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Causal Associations Between Sleep Traits and Low Grip Strength: A Bidirectional Mendelian Randomization Study

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Background: Sleep disorders and low grip strength often co-occur clinically and are geriatric symptoms that cause significant socioeconomic burden. Previous observational studies have found an association between sleep behaviors and grip strength, but the causal relationship remains unclear.

Purpose: With the Mendelian randomization (MR) approach, the study aimed to determine the causal association between sleep traits (sleep duration, insomnia, daytime napping, sleep-wake disorders, chronotype) and low grip strength.

Methods: The study used genetic variants from the genome-wide association study (GWAS) archived in UK Biobank and FinnGen. We assessed the potential causal relationship between sleep behaviors and grip strength using inverse variance weighting (IVW), weighted median (WM), and MR-Egger. Additionally, we performed sensitivity analyses using Cochran's Q test, MR Egger Intercept test, funnel plots, and leave-one-out method.

Results: We found that sleep duration is causally negatively associated with low grip strength (OR = 0.618, 95% CI = 0.424–0.900, P = 0.012). Sleep-wake disorders have a positive association with low grip strength (OR = 1.018, 95% CI = 1.002–1.034, P = 0.029). Reversely, high low grip strength risk was causally associated with increased daytime napping (OR = 1.018, 95% CI = 1.004–1.032, P = 0.011).

Conclusion: The study revealed causal associations between sleep duration, sleep-wake disorders, and low grip strength. Understanding their relationship helps in early clinical intervention to improve the life quality of the elderly.

Keywords: sleep, low grip strength, Mendelian randomization

Introduction

Low grip strength is a common debilitating dysfunction, and not only predicts a decline in muscle mass and function, but is also associated with falls and reduced mobility.[1] Meta-analyses have demonstrated that low grip strength elevates the risk of a variety of diseases, including cardiovascular diseases,[2] type 2 diabetes,[3] obesity,[4] and chronic obstructive pulmonary disease.[5] In addition, multiple previous studies support the association of weak grip strength with increased all-cause mortality in the general and old population.[6–8]

Sleep quality is a key evaluator of sleep, and sleep quality is recognized as one of the key factors affecting grip strength.[9] Previous studies have demonstrated that poor sleep quality was associated with decreased muscle mass and decreased grip strength.[10,11] This may be due to the fact that poor sleep quality affects the metabolism of hormones, among which insulin-like growth factor 1 (IGF-1) is a central factor to muscle protein synthesis.[12] Sleep patterns are also significant for sleep health,[13] yet sleep patterns change with age independent of other factors such as comorbidities and medications.[14] Several prospective cohorts have also examined the strong correlation between circadian rhythm disruption and skeletal muscle damage in humans.[15,16] Epidemiological studies have shown that poor sleep quality is prevalent

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in the old, with about half or more complaining about their sleep problems.[17,18] Therefore, it is essential to explore the effects of sleep on grip strength levels in the elderly.

Most of the current studies on sleep and grip strength are observational and are susceptible to confounding factors, making it difficult to confirm a causal relationship. In addition, most of these studies utilized cross-sectional designs, so it is difficult to infer causality and the direction of causality. To strengthen causal inference, we apply a novel genetically informed method. Mendelian randomization (MR) is an approach that uses genetic variants as instruments to estimate the causal effects of the exposure on outcome.[19] Since genotypes are randomly assigned from parents to offspring, they are not subject to reverse causality and confounding factors.[20]

As mentioned earlier, there may be a correlation between sleep traits and low grip strength, but evidence of causality is lacking. This study aimed to investigate the causal relationship between several sleep traits and low grip strength and shed light on the causal directions, providing a theoretical basis for clinical improvement of life quality in the elderly.

Materials and Methods

Study Design

We used a bidirectional, two-sample MR design to examine the relationship between sleep traits and low grip strength. Analyses were conducted using sleep traits: (i) as the exposure to assess whether sleep traits have a causal effect on low grip strength and sleep traits, and (ii) as the outcome to assess whether low grip strength has a causal effect on sleep traits. Summary data for all exposure and outcome variables were obtained from large-scale genome-wide association studies (GWAS) of individuals of European ancestry. We assessed the role of five different sleep traits on low grip strength. These included sleep duration, insomnia, sleep-wake disorders, daytime napping, and chronotype. In addition, Figure 1 summarizes the core MR assumptions for the study design.[21]

This study is reported as per the Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization (STROBE-MR) guideline (Supplementary Table S1).[22] All original studies included in the GWAS datasets were ethically approved, and informed consent was obtained from all participants.

