Nature and Science of Sleep

ORIGINAL RESEARCH

Evaluation of Joint Effect of Frailty and Sleep Health on Cardiometabolic Multimorbidity in Aging Population

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Background: Sleep and frailty are established influencing factors for cardiometabolic diseases (CMDs). However, their joint effects on cardiometabolic multimorbidity (CMM) in older adults remain poorly understood. This study aimed to assess the joint effect of sleep health and frailty on CMD prevalence and severity, with an emphasis on subgroup-specific health risk profiles.

Methods: This study analyzed 8944 adults aged ≥60 years from the National Health and Nutrition Examination Survey (NHANES, 2007–2018). Weighted Logistic and quasi-Poisson regression models were used to assess the associations between sleep health, frailty, and CMD/CMM burden. Mediation analyses were used to examine the indirect effects of frailty index (FI) on the associations between sleep and CMM. Further cross-stratification of the population was conducted to evaluate the differences in characteristic indicators of health risks and biological aging.

Results: Poor sleep and frailty exhibited dose-dependent joint effects on CMD risk. After full adjustment, poor sleep combined with frailty had an incidence rate ratio (IRR) of 2.01 (95% CI: 1.78, 2.27) for existing cumulative number of CMDs (p for interaction = 0.006). The indirect effect of the FI explained 57.80% of the relationship between sleep health and the cumulative number of CMDs. Frailty was mainly manifested as differences in individual inflammation and aging indicators (eg, Systemic inflammation response index, Phenoage acceleration), while poor sleep was more reflected in changes in metabolic indicators (eg, Metabolic score for insulin resistance).

Conclusion: Poor sleep and frailty jointly amplified associations with CMM in older US adults. The relationship between sleep and CMM could be partially explained by FI. Elderly individuals with poor sleep should focus on changes on metabolic indicators, while those combined with frailty need to pay extra attention to aging and inflammation indicators.

Keywords: sleep, frailty, cardiometabolic diseases, multimorbidity

Introduction

As the global population ages and chronic diseases grow, there is an urgent need to understand how lifestyle factors and physiological vulnerabilities cumulatively impact health outcomes. Recent projections indicate that by 2050, the prevalence rate of hypertension among the elderly in the United States will exceed 80%, and the prevalence rate of diabetes will be close to 40%.[1] Among older adults, cardiometabolic diseases (CMDs), including hypertension, heart disease, type 2 diabetes, and stroke, constitute leading contributors to morbidity and mortality.[2–4] Any combination of these diseases is linked to a multiplicative increase in the mortality risk[5,6] and further complicates the management of diseases and healthcare services. Cardiometabolic multimorbidity (CMM) has become a major public health challenge. Identifying modifiable risk factors as well as their combined effect with age-associated vulnerabilities is imperative to devise effective preventive and intervention strategies.

Sleep represents a critical modifiable behavioral factor. Approximately 50% of older adults experience sleep-related complaints,[7] such as difficulty in initiating or maintaining sleep.[8] The most common sleep issues (such as insomnia,

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fragmented sleep, and sleep apnea) in the older adults[9] are linked to adverse cardiometabolic outcomes.[10,11] Inadequate or poor-quality sleep may impair cardiovascular function by increasing systemic inflammation, metabolic dysregulation, and accelerating cellular aging.[12,13] Concurrently, frailty, characterized by diminished physiological reserves and increased sensitivity to stress, is a critical marker of vulnerability in aging population.[14,15] Frail individuals are particularly vulnerable to adverse health events, including the accelerated progression of CMDs and multimorbidity.[16,17] Despite their distinct pathophysiological underpinnings,[18,19] sleep problems and frailty often coexist,[20,21] potentially interacting to amplify health risks in elderly people.

Though previous studies have independently examined the association between sleep or frailty with health outcomes, a comprehensive understanding of their combined effects remains limited.[22,23] Considering the bidirectional connection between sleep and frailty, this knowledge gap is particularly salient.[24] Poor sleep may accelerate the onset of frailty, and frailty may further disrupt sleep architecture, continuously exacerbating health risks. To tackle this issue, our study was designed to achieve the following objectives: (1) investigate associations between sleep health and CMDs/CMM, and (2) explore the joint and mediating effects of sleep and frailty on these outcomes, with emphasis on subgroup disparities.

Methods

Data Source and Study Population

The NHANES is a research initiative from Centers for Disease Control and Prevention (CDC) whose objective is to assess the health and nutritional status among the non-institutionalized demographic. The NHANES provides a nationally representative sample of the US population by using a complex, multi-stage, probability-clustered sampling design. Respondents complete structured home interviews and undergo a series of evaluations, including physical examinations, laboratory tests, and interviews at the Mobile Examination Center (MEC).

This study utilized data from the NHANES (2007–2018) involving 59,842 participants. These specific cycles were chosen due to the consistent and complete measurement of the variables required, particularly the sleep disorders questionnaire (SLQ) and physical functioning questionnaire (PFQ). From an initial sample of 11,910 adults aged ≥60 years, we excluded individuals with incomplete sleep behavior data (n = 1520), undocumented CMD status (n = 186), insufficient frailty index (FI) completion (<80% of items, n = 49), or missing covariates (n = 1211). The final analytical sample comprised 8944 older adults (Figure 1).

Sleep Health Assessment

Referring to previous studies,[22,25–27] we developed a composite sleep health score (range: 0–4) based on four dimensions: sleep duration, sleep disorders, subjective sleep continuity, and sleep satisfaction. Sleep duration was categorized as short (<7 hours/night), normal (7–9 hours/night), or long (>9 hours/night).[28–30] Sleep disorder was defined as physician diagnosis, or "How often do you snort or stop breathing" answered with "Frequently (5 or more nights a week)", or "How often feel overly sleepy during day" answered with "Almost always (≥16 days/month)". Sleep continuity was assessed by the number of nighttime urinations, with ≥2 times per night considered as sleep being easily interrupted. Subjective sleep satisfaction was assessed through self-reported trouble sleeping. Each dimension was scored as optimal (0) or suboptimal (1). Total scores classified participants into three groups: healthy (0), intermediate (1–2), or poor (3–4) sleep health status.

