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ORIGINAL RESEARCH

Bidirectional causal associations between frailty measures and sleep disturbances: a two-sample Mendelian randomization study

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Background: Observational studies have demonstrated a strong association between sleep disturbances and frailty. However, the causality remains inconclusive. We aimed to investigate the bidirectional causal relationships between frailty measures and sleep disturbances employing a two-sample Mendelian randomization (MR) analysis.

Methods: Two-sample MR analyses were performed based on large-scale genome-wide association studies (GWAS) of the European population for frailty index (FI) (N = 175,226), Fried Frailty Score (FFS) (N = 386,565), insomnia (N = 283,595), sleep duration (N = 445,966) and sleep apnea (N = 523,366). We conducted the causal estimates using the inverse variance-weighted method (IVW), with sensitivity analyses using MR-Egger, weighted median, weighted mode, and MR pleiotropy residual sum and outlier (MR-PRESSO) analysis. Cochran's Q test was performed to assess heterogeneity.

Results: We found that genetically predicted FI was associated with shorter sleep duration and sleep apnea. The genetically predicted FFS was associated with insomnia, shorter sleep duration, and sleep apnea. In the reverse direction analysis, genetic liability to insomnia, short sleep duration, and long sleep duration were associated with an increase in FI. Genetic liability to short sleep duration and long sleep duration were associated with an increase in FFS.

Conclusion: Our study provided genetic evidence supporting the bidirectional causality between frailty measures and sleep disturbances. The findings contribute to the prevention and management of frailty and sleep disturbances.

Keywords: frailty, sleep disturbances, Mendelian randomization, the elderly

Introduction

Frailty, characterized by increased vulnerability resulting from age-related declines in reserve and function across multiple physiological domains, has emerged as a global health concern in the aging world population.[1,2] Older people with frailty have an increased risk of fall, hospitalization, disability, and mortality.[3–5] The frailty index (FI) and Fried Frailty Score (FFS) are two commonly used tools to comprehensively assess frailty.[6,7] The FI quantifies frailty by considering a range of health-related deficits and capturing the cumulative impact of various physiological and clinical markers. FFS evaluates frailty based on specific criteria, including unintentional weight loss, exhaustion, low physical activity, slow walking speed, and diminished grip strength. Besides, sleep disorders pose a significant health challenge among the elderly. With sleep disruption often regarded as a common feature of "normal aging", older adults frequently experience reduced ability to initiate and maintain sleep, along with deficits in sleep physiology.[8] Similar to frailty, there exists substantial individual variability in sleep disturbances among older adults, indicating that not all individuals of the same chronological age suffer from similar degrees of sleep impairment.[8]

Sleep deprivation and loss impair physical performance, cognitive condition, and emotional well-being, thereby resulting in symptoms such as fatigue, which play an important role in frailty.[9] Furthermore, poor sleep quality has been shown to be associated with increased systemic inflammation, leading to downstream consequences affecting various bodily functions, including endocrine, cardiovascular, and cognitive changes, thereby increasing the risk of frailty.[10–14]

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Shared underlying pathophysiological pathways, such as inflammation and neurohormonal imbalance, may contribute to both frailty and sleep disorders. A recent systematic meta-analysis has identified 12 observational studies that demonstrated a significant association between insomnia and frailty in the older population.[15] Meanwhile, a cross-sectional observational study suggested frailty was independently predicted by insomnia in older adults, adjusting for socio-demographic characteristics and comorbidity.[16] Another meta-analysis examined that longer and shorter sleep duration were associated with increased risk of frailty.[17] However, the causal associations between sleep disturbances and frailty remained inconclusive, because existing evidence from observational studies limited our understanding of the causal relationships and residual confounding factors.[18,19] The issues of reverse causation and the possibility of bidirectional associations are not well established.[20] Thus, it is difficult to identify the elaborate associations between sleep disturbances and frailty to improve individual management for the elderly population.

Randomized controlled trial (RCT) is regarded as the gold standard method to infer causality. However, RCT is expensive, time-consuming, and often limited to conduct, especially for investigations on sleep. To address the challenges of causal inference in this complex relationship, Mendelian randomization (MR) has emerged as a popular tool.[21] MR uses genetic variants that are robustly associated with exposure as potentially unconfounded instruments to infer whether an observed association between the exposure and the outcome is causal or not from observational data. It becomes a faster, cheaper, and more feasible way to estimate the causal impact of the exposure on the outcome while diminishing limitations of conventional observational studies and RCTs, including confounding factors and reverse causation.

The main limitation of previous research was the measurement of frailty. Several definitions of the frailty syndrome have been proposed; however, current studies only examined the relationship using the FI.[22,23] The FFS focuses on physical frailty, which differs from the FI comprising a series of health-related issues.[24] In this study, we performed a bidirectional, two-sample MR to explore the causal relationships between frailty measures and sleep disturbances, as measured by the FI and FFS for more convincing and comprehensive conclusions.

Methods

Study Design Overview

We performed a bidirectional two-sample MR analysis to investigate the causal relationships between frailty measures and sleep disturbances (Figure 1). Our study was conducted in accordance with the Declaration of Helsinki revised in 2013, and the methods followed the STROBE-MR checklist.[25,26] The study has been approved by the Institutional Review Board of the Peking Union Medical College Hospital (Ethics Approval Number: I-24ZM0035). As our MR study was based on publicly available summary statistics, the informed consent was found in the original studies.

