Research article

Sleep patterns, global mental status and mortality risk among middle-aged urban adults

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Abstract

Background: Sleep, cognition, and mortality may be interdependent.
Objective: We explored paths between sleep, cognition and mortality and potential interactions.
Methods: The study examines the relationship among sleep, global mental status, and mortality risk using data from 1364 participants from the Healthy Aging in Neighborhood of Diversity across the Life Span (HANDLS) study. We used Cox proportional hazards models and four-way decomposition models to analyze sleep patterns and global mental status.
Results: After a median time at risk of 8.2 years, 172 deaths occurred, with rate of 16 per 1000 person-years. A 1-unit increase in the Pittsburgh Sleep Quality Index (PSQI) global score was linked to a 7% increase in mortality risk in the reduced model, but this effect was attenuated in the full model. In both reduced and fully adjusted models, the PSQI global score and sleep quality domains interacted with global mental status, with poor sleep generally associated with mortality risk in the group with better global mental status at first-visit. In four-way decomposition models, total effects (TE) of PSQI scores on mortality risk were positive and statistically significant, while being mostly controlled direct effects. However, among women, the inverse TE of global mental status on mortality risk was partially mediated by PSQI sleep latency and the PSQI global.
Conclusions: Poor global mental status is associated with greater mortality risk at better sleep quality levels and vice versa. Further longitudinal studies with multiple sleep and cognitive performance repeats are needed to corroborate these findings.

Keywords

Alzheimer's disease, global mental status, mortality, sleep, urban adults

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Introduction

A healthy cognitive functioning is necessary for daily activities such as remembering to cook dinner or taking medication. Attention, working or short-term memory, long-term memory, reasoning, and movement coordination are all examples of cognitive domains that could affect activities of daily living. Poor cognitive performance measured in mid-[1] and later-life[2] is related with an increased risk of death, although the collective understanding of the mechanisms underlying these correlations remains incomplete. Cognitive function is most likely the product of complex interactions between environmental and genetic effects throughout life, which may also determine health and death trajectories.

Simultaneously, insufficient sleep duration or quality are emerging public health concerns linked to cardiometabolic

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risk factors such as obesity and population aging. It is believed that one in every five persons suffers from health problems related to poor sleep quality or insufficient sleep durations.[3,4] Evidence is mounting that (short or long) sleep duration,[5–9] sleep disturbances,[3,10,11] and obstructive sleep apnea (OSA)[12–15] have a positive link with all-cause,[3,9,13,14,16,17] cardiovascular-,[3,5,14,18] cancer-,[3,14,17,18] and dementia-specific[7] mortality rates. Despite differing definitions of sleep duration, most research assessing short sleep[3,7,9,18] or long sleep[6,9,16] as risk factors for all-cause or cause-specific death rates[19–22] have identified 7–8 h as the ideal range for sleep duration. A recent review of 42 cohort studies discovered a U-shaped relationship between sleep duration and mortality rate.[23] In some, but not all, studies, short and long sleep were found to have a detrimental effect; additionally, study outcomes may have been influenced by methodological concerns such as reverse causation, measurement, response, and confounding biases.[23]

Furthermore, few prospective longitudinal cohort studies have been conducted so far to assess the temporal connection between sleep and broadly characterized neurodegenerative illnesses such as dementia and age-related cognitive decline.[24–35] These investigations showed that insufficient sleep length, poor sleep quality, and sleep disorders were associated with adverse outcomes suggesting poor cognitive aging.

Given the interdependence of sleep, poor cognition, and mortality, it is pertinent to understand the paths between them and potential interactions among them. Nonetheless, no study has studied the mediating and moderating link between sleep, global mental status, and mortality risk in older persons, particularly in urban middle-aged adults, to date. We hypothesize that poor sleep quality is associated with higher risk of all-cause mortality and that there is synergism with poor cognitive performance in this relationship.

In our current investigation, we first examine whether global mental health and poor sleep patterns are connected to mortality risk, regardless of potential confounders and across sex and racial groups, as well as their 2-way interactions. Second, we use 4-way decomposition models to test whether poor sleep quality and global mental status outcomes interact to determine mortality risk. Additionally, we use this method to assess whether there is bidirectional mediation of "poor sleep quality"-mortality or "global mental status "-mortality through global mental status and poor sleep quality, respectively.

Methods

Database

We selected individuals from the Healthy Aging in Neighborhoods of Diversity Across the Life Span (HANDLS) study, based on specific inclusion and exclusion criteria outlined in Figure 1.[36] HANDLS is a longitudinal, interdisciplinary, prospective cohort study of socioeconomically diverse White and African American adults in Baltimore, MD that began in 2004. Between 2004 and 2009, baseline data (wave 1, w1) were obtained by home visits and physical examinations, including a cognitive test battery on the medical research vehicles (MRV). Between 2009 and 2013, participants returned to the MRV for a follow-up in-person wave (wave 3, w3). All participants signed written informed consent forms. The HANDLS study protocol was approved by the National Institutes of Health's Institutional Review Board, National Institute of Environmental Health Sciences.

Study sample

Starting from the follow-up visit (w_3), thereafter termed first-visit, 2468 participants had complete demographic data (Figure 1). We further excluded individuals with incomplete sleep data at w_3, resulting in 1548 participants. Of those, complete data on Mini-Mental State Examination

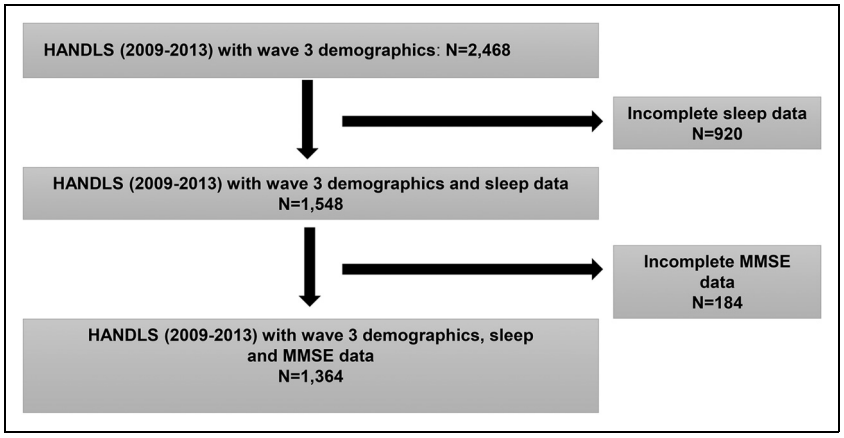

Figure 1. Participant flowchart: HANDLS 2004-2020.

(MMSE) total scores were available for 1364 individuals and no further exclusions were made beyond that point, given that all covariates were multiple imputed.

Mortality linkage

The HANDLS mortality status was collected prospectively through annual links to the National Death Index (NDI), National Center for Health Statistics.[37] Vital status information was available for all participants up to December 31, 2020 (https://www.cdc.gov/nchs/data/ndi/ndi_users_guide.pdf).