Definition of CMDs

CMDs were defined as hypertension, diabetes, heart disease, and stroke. Hypertension was diagnosed based on self-reported physician diagnosis, antihypertensive medication use, or mean systolic/diastolic blood pressure of three measurements ≥140/90 mmHg. Diabetes was confirmed through fasting glucose ≥7.0 mmol/L, hemoglobin A1c ≥6.5%, oral glucose tolerance test 2-hour ≥11.1 mmol/L, or self-reported medical history. Heart disease included physician-confirmed diagnoses of angina pectoris, myocardial infarction (MI), coronary heart disease (CHD), or congestive heart failure (HF). Stroke was defined as self-reported physician diagnosis. Participants were classified into three groups: free CMD (no diagnosis), single CMD (one diagnosis), or cardiometabolic multimorbidity (CMM; ≥ two diagnoses).[31,32]

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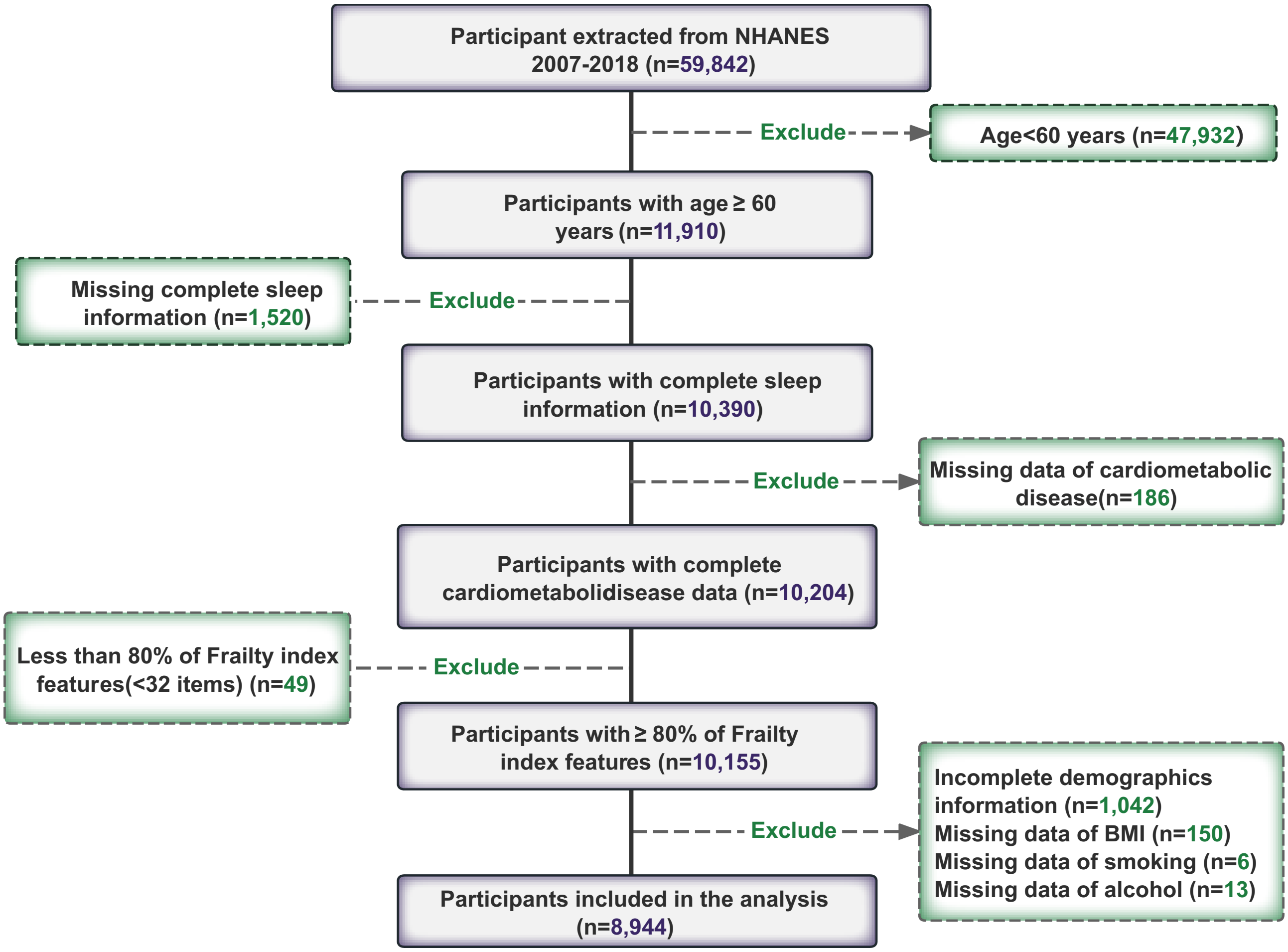

Figure 1 Flowchart of participant selection.

FI

Frailty was quantified using a 40-item FI based on deficits in physical function, cognition, comorbidities, anthropometric measures, and laboratory biomarkers[33,34] (Supplementary Table S1). Each deficit was scored from 0 (absent) to 1 (severe). The FI was computed as the ratio of deficits present to completed items (minimum 80% completion required). Participants were categorized into three groups: robust (FI ≤0.1), pre-frail (0.1< FI <0.25), and frail (FI ≥0.25).

Multifaceted Health Assessment

The present analysis evaluated multidimensional health assessments in five key domains: systemic inflammation, metabolic dysfunction, visceral adiposity, cardiometabolic risk, and biological aging. Systemic inflammation was quantified using the Systemic Inflammation Response Index (SIRI). The metabolic status was assessed using the triglyceride-glucose (TyG) index and metabolic score for insulin resistance (METS-IR). Visceral adiposity was characterized using a sex-specific visceral adiposity index (VAI). Cardiometabolic risk profiling was performed using the Cardiometabolic Index (CMI). Detailed computational algorithms for all indices are provided in the Supplementary Materials. Biological aging dynamics were analyzed using five algorithm-based metrics derived from the BioAge R package:[35] homeostatic dysregulation (HD), Klemera–Doubal method biological age (KDM), KDM acceleration (KDM-A), phenoage (PA), and PA acceleration (PAA).

Statistical Analysis

The analytical procedures rigorously accounted for the NHANES complex sampling design using survey-weighted methods to ensure national representativeness. Baseline characteristics were stratified by CMD status. To investigate the individual and joint effects of sleep health and frailty on CMDs, the number of CMDs, and changes in CMD status, we developed hierarchically adjusted Logistic regression models: Model 1 was adjusted for age, gender, and race as covariates, while Model 2 was further adjusted for socioeconomic factors (education, marital status, and poverty-to-income ratio [PIR]), body mass index (BMI), behavioral covariates (smoking, alcohol consumption, physical activity, and sedentary time). Full covariate specifications are detailed in the Supplementary Materials. Dose-response relationships in existing cumulative counts of CMD were quantified using weighted quasi-Poisson regression and expressed as incidence rate ratios (IRRs) with 95% confidence intervals (CIs). To explore the roles of frailty and sleep status in different populations, we designed three different control comparison groups: Free CMD vs Single CMD, Single CMD vs CMM, and Free CMD vs CMM. The participants were cross-categorized into nine groups based on their combined sleep status (healthy/intermediate/poor) and frailty level (robust/pre-frail/frail). The composite health risk profiles of inflammatory markers, glucose metabolism, visceral adiposity, and aging biomarkers were visualized using radar charts. Mediation analyses implemented using the R mediation package (1000 bootstrap iterations) quantified the proportional mediation of frailty in sleep-CMD associations.