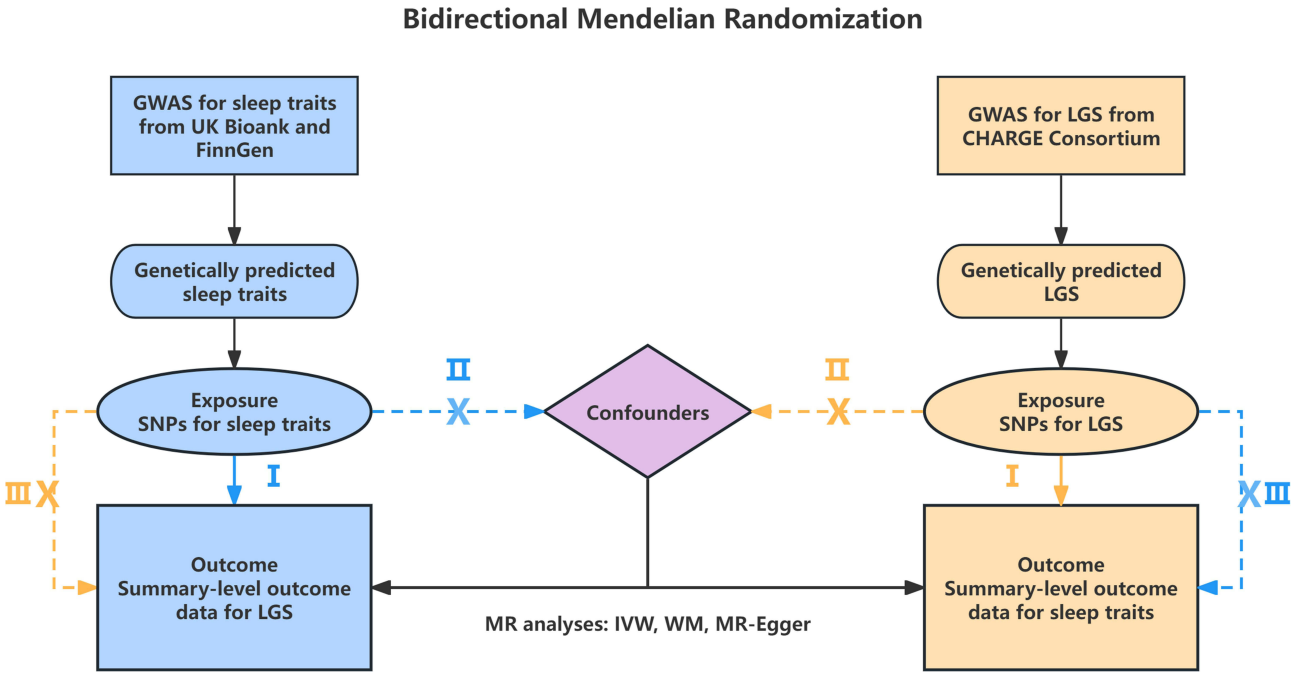

Figure 1 Study design and Mendelian Randomisation (MR) fundamental assumptions. (I) The genetic variant must be associated with the exposure. The use of weak IVs can bias MR estimates towards the confounded observational estimate in MR settings. (II) The genetic instruments should not be associated with confounders of the exposure-outcome relationship. (III) Any association between the genetic instruments and the outcome must be via the exposure.

Data Sources

Summary data for five sleep traits, including sleep duration (n = 460,099),[23,24] insomnia (n = 307,751),[25] sleep-wake disorders (n = 305,359),[25] daytime napping (n = 452,633),[26] and chronotype (n = 449,734),[27] were obtained from GWAS studies in the UK Biobank and FinnGen (R7 release). The UK Biobank is a large-scale biomedical database containing genetic and health information from approximately half a million United Kingdom participants aged between 40 and 69. The FinnGen research project collected biological samples from 500,000 participants with a median age of 63 years in Finland over six years. The details of sleep traits data sources used in this study are in Table 1.

For low grip strength, the summary data were obtained from a recent GWAS meta-analysis on muscle weakness.[28] The study included 48,596 old adults (aged from 60 to 90 years) of European ancestry with the European Working Group on Sarcopenia in Older People definition (grip strength < 30 kg Male; < 20 kg Female), adjusted for sex, age, and technical covariates.

Genetic Instruments Selection

As genetic instruments, single nucleotide polymorphisms (SNPs) associated with each trait at genome-wide significance ($P < 5\times10^{-8}$) were extracted. For phenotypes with insufficient SNPs reaching the threshold, we selected instruments with a relaxed threshold ($P < 5\times10^{-5}$). Then, SNPs were clumped to obtain independent loci using a threshold of linkage disequilibrium (LD) $r^2 < 0.001$ and a distance of 10,000 kb. When SNPs for the exposure were unavailable in the outcome phenotype data, we replaced them with proxy SNPs in high-linkage disequilibrium ($r^2 > 0.800$) using the LDlink (https://ldlink.nih.gov/?tab=ldproxy). Furthermore, we removed SNPs strongly associated with outcome ($P < 5\times10^{-8}$). Then, we considered several factors to be potential confounders of the association between sleep traits and grip strength: body mass index (BMI), fracture, poor appetite, bone mineral density, waist circumference, dementia, insulin resistance, strenuous physical activity, oxidative protein damage, age at menarche, depression, fall status, and cardiorespiratory. Furthermore, we removed SNPs with potential reverse causal effects by the Steiger filtering (Steiger $P > 0.05$).[29] Finally, to quantify the strength of instrumental variables (IVs), we calculated F-statistics. F-statistics > 10 suggests that the combined SNPs in our MR model are a sufficiently strong instrument to explain phenotypic variants.[30] The list of instruments for each phenotype is shown in Supplementary Table S2.