Sleep pattern assessment

The Pittsburgh Sleep Quality Index (PSQI) assesses sleep quality and disorders over a month,[38] with sub-scales assessing sub-optimal sleep length, daytime dysfunction, sleep disruption, sleep latency, sleep efficiency, and sleep quality.[38–40] A total score is computed by summing the sub-scales. The PSQI was utilized in two HANDLS follow-up waves (w3: 2009–2013 and w4: 2013–2017).[38] In this study, we only used w3 total and sub-scale scores. Administered during the MRV visit as part of the ACASI module,[39] this instrument consists of a scale with 19 self-report questions having response options that reflect sleeping habits for most days and nights.[38,41] These questions are integrated to generate seven component scores that reflect subjective sleep quality, sleep latency, sleep length, habitual sleep efficiency, sleep disruptions, sleeping medicine use, and daytime dysfunction. Each component was graded on a scale of 0 to 3, with "0" representing "no difficulty" and "3" indicating "severe difficulty".[38,41]

The seven component scores are summed to get a global PSQI score ranging from 0 to 21, with "0" indicating no difficulty and "21" indicating difficulty in all domains of sleep. Due to missingness of w3 data for the "sleep efficiency" component, 6 of the 7 components were employed in this investigation. Thus, with a theoretical range of 0–18, the global PSQI score totaled the components of sleep length, daytime dysfunction, sleep disturbance, sleep latency, sleep medicines, and sleep quality. The PSQI was demonstrated to have multidimensional psychometric qualities, justifying the usage of specific components in addition to the standard total score.[42] The full PSQI for another follow-up wave (wave 4) may be viewed on the HANDLS website: https://handls.nih.gov/codebooks/w04/Wave04-PSQI.pdf.

Cognitive assessment

The MMSE was the main cognitive test used in this study, reflecting global mental status at wave 3 (2009–2013). The total score was normalized (MMSEnorm) using a previously outlined process.[43]

Covariates

Additional factors were added because of their formerly known connection with cognitive performance or decline. We collected wave 3 (first-visit) data on age (continuous, years), sex (male, female), race (White, African American), poverty status (below versus above 125% of the federal poverty line), educational attainment (less than high school, high school, more than high school), and literacy (Wide Range Achievement Test, third edition [WRAT-3]) (Supplemental Methods).

In addition, we included a variety of health and behavioral characteristics such as current smoking status (0 = No versus 1 = Yes), illicit drug use (0 = No versus 1 = Yes, using any of marijuana, opiates, and cocaine), body mass index (BMI, weight/height2, $kg.m^{-2}$, continuous), self-rated health status categorized as 0 = poor/average (referent), 1 = good, and 2 = very good/excellent, the Healthy Eating Index (HEI-2010),[44] which reflects overall diet quality based on food and macronutrient-related guidelines for Americans for 2010, total energy intake (kcal/d), and depression symptomatology as assessed using the 20-item CES-D (Supplemental Methods). Finally, we considered among potential confounders, self-reported history of any cardiovascular disease as any of the following: atrial fibrillation, angina, coronary artery disease, congestive heart failure, and myocardial infarction, also measured at w3.

Statistical methods. We used Stata release 18[45] to conduct all our present analyses. We described the overall analytic sample at wave 3 as first-visit in this study, using means and proportions. Covariate data were multiple imputed using chained equations, with 5 imputations and 10 iterations. Limiting our analyses to the final selected sample (N = 1364), we compared continuous and categorical variables in the multiple imputed datasets across sex and race, respectively, using a series of linear and multinomial logit models with sex and race as the only predictors.

Survival probability and hazard rates were estimated by using time-to-event data, with the event being death from all causes and time (years) on study as the underlying time scale. First-visit age was used as time at entry in all analyses. Kaplan-Meier (K-M) estimates were presented to visualize preliminary findings, by categorizing continuous global mental status, measured by normalized MMSE, into below and above the median and poor sleep pattern, measured with PSQI total score, in a similar fashion. Accordingly, survival probabilities were compared over follow-up time, across global mental status and sleep pattern levels. χ^2 tests and the χ^2 test for trend, comparing observed and expected events with associated p-values, were used to compare survival probability estimates. To examine the association between sleep patterns at w3 and all-cause mortality, we fit a series of Cox proportional hazard regression models with sequential covariate

adjustment. In the reduced model, only age, sex, race, and poverty status were adjusted for. In the full model, all covariates described in the "Covariates" section were included, thus adjusting for other socio-economic factors (e.g., education and literacy), lifestyle and health-related factors including first-visit cardiovascular disease history. These models were then stratified according to global mental status (above versus below median) and a two-way interaction term between sleep patterns and global mental status was included in the original model. In a similar fashion, global mental status was then considered as the main exposure of interest and interaction with sleep patterns, particularly global PSQI (below and above the median) was tested.

Furthermore, the bi-directional mediating and moderating effects of global mental status and sleep patterns on all-cause mortality risk were tested using four-way decomposition models, in the overall sample, as well as stratifying by sex and by race. The reduced model was tested whereby the minimal set of potential confounders were included, namely age, sex, race and poverty status to reduce the possibility of including potential mediators in the model. Specifically, we tested the total effect of sleep patterns (global and subscales reflecting different aspects of poor sleep) on all-cause mortality, while testing for the mediating and moderating effect of global mental status at first-visit and adjusting for different sets of potential confounders. A similar approach was done to test the relationship in the opposite direction, whereby the main exposure was global mental status and the potential mediators/moderators were the global and sub-scale poor sleep pattern variables. In addition to the total effect (tereri, with 95% CI and p-value), four parameters decomposing the total effect according to mediation and interaction were also estimated with their 95% CI and p-value, namely ereri_cde (controlled direct effect: neither mediation nor interaction), ereri_interef (interaction referent: interaction only), ereri_intmed (mediated interaction: both mediation and interaction), ereri_pie (pure indirect effect: mediation only). Details related to *Med4way* command [https://github.com/anddis/med4way] and related methods are provided elsewhere.[46] Type I error was set at 0.050 for all analyses.

Results

Table 1 displays distribution of key study characteristics, overall and comparing them across sex and race groups. Female adults in this sample generally had lower literacy than their male counterparts, had higher BMI but lower proportion of current smokers and drug users, lower proportion with very good/excellent self-rated health, a higher CES-D score, and most notably poorer sleep based on the PSQI global score. After a median time at risk of 8.2 years, 172 deaths occurred, with rate of 16 per 1000 person-years. Over the time of follow-up, 15.3% of male adults died as compared to 10.8% of female adults in this sample. Racial differences were also detected, whereby African American adults were more likely to be living below poverty compared to their White counterparts (40% versus 29.6%), with lower literacy, and significantly greater proportion of current drug users (18.5% versus 10.0%) and current smokers (42.2% versus 34.6%). Depressive symptoms and the global measure of poor sleep were lower among African American adults than their White counterparts, with differences spanning most domains of sleep, excluding sleep latency. Global mental status score was lower among the African American group.

