ORIGINAL RESEARCH

Genetic Associations Between Specific Sleep-Related Phenotypes and Idiopathic Sudden Sensorineural Hearing Loss: A Mendelian Randomization Analysis

Man Li[1],*, Jinbo He[2],*, Yiting Liang[3], Fan Zou[1], Changlong Gou[4], Jing Lv[2], Xicheng Zhang[5], Dan Li[6], Zizhong Yu[1]

[1]Department of Otolaryngology, Head and Neck Surgery, Taihe Hospital, Hubei University of Medicine, Shiyan, 442000, People's Republic of China; [2]Department of Anesthesiology, Taihe Hospital, Hubei University of Medicine, Shiyan, 442000, People's Republic of China; [3]First Clinical College, Hubei University of Medicine, Shiyan, 442000, People's Republic of China; [4]Department of Ultrasound Medicine, Taihe Hospital, Hubei University of Medicine, Shiyan, 442000, People's Republic of China; [5]Biomedical Engineering College, Hubei University of Medicine, Shiyan, 442000, People's Republic of China; [6]Clinical Molecular Diagnostic Center, Taihe Hospital, Hubei University of Medicine, Shiyan, 442000, People's Republic of China

*These authors contributed equally to this work

Correspondence: Zizhong Yu, Department of Otolaryngology, Head and Neck Surgery, Taihe Hospital, Hubei University of Medicine, No. 32 Renmin South Road, Maojian District, Shiyan, Hubei, 442000, People's Republic of China, Tel +86-719-8801459, Email yurick0994@163.com; Dan Li, Clinical Molecular Diagnostic Center, Taihe Hospital, Hubei University of Medicine, No. 32 Renmin South Road, Maojian District, Shiyan, Hubei, 442000, China, Tel +86-719-8801881, Email lidan198016@163.com

Purpose: The relationship between idiopathic sleep-related phenotypes (SRPs) and sudden sensorineural hearing loss (ISSNHL) remains unclear. This study was designed to investigate the link between SRPs and ISSNHL from a genetic perspective through Mendelian randomization (MR) analysis.

Methods: ISSNHL trials were downloaded from Finngen database. SRPs were from the UK Biobank and FinnGen database. The inverse variance weighted (IVW) method was utilized, followed by confirming the robustness and reliability using the MR Egger, weighted median, simple mode, and weighted mode. The heterogeneity was determined using MR Egger and IVW, and pleiotropy by MR Egger.

Results: There were 39/27 single nucleotide polymorphisms (SNPs) related to insomnia, 68 SNPs related to sleep duration, 31 SNPs related to daytime dozing, 13 SNPs related to sleep disorders, and 20 SNPs related to sleep apnoea. The F statistics exceeded 10, suggesting minimal likelihood of weak instrument bias. There were no evidence indicating a potential causal effect of insomnia, sleep duration, sleep disorders, sleep apnoea, and on the risk of ISSHNL. However, narcolepsy was an inferred protective factor for ISSNHL. Lower risk of ISSNHL was found in relation to daytime dozing/sleeping (narcolepsy)-related SNPs.

Conclusion: This phenomenon may provide a novel and meaningful therapeutic target for ISSNHL based on sleep medicine. However, this putative causal relationship requires further experimental validation.

Keywords: ISSNHL, hearing loss, sleep-related phenotypes, Mendelian randomization

Introduction

Sudden hearing loss, medically termed idiopathic sudden sensorineural hearing loss (ISSNHL), refers to a swift and unexplained reduction in hearing capacity, typically affecting unilateral ear, and this loss can manifest abruptly or gradually over a span of up to three days.[1] Recognized as a medical emergency, ISSNHL demands immediate attention and intervention. While the estimated incidence stands at around 5 to 20 cases per 100,000 individuals annually, it is worth noting that this figure may potentially be underestimated.[2–4] The precise cause of sudden hearing loss often remains elusive, yet it may be linked to various factors or conditions such as viral infections, abnormal cellular stress responses within the cochlea, immune-mediated mechanisms, breakdown of labyrinthine membranes or barriers, and

vascular occlusion.[5,6] Nevertheless, none of these hypotheses has been conclusively validated. Recently, it has been proposed that sudden hearing loss is particularly related to genetics and sleep pattern.[7]

Sleep-related phenotypes (SRPs) encompass a range of traits or patterns linked to sleep, including sleep quality, duration, timing, presence of sleep disorders like insomnia or sleep apnea, and the broader influence of sleep on overall health. There are documented significant genetic correlations linking insomnia with psychopathological symptoms,[8] sleep duration with dementia,[9] narcolepsy with neurological disorders,[10] sleep disorders with cancer,[11] and sleep apnea with cognitive decline in mild-to-moderate Alzheimer's disease.[12] In recent times, genome-wide association studies (GWASs) have exposed that SRPs are intricate traits influenced by circadian genes, adenosigergic genes, thyroid-specific genes, genes associated with cognitive development and functioning, dopaminergic genes, and immune and clearance genes.[13] These findings shed light on the molecular mechanisms underlying SRPs and the symptoms of associated health conditions.

Previous studies have linked SRPs (sleep duration, obstructive sleep apnea, disrupted sleep, and insomnia) with hearing loss or impairment.[14–17] However, there is no established direct link between SPRs and ISSNHL from a genetic perspective by Mendelian randomization (MR) analysis. Capitalizing on results from large GWASs, our study extended the analysis to characterize the overlapping genetic architecture of SRPs and ISSNHL. Next, we speculated that there could be shared underlying genetic factors that predispose individuals to both sleep disturbances and ISSNHL. Research into these mechanisms can provide insights into the development of medications that can benefit people with ISSNHL through sleep regulation.