Data Sources

We extracted summary statistics on frailty measured by the FI from a meta-analysis of GWAS conducted in the UK Biobank (n = 164,610, mean age 64.1 years [SD = 2.8], 51.3% were female) and the Swedish TwinGene cohort (n = 10,616, mean age 58.3 years [SD = 7.9], 52.5% were female), comprising 175,226 individuals of European descent.[27] The FI was developed using self-reported questionnaire data, which included over 40 components covering various domains of mental and physical health, and has been validated as a reliable tool for measuring frailty.[27–29] The items were detailed in the Supplementary Table S1.[29] Many of the loci have been previously linked to some traits and diseases, including body mass index (BMI), smoking, depression, neuroticism, and cardiovascular disease, adding crucial evidence to support associations with frailty.[30] Summary statistics for FFS, a validated and standardized definition of frailty phenotype, were obtained from a recent large-scale GWAS with 386,565 participants of European ancestry enrolled in the UK Biobank (mean age 57 years [SD = 8], 54% were female).[31] Most loci have been identified in GWAS of various traits, such as obesity, cardiovascular disease, diabetes, and cancer, revealing confirmatory evidence for relationships between these loci with frailty.[32–34] Summary data for GWAS of insomnia and sleep apnea were obtained from the GWAS catalog, including 283,595 and 523,366 European participants.[35,36] Many loci have been associated with some traits, which increase the risk of sleep apnea, including BMI or adiposity, airway dimensions, and hearing impairment.[37–39] The summary statistics for sleep duration,

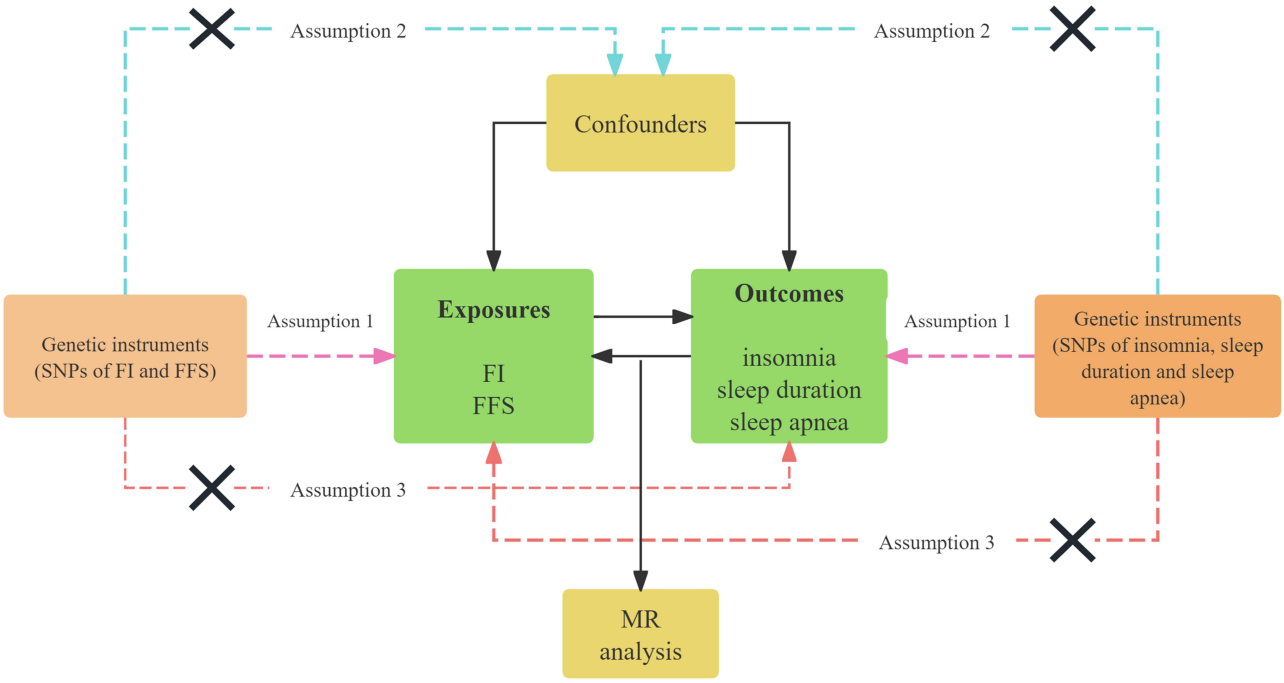

Figure 1 Overview of the MR study estimating the bidirectional association between frailty measures and sleep disturbances.
Abbreviations: SNPs, single nucleotide polymorphisms; FI, frailty index; FFS, Fried Frailty Score.

including short (≤ 5 h) and long (≥ 10 h) sleep duration, were retrieved from a GWAS and meta-analyses.[40] Only data from European ancestry (N = 445,966) were used in this MR study, including 278,003 participants from UK Biobank (mean age 56.8 years [SD = 8.0], 54.1% were female) and 167,963 participants from the Million Veteran Programme (mean age 66.8 years [SD = 11.6], 7.4% were female). These genetic loci for short or long sleep duration have been related to sleep, cognitive, and psychiatric traits as well as other disorders in the previous GWAS.[41,42] The genome-wide significance was $P < 5 * 10^{-8}$.