Figure 2 shows findings from the Kaplan-Meier curves for survival over time of follow-up across global mental status and PSQI global score groups, using the median for each as the cutoff. Poorer sleep was associated with lower survival probability over time compared to better sleep, particularly among individuals with above median global mental status ($p = 0.0002$ for log-rank test versus $p = 0.049$ for below median global mental status). Similarly, higher global mental status was associated with better survival over the period of follow-up, though only among individuals with better sleep or below median PSQI global score ($p = 0.0043$ for log-rank test versus $p = 0.99$ for the "poorer sleep" group).

Table 2 displays the findings from a series of Cox PH models with outcome being mortality risk and alternative exposures being sleep pattern measures and global mental status. In the first set of models with sleep pattern being the main exposure, analyses were run in the overall sample as two models (reduce and full model), while testing partly the interaction with global mental status and stratifying according to this potential effect modifier using the median cutoff. In reduced models adjusted for age, sex, race, and poverty status, the PSQI global score along with sleep quality, sleep latency and sleep disturbances (higher score → poorer sleep) were all positively associated with mortality risk. Specifically, a 1-unit increase in the PSQI global score was linked to a 7% increase in mortality risk in the reduced model (HR = 1.07, 95% CI: 1.03–1.11, $p = 0.001$). This effect was attenuated by adding lifestyle and health-related factors including diet, BMI, and depressive symptoms among others to HR = 1.02, 95% CI: 0.97–1.08, $p = 0.35$). Among sleep patterns, only sleep disturbances remained a statistically significant predictor of mortality risk after adjustment for lifestyle and health-related factors (HR = 1.36, 95% CI: 1.05–1.77, $p = 0.020$), suggesting 36% increase in mortality risk per unit increase in sleep disturbances, even after adjustment for factors such as self-rated health and cardiovascular disease as well as diet quality, smoking, current drug use, BMI, and CES-D scores. In both reduced and fully adjusted models, PSQI global score and the sleep quality domains interacted with global mental status (above versus below median,

Table 1. Study sample characteristics, overall by sex and by race in final analytic sample with imputed covariates (n = 1364), HANDLS 2009–2013.[a]

	Overall	Female adults	Male adults	White adults	African American adults
	(X ± SE), %	(X ± SE), %	(X ± SE), %		
	(N = 1364)	(N = 814)	(N = 550)	(N = 609)	(N = 755)
X ± SE or %±SE					
First-visit socio-demographic, SES and health-related variables, w3					
Sex, % male	40.32 ± 1.33	0.00	100.00	39.74 ± 1.98	40.79 ± 1.79
Age at w_3, y	52.33 ± 0.24	52.27 ± 0.32	52.42 ± 0.37	52.72 ± 0.35	52.02 ± 0.33
African American, %	55.35 ± 1.35	54.91 ± 1.74	56.00 ± 2.12	0.00	100.00
Poverty status, % < 125% of the 2004 federal poverty guidelines	35.34 ± 0.1.29	37.22 ± 1.69	32.55 ± 1.10*	29.56 ± 1.85	40.00 ± 1.78****
Education, Completed, %					
<HS	4.71 ± 0.58	4.45 ± 0.73	5.09 ± 0.96	7.06 ± 1.05	2.81 ± 0.60****
HS	58.20 ± 1.34	57.59 ± 1.74	59.09 ± 2.3	54.42 ± 2.05	61.25 ± 1.78
>HS	37.10 ± 1.31	37.96 ± 1.71	35.82 ± 2.05	38.52 ± 1.99	35.95 ± 1.75
Literacy, WRAT-3 score	43.85 ± 0.18	43.55 ± 0.24	44.30 ± 0.28**	46.15 ± 0.26	42.01 ± 0.24****
First-visit drug and tobacco use at w_3					
Any drug, current user, %	14.68 ± 0.98	11.87 ± 1.19	18.84 ± 01.67***	9.98 ± 1.31	18.46 ± 1.49****
Tobacco, current user, %	38.80 ± 1.39	36.27 ± 1.72	42.55 ± 2.23**	34.61 ± 1.98	42.17 ± 1.87***
BMI at w_3, kg/m^2	30.75 ± 0.21	31.98 ± 0.29	28.94 ± 0.4****	30.86 ± 0.32	30.67 ± 0.29
Self-rated health at w_3, %					
Poor/Average,	24.74 ± 1.17	27.08 ± 1.56	21.27 ± 1.74	26.01 ± 1.78	23.71 ± 1.55
Good	40.21 ± 1.33	40.96 ± 1.73	39.09 ± 2.08	38.82 ± 1.98	41.32 ± 1.79
Very good/Excellent	35.06 ± 1.29	31.97 ± 1.64	39.64 ± 2.09**	35.17 ± 1.94	34.97 ± 1.74
HEI-2010 total score at w_3	46.50 ± 0.34	46.97 ± 0.44	45.82 ± 0.50*	47.12 ± 0.55	46.01 ± 0.41*
Total energy intake at w_3, kcal/day	2079.80 ± 22.62	1853 ± 25.41	2415.40 ± 38.46****	2103.66 ± 35.13	2060.56 ± 31.79
CES-D total score at w_3	15.02 ± 0.31	15.87 ± 0.42	13.78 ± 0.44***	15.95 ± 0.49	14.28 ± 0.39***
Cardiovascular disease[b], %	18.77 ± 1.06	20.27 ± 1.41	16.55 ± 1.58*	18.88 ± 1.59	18.68 ± 01.42
MMSE, normalized	76.9±0.4	77.2±0.5	76.4±0.6	80.7±0.6	73.8±0.5***
Below median: poorer global mental status	58.1±1.3	56.6±1.7	60.4±2.0	56.8±2.0	66.8±1.7***
Above median: better global mental status	41.9±1.3	43.4±1.7	39.6±2.0	43.2±2.0	33.2±1.7
PSQI sleep quality	1.21 ± 0.02	1.29 ± 0.03	1.11 ± 0.03****	1.33 ± 0.03	1.13 ± 0.03****
PSQI sleep latency	1.53 ± 0.03	1.60 ± 0.04	1.42 ± 0.04***	1.52 ± 0.04	1.54 ± 0.04
PSQI sleep duration	1.57 ± 0.03	1.57 ± 0.03	1.55 ± 0.03	1.51 ± 0.04	1.61 ± 0.03**
PSQI sleep disturbances	1.24 ± 0.02	1.33 ± 0.02	1.12 ± 0.03****	1.31 ± 0.03	1.19 ± 0.02***
PSQI sleep medication use	0.65 ± 0.03	0.73 ± 0.04	0.53 ± 0.04***	0.75 ± 0.05	0.56 ± 0.04***
PSQI sleep daytime dysfunction	0.81 ± 0.03	0.85 ± 0.03	0.74 ± 0.03**	1.01 ± 0.04	0.65 ± 0.03****
PSQI global score	7.01 ± 0.10	7.38 ± 0.13	6.47 ± 0.15****	7.42 ± 0.16	6.69 ± 0.13****
Below median: better sleep	59.9±1.3	55.7±1.7	66.2±2.0***	56.8±2.0	62.4±1.8**
Above median: poorer sleep	40.1±1.3	44.3±1.7	33.8±2.0	43.2±2.0	37.6±1.8
Deaths, by 2020, %	12.61 ± 0.90	10.81 ± 1.09	15.27 ± 01.53***	12.32 ± 1.33	12.85 ± 1.22

HANDLS: Healthy Aging in Neighborhood of Diversity across the Lifespan; HEI-2010: Healthy Eating Index, 2010 version; HS: High school; MMSE: Mini-Mental State Examination; PSQI: Pittsburgh Sleep Quality Index; SE: Standard Error; WRAT-3: Wide Range Achievement Test, 3rd revision; X: mean.