Materials and Methods
Data Sources

SRPs were from the UK Biobank (https://ukbiobank.ac.uk/) and FinnGen database. The collected exposure phenotypes included sleeplessness, sleep duration, daytime dozing/sleeping, daytime nap, nap during day, sleep disorders, and sleep apnoea. Trials of ISSNHL were downloaded from the Finngen database (https://r10.finngen.fi/). The diagnostic criteria for ISSNHL are coded as 388.2 in the International Classification of Diseases (ICD)-9, and H91.2 in the ICD-10. ISSNHL is characterized by the following criteria: sudden onset: a rapid loss of hearing, typically occurring within 72 hours; unknown etiology: no apparent pathological factors, such as infection, trauma, or medication effects; unilateral occurrence: usually affects one ear, though bilateral hearing loss may also occur; degree of hearing loss: a threshold shift of at least 30 decibels (dB) across at least three consecutive frequencies, as determined by pure-tone audiometry. A diagnosis of ISSNHL can be made when these criteria are met. All exposure and outcome data were obtained from published data, so our study was retrospective. Dataset information was shown in Table 1. It is important to note that the

Table 1 Phenotypic Information on ISSNHL and SRPs

GWAS ID	Year	Trait	Sample	Ethnicity	SNPs No.
ISSNHL					
finn-b-H8_HL_IDIOP	2021	Sudden idiopathic hearing loss	198,083	European	16,380,424
SRPs					
ukb-b-3957	2018	Sleeplessness	462,341	European	9,851,867
ukb-a-13	2017	Sleeplessness	336,965	European	10,894,596
ukb-b-4424	2018	Sleep duration	460,099	European	9,851,867
ukb-b-5776	2018	Daytime dozing/sleeping	460,913	European	9,851,867
ebi-a-GCST011494	2021	Daytime nap	452,633	European	13,024,091
ukb-a-12	2017	Nap during day	452,633	European	13,024,091
finn-b-SLEEP	2021	Sleep disorders (combined)	216,700	European	16,380,458
finn-b-G6_SLEEPAPNO_INCLAVO	2021	Sleep apnoea	218,792	European	16,380,466

Abbreviations: ISSNHL, idiopathic sudden sensorineural hearing loss; SRPs, sleep-related phenotypes; SNPs, single nucleotide polymorphisms.

validity of MR depends on three key assumptions: (1) the instrumental variables (IVs) must be strongly associated with SRPs; (2) the IVs must not be associated with any confounding variables that affect both SRPs and ISSNHL; (3) the IVs should not directly influence ISSNHL except through its effect on SRPs.

Selection of Genetic Instrumental Variables (GIVs)

Single nucleotide polymorphisms (SNPs) are variations in a single nucleotide base pair of DNA that occur at specific positions in the genome. They can be used to infer causal relationships between exposures and outcomes, serving as GIVs in MR analysis. The conditions for selecting SNPs related to SRP as GIVs include: (1) a genome-wide significant level less than $p < 5 \times 10^{-8}$; (2) linkage disequilibrium r^2 less than 0.001, clumping distance of 10,000 kb; (3) effect allele frequency (EAF) > 0.01; (4) F-statistics (measuring the weak instrument bias) > 10, and F-statistics were computed utilizing the subsequent formula,

$$F = \frac{R^2(N - 2)}{1 - R^2}$$

In this context, R^2 represents the variance of the risk of ISSNHL elucidated by each instrument, while n denotes the sample size of the datasets.[18] The calculation of R^2 was conducted employing the subsequent formula,

$$R^2 = \frac{2 \times MAF \times (1 - MAF) \times beta^2}{2 \times MAF \times (1 - MAF) \times beta^2 + 2 \times MAF \times (1 - MAF) \times n \times SE(beta)^2}$$

MAF signifies the minor allele frequency, the estimated genetic effect on ISSNHL is denoted by the beta value, and the standard error of the genetic effect is represented by the SE(beta) value.[19]

Statistical Analysis

The TwoSampleMR and MRPRESSO of R software version 4.3.2 were used to perform all statistical analysis. The effect of SRPs on ISSNHL was estimated using the Inverse Variance Weighted (IVW) as the primary method, with p-value less than 0.05 indicating a causal relationship. For sensitivity analysis, Weighted mode, Simple mode, Weighted median, and MR Egger methods were used as complementary methods for causal estimation. MR Egger and IVW were used for analyzing heterogeneity, with a p-value of more than 0.05 considered as no heterogeneity. MR Egger's intercept indicated pleiotropy, with a p-value more than 0.05 considered as no pleiotropy. A robust result is needed to satisfy both the absence of heterogeneity and pleiotropy. Odds ratio (OR) values and 95% confidence intervals (CI) were used to represent causal effects between SRPs and ISSNHL. The methods for sensitivity analysis could be used as a reference.

Results

In this study, we totally selected 6 different sleep-related cohorts from the Finngen and UK Biobank databases, as the exposure factors. To analyze the effects of genetically predicted SRPs causing SSHL, the FinnGen data of ISSNHL (outcome) containing 198,083 SNPs was employed. The IVW was used to analyze the causality between SRPs and ISSNHL. The MR Egger and IVW analysis was carried out to analyze the heterogeneity. The pleiotropy was indicated by the Egger's intercept.

Characteristics of Instrumental Variables

The number of GIVs for the causality analysis is suggested in Table 1. The analyzed SRPs-related SNPs were from 8 datasets. There were 39 SNPs related to sleeplessness/insomnia from 462,341 individuals (ukb-b-3957), 27 SNPs related to sleeplessness (ukb-a-13) from 336,965 individuals, 68 SNPs related to sleep duration from 460,099 individuals, 31 SNPs related to daytime dozing/sleeping from 460,913 individuals, 93 SNPs related to daytime nap from 452,633, 48 SNPs related to nap during day from 452,633, 13 SNPs related to sleep disorders (combined) from 408,074 individuals, and 20 SNPs related to sleep apnoea from 412,181 individuals. In forward MR, F statistics ranged between 31.003 and 44.935, all surpassing 10, suggesting minimal risk of weak instrument bias (Table S1).

Causal Association of Daytime Dozing/Sleeping (Narcolepsy) and ISSNHL

The MR analysis was carried out using the IVW method and the forest plot showed the detailed results (Figure 1). The scatter plot illustrated the effect of each sleepless (39 SNPs and 27 SNPs), sleep duration (68 SNPs), daytime dozing/sleeping (31 SNPs), daytime nap (93 SNPs), nap during day (48 SNPs), sleep disorders (combined) (13 SNPs), and sleep apnoea (20 SNPs)-related SNPs on ISSNHL on the log-odds scale (Figure 2).

