT, BVMT, CPT-IP, spatial span, fluency, managing emotions	8
Khassawneh 2018 [16]	19/16/39	N/A	N/A	N/A	N/A	SRT, CRT, BLC, RVP, AST, SWM	7
Miller 2016 [17]	43/53/-	44.8/38.6/-	58.1/67.9/-	25.4/24.7/-	N/A	N-Back, LCT, ToL	8

ISS insomnia with objective short sleep duration, *INS* insomnia with objective normal sleep duration, *GS* good sleeper, NOS the Newcastle-Ottawa Scale,

LCT letter cancellation test, *ToL* Tower of London, *SRT* simple reaction time, *CRT* choice reaction time, *BLC* big circle-little circle, *RVP* rapid visual information processing, *AST* attention switching task, *SWM* spatial working, *TMT* trail making test, *BACS-SC* brief assessment of cognition in schizophrenia, *HVLT* Hopkins verbal learning test, *BVMT* brief visuospatial memory test, *CPT-IP* continuous performance test, *MMSE* mini-mental status examination, *SDMT* symbol digit modalities test, *BVRT* Benton visual retention test, *TWFT* Thurstone word fluency test

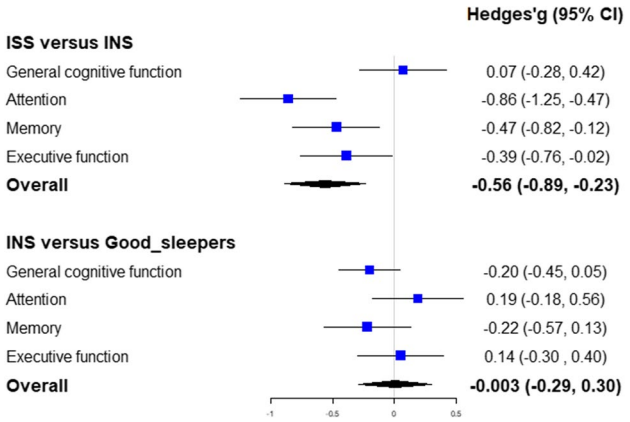

Fig. 2 Forest plot of the omnibus meta-analyses. Compared to insomnia with objective normal sleep duration (INS) phenotype, insomnia with objective short sleep duration (ISS) phenotype significantly impairs overall cognitive performance (Hedges' g = -0.56, $p < 0.001$), as well as specific cognitive domains including attention (Hedges' g = -0.86, $p<0.001$), memory (Hedges' g = -0.47, $p = 0.02$), and executive function (Hedges' g = -0.39, $p = 0.04$). Compared to good sleepers, impaired cognitive performance is not significantly different ($p > 0.05$) in the insomnia with objective normal sleep duration (INS) phenotype

correlated with altered anterior insula-superior frontal gyrus functional connectivity [24]. They suggested that functional connectivity abnormalities in the anterior insular subregions represented a neuroimaging biomarker of sleep deprivation-associated cognitive impairment. As a form of chronic sleep deprivation, the ISS phenotype is more likely to damage functional connectivity by complex phenotype-genotype associations based on the genetic underpinnings of sleep deprivation-induced impairments in human cognition [25].

The small to moderate deficits in memory and executive function were in alignment with results from the 2019 meta-analysis conducted by Wardle-Pinkston et al. [10]. In their study, the smaller effect size might be related to the mixing of the ISS and the INS phenotypes. Impaired memory and executive function emphasize the detrimental impact of the ISS phenotype on daytime performance. Memory involves an individual's ability to retain and manage information in the short-term memory, or the learning of new material and recalling them after a delay. The ISS phenotype increases hypothalamic pituitary adrenal axis and sympathetic nervous system activations, which has been proved to be positively correlated with memory deficits [26]. The executive function appears to be more complex and more impacted by the negative effects of the ISS phenotype.

Recent studies have attempted to link the ISS phenotype with altered neurocognitive function and potential increased risk of cognitive impairments, indicating lower gamma-aminobutyric acid (GABA) levels in the anterior cingulate cortex, greater waking connectivity between the retrosplenial cortex/hippocampus and various nodes of the default mode network (DMN), and decreased glutamate metabolites and brain-derived neurotrophic factor [27–29]. These results indicated that managing ISS phenotype might serve as a promising target for cognitive impairment prevention.

There were some limitations in the current meta-analysis. First, despite that the Failsafe-N analysis and publication bias results indicated our findings were relatively robust, the sample size was small. Second, the included studies

were cross-sectional and no causal relationship could be drawn. Third, cognitive measures varied greatly between the enrolled studies. Therefore, there is a need for large, multicenter, longitudinal studies using objective cognitive and sleep measures, as well as developing standardized battery of cognitive performance to facilitate comparison and replication of results.

In conclusion, this meta-analysis revealed that insomnia disorder with ISS phenotype is associated with cognitive impairments, including overall cognitive performance and specific cognitive domains. While cognitive performance is not significantly different between patients with INS phenotype and good sleepers, that suggests the possible utility of treating ISS phenotype, but not INS phenotype, to improve cognitive performance. In the future, multicenter, longitudinal studies with standardized battery of cognitive measures are needed to draw a potential causal relationship.

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Author contribution Study conception and design: BJ and DR; acquisition of data: DR and ZG; analysis and interpretation of the data and writing of this paper: BJ, DR, and ZG. All of the authors approved the submission of the final version of this paper.

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Declarations

Ethical approval None.

Conflict of interest The authors declare no competing interests.

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