Selection and Validation of Instrumental Variables

The genetic variants selected as instrumental variables (IVs) must follow three assumptions: (1) genetic variants are reliably associated with the risk factor under investigation (relevance assumption); (2) genetic variants are not associated with any known or unknown confounding factor (independence assumption); (3) genetic variants influence the outcome only through the risk factor and not through any causal pathway (exclusion restriction assumption).[43] To satisfy the relevance assumption, single nucleotide polymorphisms (SNPs) that met a significance threshold of $P < 5 * 10^{-8}$ were selected as IVs, but long sleep duration in which only two SNPs reached the threshold and the significance threshold was set as $P < 5 * 10^{-6}$ to obtain a more comprehensive result as previously reported.[44,45] To meet the independence assumption, we identified potential confounders through the PhenoScanner Database (http://www.phenoscanner.medschal.cam.ac.uk/). Besides, to ensure variable independence and account for linkage disequilibrium (LD) effects, an LD parameter (r^2) of 0.001 and a genetic distance of 10000 kb were utilized. For the exclusion restriction assumption, the selected SNPs related to outcome with $P < 5 * 10^{-5}$ were removed from the IVs. Moreover, we removed palindromic SNPs from the instrumental SNPs chosen for analysis in the harmonization process. Regarding the strength of the IVs, the F statistic ($F = \beta^2/se^2$) was employed to exclude weak instrumental biases and ensure the instrumental strength. The SNPs with F statistic < 10 indicating a weak association were excluded from the MR analysis[46] In addition, the R^2-value (the proportion of variation explained by the genetic variant) of each genetic instrument was also calculated to ensure that the eligible SNPs were strong instruments.

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Statistical Analysis for MR

Statistical analysis in this study was performed using R Software (version 4.3.3) through TwoSampleMR (version 0.5.11), MendelianRandomization (version 0.8.0), and MRPRESSO package (version 1.0). The primary analysis method employed was the inverse variance-weighted (IVW) approach.[47] Additionally, MR Egger, weighted median, and weighted mode methods were utilized as complementary analyses.[48–50] The estimates were reported as odds ratios (ORs) along with their corresponding 95% confidence intervals (CIs). Cochran's Q test was performed to assess heterogeneity among individual causal effects, with significance defined as $P < 0.05$, indicating heterogeneity.[51] We identified exposures with horizontal pleiotropy for MR-Egger regression and MR pleiotropy residual sum and outlier (MR-PRESSO) global test.[49,52] Furthermore, scatterplots were employed to evaluate the robustness and stability, and leave-one-out analysis was conducted to indicate that the causal effect of exposure on outcome was not influenced by individual SNPs. If one or more outlier SNPs were found to affect the MR estimates, they were removed and MR analysis was performed again. The variables in our study were not independent; therefore, multiple testing adjustment was not applied in the MR analysis.

Results

To ensure that the samples for exposures were independent of those for outcomes, we manually reviewed the sample descriptions of each GWAS. Besides sleep duration, there was no sample overlap between the data of the frailty measures and other sleep disturbances. We conducted simulation studies to explore the potential impact of sample overlap on causal estimates as previously reported.[53] The simulation studies indicated that while overlap could introduce bias, the effect size and direction in our analysis were unlikely to be substantially affected, with bias estimated to be less than 5%. Detailed information on SNPs used for our analyses is presented in the Supplementary Tables S2–S17. The F statistics of all SNPs were more than 10, and it meant there were no weak IVs. The results of leave-one-out sensitivity analysis, forest plot, scatter plot, and funnel plot were shown in Supplementary Figures S1–S16.

Causal Effects of Frailty measures on Sleep Disturbances

For the effect of FI on insomnia, it demonstrated that the genetic predisposition to FI was statistically significantly associated with increased risk of insomnia (OR 1.21, 95% CI: 1.10, 1.32, $P < 0.001$). It indicated that one standard deviation increase in quantile-normalized FI could elevate the risk of insomnia by 21%. However, the results of MR-Egger and weighted mode showed that FI was not related to the risk of insomnia (Figure 2). Heterogeneity among SNPs was detected by the Cochran's Q test (Q = 28.364, $P = 0.003$). The results of the MR-PRESSO test revealed that IVs of FI and insomnia had horizontal pleiotropy after the removal of outlier SNPs (MR-PRESSO: $P = 0.008$), however, the MR-Egger regression did not find the presence of pleiotropy (MR-Egger intercept: $P = 0.085$) (Table 1). For the effect of FFS on insomnia, the IVW analysis suggested that the genetic predisposition to FFS was statistically significantly associated with insomnia (OR 1.28, 95% CI: 1.18, 1.38, $P < 0.001$). It revealed that one standard deviation increase in quantile-normalized FFS could elevate the risk of insomnia by 28%. The weighted median and weighted mode methods were consistent with this result. However, the MR-Egger method showed no evidence of a causal association between FFS and insomnia (OR 1.32, 95% CI: 0.99, 1.75, $P = 0.072$) (Figure 2). In addition, there was no heterogeneity by the Cochran's Q test ($Q = 30.104$, $P = 0.146$). The MR-Egger regression and MR-PRESSO test did not detect any pleiotropy (MR-Egger intercept: $P = 0.821$; MR-PRESSO: $P = 0.191$) (Table 1).