The results revealed a significant causal relationship between daytime dozing/sleeping and ISSNHL (OR = 0.058; 95% CI: 0.008–0.417; p = 0.005). As shown in Table S1, simple mode methods demonstrated a similar causal association (OR = 0.003; 95% CI: 0.000–0.701; p = 0.045). We further examine whether daytime nap or nap during day-related SNPs is a causal genetic factor for ISSNHL. As analyzed by the IVW method, there was no evidence of significant association between daytime nap-related SNPs and ISSNHL (OR = 1.009; 95% CI: 0.365–2.79; p = 0.986) or nap during day-related SNPs and ISSNHL (OR = 1.212; 95% CI: 0.396–3.707; p = 0.737).

According to risk estimation using two datasets (ukb-b-3957 and ukb-a-13), there were no obvious evidence proving a causal relationship between sleeplessness and ISSNHL (ukb-b-3957-IVW: OR = 1.119; 95% CI: 0.344–3.641; p = 0.852) (ukb-a-13-IVW: OR = 0.830; 95% CI: 0.217–3.173; p = 0.785). As for sleep duration, we found no obvious causal relationship to ISSNHL after analysis by IVW method (OR = 0.761; 95% CI: 0.289–1.998; p = 0.579). The obtained results did not show a causal effect of sleep disorders on the risk of ISSNHL (OR = 1.055; 95% CI: 0.663–1.679; p = 0.820). As for sleep apnoea, the IVW results showed that it was also not significant related to the risk of ISSHNL (OR = 0.923; 95% CI: 0.617–1.379; p = 0.694).

Heterogeneity Analysis

Heterogeneity in MR refers to the variation in the causal effect estimates of SRPs on ISSNHL across different genetic variants used as IVs. These variants might not all estimate the same causal effect size. The MR Egger and IVW methods were used to analyze the heterogeneity. The visualization of heterogeneity was shown in Funnel plots (Figure 3). There was limited evidence of heterogeneity in SRPs-related SNP effect estimates for MR Egger (sleeplessness, p = 0.350 and p = 0.269; sleep duration, p = 0.084; daytime dozing/sleeping, p = 0.585; daytime nap, p = 0.194; nap during day, p = 0.47; sleep disorders, p = 0.846; sleep apnoea, p = 0.227) and IVW methods (sleeplessness, p = 0.388 and p = 0.270; sleep duration, p = 0.096; daytime dozing/sleeping, p = 0.636; daytime nap, p = 0.086; nap during day, p = 0.37; sleep disorders, p = 0.893; sleep apnoea, p = 0.273) (Table S1).

Pleiotropy Analysis

Pleiotropy analysis was performed to confirm that the SNPs utilized as IVs affect the outcome (ISSNHL) via the exposure of interest (SRPs) and not through other phenotypic traits. MR Egger method was utilized, and the pleiotropy was indicated by MR Egger's intercept. MR Egger analysis showed limited evidence of directional pleiotropy for the analyzed SRPs-related SNPs (sleeplessness, p = 0.731 and p = 0.348; sleep duration, p = 0.731; daytime dozing/sleeping, p = 0.994; daytime nap, p = 0.006; nap during day, p = 0.066; sleep disorders, p = 0.834; sleep apnoea, p = 0.765) (Table S1). The leave-one-out plots were produced to assess the influence of individual SNPs on the causal effect of genetically predicted SRPs on ISSNHL (Figure S1).