[a]Values are means (X) ±SE for continuous variables and % for categorical variables.

[b]Self-reported history of cardiovascular disease included atrial fibrillation, angina, coronary artery disease, congestive heart failure, or myocardial infarction, ranging from 0 to 5.

*$p < 0.10$; ** $p < 0.05$; *** $p < 0.010$; ****$p < 0.001$, *t*-test for null hypothesis of no between-sex or between-race differences.

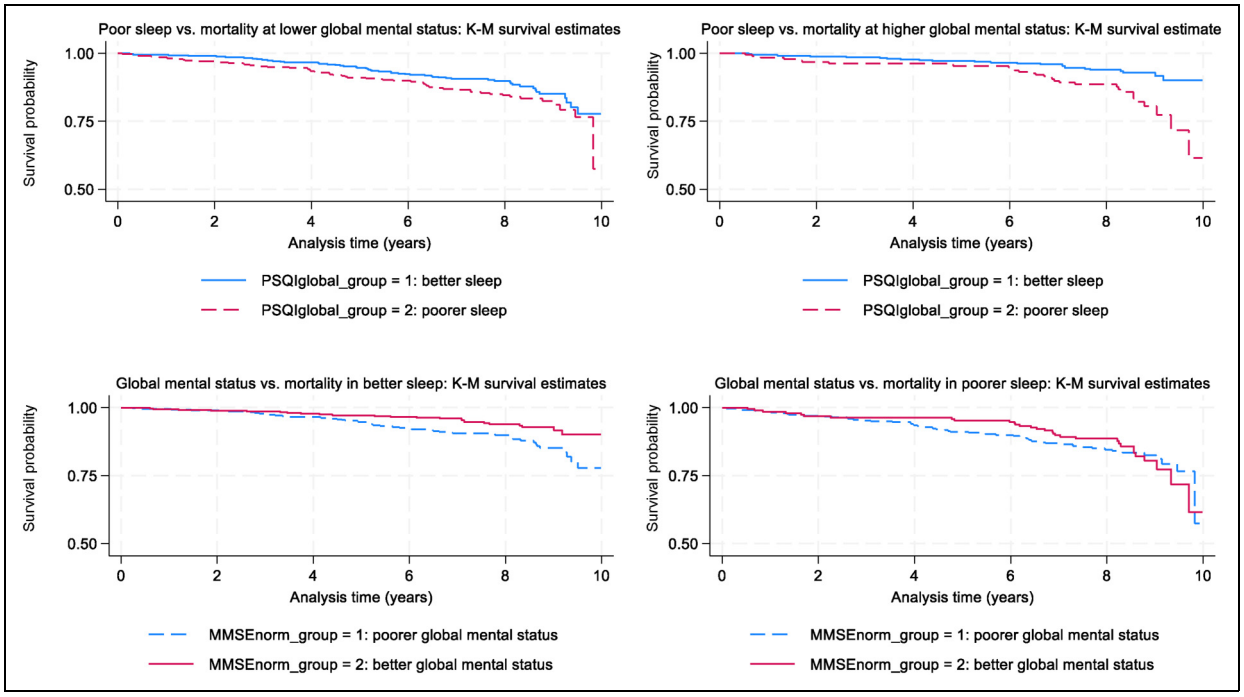

Figure 2. Poor sleep, global mental status and mortality: Kaplan-Meier survival curves, HANDLS 2009-2020.

$p < 0.10$), whereby poor sleep was found to be generally associated with mortality risk in the group with better global mental status at first-visit as measured by normalized MMSE. For instance, a unit increase in PSQI sleep quality (higher score → poorer sleep), was associated with 77% greater mortality risk in the reduced model, which was attenuated to 45% increased mortality risk ($p < 0.10$) in the fully adjusted model, within the better global mental status stratum. This association was not detected in the poorer global mental status stratum for sleep quality domain and was weaker in the reduced model for PSQI global (HR = 1.14 in the "better global mental status stratum" versus HR = 1.04 in the "poorer global mental status stratum", Model 1).

In a similar fashion, also based on Table 2 findings, there was an interaction between global mental status as the main exposure and PSQI global score as the potential effect modifier ($p = 0.04$) in both the reduced and the fully adjusted models. However, in the stratified analysis, an inverse relationship between global mental status and mortality risk was only marginally significant ($p < 0.10$) in the reduced model with the better sleep stratum.

Table 3 shows findings from four-way decomposition models, including as exogenous variables, age, sex, race and poverty status and as main exposure the PSQI global and sub-scores, with the potential mediator/moderator being normalized MMSE z-score. Findings indicated that the total effects were statistically significant for global PSQI overall and across a number of strata and that they were largely controlled direct effects, with little evidence of interaction or mediation through normalized MMSE z-score.

Table 4 shows findings from four-way decomposition models, also using the minimal set of exogenous variables, with exposure being normalized MMSE z-score and the potential mediators/moderators being the sleep patterns. Models were carried out overall and across sex and race groups. In contrast to the previous models, among women, the inverse total effect of global mental status (normalized MMSE z-score) with mortality risk was partially mediated (10–15%) by PSQI sleep latency (Total effect = −0.23, $p = 0.013$, Pure indirect effect = −0.044, $p = 0.025$) as well as the PSQI global (Total effect = −0.21, $p = 0.024$, Pure indirect effect = −0.034, $p = 0.038$). Stratification by race did not yield statistically significant total effects with few exceptions among White adults, whereby global mental status was inversely related to mortality risk which was mainly a controlled direct effect when considering sleep disturbance and sleep medications as potential mediators or moderators.