In the analysis of the effect of FI on short sleep duration, our study indicated a genetic predisposition to FI increased the risk of short sleep duration (OR 1.89, 95% CI: 1.28, 2.79, $P = 0.001$) based on IVW method, which showed that one standard deviation increase in quantile-normalized FI could elevate the risk of insomnia by 89%, but MR-Egger and weighted mode methods were not significant (Figure 2). There was no heterogeneity and horizontal pleiotropy, according to Cochran's Q ($Q = 8.648$, $P = 0.124$), MR-Egger intercept ($P = 0.388$), and MR-PRESSO ($P = 0.194$) tests (Table 1). The IVW method showed a causal relationship between FFS and short sleep duration (OR 2.65, 95% CI: 1.89, 3.72, $P < 0.001$). It demonstrated that one standard deviation increase in quantile-normalized FFS could elevate the risk of insomnia by 165%. The weighted median and weighted mode methods were consistent with this result (Figure 2).

Exposure	Outcome	No.of SNP	Method	OR(95% CI)	P
FI	insomnia	12	IVW	1.21 (1.10 to 1.32)	0.000
			MR Egger	0.55 (0.24 to 1.24)	0.178
			Weighted median	1.11 (1.00 to 1.23)	0.043
			Weighted mode	1.07 (0.93 to 1.23)	0.390
	short sleep duration	6	IVW	1.89 (1.28 to 2.79)	0.001
			MR Egger	15.00 (0.22 to 1014.54)	0.276
			Weighted median	1.64 (1.09 to 2.46)	0.017
			Weighted mode	1.49 (0.79 to 2.81)	0.275
	long sleep duration	7	IVW	1.15 (0.66 to 1.98)	0.627
			MR Egger	1.99 (0.00 to 1665.13)	0.849
			Weighted median	1.34 (0.71 to 2.51)	0.367
			Weighted mode	1.86 (0.66 to 5.25)	0.286
	sleep apnea	8	IVW	1.21 (1.04 to 1.41)	0.015
			MR Egger	0.73 (0.40 to 1.33)	0.343
			Weighted median	1.25 (1.02 to 1.53)	0.030
			Weighted mode	1.38 (1.01 to 1.88)	0.084
FFS	insomnia	24	IVW	1.28 (1.18 to 1.38)	0.000
			MR Egger	1.32 (0.99 to 1.75)	0.072
			Weighted median	1.27 (1.15 to 1.40)	0.000
			Weighted mode	1.26 (1.05 to 1.50)	0.017
	short sleep duration	19	IVW	2.65 (1.89 to 3.72)	0.000
			MR Egger	5.31 (1.07 to 26.33)	0.057
			Weighted median	2.24 (1.47 to 3.40)	0.000
			Weighted mode	2.24 (1.06 to 4.74)	0.049
	long sleep duration	23	IVW	3.06 (1.81 to 5.18)	0.000
			MR Egger	3.93 (0.55 to 28.30)	0.189
			Weighted median	3.46 (1.87 to 6.41)	0.000
			Weighted mode	3.08 (0.92 to 10.29)	0.081
	sleep apnea	21	IVW	1.57 (1.28 to 1.94)	0.000
			MR Egger	2.94 (1.41 to 6.13)	0.009
			Weighted median	1.76 (1.35 to 2.30)	0.000
			Weighted mode	2.09 (1.35 to 3.23)	0.003

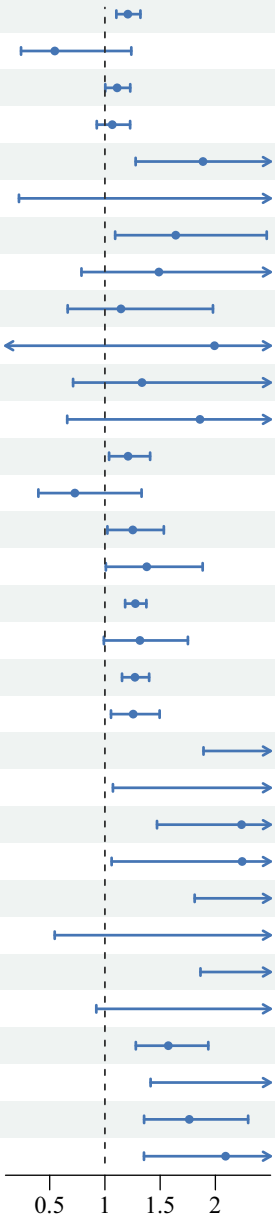

Figure 2 MR estimates for the causal effect of frailty measures on sleep disturbances.
Abbreviations: FI, frailty index; FFS, Fried Frailty Score; SNPs, single nucleotide polymorphisms; IVW, inverse variance-weighted method; CI, confidence interval; OR, odds ratio.

Besides, the Cochran's Q test (Q = 25.275, $P = 0.118$) showed no significant heterogeneity). The MR-Egger regression ($P = 0.396$) and MR-PRESSO ($P = 0.152$) tests did not show the presence of pleiotropy (Table 1).