Statistical Analyses

This study used the random-effect inverse-variance weighted (IVW) method to estimate overall causal effects. It is considered the most predictive method, assuming no directional pleiotropy.[31] Then, we conducted the weighted-Median method, which gives a credible estimate of effect when up to half of the weight is derived from valid IVs.[32] In addition, the MR-Egger method provided a causal estimate using the slope of the weighted linear regression against horizontal pleiotropy.[33]

We conducted several sensitivity analyses to further estimate the MR results' robustness. Cochran's Q statistic evaluated Heterogeneity across IVs.[34] We performed the MR-Egger intercept test to assess horizontal pleiotropy.[35] The stability of these genetic variants is measured by funnel plots and leave-one-out method.[33] In addition, Mendelian Randomization Pleiotropy Residual Sum and Outlier (MR-PRESSO) was used to identify potential pleiotropic outliers and provided estimates after excluding these outlier SNPs.[35] Moreover, we looked up each instrument SNP and their proxies ($r^2 > 0.80$) in the PhenoScanner database to assess associations with potential confounding ($P < 1 \times 10^{-5}$). We assessed the effects of manually removing these SNPs from the MR analysis to rule out possible pleiotropic effects. Finally, because some exposure data were derived from UK Biobank and outcome data were derived from several GWAS meta-analysis results, there is some inevitable partial sample overlap. We used MRlap method to assess the potential resulting bias.[36] If the difference between the raw and adjusted IVW effects was insignificant ($P > 0.05$), the raw IVW estimates could be trusted. Conversely, if we found the difference significant ($P < 0.05$), we prioritize the adjusted IVW estimates as it is not affected by sample overlap.

Table 1 Details of GWAS Datasets About Sleep Traits

Exposures	Type	Definition	Sample size	Populations	Consortium	Sources
Sleep duration	Categorical Ordered	Reported in whole hours: Short sleep duration (<6 vs 7 or 8 h); Long sleep duration (>9 vs 7 or 8 h)	460,099	European	MRC-IEU (UKB)	https://gwas.mrcieu.ac.uk/datasets/ukb-b-4424/[23]
Insomnia	Categorical Ordered	Self-reported: usually;Sometimes or rarely; Never	307,751	European	FinnGen	Kurki MI et al[25]
Sleep-wake disorders	Categorical Ordered	Sleep-wake phase disorder; Delayed sleep-wake phase disorder	305,359	European	FinnGen	Kurki MI et al[25]
Daytime napping	Categorical Ordered	Self-reported: Never/Rarely; Sometimes; Always	452,633	European	UKB	Dashti HS et al[26]
Chronotype	Categorical Ordered	Self-report: Definitely morning; More morning than evening; Do not know; More evening than morning; Definitely evening	449,734	European	UKB	Jones SE et al[27]

Abbreviations: UKB, UK biobank; MRC-IEU, Medical Research Center-Integrative Epidemiology Center (UK Bristol).

All statistical analyses were conducted in the R software (version 4.2.2) using the TwoSampleMR, MR-PRESSO, and MRlap packages.[37] Effect estimates are reported in odds ratio (OR) with 95% confidence intervals (CI), and $P < 0.05$ was considered statistically significant.

Results

Causal Effects of Sleep Traits and Low Grip Strength

The F-statistics for five sleep traits were above of 10 (12.09–32.67), indicating that the selected IVs has enough power to avoid potential weak instruments bias effectively.[38,39] The summary results of all the analyses for sleep traits on low grip strength are shown in Figure 2 and Table 2.

We obtained 36 significant independent SNPs as IVs for sleep duration, excluding 24 confounder-associated variants, 1 incompatible SNP, and 10 palindromic SNPs. The IVW result showed that sleep duration was negatively associated with low grip strength (OR = 0.62, 95% CI = 0.42–0.90, $P = 0.012 < 0.05$) (Figure 3). The weighted median and MR-Egger results showed the same direction as those of IVW (OR < 1.00). Moreover, the MR-Egger