Discussion

To our knowledge, this is the first study to comprehensively examine the independent and the bi-directional mediating/moderating effects of sleep and global mental status on mortality risk among middle-aged urban adults. After a median time at risk of 8.2 years, 172 deaths occurred, with rate of 16 per 1000 person-years. A 1-unit increase in the PSQI global score was linked to a 7% increase in

Table 2. Cox PH for global mental status, sleep pattern measures and mortality risk: overall and stratified analyses: HANDLS 2009–2020.[a]

	Model 1[b]			Model 2[c]		
	Log_e(HR)	SE	p	Log_e(HR)	SE	p
X = Sleep pattern measures						
PSQI sleep quality	**0.231**	**0.089**	**0.010**	0.0380	0.106	0.72
PSQI sleep latency	**0.241**	**0.076**	**0.002**	0.0853	0.085	0.32
PSQI sleep duration	**0.156**	**0.082**	**0.060**	0.037	0.084	0.66
PSQI sleep disturbances	**0.503**	**0.11**	**<0.0001**	**0.311**	**0.134**	**0.020**
PSQI sleep medication use	0.073	0.063	0.25	0.019	0.069	0.78
PSQI sleep daytime dysfunction	0.134	0.087	0.13	−0.069	0.109	0.53
PSQI global score	**0.068**	**0.019**	**0.001**	0.025	0.026	0.35
Interaction with global mental status						
PSQI sleep quality	**0.384**	**0.184**	**0.04**	**0.419**	**0.187**	**0.030**
PSQI sleep latency	0.223	0.156	0.15	0.236	0.158	0.14
PSQI sleep duration	0.045	0.17	0.79	0.056	0.176	0.75
PSQI sleep disturbances	0.236	0.224	0.29	0.247	0.225	0.27
PSQI sleep medication use	0.167	0.133	0.21	0.174	0.135	0.19
PSQI sleep daytime dysfunction	0.177	0.181	0.33	0.220	0.185	0.23
PSQI global score	***0.075***	***0.041***	***0.069***	***0.078***	***0.042***	***0.063***
Poorer global mental status stratum						
PSQI sleep quality	0.088	0.109	0.42	−0.092	0.128	0.47
PSQI sleep latency	***0.160***	***0.094***	***0.09***	0.043	0.10	0.68
PSQI sleep duration	0.143	0.100	0.15	0.053	0.10	0.61
PSQI sleep disturbances	**0.390**	**0.134**	**0.004**	0.258	0.166	0.12
PSQI sleep medication use	0.0084	0.079	0.92	−0.034	0.084	0.69
PSQI sleep daytime dysfunction	0.048	0.109	0.65	−0.119	0.134	0.37
PSQI global score	***0.040***	***0.024***	***0.098***	0.0010	0.032	0.97
Better global mental status stratum						
PSQI sleep quality	**0.569**	**0.162**	**<0.0001**	***0.375***	***0.205***	***0.067***
PSQI sleep latency	**0.397**	**0.132**	**0.003**	0.167	0.156	0.29
PSQI sleep duration	0.164	0.148	0.27	−0.0239	0.164	0.88
PSQI sleep disturbances	**0.691**	**0.198**	**<0.0001**	0.336	0.244	0.17
PSQI sleep medication use	***0.209***	***0.110***	***0.057***	0.139	0.127	0.28
PSQI sleep daytime dysfunction	***0.289***	***0.152***	***0.058***	0.021	0.213	0.92
PSQI global score	**0.133**	**0.037**	**<0.0001**	0.076	0.051	0.136
X = Global mental status (above versus below median)						
Overall	−0.137	0.170	0.42	0.012	0.178	0.94
Interaction analysis with global PSQI (above versus below median)	**0.657**	**0.328**	**0.04**	**0.716**	**0.331**	**0.031**
Better sleep stratum (below median global PSQI)	***−0.486***	***0.254***	***0.06***	−0.428	0.264	0.11
Poorer sleep stratum (above median global PSQI)	0.316	0.232	0.17	***0.495***	***0.252***	***0.05***

HANDLS: Healthy Aging in Neighborhood of Diversity across the Lifespan; HEI-2010: Healthy Eating Index, 2010 version; HS: High school; MMSE: Mini-Mental State Examination; PSQI: Pittsburgh Sleep Quality Index; SE: Standard Error; WRAT-3: Wide Range Achievement Test, 3rd revision.
[a]Based on Cox PH models with exposure being either of 6 sleep sub-scale patterns and global score or normalized MMSE (above versus below median). Models with sleep patterns as main exposures were also stratified by normalized MMSE (above versus below median) and 2-way interactions were tested separately. In models with normalized MMSE as the main binary exposure, stratification was further conducted by global PSQI (above versus below median), and interaction analysis was tested separately.
[b]Model 1 included as covariates age, sex, race and poverty status.
[c]Model 2 is Model 1 + lifestyle and health-related factors as described in Covariates section.

mortality risk in the reduced model (HR = 1.07, 95% CI: 1.03–1.11, p = 0.001), an effect markedly attenuated in the full model (HR = 1.02, 95% CI: 0.97–1.08, p = 0.35). Sleep quality was robust to such adjustment (per unit, HR = 1.36, 95% CI: 1.05–1.77, p = 0.020). In both reduced and fully adjusted models, PSQI global score and the sleep quality domains interacted with global mental status (above versus below median, $p < 0.10$), whereby poor sleep was found to be generally associated with mortality risk in the group with better global mental status at first-visit (above median normalized MMSE). An inverse relationship between global mental status and morality risk was only marginally significant ($p < 0.10$) in the reduced model with the better sleep stratum, despite a significant 2-way interaction between global mental status and global PSQI score (above versus below median). In four-way

Table 3. Four-way decomposition of the effect of PSQI global and sub-scores versus mortality risk: mediation and moderation through global mental status: HANDLS 2009–2020[a,b].