No significant association between FI and long sleep duration was observed (OR 1.1.5, 95% CI: 0.66, 1.98, $P = 0.627$), and the effects generated by four methods for the association were consistent (Figure 2). The sensitivity test did not find any evidence for heterogeneity (Cochran's Q test: $Q = 9.121$, $P = 0.167$). There was no pleiotropy in the MR-Egger regression ($P = 0.878$) and MR-PRESSO test ($P = 0.192$) (Table 1). The causal relationship between FFS and long sleep duration was observed using IVW and weighted median methods (OR 3.06, 95% CI: 1.81, 5.18, $P < 0.001$; OR 3.46, 95% CI: 1.87, 6.41, $P < 0.001$), which reported that one standard deviation increase in quantile-normalized FFS could elevate the risk of insomnia by 206%. However, MR-Egger and weighted mode methods did not indicate the result (Figure 2). After the adjustment of outliers, the presence of heterogeneity was still observed in the Cochran's Q test ($Q =$

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Table 1 The Causal Estimates Between Frailty Measures and Sleep Disturbances in the Sensitivity Analysis

Exposure	Outcome	Heterogeneity		Horizontal Pleiotropy	
		Q	P	MR-Egger Intercept (P)	MR-PRESSO Global P
FI	Insomnia	28.364	0.003	0.085	0.008
	Short sleep duration	8.648	0.124	0.388	0.194
	Long sleep duration	9.121	0.167	0.878	0.192
	Sleep apnea	3.898	0.791	0.140	0.683
FFS	Insomnia	30.104	0.146	0.821	0.191
	Short sleep duration	25.275	0.118	0.396	0.152
	Long sleep duration	36.680	0.026	0.800	0.039
	Sleep apnea	26.166	0.160	0.099	0.192
Insomnia	FI	24.072	0.088	0.096	0.117
	FFS	28.304	0.013	0.638	0.016
Short sleep duration	FI	20.913	0.052	0.490	0.077
	FFS	11.723	0.385	0.989	0.502
Long sleep duration	FI	11.638	0.769	0.431	0.778
	FFS	12.561	0.765	0.381	0.796
Sleep apnea	FI	7.479	0.113	0.108	0.165
	FFS	8.826	0.032	0.268	0.099

Abbreviations: FI, frailty index; FFS, Fried Frailty Score.

36.680, P = 0.026). The MR-Egger regression (P = 0.800) revealed no pleiotropy among IVs, however, the MR-PRESSO test found the presence of pleiotropy (P = 0.039) (Table 1).

The MR study found that the genetic predisposition to FI was statistically significantly associated with sleep apnea (OR 1.21, 95% CI: 1.04, 1.41, P = 0.015; OR 1.25, 95% CI: 1.02, 1.53, P = 0.030) based on the IVW and weighted median methods (Figure 2). It revealed that one standard deviation increase in quantile-normalized FI could elevate the risk of insomnia by 21%. In addition, the MR results were robust in several sensitivity analyses. The Cochran's Q test did not show any heterogeneity (Q = 3.898, P = 0.791. The MR-Egger regression (P = 0.140) and MR-PRESSO test (P = 0.683) did not find significant horizontal pleiotropy (Table 1). All four MR methods supported that sleep apnea was suggestively associated with the higher FFS (IVW, OR 1.57, 95% CI: 1.28, 1.94, $P < 0.001$) (Figure 2). It showed that one standard deviation increase in quantile-normalized FFS could elevate the risk of insomnia by 57%. Heterogeneity and horizontal pleiotropy were not found in the sensitivity analyses (Cochran's Q test: Q = 26.166, P = 0.160; MR-Egger intercept: P = 0.099; MR-PRESSO: P = 0.192) (Table 1).

Causal Effects of Sleep Disturbances on Frailty Measures

For the effect of sleep disturbances on FI, the reverse MR study revealed that genetically predicted insomnia (β 0.43, 95% CI: 0.27, 0.59, $P < 0.001$), short sleep duration (β 0.12, 95% CI: 0.07, 0.18, $P < 0.001$) and long sleep duration (β 0.03, 95% CI: 0.00, 0.06, P = 0.030) were statistically significantly associated with an increase in FI, based on the IVW method, while no significant association was found for genetically predicted sleep apnea with FI (β 0.02, 95% CI: −0.11, 0.14, P = 0.774) based on the IVW method (Figure 3). All MR results remained robust across several sensitivity analyses. The results of Cochran's Q test showed no significant heterogeneity (insomnia: Q = 24.072, P = 0.088; short sleep duration: Q = 20.913, P = 0.052; long sleep duration: Q = 11,638, P = 0.769; sleep apnea: Q = 7.479, P = 0.113). The results of the MR-Egger regression (insomnia: P = 0.096; short sleep duration: P = 0.490; long sleep duration: P = 0.431; sleep apnea: P = 0.108) and MR-PRESSO test (insomnia: P = 0.117; short sleep duration: P = 0.077; long sleep duration: P = 0.778; sleep apnea: P = 0.165) revealed no significant horizontal pleiotropy (Table 1).

For the effect of sleep disturbances on FFS, the reverse MR study revealed that genetically predicted insomnia (β 0.14, 95% CI: 0.02, 0.25, P = 0.021), short sleep duration (β 0.08, 95% CI: 0.06, 0.11, $P < 0.001$) and long sleep duration