Stratified analyses were conducted by age, gender, and BMI to evaluate the impact of sleep on CMD. Sleep continuity (the number of nighttime urinations) was removed from the sleep health score to examine the robustness of the results. Sensitivity analyses confirmed the robustness by alternatively modeling frailty as a log-transformed continuous variable and stratified analyses. We used the following methods to examine the robustness of the joint effect: (1) constructed an unordered multinomial logistic regression model; (2) stratified by age and gender. All analyses were conducted using R (version 4.3.1). All tests were two-sided, with a statistical significance level set at $\alpha=0.05$.

Results

Participant Characteristics Stratified by CMD Status

The final analytical sample included 8944 participants, representing a weighted population of 49,340,699 adults. Table 1 summarized baseline characteristics stratified by CMD status. Participants had an average age of 69.45 ± 6.72 years, with 54.5% female. Sleep health categories were distributed as: healthy (28.2%), intermediate (61.4%), and poor (10.4%). Frailty status included robust (30.6%), pre-frail (50.5%), and frail (18.9%).

Compared to free-CMD individuals, participants with single-CMD were older, more likely to have obesity, lower socioeconomic status (education and income), reduced physical activity, poor sleep health (eg, abnormal sleep duration, sleep disorders, sleep disruption), and elevated frailty level ($p<0.05$). These trends intensified in participants with cardiometabolic multimorbidity (CMM), who also exhibited higher proportions of males and non-drinkers ($p<0.05$).

The most common CMD combinations among participants were: isolated hypertension, hypertension with diabetes, hypertension with heart disease, and hypertension with diabetes and heart disease. Weighted and unweighted results showed similar patterns (Supplementary Figure S1).

Associations of Sleep Status, Frailty Levels, and CMD Burden

In fully adjusted models, poor sleep status was significantly associated with hypertension [odds ratio (OR) (95% CI): 2.33 (1.68, 3.22)], diabetes [OR (95% CI): 1.87 (1.46, 2.40)], heart disease [OR (95% CI): 2.38 (1.75, 3.23)], and stroke [OR (95% CI): 2.51 (1.77, 3.54)]. A graded association was observed between frailty and CMD risk (Figure 2 and Supplementary Tables S2-S3). Sleep status [IRR (95% CI): 1.42 (1.32, 1.52)] and frailty level [IRR (95% CI): 1.84 (1.70, 2.00)] were independently associated with higher cumulative CMD burden (Table 2). Stratified analyses by three CMD status groups revealed that poor sleep status was linked to both single CMD [OR (95% CI): 3.06 (2.08, 4.51)] and CMM [OR (95% CI): 5.63 (3.84, 8.25)] among CMD-free individuals. Among participants with existing CMD, poor sleep status was associated with a 1.89-fold higher odds ratio of CMM [OR (95% CI): 1.89 (1.45, 2.45)]. Significant associations between frailty and CMD status were found in all three control groups (Table 3).

Table 1 Baseline Characteristics According to the CMD Status: NHANES, 2007–2018

Characteristic	Overall N = 8944 (100.0%)	Free CMD N = 1702 (23.4%)	Single CMD N = 3766 (42.9%)	CMM N = 3476 (33.7%)	P^a
Age	69.45 ± 6.72	67.27 ± 6.08	69.56 ± 6.69	70.83 ± 6.79	<0.001
Age group					<0.001
60–69 years	4622 (54.5%)	1075 (69.2%)	1960 (53.5%)	1587 (45.6%)	
70–79 years	2785 (30.2%)	446 (23.1%)	1165 (31.3%)	1174 (33.8%)	
≥80 years	1537 (15.2%)	181 (7.7%)	641 (15.2%)	715 (20.5%)	
Gender					<0.001
Male	4452 (45.5%)	836 (43.6%)	1767 (42.6%)	1849 (50.5%)	
Female	4492 (54.5%)	866 (56.4%)	1999 (57.4%)	1627 (49.5%)	
Race					<0.001
Non-Hispanic White	4431 (79%)	938 (85.4%)	1874 (80.0%)	1619 (73.2%)	
Non-Hispanic Black	1884 (8.3%)	233 (4.3%)	801 (8.2%)	850 (11.3%)	
Mexican American	1023 (3.8%)	189 (3.1%)	423 (3.6%)	411 (4.6%)	
Other Hispanic	895 (3.5%)	197 (3.1%)	377 (3.5%)	321 (3.7%)	
Other/multiracial	711 (5.4%)	145 (4.1%)	291 (4.7%)	275 (7.1%)	
Education					<0.001
< High School	2549 (17.2%)	379 (11.2%)	1015 (16.3%)	1155 (22.6%)	
High School	2128 (24.9%)	342 (19.8%)	919 (25.7%)	867 (27.3%)	
> High School	4267 (57.9%)	981 (69%)	1832 (57.9%)	1454 (50.1%)	
Marital status					0.007
Married/Living with partner	5214 (64.3%)	1085 (69.7%)	2175 (63.7%)	1954 (61.3%)	
Never married /Separated /Widowed / Divorced	3730 (35.7%)	617 (30.3%)	1591 (36.3%)	1522 (38.7%)	
PIR					<0.001
< 1.3	2584 (17.3%)	383 (11.1%)	1053 (16.9%)	1148 (22.1%)	
1.3–3.5	3737 (40.0%)	657 (34.0%)	1571 (39.8%)	1509 (44.3%)	
≥ 3.5	2623 (42.7%)	662 (54.9%)	1142 (43.3%)	819 (33.6%)	
BMI					<0.001
Underweight/Normal	2221 (24.6%)	605 (36.2%)	1017 (25.3%)	599 (15.7%)	
Overweight	3228 (35.7%)	653 (37.4%)	1418 (37.9%)	1157 (31.7%)	
Obese	3495 (39.7%)	444 (26.4%)	1331 (36.8%)	1720 (52.6%)	
Smoke					<0.001
Never	4367 (49.2%)	878 (53.9%)	1912 (50.5%)	1577 (44.2%)	
Former	3456 (39.9%)	606 (34.5%)	1385 (39.2%)	1465 (44.4%)	
Current	1121 (10.9%)	218 (11.6%)	469 (10.3%)	434 (11.4%)	
Alcohol	5782 (68.6%)	1144 (71.6%)	2454 (70.2%)	2184 (64.6%)	0.014
Physical activities					<0.001
Less physical activities	4904 (50.0%)	779 (40.4%)	1963 (47.8%)	2162 (59.4%)	
MVPA	4040 (50.0%)	923 (59.6%)	1803 (52.2%)	1314 (40.6%)	
Sedentary time (hours)	7.12 ± 12.00	6.11 ± 4.87	7.29 ± 14.16	7.61 ± 12.45	<0.001
Sleep status group					
Healthy	2210 (28.2%)	570 (36.3%)	992 (29.2%)	648 (21.2%)	<0.001
Intermediate	5643 (61.4%)	1038 (60.5%)	2381 (61.2%)	2224 (62.3%)	
Poor	1091 (10.4%)	94 (3.1%)	393 (9.6%)	604 (16.5%)	
Sleep duration					<0.001
<7h	2775 (25.7%)	465 (21.0%)	1165 (25.9%)	1145 (28.7%)	
7–9h	5483 (66.9%)	1134 (74.1%)	2335 (66.9%)	2014 (62.1%)	
>9h	686 (7.3%)	103 (4.9%)	266 (7.2%)	317 (9.2%)	
Trouble sleeping	2670 (33%)	397 (27.7%)	1041 (31.7%)	1232 (38.4%)	<0.001
Sleep disorders	958 (10.9%)	105 (5.8%)	329 (9.5%)	524 (16.1%)	<0.001
Sleep disruption	4235 (41.4%)	607 (30.7%)	1721 (40.7%)	1907 (49.6%)	<0.001
Frailty level group					<0.001
Robust	2500 (30.6%)	818 (51.2%)	1211 (32.2%)	471 (14.1%)	
Pre-frail	4449 (50.5%)	729 (42.2%)	1959 (53.4%)	1761 (52.7%)	
Frail	1995 (18.9%)	155 (6.7%)	596 (14.4%)	1244 (33.1%)	