Discussion

Recently, several findings supported that the polygenic liability for SRPs was related to increased risk of cognitive impairment, and O'Connell et al provided evidence showcasing significant polygenic overlap between SRPs and psychiatric disorders.[20] The present study introduced GWAS summary statistics from SRPs (sleeplessness, sleep duration, daytime dozing, sleep disorders, daytime napping or nap during day, and sleep apnoea) and ISSNHL to illuminate the shared underlying genetic architecture. We found there was limited evidence of effects of sleeplessness, sleep duration, daytime napping or nap during day, sleep disorders (combined), and sleep apnoea on ISSNHL risk. However, lower risk of ISSNHL was found in relation to daytime dozing/sleeping-related SNPs. It is noteworthy that this
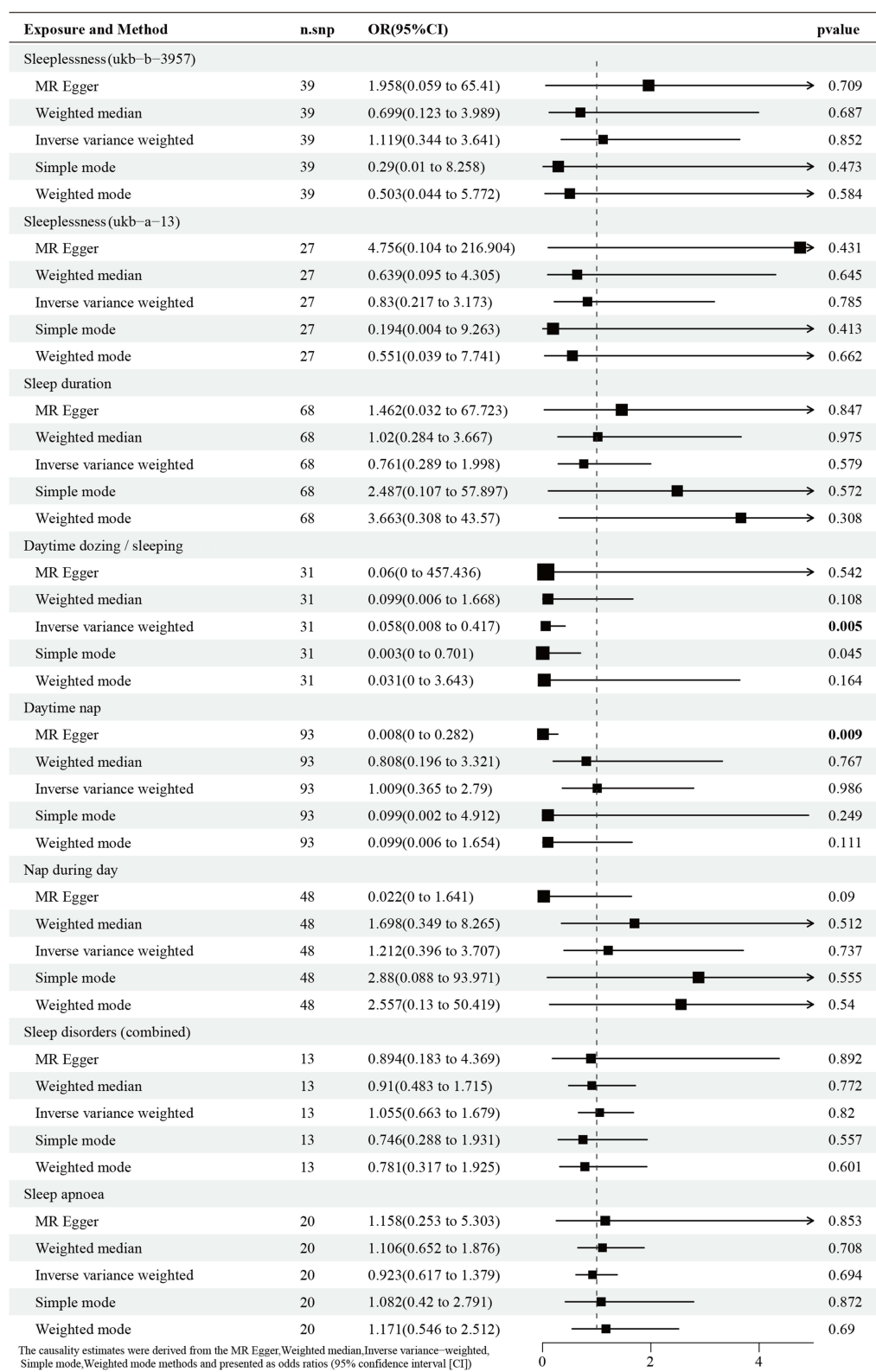
Exposure and Method	n.snp	OR(95%CI)		pvalue
Sleeplessness (ukb–b–3957)				
MR Egger	39	1.958(0.059 to 65.41)		0.709
Weighted median	39	0.699(0.123 to 3.989)		0.687
Inverse variance weighted	39	1.119(0.344 to 3.641)		0.852
Simple mode	39	0.29(0.01 to 8.258)		0.473
Weighted mode	39	0.503(0.044 to 5.772)		0.584
Sleeplessness (ukb–a–13)				
MR Egger	27	4.756(0.104 to 216.904)		0.431
Weighted median	27	0.639(0.095 to 4.305)		0.645
Inverse variance weighted	27	0.83(0.217 to 3.173)		0.785
Simple mode	27	0.194(0.004 to 9.263)		0.413
Weighted mode	27	0.551(0.039 to 7.741)		0.662
Sleep duration				
MR Egger	68	1.462(0.032 to 67.723)		0.847
Weighted median	68	1.02(0.284 to 3.667)		0.975
Inverse variance weighted	68	0.761(0.289 to 1.998)		0.579
Simple mode	68	2.487(0.107 to 57.897)		0.572
Weighted mode	68	3.663(0.308 to 43.57)		0.308
Daytime dozing / sleeping				
MR Egger	31	0.06(0 to 457.436)		0.542
Weighted median	31	0.099(0.006 to 1.668)		0.108
Inverse variance weighted	31	0.058(0.008 to 0.417)		**0.005**
Simple mode	31	0.003(0 to 0.701)		0.045
Weighted mode	31	0.031(0 to 3.643)		0.164
Daytime nap				
MR Egger	93	0.008(0 to 0.282)		**0.009**
Weighted median	93	0.808(0.196 to 3.321)		0.767
Inverse variance weighted	93	1.009(0.365 to 2.79)		0.986
Simple mode	93	0.099(0.002 to 4.912)		0.249
Weighted mode	93	0.099(0.006 to 1.654)		0.111
Nap during day				
MR Egger	48	0.022(0 to 1.641)		0.09
Weighted median	48	1.698(0.349 to 8.265)		0.512
Inverse variance weighted	48	1.212(0.396 to 3.707)		0.737
Simple mode	48	2.88(0.088 to 93.971)		0.555
Weighted mode	48	2.557(0.13 to 50.419)		0.54
Sleep disorders (combined)				
MR Egger	13	0.894(0.183 to 4.369)		0.892
Weighted median	13	0.91(0.483 to 1.715)		0.772
Inverse variance weighted	13	1.055(0.663 to 1.679)		0.82
Simple mode	13	0.746(0.288 to 1.931)		0.557
Weighted mode	13	0.781(0.317 to 1.925)		0.601
Sleep apnoea				
MR Egger	20	1.158(0.253 to 5.303)		0.853
Weighted median	20	1.106(0.652 to 1.876)		0.708
Inverse variance weighted	20	0.923(0.617 to 1.379)		0.694
Simple mode	20	1.082(0.42 to 2.791)		0.872
Weighted mode	20	1.171(0.546 to 2.512)		0.69

The causality estimates were derived from the MR Egger, Weighted median, Inverse variance–weighted, Simple mode, Weighted mode methods and presented as odds ratios (95% confidence interval [CI])

(x-axis: 0   2   4)