Exposure	Outcome	No.of SNP	Method	Beta(95% CI)	P
insomnia	FI	17	IVW	0.43 (0.27 to 0.59)	0.000
			MR Egger	0.05 (−0.39 to 0.50)	0.824
			Weighted median	0.26 (0.06 to 0.45)	0.009
			Weighted mode	0.21 (−0.04 to 0.45)	0.123
	FFS	15	IVW	0.14 (0.02 to 0.25)	0.021
			MR Egger	−0.08 (−0.96 to 0.81)	0.865
			Weighted median	0.17 (0.04 to 0.30)	0.009
			Weighted mode	0.20 (−0.04 to 0.44)	0.124
short sleep duration	FI	13	IVW	0.12 (0.07 to 0.18)	0.000
			MR Egger	0.05 (−0.14 to 0.24)	0.587
			Weighted median	0.11 (0.05 to 0.18)	0.001
			Weighted mode	0.16 (0.03 to 0.30)	0.032
	FFS	12	IVW	0.08 (0.06 to 0.11)	0.000
			MR Egger	0.08 (−0.06 to 0.22)	0.278
			Weighted median	0.09 (0.05 to 0.12)	0.000
			Weighted mode	0.09 (0.04 to 0.15)	0.008
long sleep duration	FI	17	IVW	0.03 (0.00 to 0.06)	0.030
			MR Egger	−0.00 (−0.08 to 0.08)	0.975
			Weighted median	0.03 (−0.01 to 0.07)	0.093
			Weighted mode	0.05 (−0.02 to 0.12)	0.163
	FFS	18	IVW	0.03 (0.01 to 0.04)	0.000
			MR Egger	0.01 (−0.03 to 0.05)	0.571
			Weighted median	0.02 (0.00 to 0.04)	0.023
			Weighted mode	0.02 (−0.02 to 0.05)	0.289
sleep apnea	FI	5	IVW	0.02 (−0.11 to 0.14)	0.774
			MR Egger	0.55 (0.08 to 1.01)	0.105
			Weighted median	0.00 (−0.12 to 0.13)	0.950
			Weighted mode	0.10 (−0.05 to 0.25)	0.272
	FFS	4	IVW	0.10 (−0.01 to 0.21)	0.066
			MR Egger	0.74 (−0.09 to 1.56)	0.221
			Weighted median	0.09 (0.00 to 0.17)	0.044
			Weighted mode	0.02 (−0.14 to 0.19)	0.816

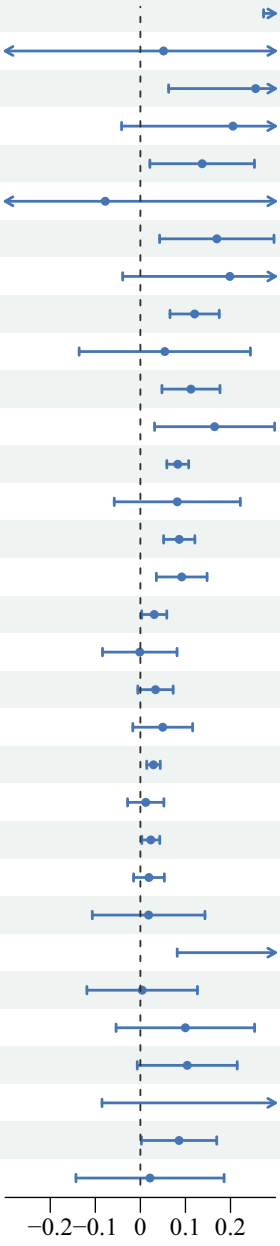

Figure 3 MR estimates for the causal effect of sleep disturbances on frailty measures.
Abbreviations: FI, frailty index; FFS, Fried Frailty Score; SNPs, single nucleotide polymorphisms; IVW, inverse variance-weighted method; CI, confidence interval; OR, odds ratio.

(β 0.03, 95% CI: 0.01, 0.04, $P < 0.001$) were statistically significantly associated with an increase in FFS, based on the IVW method, while no significant association was found for sleep apnea with FFS (β 0.10, 95% CI: −0.01, 0.21, $P = 0.066$) (Figure 3). The Cochrane's Q test and MR-PRESSO test regarding the association of insomnia with FFS suggested the presence of heterogeneity and horizontal pleiotropy (Cochran's Q test: $Q = 28.304$, $P = 0.013$; MR-PRESSO: $P = 0.016$). In addition, heterogeneity was identified in the analysis between sleep apnea and FFS (Cochran's Q test: $Q = 8.826$, $P = 0.032$). Other MR results remained robust across several sensitivity analyses. There was no significant heterogeneity by the Cochran's Q test (short sleep duration: Q = 11.723, $P = 0.385$; long sleep duration: Q = 12.561, $P = 0.765$). There was no significant horizontal pleiotropy by MR-Egger regression (insomnia: P = 0.638; short

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sleep duration: $P = 0.989$; long sleep duration: $P = 0.381$; sleep apnea: $P = 0.268$) and MR-PRESSO test (short sleep duration: $P = 0.502$; long sleep duration: $P = 0.796$; sleep apnea: $P = 0.099$) (Table 1).

Discussion

In this study, we employed MR to explore the bidirectional causal relationships between frailty measures and sleep disturbances, measured by FI and FFS. Our findings suggested a causal link that increased FI was associated with shorter sleep duration and sleep apnea. The genetically predicted FFS demonstrated a causal association with insomnia, shorter sleep duration, and sleep apnea. In the reverse MR analysis, we found that genetically predicted sleep disturbances, including insomnia, short sleep duration, and long duration causally contributed to an elevation in FI. Our study revealed that genetically predicted sleep disturbances, including short sleep duration and long duration, were causally related to increased risk of frailty measured by FFS. However, no significant effect was observed for sleep apnea on the risk of frailty. Furthermore, sensitivity analysis showed horizontal pleiotropy in the causal effect of FI on insomnia, FFS on long sleep duration, and insomnia on FFS, suggesting cautious interpretations of the results. Compared to previous studies, we applied two different measuring tools, which enhanced the accuracy of the results.[22,23] Regarding sleep apnea and frailty, the study conducted by Deng et al demonstrated that sleep apnea increased the risk of frailty, whereas our study did not provide the finding.[23] Besides, other findings were generally consistent with previous literature.