Notes: [a]*P* value adjusted after Bonferroni correction. Unweighted N (weighted %) for categorical variables: Chi-squared test with Rao & Scott's second-order correction. Weighted Mean ± SD for continuous variables: Kruskal–Wallis rank-sum test for complex survey samples.

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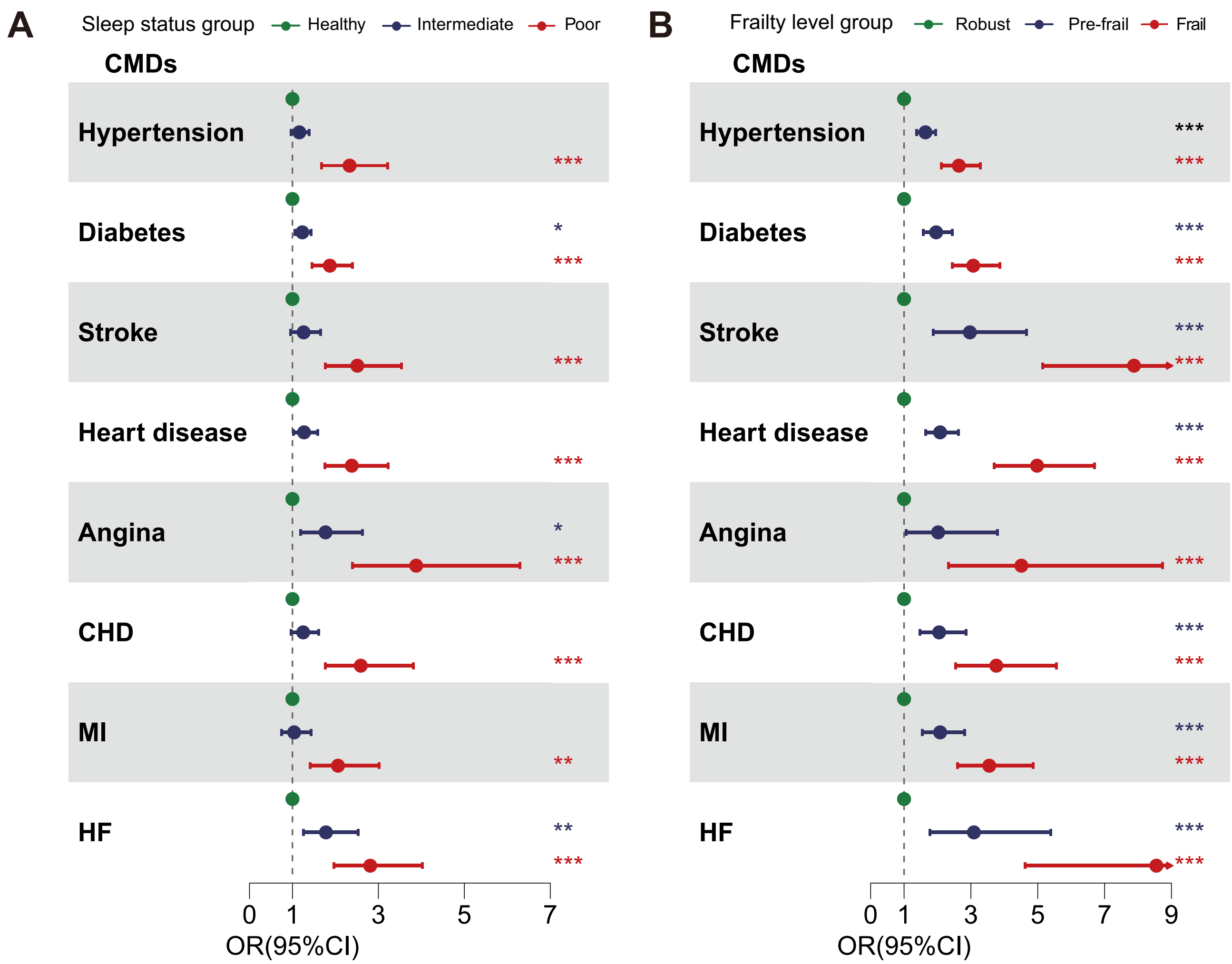

Figure 2 Associations of sleep status and frailty level with cardiometabolic diseases.
Note: Forest plots show adjusted ORs with 95% CI for (**A**) sleep status and (**B**) frailty level. Models were adjusted for age, gender, race, education, marital status, PIR, BMI, smoking, alcohol consumption, physical activity, and sedentary time. *P* values were corrected by the Benjamini & Hochberg method: **p* <0.05, ***p* <0.01, ****p* <0.001.

Joint Effects of Sleep Status and Frailty Level on the CMD Burden

We further explored the joint effect of frailty and sleep status on CMD burden. The results showed that the strength of these associations increased progressively with worsening sleep status or increasing frailty level (Supplementary Figure S2).

Table 2 Association Between Sleep Status and Frailty Level with the Number of CMDs

	Characteristic	Model 1[a]				Model 2[b]			
		IRR	95% CI	p	Adjusted p[c]	IRR	95% CI	p	Adjusted p[c]
Number of CMDs	**Sleep Status Group**								
	Healthy	Ref.	Ref.			Ref.	Ref.		
	Intermediate	1.16	1.10, 1.24	<0.001	<0.001	1.11	1.04, 1.17	<0.001	0.001
	Poor	1.62	1.50, 1.74	<0.001	<0.001	1.42	1.32, 1.52	<0.001	<0.001
	Frailty level group								
	Robust	Ref.	Ref.			Ref.	Ref.		
	Pre-frail	1.53	1.42, 1.63	<0.001	<0.001	1.41	1.31, 1.51	<0.001	<0.001
	Frail	2.17	2.02, 2.34	<0.001	<0.001	1.84	1.70, 2.00	<0.001	<0.001

Notes: [a]Adjusted for age, gender, race. [b]Adjusted for age, gender, race, education, marital status, PIR, BMI, smoking, alcohol, physical activity, and sedentary time. [c]Benjamini and Hochberg correction for multiple testing.
Abbreviations: IRR, Incidence Rate Ratio; CI, Confidence Interval.