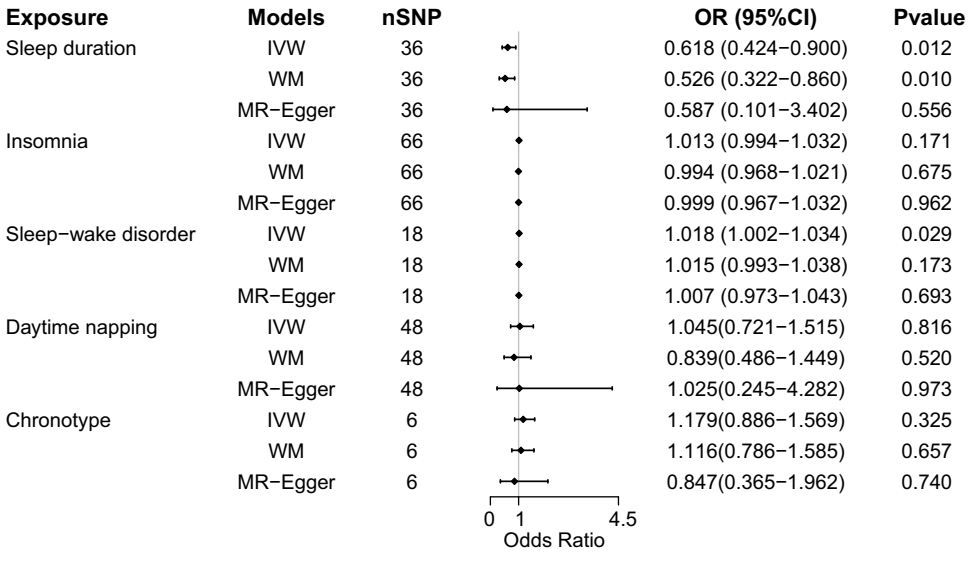

Figure 2 Forest plot for Mendelian randomization (MR) effect estimates with IVW, WM, and MR-Egger: causal effects for sleep traits on low grip strength. OR: odds ratio; CI: confidence interval; IVW: inverse-variance weighted; WM: weighted median; nSNP: number of single nucleotide polymorphisms. Horizontal lines represent 95% confidence interval.

Table 2 MR Analyses with Heterogeneity, Sensitivity, and Pleiotropy Evaluation for Causal Effects of Sleep Traits on LGS

Exposure	Outcome	SNPs	Cochran's Q test (P)	MR Egger Intercept (P)	MR		
					Method	OR (95% CI)	P
Sleep duration	LGS	36	0.193	0.954	IVW	0.618 (0.424–0.900)	0.012
					WM	0.526 (0.322–0.860)	0.010
					MR-Egger	0.587 (0.101–3.402)	0.556
Insomnia	LGS	66[a]	0.390	0.321	IVW	1.013 (0.994–1.032)	0.171
					WM	0.994 (0.968–1.021)	0.675
					MR-Egger	0.999 (0.967–1.032)	0.962
Sleep-wake disorders	LGS	18[a]	0.408	0.525	IVW	1.018 (1.002–1.034)	0.029
					WM	1.015 (0.993–1.038)	0.173
					MR-Egger	1.007 (0.973–1.043)	0.693
Daytime napping	LGS	48	0.701	0.978	IVW	1.045 (0.721–1.515)	0.816
					WM	0.839 (0.492–1.431)	0.520
					MR-Egger	1.025 (0.245–4.281)	0.973
Chronotype	LGS	6[a]	0.910	0.500	IVW	1.161 (0.862–1.563)	0.325
					WM	1.083 (0.763–1.538)	0.657
					MR-Egger	0.855 (0.361–2.026)	0.740

Notes: [a]Using $P < 5\times10^{-5}$ threshold when the eligible single nucleotide polymorphism (SNP) numbers were insufficient (nSNP <3).
Abbreviations: LGS, Low grip strength; SNP, Single-nucleotide polymorphism; MR, Mendelian Randomization; OR, odds ratio; IVW, Inverse-Variance Weighted; WM, Weighted Median.

intercept test showed no significant horizontal pleiotropy ($P > 0.05$), and MR-PRESSO did not identify any pleiotropic outliers. Funnel plot and leave-one-out analysis showed no single SNP biased effect estimates (Supplementary Figures S1 and S2). MRlap analysis showed no significant difference between the raw and adjusted IVW estimates ($P > 0.05$).

For sleep-wake disorders, we got 18 IVs using relaxed P-value thresholds ($P < 5\times10^{-5}$) after removing 1 palindromic SNP. Notably, for the large-scale GWAS study on sleep-wake disorders (n = 305,359) that we used, relaxing the P-value

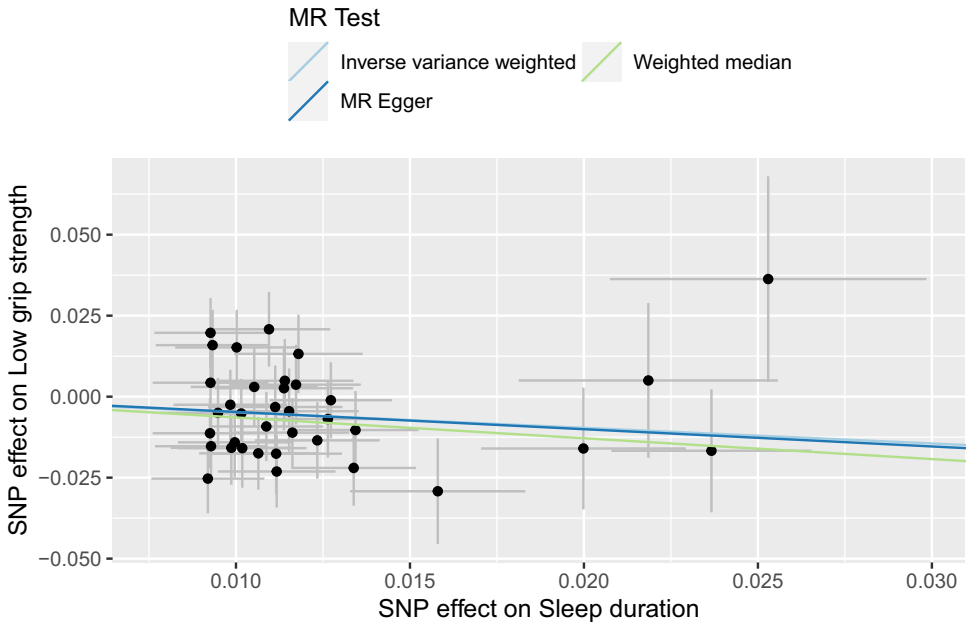

Figure 3 Scatterplot of the effect of each single genetic instrument on sleep duration and low grip strength. The slope of each line corresponds to the estimated MR effect in different models, and the horizontal and vertical lines indicate each correlation's 95% confidence interval.