The study revealed a bidirectional association between frailty and insomnia. Existing literature focusing on the relationship between insomnia and frailty mostly reported that insomnia was associated with frailty, however, few studies have examined the effect of frailty on insomnia.[15–17] Our results were consistent with the previous study that a 2-year longitudinal analysis demonstrated that insomnia was a prognostic risk factor for frailty and frailty also predicted severe insomnia symptoms, adjusting for socio-demographic variables, health conditions, and health behaviors.[54] The current studies have highlighted the roles of chronic pain and depression in insomnia.[55–57] Frailty as a count of mental and physical disorders, including multiple chronic conditions with pain and discomfort, could lead to difficulty falling or staying asleep. In addition, regular medication use for this might be also a risk factor for insomnia.[58] While, insomnia is also thought to be a risk factor for depression and promote or exacerbate frailty.[59] Furthermore, frail individuals may experience impaired thermoregulation due to a decrease in muscle mass and metabolic activity, which can disturb sleep by making it challenging to maintain an optimal core temperature.[58,60–69]

Our findings indicated a significant genetic correlation between frailty and sleep duration. We have observed that genetic susceptibility to frailty was shown to be a risk factor for short sleep duration, which has not been reported in previous studies. Furthermore, reverse direction analysis has shown that shorter sleep duration could increase the likelihood of frailty, which was the same as the results of other studies.[17,70,71] In the reverse analysis, we found that long sleep duration was causally associated with frailty, which was consistent with the previous literature. A study comprising 7623 older adults demonstrated that long sleep duration was significantly associated with frailty incidence among older adults even after adjustment for confounding factors.[72] Another community-based cohort study corroborated this finding, suggesting that older adults with long sleep duration had an elevated incidence of frailty.[70]

Furthermore, our study found that frailty was strongly correlated with sleep apnea; however, no causal effect of sleep apnea on frailty was observed. Researchers have indicated that participants with an intermediate or high risk of obstructive sleep apnea were more likely to be frail.[73] A systematic review and meta-analysis demonstrated that sleep-disordered breathing was correlated with frailty.[74] The inconsistent results were probably caused by some unknown confounders. The heterogeneity was identified in the analysis between sleep apnea and FFS, which may cause some bias, indicating cautious interpretations of the results. Another reason might be that the statistical power of our analysis was not sufficient to detect the weak effects of sleep apnea on frailty, suggesting a need for larger studies. Further understanding of the relationship between sleep apnea and frailty may guide the comprehensive management of patients with sleep apnea.

Our research demonstrated that the causal relationships between frailty measures and sleep disturbances is bidirectional. Although pathophysiological mechanisms underlying the associations remained uncertain, several shared pathways might be considered. Some studies have shown that both short sleep duration and long sleep duration were associated with increasing risk of sarcopenia.[75] Sleep deprivation affects many important physiological functions of the body, such as protein synthesis,

muscle growth, and hormone production, which could lead to sarcopenia.[76,77] Furthermore, sarcopenia has been regarded as a strong indicator of reduced physical performance and played an essential role in the process of frailty.[78] Frailty-related physical and cognitive decline decreases daily physical activity, which may interfere with normal sleep-wake cycles and contribute to sleep disorders.[79] Simultaneously, sleep disturbances are linked to neurodegenerative changes and cognitive impairment, which could exacerbate frailty by reducing the ability to maintain physical and social functions.[80] In addition, previous studies found that some adipokines, such as adiponectin, leptin, and ghrelin, played important roles in sleep disorders.[81] An observational study showed a significant association between plasma adiponectin levels and obstructive sleep apnea.[82] A systematic review and meta-analysis covering a total of 2250 participants indicated that short sleep duration is correlated with elevated ghrelin levels, while sleep deprivation had a significant effect on the levels of both leptin and ghrelin.[83] There was a strong positive relationship between ghrelin and the apnea–hypopnea index or the Epworth sleepiness scale.[84] Similarly, it has been shown that higher plasma adiponectin was an independent risk factor for frailty status.[85,86] Also, researchers found that higher leptin levels increased the risk of exhaustion and muscle weakness, which led to frailty.[87] Moreover, frailty can lead to a significant effect on sleep quality through changes in circadian rhythms and hormones, notably in cortisol and melatonin, which are crucial for sleep quality.[61–64] The low testosterone has been found to be associated with frailty.[66,67] Other studies have indicated the relationship between low level of testosterone and sleep quality.[68,69] Therefore, the associations between frailty and impaired sleep may be also explained by testosterone. In addition, it has been shown that impaired sleep was associated with reduced growth hormone and insulin-like growth factor-1, which affected muscle metabolism, strength, and function, leading to frailty.[76] Also, increasing evidence found possible associations between sleep disorders and glucose imbalance.[88,89] Several studies concluded that sarcopenia was related to insulin resistance, diabetes, and metabolic syndrome.[90,91] Insulin resistance exerts a strong effect on muscle mass by promoting muscle catabolism and inhibiting anabolism.[92]