Table 3 Association Between Sleep Status and Frailty Level with the Distribution of CMD Status

	Characteristic	Model 1[a]				Model 2[b]			
		OR	95% CI	p	Adjusted p[c]	OR	95% CI	p	Adjusted p[c]
Free CMD vs Single CMD	**Sleep status group**								
	Healthy	Ref.	Ref.			Ref.	Ref.		
	Intermediate	1.17	0.97, 1.42	0.103	0.155	1.12	0.92, 1.37	0.246	0.396
	Poor	3.60	2.47, 5.23	<0.001	<0.001	3.06	2.08, 4.51	<0.001	<0.001
	Frailty level group								
	Robust	Ref.	Ref.			Ref.	Ref.		
	Pre-frail	1.85	1.53, 2.24	<0.001	<0.001	1.67	1.38, 2.03	<0.001	<0.001
	Frail	3.08	2.24, 4.24	<0.001	<0.001	2.43	1.72, 3.44	<0.001	<0.001
Single CMD vs CMM	**Sleep status group**								
	Healthy	Ref.	Ref.			Ref.	Ref.		
	Intermediate	1.33	1.14, 1.56	<0.001	0.001	1.19	1.02, 1.39	0.029	0.047
	Poor	2.34	1.81, 3.02	<0.001	<0.001	1.89	1.45, 2.45	<0.001	<0.001
	Frailty level group								
	Robust	Ref.	Ref.			Ref.	Ref.		
	Pre-frail	2.32	1.88, 2.86	<0.001	<0.001	2.04	1.65, 2.53	<0.001	<0.001
	Frail	5.63	4.19, 7.57	<0.001	<0.001	4.19	3.08, 5.69	<0.001	<0.001
Free CMD vs CMM	**Sleep status group**								
	Healthy	Ref.	Ref.			Ref.	Ref.		
	Intermediate	1.60	1.30, 1.98	<0.001	<0.001	1.42	1.12, 1.80	0.004	0.007
	Poor	8.49	5.85, 12.31	<0.001	<0.001	5.63	3.84, 8.25	<0.001	<0.001
	Frailty level group								
	Robust	Ref.	Ref.			Ref.	Ref.		
	Pre-frail	4.17	3.32, 5.25	<0.001	<0.001	3.29	2.61, 4.14	<0.001	<0.001
	Frail	16.35	11.54, 23.16	<0.001	<0.001	9.53	6.65, 13.64	<0.001	<0.001

Note: [a]Adjusted for age, gender, race. [b]Adjusted for age, gender, race, education, marital status, PIR, BMI, smoking, alcohol, physical activity, and sedentary time. [c]Benjamini and Hochberg correction for multiple testing.
Abbreviations: OR, Odds Ratio; CI, Confidence Interval.

Poisson regression further quantified the effect of co-exposure on the cumulative number of CMD [IRR (95% CI): 2.01 (1.78, 2.27)] (Figure 3A). The multiplicative interaction between frailty and sleep status had a p-value of 0.006. We modified the subgrouping of sleep (healthy [0–1 scores]/unhealthy [2–4 scores]) and frailty (non-frail [FI<0.21]/frail [FI≥0.21]) to reduce the bias in data distribution caused by an excess of subgroups and evaluate the robustness of the findings. Unhealthy sleep combined with frailty had significant associations with CMDs. In three control comparison groups, participants with both unhealthy sleep and frailty had an OR of 2.06 for single CMD [95% CI: 1.48, 2.88], while the OR for CMM increased to 5.71 [95% CI: 4.16, 7.83]. In the subgroup who had been diagnosed with at least one CMD, poor sleep combined with frailty was significantly associated with the prevalence of CMM [OR (95% CI): 2.98 (2.40, 3.70)] (Figure 3B and Supplementary Table S4).

Mediation Effects of FI on Sleep Health Score and CMDs, the Number of CMDs, and CMD Status Distribution Associations

To further explore the role of frailty in the association among sleep status, number of CMDs, and changes in CMD status, we conducted a mediation analysis. The correlation between sleep health scores and cumulative number of CMDs was significantly mediated by FI, with a mediation proportion of 57.80%. Compared with the population without CMD, the mediating proportion of FI on the occurrence of CMD was 34.02%, and the mediating proportion of FI on the occurrence of CMM was 46.74%. In the subgroup of patients with at least one type of CMD, significant mediating effect of FI between sleep and CMM was found, but the direct effect was not significant (p_{ADE} = 0.160, p_{ACME} <0.001, Prop. = 73.16%) (Figure 4 and Supplementary Table S5). Additionally, FI played a significant mediating role in the associations