X = sleep patterns, z-scores	tereri	ereri_cde	ereri_intref	ereri_intmed	ereri_pie
Overall, N = 1364					
PSQI global score	**0.338 ± 0.104** **p = 0.001**	**0.347 ± 0.106** **p = 0.001**	−0.006 ± 0.0118 p = 0.610	−0.0137 ± 0.008 p = 0.120	0.0106 ± 0.0080 p = 0.189
PSQI sleep quality	**0.259 ± 0.0958** **p = 0.007**	**0.269 ± 0.0965** **p = 0.005**	−0.0071 ± 0.0141 p = 0.614	−0.0096 ± 0.0065 p = 0.141	0.0068 ± 0.0054 p = 0.208
PSQI sleep latency	**0.298 ± 0.106** **p = 0.005**	**0.304 ± 0.107** **p = 0.005**	−0.0054 ± 0.0084 p = 0.521	−0.0120 ± 0.0110 p = 0.277	0.0122 ± 0.00968 p = 0.205
PSQI sleep duration	***0.152 ± 0.0902*** ***p = 0.092***	0.136 ± 0.0918 p = 0.137	0.00455 ± 0.0095 p = 0.634	0.00430 ± 0.0064 p = 0.503	0.0066 ± 0.00653 p = 0.311
PSQI sleep disturbances	**0.430 ± 0.109** **p < 0.0001**	**0.433 ± 0.111** **p < 0.0001**	−0.00373 ± 0.0070 p = 0.594	−0.00565 ± 0.00642 p = 0.379	0.00601 ± 0.00610 p = 0.325
PSQI sleep medication use	0.0989 ± 0.0793 p = 0.213	0.103 ± 0.0800 p = 0.197	−0.0057 ± 0.0073 p = 0.436	−0.0043 ± 0.0041 p = 0.301	0.0054 ± 0.0049 p = 0.264
PSQI sleep daytime dysfunction	***0.151 ± 0.0877*** ***p = 0.085***	***0.159 ± 0.0879*** ***p = 0.070***	−0.0083 ± 0.0103 p = 0.420	0.00059 ± 0.0035 p = 0.866	−0.00061 ± 0.0036 p = 0.866
Females, N = 814					
PSQI global score	**0.371 ± 0.144** **p = 0.010**	**0.352 ± 0.147** **p = 0.017**	−0.00381 ± 0.0139 p = 0.785	0.00099 ± 0.0113 p = 0.930	0.0209 ± 0.0144 p = 0.146
PSQI sleep quality	**0.297 ± 0.132** **p = 0.025**	**0.294 ± 0.134** **p = 0.028**	−0.0114 ± 0.0161 p = 0.479	−0.0033 ± 0.00801 p = 0.680	0.0176 ± 0.0120 p = 0.141
PSQI sleep latency	**0.392 ± 0.161** **p = 0.015**	**0.375 ± 0.159** **p = 0.019**	−0.00769 ± 0.0182 p = 0.673	−0.0019 ± 0.0176 p = 0.912	0.0270 ± 0.0168 p = 0.108
PSQI sleep duration	0.0914 ± 0.117 p = 0.437	0.0162 ± 0.115 p = 0.888	0.0348 ± 0.0291 p = 0.232	0.0196 ± 0.0131 p = 0.135	0.0207 ± 0.0141 p = 0.141
PSQI sleep disturbances	**0.404 ± 0.144** **p = 0.005**	**0.391 ± 0.147** **p = 0.008**	−0.00215 ± 0.0136 p = 0.875	0.0018 ± 0.0074 p = 0.805	0.0137 ± 0.0111 p = 0.217
PSQI sleep medication use	0.173 ± 0.113 p = 0.126	0.173 ± 0.113 p = 0.126	−0.00582 ± 0.0161 p = 0.719	−0.00047 ± 0.0032 p = 0.881	0.00652 ± 0.0082 p = 0.425
PSQI sleep daytime dysfunction	0.172 ± 0.123 p = 0.160	0.179 ± 0.126 p = 0.155	−0.0081 ± 0.0155 p = 0.603	−0.00016 ± 0.0012 p = 0.885	0.0013 ± 0.0080 p = 0.871
Males, N = 550					
PSQI global score	0.312 ± 0.153 p = 0.042	0.315 ± 0.151 p = 0.037	0.019 ± 0.040 p = 0.639	−0.0250 ± 0.018 p = 0.168	0.0023 ± 0.0084 p = 0.782
PSQI sleep quality	0.232 ± 0.144 p = 0.107	0.206 ± 0.137 p = 0.134	0.032 ± 0.0466 p = 0.483	−0.0071 ± 0.0164 p = 0.665	0.00037 ± 0.0023 p = 0.873
PSQI sleep latency	0.208 ± 0.143 p = 0.145	0.223 ± 0.144 p = 0.122	0.0063 ± 0.0247 p = 0.797	−0.0216 ± 0.0168 p = 0.198	0.00041 ± 0.0119 p = 0.972
PSQI sleep duration	0.231 ± 0.144 p = 0.109	0.231 ± 0.142 p = 0.106	0.00494 ± 0.021 p = 0.814	−0.0047 ± 0.0080 p = 0.559	0.000051 ± 0.0031 p = 0.987
PSQI sleep disturbances	**0.501 ± 0.180** **p = 0.005**	**0.506 ± 0.176** **p = 0.004**	0.0159 ± 0.0376 p = 0.673	−0.0213 ± 0.0183 p = 0.243	−0.000010 ± 0.0077 p = 0.999

(continued)

Table 3. Continued.

X = sleep patterns, z-scores	tereri	ereri_cde	ereri_intref	ereri_intmed	ereri_pie
PSQI sleep medication use	0.0666 ± 0.118 p = 0.576	0.0753 ± 0.120 p = 0.531	0.00063 ± 0.014 p = 0.964	−0.0099 ± 0.010 p = 0.337	0.00057 ± 0.0094 p = 0.951
PSQI sleep daytime dysfunction	0.093 ± 0.122 p = 0.443	0.0821 ± 0.121 p = 0.499	0.0077 ± 0.026 p = 0.771	0.0045 ± 0.0099 p = 0.646	−0.000698 ± 0.0027 p = 0.801
White adults, N = 609					
PSQI global score	**0.316 ± 0.152** **p = 0.038**	***0.270 ± 0.152*** ***p = 0.076***	0.044 ± 0.0510 p = 0.378	***−0.0314 ± 0.0186*** ***p = 0.091***	***0.0321 ± 0.0185*** ***p = 0.084***
PSQI sleep quality	**0.290 ± 0.146** **p = 0.048**	0.246 ± 0.150 p = 0.100	0.042 ± 0.048 p = 0.380	−0.022 ± 0.0147 p = 0.129	0.0233 ± 0.0154 p = 0.132
PSQI sleep latency	**0.382 ± 0.170** **p = 0.025**	**0.339 ± 0.169** **p = 0.045**	0.044 ± 0.053 p = 0.404	−0.0337 ± 0.0221 p = 0.128	***0.0319 ± 0.019*** ***p = 0.098***
PSQI sleep duration	0.034 ± 0.119 p = 0.772	−0.0028 ± 0121 p = 0.981	−0.0031 ± 0.0115 p = 0.783	0.0116 ± 0.014 p = 0.436	0.029 ± 0.018 p = 0.121
PSQI sleep disturbances	***0.286 ± 0.150*** ***p = 0.057***	***0.260 ± 0.1501*** ***p = 0.084***	0.0128 ± 0.0318 p = 0.687	−0.0116 ± 0.0150 p = 0.440	0.024 ± 0.016 p = 0.140
PSQI sleep medication use	0.122 ± 0.114 p = 0.286	0.0950 ± 0.116 p = 0.416	0.0245 ± 0.032 p = 0.451	−0.0069 ± 0.0083 p = 0.406	0.0094 ± 0.011 p = 0.397
PSQI sleep daytime dysfunction	0.120 ± 0.124 p = 0.335	0.089 ± 0.128 p = 0.485	0.0312 ± 0.039 p = 0.427	0.0066 ± 0.010 p = 0.524	−0.0075 ± 0.011 p = 0.523
African American adults, N = 755					
PSQI global score	**0.448 ± 0.158** **p = 0.005**	**0.480 ± 0.174** **p = 0.006**	−0.0245 ± 0.023 p = 0.305	−0.0079 ± 0.0099 p = 0.422	−0.00017 ± 0.0070 p = 0.980
PSQI sleep quality	**0.294 ± 0.137** **p = 0.032**	**0.323 ± 0.148** **p = 0.029**	−0.0264 ± 0.022 p = 0.247	−0.0028 ± 0.0054 p = 0.602	0.00052 ± 0.0024 p = 0.832
PSQI sleep latency	**0.333 ± 0.151** **p = 0.027**	**0.317 ± 0.157** **p = 0.044**	0.0125 ± 0.0348 p = 0.719	0.00476 ± 0.0125 p = 0.705	−0.0011 ± 0.0099 p = 0.909
PSQI sleep duration	**0.337 ± 0.148** **p = 0.023**	**0.339 ± 0.158** **p = 0.032**	−0.0015 ± 0.031 p = 0.960	−0.00014 ± 0.0030 p = 0.961	0.00031 ± 0.0025 p = 0.901
PSQI sleep disturbances	**0.632 ± 0.171** **p < 0.0001**	**0.669 ± 0.185** **p < 0.0001**	−0.031 ± 0.023 p = 0.183	−0.00585 ± 0.0078 p = 0.458	−0.00016 ± 0.0039 p = 0.967
PSQI sleep medication use	0.079 ± 0.112 p = 0.478	0.0823 ± 0.124 p = 0.508	−0.0032 ± 0.025 p = 0.901	−0.00081 ± 0.0067 p = 0.904	0.0014 ± 0.0066 p = 0.827
PSQI sleep daytime dysfunction	***0.213 ± 0.127*** ***p = 0.094***	***0.237 ± 0.137*** ***p = 0.083***	−0.0225 ± 0.0215 p = 0.295	−0.00147 ± 0.00418 p = 0.725	0.00041 ± 0.0018 p = 0.824