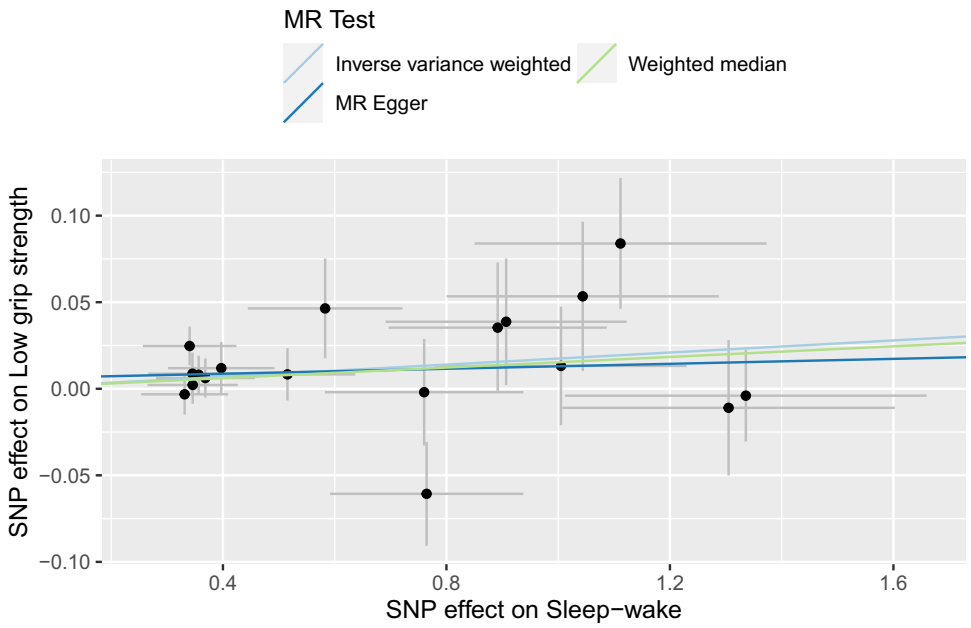

Figure 4 Scatterplot of the effect of each single genetic instrument on sleep-wake disorders and low grip strength. The slope of each line corresponds to the estimated MR effect in different models, and the horizontal and vertical lines indicate each correlation's 95% confidence interval.

thresholds may have increased the true positive discovery at the cost of adding few additional false positive results.[40] We found sleep-wake disorders was significantly associated with low grip strength (IVW: OR = 1.02, 95% CI = 1.00–1.03, P = 0.020 < 0.05) (Figure 4). Consistent with the IVW result, the Weighted median and MR-Egger showed a positive causal direction (OR > 1.00). The Cochran's Q and MR-Egger intercept tests showed no obvious heterogeneity and horizontal pleiotropy ($P > 0.05$). In addition, no outlier IVs were identified in the MR-PRESSO analysis. Funnel plots and leave-one-out analyses showed single SNP did not bias the result (Supplementary Figures S3 and S4). MRlap analysis showed no significant differences between the raw and adjusted IVW P-values for sleep-wake disorders ($P > 0.05$).

Besides, we did not find a significant causal relationship between the genetically predicted insomnia, daytime napping, and chronotype with low grip strength (IVW P > 0.05). In the sensitivity analyses, the MR-PRESSO results for chronotype showed rs76277841 played a contradictory role with other SNPs. However, we still could not find a causal relationship between chronotype and low grip strength after removing it (OR = 0.95, 95% CI = 0.65–1.40, $P = 0.802$). MRlap analyses for these three sleep traits similarly showed no significant difference between the raw and adjusted (for sample overlap) IVW P-values ($P > 0.05$). The visualization of the sensitivity analyses is shown in Supplementary Figures S5–S13.

Causal Effects of Low Grip Strength on Sleep Traits

In reverse analyses, we found a significant positive association low grip strength and between daytime napping (IVW: OR = 1.02, 95% CI = 1.00–1.03, $P = 0.011 < 0.05$) (Figure 5). Notably, the IVs used for daytime napping had removed the specific SNP (rs3771501), influencing the effect estimates found by the leave-one-out analysis. Similar to the IVW result, the Weighted median and MR-Egger also showed a positive causal direction (OR > 1.00). Cochran's Q and MR-Egger intercept tests showed no significant heterogeneity or horizontal pleiotropy ($P > 0.05$). MR-PRESSO did not identify any outliers. Furthermore, funnel plots and leave-one-out analysis verified the robustness of the findings (Supplementary Figures S14 and S15). MRlap analysis showed a significant difference between the raw and adjusted IVW P-values ($P = 0.007 < 0.05$). However, the MRlap corrected results were consistent with the primary MR analysis result (corrected IVW: OR = 1.08, 95% CI = 0.94–1.23, $P = 0.044 < 0.05$), which confirms that the IVW method is robust. The results of reverse MR are summarized in Figure 6 and Table 3.