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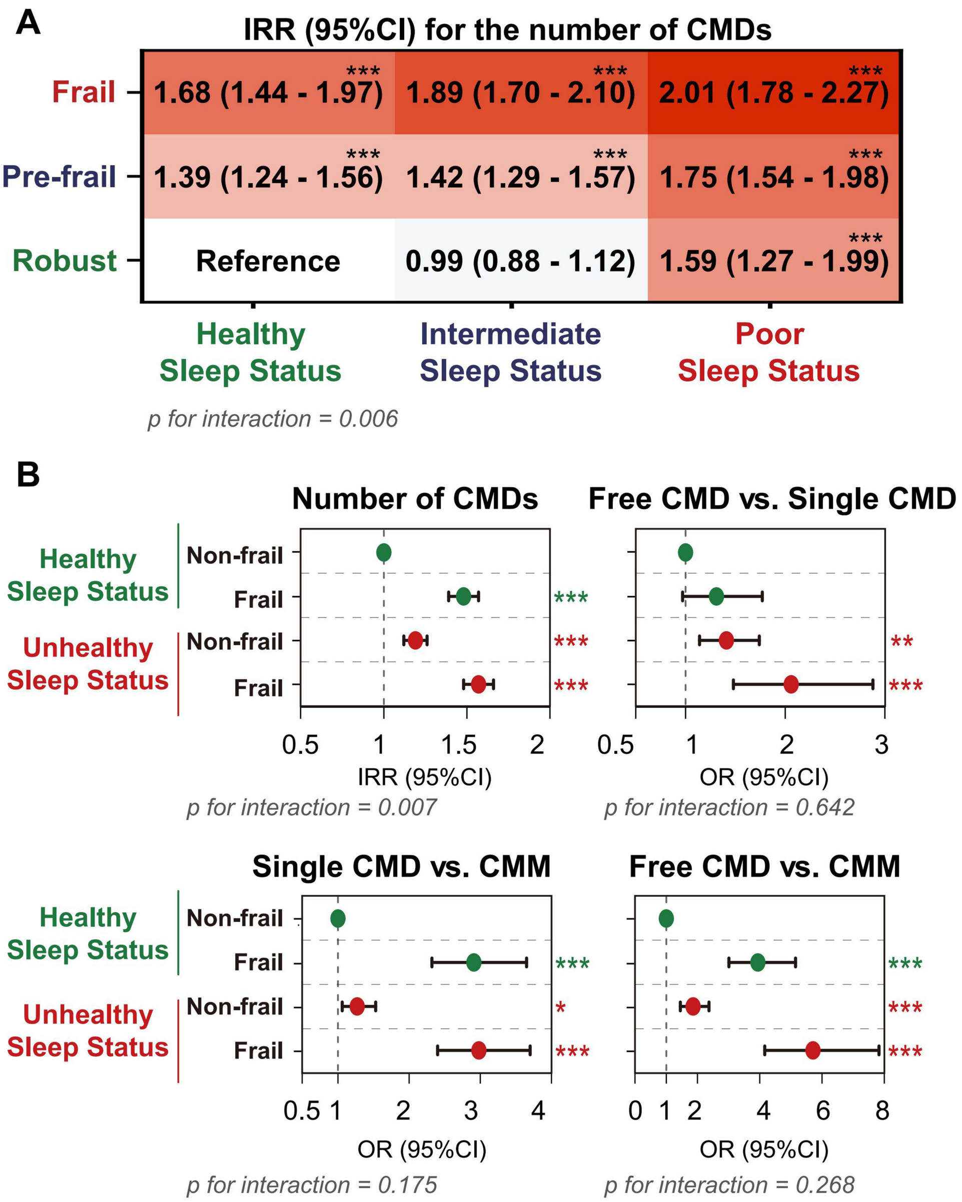

Figure 3 Joint effects of sleep status and frailty level on cardiometabolic disease burden.

Notes: (**A**) IRR for sleep status and frailty on CMDs cumulative number. (**B**) IRR and OR for re-grouped sleep status and frailty on CMDs cumulative number and status distribution. Models were adjusted for age, gender, race, education, marital status, PIR, BMI, smoking, alcohol consumption, physical activity, and sedentary time. *P* values were corrected by the Benjamini & Hochberg method: *p <0.05, **p <0.01, ***p <0.001.

between sleep health scores and hypertension, diabetes, angina pectoris, CHD, and heart failure, with mediation proportions of 43.78%, 52.51%, 37.49%, 51.47%, 59.49%, and 62.45%, respectively. In the mediation analysis of FI in sleep health scores and MI and stroke, no direct effect was found, but the mediation effect was significant, with mediation proportion of 54.38% and 81.26%, respectively (Supplementary Figure S3 and Table S5).

Radar Chart of Healthy and Aging Risk in Stratified Populations

Given the results of mediation analysis, we stratified the population to explore whether there were differences in the performance across five dimensions: inflammation level, metabolic function, obesity, cardiometabolic risk, and biological aging. Figure 5 showed a clear upward trend in the weighted mean values of inflammatory (eg, SIRI) and all biological aging indicators with increasing frailty levels. Under different frailty level groups, differences in the performance of health and aging indicators were observed between different sleep statuses. In the robust group, participants with poor

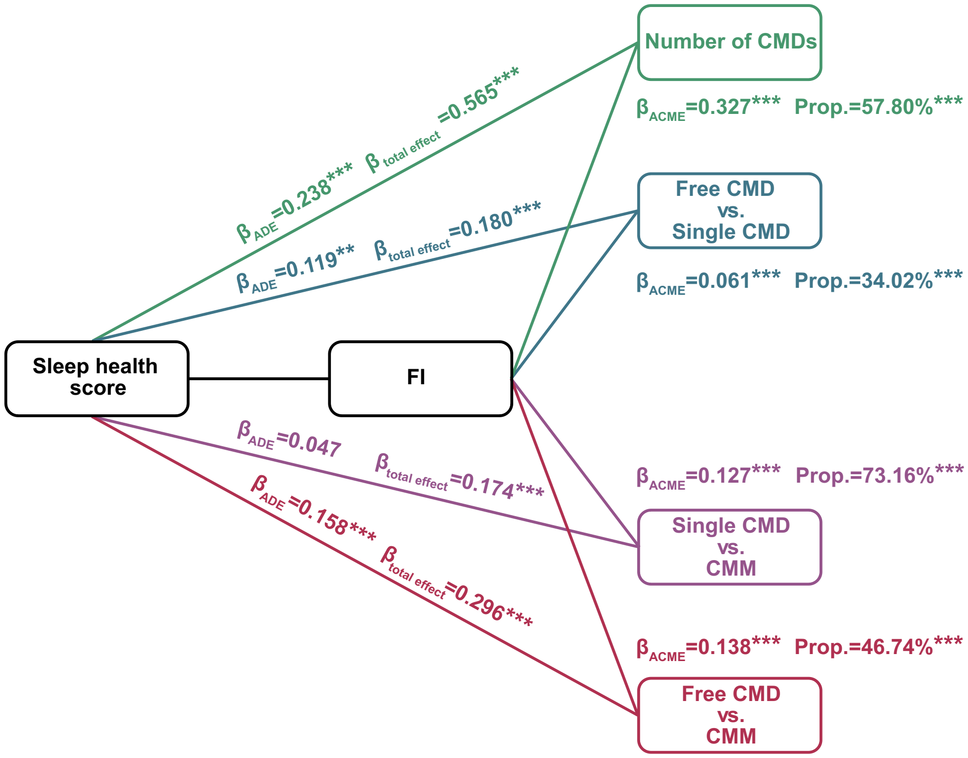

Figure 4 Mediation analysis of FI on the associations between sleep health and CMDs cumulative number, and status distribution.
Notes: ***p* <0.01, ****p* <0.001. Models were adjusted for age, gender, race, education, marital status, PIR, BMI, smoking, alcohol consumption, physical activity, and sedentary time.
Abbreviations: ADE, Average Direct Effect; ACME, Average Causal Mediation Effect; Prop., Proportion of Mediation.

sleep exhibited higher weighted means of BMI, SIRI, METS-IR, and CMI than those with healthy sleep ($p<0.05$). Among the pre-frail participants, those with poor sleep status showed statistically significant differences in SIRI, PA, PAA, and HD compared to those with healthy sleep ($p<0.05$). In the frail group, individuals with poor sleep status exhibited progressively higher BMI, VAI, PA, and CMI than those with healthy sleep status. However, differences were only statistically significant for BMI, METS-IR, PA, and KDM-A ($p<0.05$) (Supplementary Table S6–S8).