Figure 1 Forest plot of the potential impacts of SRPs-related SNPs on ISSNHL. The analyzed SRPs included sleeplessness (ukb-b-3957 and ukb-a-13), sleep duration, daytime dozing/sleeping, daytime nap, nap during day, sleep disorders (combined), and sleep apnoea.
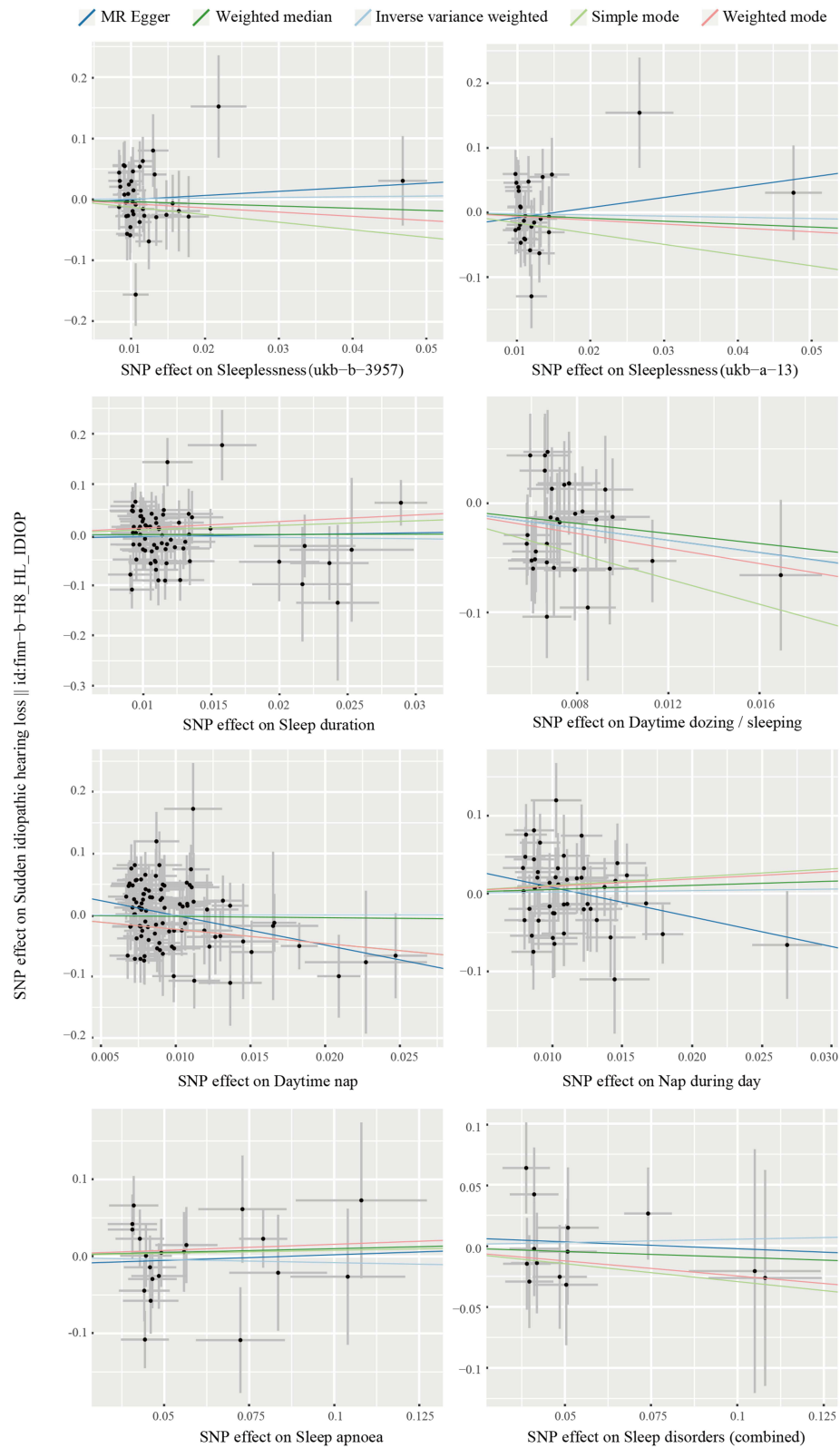
Figure 2 Scatter plot demonstrates the effect of each SRPs-related genetic variant on ISSNHL on the log-odds scale. The analyzed SRPs included sleeplessness (ukb-b-3957 and ukb-a-13), sleep duration, daytime dozing/sleeping, daytime nap, nap during day, sleep disorders (combined), and sleep apnoea. Each dot represents effect sizes of each SNP on ISSNHL (y-axis) and SRPs (x-axis). Regression slopes show the estimated causal effect of SRPs on ISSNHL.
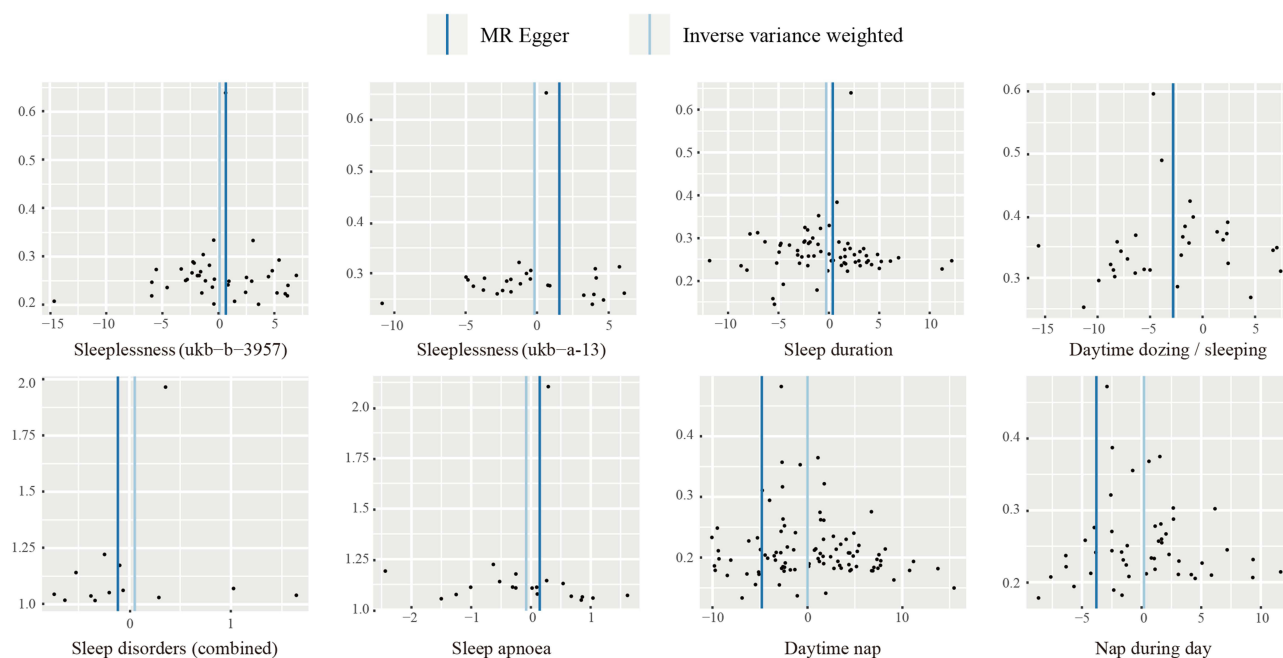
Figure 3 Funnel plot of the causal effect of SRPs-related SNPs on ISSNHL. The analyzed SRPs included sleeplessness/insomnia (ukb-b-3957 and ukb-a-13), sleep duration, daytime dozing/sleeping, daytime nap, nap during day, sleep disorders (combined), and sleep apnoea (including avohilmo).

is the inaugural two-sample MR study examining the causal relation between SRPs and ISSNHL from a genetic perspective.