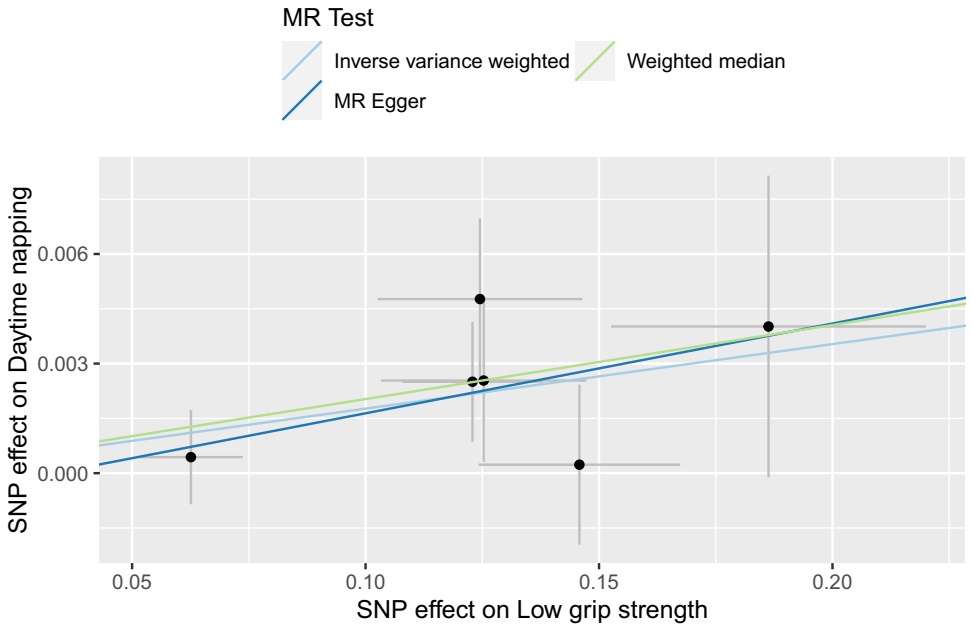

Figure 5 Scatterplot of the effect of each single genetic instrument on low grip strength and daytime napping. The slope of each line corresponds to the estimated MR effect in different models, and the horizontal and vertical lines indicate each correlation's 95% confidence interval.

Outcome	Model	nSNP	OR (95%CI)	Pvalue
Sleep duration	IVW	7	0.996 (0.979−1.012)	0.609
	WM	7	0.995 (0.975−1.015)	0.602
	MR−Egger	7	0.997 (0.949−1.048)	0.911
Insomnia	IVW	137	1.032 (0.940−1.134)	0.503
	WM	137	1.072 (0.927−1.241)	0.352
	MR−Egger	137	1.047 (0.885−1.281)	0.659
Sleep−wake disorder	IVW	106	0.900 (0.665−1.220)	0.498
	WM	106	0.995 (0.636−1.556)	0.982
	MR−Egger	106	0.739 (0.411−1.330)	0.316
Daytime napping	IVW	6	1.018 (1.004−1.032)	0.011
	WM	6	1.020 (1.003−1.038)	0.022
	MR−Egger	6	1.025 (0.982−1.070)	0.324
Chronotype	IVW	3	1.060 (0.934−1.202)	0.368
	WM	3	1.065 (0.900−1.260)	0.465
	MR−Egger	3	1.189 (0.953−1.484)	0.367

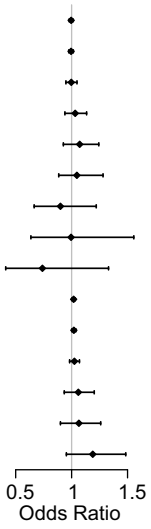

Figure 6 Forest plot for Mendelian randomization (MR) effect estimates with IVW, WM, and MR-Egger: causal effects for low grip strength on sleep traits. OR: odds ratio; CI: confidence interval; IVW: inverse-variance weighted; WM: weighted median; nSNP: number of single nucleotide polymorphisms. Horizontal lines represent 95% confidence interval.

However, we failed to find a potential causal relationship between genetically predicted low grip strength and sleep duration, insomnia, sleep-wake disorders, and chronotype (IVW $P > 0.05$). Moreover, MRlap analyses revealed a significant difference between raw and corrected IVW P-values for low hand grip strength to Insomnia ($P = 0.049 < 0.05$) and Sleep-wake disorders analyses ($P = 0.004 < 0.05$). Similarly, the corrected results of low grip strength to Insomnia and Sleep-wake disorders were consistent with the primary MR results (corrected IVW: $P = 0.856$ and $0.428 > 0.05$). For the MRlap result for low grip strength to chronotype, no significant difference was

Table 3 MR Analyses with Heterogeneity, Sensitivity, and Pleiotropy Evaluation for Causal Effects of LGS on Sleep Traits