Sensitivity Analyses

When we repeated the analyses of the relationship between sleep and CMD burden stratified by age, gender, and BMI, the results did not change significantly from the original analysis (Supplementary Figures S4 and S5). Sleep continuity was removed from the sleep health score in order to remove the possibility of a reverse confounding effect from frequent nighttime urination. After reclassifying sleep status [healthy (0–1 scores), intermediate (2 scores), poor (3 scores)] and repeating the analysis, the results were consistent with the main analysis (Supplementary Table S9). Similar results were obtained when we replaced the frailty level group with a logarithmic transformation of the FI as a continuous variable (Supplementary Table S10). When we repeated the analyses of the relationship between frailty and CMD burden stratified by age, gender, and BMI, the results were similar to before (Supplementary Figures S6 and S7). The stratified analyses identified several statistically significant interactions; however, the majority appeared to lack clinical significance. We used the CMDs status as the dependent variable and constructed an unordered multinomial logistic regression model with repeated joint effects analyses, obtaining similar results (Supplementary Table S11). When we stratified by age and gender, the joint effects of sleep status and frailty on CMDs were similar to the main analysis results. Notably, in the Free CMD vs Single CMD comparison group, the joint effect was significant in females but not in males (Supplementary Tables S12 and S13).

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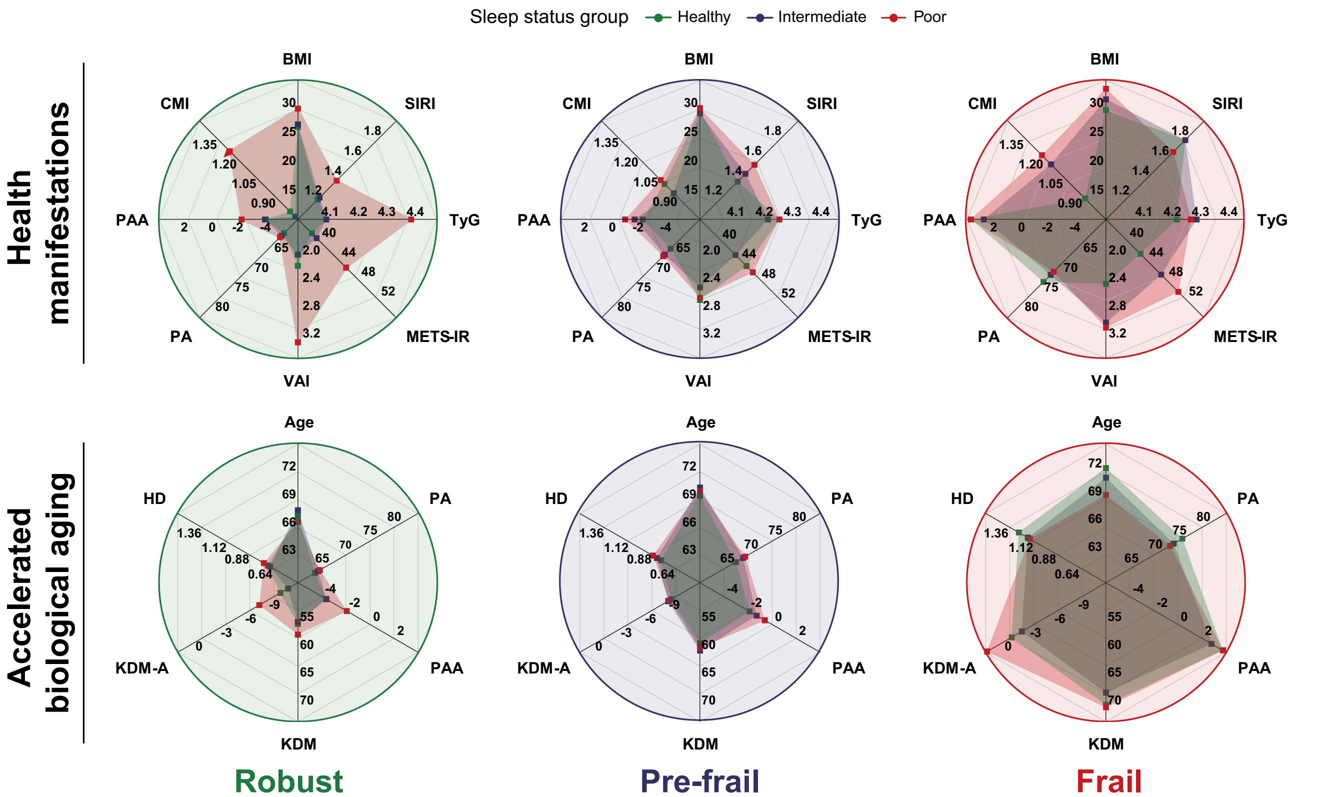

Figure 5 Health manifestations and acceleration biological aging profiles stratified by frailty levels.

Note: Weighted mean values of inflammation, metabolism, obesity, cardiometabolic risk, and aging indicators among participants with different levels of frailty.

Abbreviations: Inflammation level: SIRI, Systemic Inflammation Response Index. Metabolism function: METS-IR, Metabolic Score for Insulin Resistance; TyG, Triglyceride-glucose Index. Obesity: BMI, Body Mass Index (kg/m2); VAI, Visceral Adiposity Index. Cardiometabolic risk: CMI, Cardiometabolic Index. Biological aging: HD, Homeostatic Dysregulation; KDM, Klemera-Doubal Biological Age; KDM-A, KDM Acceleration; PA, Phenoage; PAA, Phenoage Acceleration.

Discussion

The present study provides valuable theoretical insights into the joint effect of poor sleep and frailty on CMDs and multimorbidity in older adults. We used a nationally representative sample in US to show that poor sleep and frailty act both independently and jointly to amplify CMD risk, multimorbidity burden, and the pace of biological aging. These findings will help to enhance our understanding of the multifactorial mechanisms that drive age-related health decline.

Individuals with either poor sleep status or frailty exhibited more associations with CMDs and greater multimorbidity. This pattern was observed in three controlled comparisons (Free CMD vs Single CMD, Single CMD vs CMM, and Free CMD vs CMM), and was consistent with previous reports.[36,37] The complex association between frailty and sleep disorders[24,38,39] may lead to the greater risk of CMD and CMM in both poor sleep and frailty. These various pathophysiological interactions create a vicious feedback,[40] which eventually leads to adverse cardiometabolic outcomes. Our findings point to a logical correlation between the severity of poor sleep or frailty and CMD prevalence. The prevalence of severe CMDs (eg, HF) or excessive CMM can lead to reduced physical function and disturbed sleep.[41,42] Further research is needed to establish causal pathways.