There are several ideas concerning the pathogenesis of ISSNHL that include some of the autoimmune causes such as vascular compromise, chronic inflammation, and viral infection. Several studies have examined the association between SRPs and hearing loss, as well as hearing impairment.[14–17] In adults with severe obstructive sleep apnea–hypopnea syndrome (OSA-HS), high-frequency hearing loss was detected.[21]

Chen et al revealed that ISSNHL could potentially be one of the auditory complications linked to OSA.[22] Subsequently, Li et al found that individuals at high risk for OSA had d 1.64-fold increased risk of hearing impairment compared to those at low risk for OSA (95% CI: 1.02–2.69, P < 0.05).[23] In two cross-sectional studies, noise exposure is related with poorer hearing, and sleep duration ≥8 hours/night was negatively correlated with hearing loss in the Chinese participants, especially when exposed to noise.[24] In a longitudinal study conducted among a Japanese general population, individuals with hearing loss at 4,000 hz at baseline demonstrated a significantly higher risk of longer sleep duration (≥8 hours) after 8 years.[25]

A large population-based UK Biobank study reported that a heightened risk of hearing loss may be associated with sleep complaints (evening preference, difficulty getting up in the morning, sleeplessness, daytime sleepiness, and snoring at night).[26] Increased risks of ISSNHL have been observed among participants sleeping fewer than 7 hours per night (OR = 1.61, 95% CI = 1.09–2.37), which have been confirmed in a case–control study.[27] In addition, 61.8% of patients with ISSNHL suffered from insomnia prior to the insult of hearing loss, according to Yang et al.[28] Instead, among older adults, longer sleep duration (more than 8 hours) is marginally associated with poorer high-frequency hearing.[29] As indicated by a representative and prospective cohort study, a heightened risk of subjective hearing impairment among middle-aged and older adults was linked to insufficient nocturnal sleep, whereas moderate napping may reduce hearing loss risk.[30] Summarily, maintaining stable sleep patterns within the recommended duration may serve as a beneficial strategy for averting the onset of hearing loss.

From a genetic perspective, the dysregulation of circadian clock genes may explain why the patients with ISSNHL exhibit lower sleep quality and more disruptive modes compared to healthy controls without hearing loss.[31] Many researchers believe that the initial degree of hearing loss is a crucial factor in determining prognosis.[32] A correlation

analysis of nine circadian rhythm gene expressions was conducted in 22 patients with severe sudden sensorineural hearing loss (SSNHL, hearing threshold >90 dB HL) and 16 patients with non-severe SSNHL (hearing threshold ≤90 dB HL).[28] However, no significant differences were observed between the two groups. Thus, the sleep phenotype may have a weak correlation with the severity of hearing loss, with significant differences only between diseased and healthy groups. Additionally, we found no other study regarding the relationship between sleep phenotype and hearing impairment severity. However, the genetic basis of the causal relationship between ISSNHL and a broad spectrum of sleep behaviors is still warranted. As a genetic technique, MR method utilizes the genetic variants related to the exposure of interest to conclude the causal pathways between an outcome and exposure. Previous studies have utilized MR analysis to explore the causal relationship between ISSNHL and C-reactive protein,[33] free thyroxine,[34] triglyceride-glucose, blood glucose,[35] and high-density lipoprotein cholesterol.[36] However, these studies only examined the relationship between ISSNHL and biochemical parameters. From our MR results, there was no clear causal relationship between sleep disorders (combined) and ISSNHL. More specifically, MR analysis showed no significant causal effects of sleeplessness, sleep duration, or sleep apnoea on ISSNHL.

Daytime dozing or sleeping refers to the propensity or tendency to nod off or fall asleep during daylight hours despite intending to stay awake. This inclination is distinct from subjective feelings of tiredness or fatigue, which may not necessarily result in drowsiness. However, the implicit connotation of the term "daytime nap" extends beyond merely occurring during daytime hours; it encompasses sleep that is deliberate, managed, premeditated, and distinctly demarcated with a clear start and finish. From our results, it should be noted that daytime dozing or sleeping was linked to a decreased risk of ISSNHL. On these grounds, we considered that compared to excessive daytime dozing, daytime napping may be linked with a favorable consequence of ISSNHL, considering its intentionality and various benefits including improved mood, alertness, and cognitive function. Unlike napping, dozing is often unplanned and may occur involuntarily during the day.

In modern society, consolidated daytime napping is encouraged in sleep-deprived population, presumably to address daytime sleepiness. The benefits of daytime napping remain controversial because of napping duration and frequency for instance, in Alzheimer's disease.[37,38] From the genetic perspective, MR results suggested that daytime napping or napping during day was not associated with the risk of ISSNHL. This may be attributed to the inherent limitations of the study, wherein we encounter unavoidable instances of unspecific or incomplete questionnaire data obtained from the GWAS. Here, we were unable to obtain the detailed information about habitual daytime napping, such as duration, frequency, or timing. This may contribute to the results that daytime napping showed no genetic effects on ISSNHL risk.

Common treatments for ISSNHL often involve systemic and/or trans-tympanic corticosteroids to mitigate inflammation or vasoactive agents like prostaglandins to improve cochlear blood flow.[39] Around 60% of ISSNHL patients undergo some level of spontaneous remission.[40] Recent studies suggest that prompt intervention for sleep-related phenotypes (such as obstructive sleep apnea, insomnia, and sleep disturbances) might effectively enhance the auditory health of ISSNHL patients.[22,28,41] After a combined analysis of genetic factors based on MR method, we proposed a phenotypic relationship between daytime dozing and ISSNHL. Meanwhile, we presented an underlying mechanism of ISSNHL that these dysregulated genes may be implicated in central nervous system and neurotransmitters. However, such a putative causal mechanism requires further experimental validation. According to the results of this study, ISSNHL may be alleviated by moderate daytime napping that may be dependent on napping duration, frequency, or timing.