Besides, inflammation was regarded as a potential pathway between frailty and sleep disturbances. Previous studies reported that sleep disturbances induced inflammatory responses, with increased levels of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP).[93–95] According to recent studies, elevated inflammatory marker levels, such as IL-6, TNF-α, and CRP, have been identified in individuals with frailty.[96,97] Higher levels of inflammatory reactions might cause muscle loss and protein degradation, increasing the risk of frailty.[98] Moreover, chronic inflammation was found to be associated with some diseases, such as depression and cardiovascular disease, thus impairing cognitive action and physical function.[93,99] Therefore, the inflammatory process was considered a major mediator between frailty risk and sleep disturbances.[98] Also, existing research demonstrated that sleep deprivation affected the innate and adaptive immune parameters, leading to changes in the defense system and increasing the risk for chronic disease.[100,101] Additionally, there has been evidence suggesting that dysregulated autonomic function, such as decreased heart rate variability, is common in both sleep disturbances and frailty, leading to poor cardiovascular health and systemic homeostasis.[102,103]

Our study confirmed the bidirectional causality between frailty measures and sleep disturbances, even though some findings with small effect sizes, which are still instructive for clinical practice. For instance, sleep duration has been associated with cognitive decline, particularly in older adults.[104,105] Thus, even small effect sizes may have a greater influence on vulnerable populations requiring attention in clinical practice. Future research should consider the distribution and impact of these effect sizes in different populations and how these effects could be enhanced by improving sleep quality. Existing interventions have proven effective in the recovery of insomnia and exert a positive effect on daily life.[106,107] These results highlighted the role of assessing and improving sleep quality in frailty management, which could inform clinical and public health decision-making aiming to avoid the process of frailty.

There are some advantages in this study. First, to the best of our knowledge, this is the first MR study employing the GWAS to investigate the bidirectional relationships between frailty measures and sleep disturbances, using two different frailty definitions, based on FI and FFS. Second, the genetic data were from a large sample European population, which strengthened the reliability of results and avoided possible heterogeneity. Furthermore, the IVW estimates were examined by multiple MR sensitivity analyses to detect heterogeneity and horizontal pleiotropy. Nevertheless, several limitations should be considered in the current study. First, the GWAS data we utilized were derived from European countries, and the causalities might not be generalizable for other populations. The previous study indicated that 81% of individuals in GWAS were European descent

and it limited the generalizability of existing genetic findings to global populations.[108] Although reducing bias due to population stratification, it is necessary to acknowledge that our conclusions are more applicable to European ancestry and require further validation in non-European ancestry, which is the common limitation and challenge in the GAWS. Future studies should involve a much broader range of populations to improve the generalizability of genomics. Second, there was some overlap with the UK Biobank samples. Although we evaluated potential bias by calculating type I error rates, which would not affect the MR estimates, the results should be treated cautiously. Third, we only employed FI and FFS as assessment tools for quantifying frailty, and more studies including other frailty screening instruments are needed to confirm our findings. Fourth, the characteristics we focused on were widely representative and recognized indicators of sleep disturbances including insomnia, sleep duration and sleep apnea, which could not fully reflect the complexity and diversity of sleep disturbances. Fifth, although we utilized a large GWAS database, limited SNPs were selected for long sleep duration reaching the genome-wide significance ($P < 5 * 10^{-8}$). We have chosen a relaxed threshold ($P < 5 * 10^{-6}$) for identifying genetic variants, which might influence the validity of genetic instruments and increase the risk of weak instrument bias. To address this, we implanted multiple measures, such as F statistic and R^2 value to assess and ensure the reliability of conclusions. Sixth, it is necessary to acknowledge that we employed multiple complementary methods to elevate the validity of the MR assumptions and to reduce bias, however, identifying all sources of heterogeneity remains challenging. Heterogeneity and horizontal pleiotropy still existed in the sensitivity analyses after removing outliners, which could introduce bias. Last, we usually assume that the association between genetic instrumental variables and exposure or outcome is linear in MR analyses.[109,110] When exposure or outcome is binary, we need to hypothesize that causality is linear and homogeneous across individuals, which may be less reasonable in binary variables. The binary nature may cause challenges in the validity of MR assumptions. And our results should be interpreted as causal estimations in continuous variables, which were represented by binary variables.[109,110] In summary, our findings should also be interpreted with caution, and future studies are required to verify the causality.

Conclusions

In summary, the study provided bidirectional causal associations between frailty and sleep disturbances. A better understanding of the relationships between frailty and sleep disturbances could contribute to better prediction and intervention at sleep performance for potential risk of frailty and guide more comprehensive management. Further and more multiple studies are still needed to examine the causality inferred in our study.

Abbreviations

MR, Mendelian randomization; GWAS, Genome-wide association studies; FI, Frailty index; FFS, Fried Frailty Score; IVW, Inverse variance-weighted; MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier; RCT, Randomized controlled trial; SNPs, Single nucleotide polymorphisms; IVs, Instrumental variables; LD, Linkage disequilibrium; ORs, Odds ratios; CIs, Confidence intervals; IL-6, Interleukin-6; TNF-α, Tumor necrosis factor-α; CRP, C-reactive protein.

Data Sharing Statement

The data used in this study were obtained from public GWAS data. The data generated and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval

The study has been approved by the Institutional Review Board of the Peking Union Medical College Hospital (Ethics Approval Number: I-24ZM0035) and the informed consent was found in the original studies.

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

Lu Che and Han Zang are co-first authors for this study. The authors report no conflicts of interest in this work.

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