Frailty was a key mediating factor between poor sleep and CMDs or CMM, similar to previous studies.[43] Mediation analysis showed that frailty explained 57.80% of the cumulative burden of poor sleep status on CMDs, especially 81.26% for stroke and 62.45% for HF. In addition, individuals with poor sleep status or frailty showed increased numbers of inflammatory and metabolic markers, along with accelerated biological aging. These findings are highly consistent with the systemic physiological reserve depletion characteristic of frailty:[44] poor sleep may accelerate biological aging[45] and metabolic dysregulation,[46] leading to the premature appearance of frailty phenotypes (eg, sarcopenia and immunosenescence).[47] These phenotypes can in turn impair cardiovascular and pancreatic functions through metabolic inflammatory pathways (such as elevated IL-6 and TNF-α).[48]

Both poor sleep and frailty were associated with poor health performance, but they showed different health characteristics. Frailty was primarily characterized by inflammation and accelerated aging, while poor sleep more likely to manifest as metabolic imbalance (eg, imbalances in energy intake and expenditure, and increased secretion of appetite hormones),[49] which further contributed to obesity. Evidence showed that visceral adiposity significantly increases the risk of cardiovascular disease and type 2 diabetes, while fat deposition in the abdomen and neck can contribute to sleep breathing apnea,[50] both of them increase the cardiometabolic burden. Consequently, we propose that non-frail individuals need focus on metabolic parameters (eg, BMI, METS-IR) which can be improved through diet, exercise, psychotherapy, etc. Frail individuals require additional attention to inflammatory and aging markers. Age-related alterations in body composition, metabolism, and pharmacokinetics can induce or exacerbate coexisting conditions.[50]

Previous studies found that individuals with both circadian syndrome and frailty were more likely to have new-onset cardiovascular disease.[51] However, the joint effect of sleep and frailty in the Free CMD vs Single CMD comparison group was only significant in females in our study. This may be due to the fact that females are more susceptible to long-term wakefulness and circadian rhythm disruption, making them more likely to develop metabolic disorders.[52] At the same time, females often experience a heavier frailty burden than males.[53] On one hand, the downregulation of estrogen associated with aging reduces the protective effect of immune-regulating genes.[54,55] On the other hand, there are gender differences in immune responses and inflammatory signaling pathways. The Y chromosome carried by males encodes some inflammatory pathway genes that have higher innate pro-inflammatory activity and lower adaptive immunity.[56] This gap will further increase after the age of 65.[53] This condition will significantly increase the risk of frailty in women, while also amplifying the risk of CMD when combined with unhealthy sleep. However, it does not mean that elderly men can ignore sleep and frailty issues. Frailty was related to the prognosis of CMD patients, especially elderly men.[57] In our study, unhealthy sleep coexisting with frailty was associated with the development of CMM. Therefore, we recommend that both males and females focus on the prevention and intervention of sleep issues and frailty.

This study had several limitations. First, although we used a large sample size and complex statistical models, the cross-sectional design was insufficient for concluding causal (eg, whether CMD drives sleep deterioration/frailty).[58,59] Second, in large-scale population studies, polysomnography—widely regarded as the gold standard for assessing sleep cycles and sleep disorders, is often difficult to implement due to its high cost. The collection of sleep behavior data mainly relied on subjective reports, which may lead to recall bias or misclassification. Although we have made efforts to conduct a comprehensive assessment of sleep disorders, we have focused only on the more common clinical manifestations such as snoring, apnea, and daytime sleepiness. These symptoms were merely characteristic manifestations of insomnia or sleep apnea, which may lead to an underestimation of the prevalence of sleep disorders. Future research should consider other sleep disorders (eg, parasomnias, circadian rhythm sleep-wake disorders, and restless legs syndrome) and further expand by incorporating low-cost and easily applicable objective measurements (eg, actigraphy). Third, although we selected as many covariates as possible, residual confounding (eg, medications, genetic predisposition) may still exist. Fourth, although previous studies have reported the potential of using Poisson models for estimating IRRs,[60–63] the IRRs in this study were based on cross-sectional data considerations. They only reflected the relative ratios of the existing CMD burden (number of diseases) rather than the incidence rates over time. Finally, the applicability of the NHANES data to populations outside the United States requires careful consideration because of potential factors such as genetic and cultural differences.

Conclusion

Our findings indicated that sleep health was associated with CMDs and status distribution in older adults. Frailty level and sleep had a joint effect, amplifying the strength of association with the cumulative incidence of CMDs. FI was a key mediating factor in the Sleep-CMM association. These findings will contribute to a better understanding of the relationships and underlying mechanisms among sleep health, frailty, CMD, and CMM. The differences in health risk indicators among populations with different sleep statuses and frailty levels suggested targeted detection for different groups: Elderly individuals with poor sleep should focus on changes on metabolic indicators, while those combined with frailty need pay extra attention to aging and inflammation indicators.

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Abbreviations

CMD, Cardiometabolic disease; CMM, Cardiometabolic multimorbidity; FI, Frailty index; NHANES, National Health and Nutrition Examination Survey; MI, Myocardial infarction; CHD, Coronary heart disease; HF, Heart failure; BMI, Body mass index; SIRI, Systemic inflammation response index; TyG, Triglyceride-glucose; VAI, Visceral adiposity index; CMI, Cardiometabolic index; METS-IR, Metabolic score for insulin resistance; HD, Homeostatic dysregulation; KDM, Klemera-Doubal method biological age; KDM-A, Klemera-Doubal method biological age acceleration; PA, Phenoage; PAA, Phenoage acceleration; PIR, Poverty index ratio; MVPA, Moderate to vigorous intensity physical activity; OR, Odds ratio; IRR, Incidence rate ratio; CI, Confidence interval.

Data Sharing Statement

The NHANES data supporting the results of this study are available online through https://wwwn.cdc.gov/nchs/nhanes/Default.aspx.

Ethics Approval and Consent to Participate

NHANES study protocol was reviewed and approved by the National Center for Health Statistics Ethics Review Board, as detailed on their official website (https://www.cdc.gov/nchs/nhanes/about/erb.html?CDC_AAref_Val). According to Article 32, Items 1 and 2 of the "Ethical Review Measures for Life Science and Medical Research Involving Humans" (released on February 18, 2023) in China, this study meets the criteria for exemption from ethical review. Therefore, this study does not require approval from an ethics review committee. This study adhered to the ethical standards of the Declaration of Helsinki.

Author Contributions

Conceptualization: QZ; Data curation, Methodology and Visualization: XP and AT; Formal analysis: XP, AT, and JT; Validation: XP, AT, and YM; Project administration and Supervision: QZ, AT, and JT; Funding acquisition: QZ; Writing – original draft: XP; Writing – review and editing: QZ, XP, AT, JT, and YM. All authors drafted, substantially revised, or critically reviewed the article, and agreed on the final version of the manuscript. Furthermore, all authors have agreed on the journal to which the manuscript will be submitted and take responsibility for all aspects of the work.

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Disclosure

The authors declare no conflict of interest.

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