HANDLS: Healthy Aging in Neighborhood of Diversity across the Lifespan; HEI-2010: Healthy Eating Index, 2010 version; HS: High school; MMSE: Mini-Mental State Examination; PSQI: Pittsburgh Sleep Quality Index; SE: Standard Error; WRAT-3: Wide Range Achievement Test, 3rd revision.

[a]Four-way decomposition model with main exposures being sleep patterns and mediating-moderating factor being normalized MMSE (continuous score). Exposures and moderator/mediators are transformed into a standardized z-score. Values of zero on each correspond to the sample mean and a value of 1 is mean + 1 SD.

[b]Model adjusted for age, sex, race and poverty status.

Table 4. Four-way decomposition of the effect of global mental status versus mortality risk: mediation and moderation through PSQI global and sub-scores: HANDLS 2009–2020[a,b].

X = normalized MMSE, z-score	tereri	ereri_cde	ereri_intref	ereri_intmed	ereri_pie
Overall, N = 1364					
PSQI global score	−0.105 ± 0.073 p = 0.15	−0.110 ± 0.072 p = 0.13	+0.043 ± 0.30 p = 0.15	−0.011 ± 0.007 p = 0.15	**−0.028 ± 0.011** **p = 0.011**
PSQI sleep quality	−0.097 ± 0.072 p = 0.18	***−0.124 ± 0.069*** ***p = 0.073***	***+0.047 ± 0.029*** ***p = 0.096***	−0.008 ± 0.006 p = 0.16	***−0.013 ± 0.008*** ***p = 0.098***
PSQI sleep latency	−0.116 ± 0.071 0.10	−0.102 ± 0.072 p = 0.16	+0.027 ± 0.027 p = 0.31	−0.009 ± 0.009 p = 0.31	**−0.031 ± 0.012** **p = 0.009**
PSQI sleep duration	−0.094 ± 0.073 p = 0.20	−0.083 ± 0.073 p = 0.26	−0.004 ± 0.006 p = 0.47	+0.004 ± 0.006 p = 0.49	−0.011 ± 0.008 p = 0.16
PSQI sleep disturbances	−0.086 ± 0.074 p = 0.25	−0.083 ± 0.074 0.26	+0.026 ± 0.027 0.34	−0.004 ± 0.005 p = 0.41	**−0.025 ± 0.011** **p = 0.027**
PSQI sleep medication use	−0.107 ± 0.07 p = 0.14	−0.110 ± 0.073 p = 0.13	+0.011 ± 0.013 p = 0.40	−0.003 ± 0.004 p = 0.31	−0.005 ± 0.005 p = 0.28
PSQI sleep daytime dysfunction	−0.103 ± 0.07 p = 0.15	***−0.127 ± 0.071*** ***p = 0.074***	+0.023 ± 0.019 p = 0.22	+0.000 ± 0.003 p = 0.87	+0.001 ± 0.004 p = 0.87
Females, N = 814					
PSQI global score	**−0.210 ± 0.094** **p = 0.025**	***−0.180 ± 0.096*** ***p = 0.060***	+0.002 ± 0.032 p = 0.95	+0.002 ± 0.009 p = 0.84	**−0.0344 ± 0.017** **p = 0.038**
PSQI sleep quality	**−0.219 ± 0.091** **p = 0.016**	**−0.212 ± 0.091** **p = 0.020**	+0.017 ± 0.032 p = 0.61	−0.002 ± 0.007 p = 0.78	***−0.022 ± 0.013*** ***p = 0.098***
PSQI sleep latency	**−0.227 ± 0.091** **p = 0.013**	**−0.194 ± 0.094** **p = 0.040**	+0.011 ± 0.043 p = 0.80	−0.000 ± 0.014 p = 0.97	**−0.044 ± 0.020** **p = 0.025**
PSQI sleep duration	−0.155 ± 0.104 p = 0.14	***−0.178 ± 0.097*** ***p = 0.066***	+0.007 ± 0.022 p = 0.74	+0.018 ± 0.012 p = 0.14	−0.002 ± 0.014 p = 0.89
PSQI sleep disturbances	**−0.197 ± 0.100** **p = 0.040**	***−0.171 ± 0.097*** ***p = 0.077***	−0.003 ± 0.033 p = 0.93	+0.002 ± 0.006 p = 0.73	***−0.025 ± 0.014*** ***p = 0.088***
PSQI sleep medication use	**−0.209 ± 0.092** **p = 0.023**	**−0.208 ± 0.090** **p = 0.021**	+0.005 ± 0.023 p = 0.82	−0.000 ± 0.003 p = 0.94	−0.006 ± 0.007 p = 0.44
PSQI sleep daytime dysfunction	**−0.208 ± 0.092** **p = 0.024**	**−0.214 ± 0.093** **p = 0.021**	+0.007 ± 0.020 p = 0.71	−0.000 ± 0.001 p = 0.90	−0.001 ± 0.006 p = 0.87
Males, N = 550					
PSQI global score	−0.012 ± 0.113 p = 0.92	−0.031 ± 0.112 p = 0.78	+0.057 ± 0.048 p = 0.23	−0.019 ± 0.014 p = 0.17	−0.019 ± 0.014 p = 0.17
PSQI sleep quality	+0.023 ± 0.116 p = 0.84	−0.019 ± 0.110 p = 0.86	+0.051 ± 0.046 p = 0.26	−0.006 ± 0.013 p = 0.66	−0.003 ± 0.008 p = 0.67
PSQI sleep latency	−0.017 ± 0.110 p = 0.88	−0.004 ± 0.112 p = 0.97	+0.024 ± 0.013 p = 0.45	−0.017 ± 0.013 p = 0.20	−0.020 ± 0.014 p = 0.16
PSQI sleep duration	+0.022 ± 0.117 p = 0.85	−0.002 ± 0.110 p = 0.99	+0.034 ± 0.040 p = 0.40	−0.004 ± 0.007 p = 0.56	−0.006 ± 0.009 p = 0.53
PSQI sleep disturbances					

(continued)

Table 4. Continued.