In any case, although these findings may not encapsulate the complete genetic etiology of these traits, they offer valuable insights and lay the groundwork for deep exploration into the shared genetic architecture of SRPs and ISSNHL. Here, we found that 31 independent SNPs from daytime dozing suggested potential functions relevant to ISSNHL. However, some limitations need to be taken into consideration. First, this study did not collect information on duration, frequency and timing of daytime dozing or napping because of the unspecific or incomplete questionnaire data obtained from the GWAS. Incorporating this data in future research could facilitate the identification of relevant genetic associations. Second, the participants in the GWAS study were predominantly of European descent. Consequently, it is uncertain whether these findings can be reliably generalized to individuals from other ethnic backgrounds. Third, this study analyzed SNPs-related ISSNHL and several SRPs that may cause the risks of false discovery. Consequently, independent replications are necessary, followed by investigation of molecular mechanisms.

Summarily, this study provided evidence that SRPs (sleeplessness, sleep duration, daytime dozing, daytime napping, sleep disorders, and sleep apnoea) shared a genetic basis with ISSNHL. This MR analysis found that daytime napping was associated with ISSNHL, and daytime napping might be a protective factor for ISSNHL from a genetic perspective. This phenomenon may provide a novel and meaningful therapeutic target for ISSNHL based on sleep medicine. However, as most participants in the GWAS studies were of European descent, this assumed causal relationship has limitations and requires further experimental validation to assess its applicability across different populations.

Data Sharing Statement

All data generated or analysed during this study are included in this article and its supplementary information files.

Ethics Approval and Informed Consent

This study complies with the Declaration of Helsinki. The research data of study were from the FinnGen database (https://r10.finngen.fi/) and UK Biobank (https://ukbiobank.ac.uk/). Because the information in the databases does not require the patient's explicit consent, the ethical approval was waived by the Ethics Committee of Taihe Hospital, Hubei University of Medicine (Approval No.: 2024KS100). The informed patient consent is not required due to the retrospective nature of the study.

Consent for Publication

All authors have agreed to the publication of this study.

Author Contributions

D.L. and Z.Y. designed research. Y.L., F.Z., C.G., J.L. and X.Z. contributed to investigation and data collection. M.L. and J.H. analyzed data and drafted the initial manuscript. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Disclosure

The authors declare no conflicts of interest in this work.

References

1. Jung WW, Hoegerl C. Sudden sensorineural hearing loss and why it's an emergency. *Cureus*. 2022;14:e21418.
2. Nakashima T, Sato H, Gyo K, et al. Idiopathic sudden sensorineural hearing loss in Japan. *Acta Otolaryngol*. 2014;134:1158–1163. doi:10.3109/00016489.2014.919406
3. Kitoh R, Nishio SY, Ogawa K, et al. Nationwide epidemiological survey of idiopathic sudden sensorineural hearing loss in Japan. *Acta Otolaryngol*. 2017;137:S8–s16. doi:10.1080/00016489.2017.1297537
4. Im GJ, Park E. Sudden sensorineural hearing loss. *Hanyang Med Rev*. 2015;35:92–96. doi:10.7599/hmr.2015.35.2.92
5. Yamada S, Kita J, Shinmura D, et al. Update on findings about sudden sensorineural hearing loss and insight into its pathogenesis. *J Clin Med*. 2022;12(1):11. doi:10.3390/jcm12010011
6. Xie W, Karpeta N, Tong B, et al. Etiological analysis of patients with sudden sensorineural hearing loss: a prospective case-control study. *Sci Rep*. 2023;13:5221. doi:10.1038/s41598-023-32085-7
7. Liu M, Zhang H, Wang Z, et al. Independent and combined associations of sleep duration, bedtime, and polygenic risk score with the risk of hearing loss among middle-aged and old Chinese: the Dongfeng-Tongji cohort study. *Research*. 2023;6:0178. doi:10.34133/research.0178
8. Fila-Witecka K, Malecka M, Senczyszyn A, et al. Sleepless in solitude-insomnia symptoms severity and psychopathological symptoms among university students during the COVID-19 pandemic in Poland. *Int J Environ Res Public Health*. 2022;20:19. doi:10.3390/ijerph20010019

9. Sabia S, Fayosse A, Dumurgier J, et al. Association of sleep duration in middle and old age with incidence of dementia. *Nat Commun*. 2021;12:2289. doi:10.1038/s41467-021-22354-2

10. Maestri M, Romigi A, Schirru A, et al. Excessive daytime sleepiness and fatigue in neurological disorders. *Sleep Breath*. 2020;24:413–424.

11. Mogavero MP, DelRosso LM, Fanfulla F, Bruni O, Ferri R. Sleep disorders and cancer: state of the art and future perspectives. *Sleep Med Rev*. 2021;56:101409. doi:10.1016/j.smrv.2020.101409

12. Jorge C, Targa A, Benítez ID, et al. Obstructive sleep apnoea and cognitive decline in mild-to-moderate alzheimer's disease. *Eur Respir J*. 2020;56:1.

13. Garfield V. Sleep duration: a review of genome-wide association studies (GWAS) in adults from 2007 to 2020. *Sleep Med Rev*. 2021;56:101413. doi:10.1016/j.smrv.2020.101413

14. Long L, Tang Y. Association between sleep duration and hearing threshold shifts of adults in the United States: national health and nutrition examination survey, 2015-2016. *BMC Public Health*. 2023;23:2305. doi:10.1186/s12889-023-17204-3

15. Kayabasi S, Hizli O, Yildirim G. The association between obstructive sleep apnea and hearing loss: a cross-sectional analysis. *Eur Arch Otorhinolaryngol*. 2019;276:2215–2221. doi:10.1007/s00405-019-05468-8

16. Clarke NA, Hoare DJ, Killan EC. Evidence for an association between hearing impairment and disrupted sleep: scoping review. *Am J Audiol*. 2019;28:1015–1024. doi:10.1044/2019_AJA-19-0026