Exposure	Outcome	SNPs	Cochran's Q test (P)	MR Egger Intercept (P)	MR		
					Method	OR (95% CI)	P
LGS	Sleep duration	7	0.973	0.955	IVW	0.996 (0.979–1.012)	0.609
					WM	0.995 (0.975–1.015)	0.602
					MR-Egger	0.997 (0.949–1.048)	0.911
LGS	Insomnia	137 [a]	0.501	0.883	IVW	1.032 (0.940–1.134)	0.503
					WM	1.072 (0.927–1.241)	0.352
					MR-Egger	1.047 (0.855–1.281)	0.659
LGS	Sleep-wake disorders	106 [a]	0.986	0.444	IVW	0.900 (0.665–1.220)	0.498
					WM	0.995 (0.636–1.556)	0.982
					MR-Egger	0.739 (0.411–1.330)	0.316
LGS	Daytime napping	6	0.722	0.756	IVW	1.018 (1.004–1.032)	0.011
					WM	1.020 (1.003–1.038)	0.022
					MR-Egger	1.025 (0.982–1.070)	0.324
LGS	Chronotype	3 [a]	0.316	0.445	IVW	1.060 (0.934–1.202)	0.368
					WM	1.065 (0.900–1.260)	0.465
					MR-Egger	1.189 (0.953–1.484)	0.367

Notes: [a] Using $P < 5\times10^{-5}$ threshold when the eligible single nucleotide polymorphism (SNP) numbers were insufficient (nSNP <3).
Abbreviations: LGS, Low grip strength; SNP, Single-nucleotide polymorphism; MR, Mendelian Randomization; OR, odds ratio; IVW, Inverse-Variance Weighted; WM = Weighted Median.

observed between the raw and adjusted IVW P-values (P > 0.05). All sensitivity analyses showed that the results are robust (Supplementary Figure S16–S27).

Discussion

Using bi-directional two-sample MR with genetic instruments selected from large-scale GWAS, we found evidence supporting a potential causal relationship between sleep traits and reduced risk for low grip strength. The study is the first bi-directional MR study to investigate causality between sleep traits and low grip strength. Low grip strength is an early marker of age-related functional decline and a strong predictor of morbidity and mortality in various diseases.[41] Previous studies have revealed the association of grip strength with physical functioning and independence in community-dwelling older adults.[42] Therefore, preventing low grip strength is important for improving population health, especially among older adults. Based on the results, we revealed a significant negative causal effect of sleep duration on low grip strength, indicating that longer sleep duration is associated with a lower occurrence of low grip strength. In addition, the result proposes a causality association between low grip strength risk and sleep-wake disorders. Reversely, low grip strength achieved a significant causal effect with daytime napping. However, there was no evidence of a causal association between insomnia, chronotype and low grip strength.

Sleep duration is a key trait in sleep quality.[43] Aging disrupts circadian rhythms and is a risk factor for decreased sleep duration;[44] it also increases the risk of falls, representing the risk of decreased muscle strength.[45] As two corollaries of aging, however, researches on the correlation between sleep duration and grip strength in older adults are controversial.[9,46] An observational study has shown no evidence of a correlation between lower sleep duration and sarcopenia.[47] However, a systematic review including 21 cross-sectional, 3 prospective studies, and 92,363 subjects indicated the robust association between sleep duration and muscle health.[48] Typically, previous studies concluded that the shorter the sleep duration, the lower the skeletal muscle mass index and the higher risk of low grip strength.[49] The old adults with mid-sleep (6–7 h) had significantly higher hand grip strength than those with short-sleep (≤ 5 h).[50] However, recent studies have suggested that either too long or too short sleep duration may lead to sarcopenia and manifest as low grip strength.[51,52] Our findings support an appropriate increase in sleep duration, which may be a protective factor for low grip strength, improving quality of life in older adults. Skeletal muscle is composed of 80% protein.[53] When sleep is

reduced, the metabolic state of protein is reduced anabolism and/or increased catabolism, which partially explains the decrease in muscle mass when sleep is reduced, and also fits with our results.[54] IGF-1 is a key protein for muscle growth and directly upregulates skeletal muscle protein synthesis through activation of PI3k/Akt/mTOR.[53] Sleep deprivation leads to a decrease in circulating IGF-1, which in turn affects muscle synthesis.[55] Besides the involvement of protein metabolism in muscle synthesis, glucose also has an effect on muscle metabolism. Muscle is the largest organ in the human body and consumes a large amount of glucose every day to maintain its energy supply and glucose homeostasis.[56,57] Reduced sleep induces insulin resistance, leading to reduced glucose uptake by muscles and reduced muscle synthesis.[58,59] In addition, skeletal muscle possesses a sleep-regulated cell-autonomous molecular clock, and maintaining adequate sleep is essential for muscle mass, growth, and metabolic regulation.[60–62]

Daytime napping appeared to be a beneficial strategy to enhance the recovery process and counteract some of the adverse effects of sleep deprivation on physical and cognitive performance.[63] In observational studies, a higher risk of functional limitations (low grip strength and propensity to fall) was associated with increased daytime napping, but this could not be fully explained by adjusting for demographics or health status.[64] Using MR analyses, we found the causality and its direction: low grip strength may be a causative factor for daytime napping. Previous studies corroborated the plausibility of the results: low hand grip strength was an important symptom of frailty and tended to be highly associated with daytime napping.[65,66] However, the clinical significance of this result should be interpreted cautiously as the OR was very close to 1 (OR = 1.018). Increased physical activity increases muscle mass and reduces the incidence of low grip strength.[67] This may help to reduce the incidence of daytime napping, and thus reduce the risk of multiple diseases associated with excessive daytime sleepiness.[68]