17. Aazh H, Heinonen-Guzejev M, Moore BCJ. The relationship between hearing loss and insomnia for patients with tinnitus(). *Int J Audiol*. 2020;59:68–72. doi:10.1080/14992027.2019.1654621

18. Burgess S, Thompson SG. Avoiding bias from weak instruments in Mendelian randomization studies. *Int J Epidemiol*. 2011;40:755–764. doi:10.1093/ije/dyr036

19. Burgess S, Dudbridge F, Thompson SG. Combining information on multiple instrumental variables in Mendelian randomization: comparison of allele score and summarized data methods. *Stat Med*. 2016;35:1880–1906. doi:10.1002/sim.6835

20. O'Connell KS, Frei O, Bahrami S, et al. Characterizing the genetic overlap between psychiatric disorders and sleep-related phenotypes. *Biol Psychiatry*. 2021;90:621–631. doi:10.1016/j.biopsych.2021.07.007

21. Li X, Chen WJ, Zhang XY, et al. Inner ear function in patients with obstructive sleep apnea. *Sleep Breath*. 2020;24:65–69. doi:10.1007/s11325-019-01891-7

22. Chen CK, Shen SC, Lee LA, et al. Idiopathic sudden sensorineural hearing loss in patients with obstructive sleep apnea. *Nat Sci Sleep*. 2021;13:1877–1885. doi:10.2147/NSS.S331880

23. Li Y, Wang X, Cui J, et al. Increasing obstructive sleep apnea risk is associated with hearing impairment in middle-aged Chinese men-A cross-sectional study. *PLoS One*. 2022;17:e0268412. doi:10.1371/journal.pone.0268412

24. Wu E, Ni J, Zhu Z, et al. Association of sleep duration and noise exposure with hearing loss among Chinese and American adults: two cross-sectional studies. *BMJ Open*. 2022;12:e062535. doi:10.1136/bmjopen-2022-062535

25. Nakajima K, Kanda E, Hosobuchi A, Suwa K. Subclinical hearing loss, longer sleep duration, and cardiometabolic risk factors in Japanese general population. *Int J Otolaryngol*. 2014;2014:218218. doi:10.1155/2014/218218

26. Yévenes-Briones H, Caballero FF, Estrada-deLeón DB, et al. Duration and quality of sleep and risk of self-reported hearing loss: the UK biobank study. *Ear Hear*. 2023;44:1182–1189. doi:10.1097/AUD.0000000000001360

27. Nakamura M, Aoki N, Nakashima T, et al. Smoking, alcohol, sleep and risk of idiopathic sudden deafness: a case-control study using pooled controls. *J Epidemiol*. 2001;11:81–86. doi:10.2188/jea.11.81

28. Yang CH, Hwang CF, Lin PM, et al. Sleep disturbance and altered expression of circadian clock genes in patients with sudden sensorineural hearing loss. *Medicine*. 2015;94:e978. doi:10.1097/MD.0000000000000978

29. Jiang K, Spira AP, Reed NS, Lin FR, Deal JA. Sleep characteristics and hearing loss in older adults: the national health and nutrition examination survey 2005-2006. *J Gerontol a Biol Sci Med Sci*. 2022;77:632–639. doi:10.1093/gerona/glab214

30. Cui X, Lu Z, Guo X, et al. Association of nocturnal sleep duration and midday napping with subjective poor hearing among middle-aged and older adults in China. *Front Public Health*. 2023;11:1160294. doi:10.3389/fpubh.2023.1160294

31. Lee SY, Choe G, Lee HS, et al. Sleep disturbance and dysregulation of circadian clock machinery in sudden sensorineural hearing loss. *Acta Otolaryngol*. 2023;143:692–698. doi:10.1080/00016489.2023.2244010

32. Wilson WR, Byl FM, Laird N. The efficacy of steroids in the treatment of idiopathic sudden hearing loss. A double-blind clinical study. *Arch Otolaryngol*. 1980;106:772–776. doi:10.1001/archotol.1980.00790360050013

33. Zhou T, Chen M, Yuan Z, et al. Inflammatory markers and the risk of idiopathic sudden sensorineural hearing loss: a Mendelian randomization study. *Front Neurol*. 2023;14:1111255. doi:10.3389/fneur.2023.1111255

34. Strich D, Karavani G, Edri S, Gillis D. TSH enhancement of FT4 to FT3 conversion is age dependent. *Eur J Endocrinol*. 2016;175:49–54. doi:10.1530/EJE-16-0007

35. Wang Y, Liu H, Nie X, Lu N, Wang X. L− shaped association of triglyceride glucose index and sensorineural hearing loss: results from a cross-sectional study and Mendelian randomization analysis. *Front Endocrinol*. 2024;15:1339731. doi:10.3389/fendo.2024.1339731

36. Pu K, Li L, Qiu Y, Song H. Lipids and sudden sensorineural hearing loss: a bidirectional two-sample Mendelian randomization analysis. *Auris Nasus Larynx*. 2023;51:365–370. doi:10.1016/j.anl.2023.11.006

37. Cross N, Terpening Z, Rogers NL, et al. Napping in older people 'at risk' of dementia: relationships with depression, cognition, medical burden and sleep quality. *J Sleep Res*. 2015;24:494–502. doi:10.1111/jsr.12313

38. Li J, Cacchione PZ, Hodgson N, et al. Afternoon napping and cognition in Chinese older adults: findings from the china health and retirement longitudinal study baseline assessment. *J Am Geriatr Soc*. 2017;65:373–380. doi:10.1111/jgs.14368

39. Chandrasekhar SS, Tsai Do BS, Schwartz SR, et al. Clinical practice guideline: sudden hearing loss (Update). *Otolaryngol Head Neck Surg*. 2019;161:S1–s45. doi:10.1177/0194599819859885

40. Chaushu H, Ungar OJ, Abu Eta R, et al. Spontaneous recovery rate of idiopathic sudden sensorineural hearing loss: a systematic review and meta-analysis. *Clin Otolaryngol*. 2023;48:395–402. doi:10.1111/coa.14036

41. Yeo CD, Yeom SW, You YS, Kim JS, Lee EJ. Association of sudden sensorineural hearing loss with increased risk of insomnia: a nationwide population-based cohort study. *J Clin Sleep Med*. 2022;18:1335–1342. doi:10.5664/jcsm.9864