Almost all sleep-related phenotypes can be categorized as sleep-wake disorders (or sleep disorders) according to American Psychiatric Association definition.[69] The causal associations of sleep duration, sleep-wake disorders to low grip strength, and low grip strength to daytime napping may be related to circadian rhythm mechanisms in skeletal muscle.[70] Causes of sleep disorders include delayed circadian rhythm with aging, lower physical function and/or activity, and decreased social interactions.[71,72] Studies have shown that long-term sleep disorders alter the body's normal biological rhythms, and indirectly impair skeletal muscle structure, function, and metabolism.[16] In addition to the aforementioned effects of protein metabolism on muscle production, previous studies have shown that patients with sleep disorders are predisposed to develop metabolic syndrome.[16] And the pathological processes that characterize metabolic syndrome, insulin resistance and persistent inflammation, weaken muscle mass.[73] Moreover, the rhythmicity of skeletal muscle itself is thought to affect sleep. The skeletal muscle clock gene regulates sleep homeostasis, and knockout BMAL1 mice exhibit an attenuated rhythm of sleep-wake distribution during 24 hours.[74]

Circadian clock genes regulate skeletal muscle rhythms.[60,61] More than 2300 circadian clock genes are expressed in human skeletal muscle, and these genes regulate the expression of downstream clock-control genes (CCGs) through transcriptional, translational, and epigenetic means, thereby effectively regulating the rhythmicity of organisms at physiological, metabolic, and behavioral levels.[75] Among them, skeletal muscle-specific CCGs include myogenic differentiation 1 (Myod1),[76] Atrogin-1,[77] dynamin-related protein 1 (Drp1),[78] Bcl-2 nineteen-kilodalton interacting protein 3 (BNIP3),[79] and so on. These tissue-specific genes not only maintain skeletal muscle mass and prevent muscle atrophy by regulating muscular dystrophy factor, but also interact with the central clock to influence sleep behavior.[80] For example, Myod1 is a key upstream factor involved in myogenic differentiation and also regulates the expression of core clock genes.[80,81] Despite certain results, the complex mechanisms by which skeletal muscle circadian rhythms affect sleep behavior need to be supported by more researches.

Our study used bidirectional two-sample MR to explore causality and reverse causality between multiple sleep traits and low grip strength based on large sample size databases. Both directions yielded significant results, albeit with some weak effect sizes, suggesting some degree of potential interaction between sleep and grip strength. This may give a universal positive signal that increasing muscle mass to increase grip strength, or consciously improving sleep habits, can consequently improve quality of life and health in old populations.

Several limitations should be considered in our study. Firstly, although we drew on the largest available GWAS data, some traits found insufficient genome-wide significant SNPs. Therefore, we used relaxed P-value thresholds for some analyses, which may result in weak instruments bias.[82] Although the F-statistics results assured the efficacy of the genetic

instruments, some bias (eg, false positives) may still exist with the relaxed thresholds.[40] Secondly, despite selecting strongly associated SNPs, common SNPs do not yet explain much total variance in complex traits and so cannot be considered exact proxies of the exposure. Thirdly, there was some difference in age between the populations for exposure and outcome. The samples in the exposure data from the UK Biobank ranged in age from 40 to 69 years, and the median age of samples from the FinnGen database was 63 years. For outcome, SNPs associated with low grip strength were identified in the CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology) Study of individuals aged 60 to 90. Therefore, we could not avoid bias from age differences. Due to the low hand grip strength being an important symptom of frailty, the GWAS data on low hand grip strength are restricted to an older population, which might limit the generalizability of the findings to younger populations. However, age differences in two-sample MR studies generally do not increase the likelihood of incorrectly inferring a causal association.[83] Moreover, datasets restricted to European ancestry limited the bias due to population stratification and clinical generalizability to other populations. However, despite some limitations, our findings are novel and provide data support and a theoretical basis for clinical improvement of quality of life in older adults.

Conclusion

This study leverages MR to explore causal associations regarding sleep traits and low grip strength risk. Our findings validate a potential causal association between sleep-related phenotypes and low grip strength risk, including sleep duration, sleep-wake disorders, and daytime napping. Furthermore, we speculate on possible physiological mechanisms from the skeletal muscle circadian rhythms perspective. Effective interventions are of great necessity to improve the elderly sleep and muscle function from an early stage. These findings have implications for establishing feasible disease screening and prevention strategies.

Data Sharing Statement

The data presented in this study are available on reasonable request from the corresponding author. Original data on sleep traits and low grip strength were obtained from the IEU GWAS database (https://gwas.mrcieu.ac.uk/), Finngen database (https://www.finngen.fi/en), and original GWAS studies.

Ethics Approval

The ethics committee of Beijing Sport University strictly adheres to the Declaration of Helsinki and the International Ethical Guidelines for Health-related Research Involving Humans. The present study uses legally obtained publicly available data, meeting the conditions for exemption from review as stated in the Measures for Ethical Review Methods for Life Sciences and Medical Research Involving Humans.

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Author contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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