X = normalized MMSE, z-score	tereri	ereri_cde	ereri_intref	ereri_intmed	ereri_pie
	+0.013 ± 0.116 p = 0.91	+0.000 ± 0.114 p = 1.000	+0.053 ± 0.051 p = 0.29	−0.015 ± 0.013 p = 0.25	−0.026 ± 0.018 p = 0.15
PSQI sleep medication use	−0.020 ± 0.112 p = 0.86	−0.007 ± 0.114 p = 0.95	+0.000 ± 0.013 p = 1.00	−0.008 ± 0.008 p = 0.33	−0.005 ± 0.009 p = 0.54
PSQI sleep daytime dysfunction	−0.011 ± 0.110 p = 0.92	−0.033 ± 0.110 p = 0.76	+0.016 ± 0.026 p = 0.54	+0.004 ± 0.009 p = 0.65	+0.002 ± 0.004 p = 0.70
White adults, N = 609					
PSQI global score	***−0.0186 ± 0.101*** ***p = 0.066***	**−0.235 ± 0.090** **p = 0.009**	***+0.101 ± 0.061*** ***p = 0.097***	−0.025 ± 0.016 p = 0.13	***−0.027 ± 0.017*** ***p = 0.097***
PSQI sleep quality	***−0.176 ± 0.100*** ***p = 0.079***	**−0.242 ± 0.087** **p = 0.005**	***+0.102 ± 0.054*** ***p = 0.063***	−0.018 ± 0.013 p = 0.16	−0.017 ± 0.013 p = 0.17
PSQI sleep latency	***−0.190 ± 0.100*** ***p = 0.058***	**−0.204 ± 0.093** **p = 0.028**	+0.080 ± 0.058 p = 0.16	−0.025 ± 0.019 p = 0.18	***−0.041 ± 0.021*** ***p = 0.050***
PSQI sleep duration	***−0.178 ± 0.100*** ***p = 0.077***	***−0.193 ± 0.098*** ***p = 0.050***	+0.004 ± 0.013 p = 0.73	+0.010 ± 0.013 p = 0.43	+0.000 ± 0.017 p = 0.98
PSQI sleep disturbances	**−0.197 ± 0.099** **p = 0.046**	**−0.200 ± 0.096** **p = 0.036**	+0.033 ± 0.042 p = 0.43	−0.008 ± 0.011 p = 0.49	−0.022 ± 0.015 p = 0.12
PSQI sleep medication use	**−0.200 ± 0.098** **p = 0.042**	**−0.239 ± 0.099** **p = 0.012**	+0.049 ± 0.036 p = 0.16	−0.006 ± 0.008 p = 0.41	−0.004 ± 0.006 p = 0.41
PSQI sleep daytime dysfunction	−0.157 ± 0.103 p = 0.13	**−0.255 ± 0.092** **p = 0.006**	***+0.090 ± 0.051*** ***p = 0.076***	+0.006 ± 0.010 p = 0.53	+0.002 ± 0.005 p = 0.63
African American adults, N = 755					
PSQI global score	−0.003 ± 0.110 p = 0.98	+0.003 ± 0.111 p = 0.98	+0.026 ± 0.039 p = 0.50	+-0.006 ± 0.008 p = 0.43	−0.025 ± 0.016 p = 0.12
PSQI sleep quality	−0.012 ± 0.107 p = 0.91	−0.024 ± 0.106 p = 0.82	+0.021 ± 0.032 p = 0.50	−0.002 ± 0.005 p = 0.61	−0.006 ± 0.011 p = 0.55
PSQI sleep latency	−0.018 ± 0.109 p = 0.87	+0.013 ± 0.112 p = 0.91	−0.010 ± 0.021 p = 0.66	***+0.004 ± 0.010*** ***p = 0.070***	***−0.025 ± 0.015*** ***p = 0.087***
PSQI sleep duration	−0.019 ± 0.106 p = 0.86	−0.013 ± 0.105 p = 0.90	+0.002 ± 0.034 p = 0.95	−0.000 ± 0.003 p = 0.96	−0.007 ± 0.011 p = 0.54
PSQI sleep disturbances	+0.030 ± 0.113 p = 0.79	+0.005 ± 0.109 p = 0.97	+0.049 ± 0.054 p = 0.36	−0.005 ± 0.007 p = 0.47	−0.019 ± 0.020 p = 0.34
PSQI sleep medication use	−0.029 ± 0.106 p = 0.78	−0.024 ± 0.106 p = 0.82	−0.000 ± 0.001 p = 0.95	−0.001 ± 0.006 p = 0.90	−0.005 ± 0.008 p = 0.52
PSQI sleep daytime dysfunction	−0.030 ± 0.105 p = 0.77	−0.030 ± 0.108 p = 0.78	+0.004 ± 0.014 p = 0.78	−0.001 ± 0.003 p = 0.72	−0.003 ± 0.008 p = 0.71

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[a]Four-way decomposition model with main exposures being normalized MMSE (continuous score) and mediating-moderating factor being each of 7 sleep patterns continuous scores. Exposures and moderator/mediators are transformed into a standardized z-score. Values of zero on each correspond to the sample mean and a value of 1 is mean + 1 SD.

[b]Model adjusted for age, sex, race, and poverty status.

decomposition models, total effects of PSQI scores were positive and statistically significant, while being mostly controlled direct effects. In contrast, among women, the inverse total effect of global mental status (normalized MMSE z-score) with mortality risk was partially mediated by PSQI sleep latency (Total effect = −0.23, p = 0.013, Pure indirect effect = −0.044, p = 0.025) as well as the PSQI global (Total effect = −0.21, p = 0.024, Pure indirect effect = −0.034, p = 0.038). These effect sizes can be interpreted on the scale of Log_e(HR), and thereby a total effect of −0.23 is equivalent to a hazard ratio of 0.79, suggestive of a reduction in risk of all-cause mortality by 21%.

Although there is a link between poor cognitive function assessed in mid-[1] to late-life[2] and a higher risk of death, the underlying mechanisms are not recognized. The intricate interactions between genetic and environmental influences throughout life, which may also affect health and mortality trajectories, are most likely the source of cognitive function. In addition to the social and physical consequences, problems in cognitive function may indicate underlying biological abnormalities or hereditary issues that go beyond neurodegenerative illnesses. It's significant to note that a meta-analysis of over 60 research concluded that cognitive impairment, including overt dementia, was linked to a higher risk of all-cause mortality.[47] In a systematic review,[48] dementia was also linked to higher mortality among COVID-19 patients.

Prolonged sleep is associated with an increased risk of death in older individuals due to factors like sleep fragmentation, weariness, depression, and inactivity.[49,50] Short sleep is linked to obesity, diabetes, hypertension, cardiovascular disease, and cancer.[51–57] Upregulation of appetite, increased time to eat, reduced energy expenditure, and altered glucose metabolism contribute to the obesogenic consequences of shorter sleep durations.[58] Sleep disturbance is linked to heightened systemic inflammation, leading to neuronal damage and mortality.[59–61] Despite these well-defined biological mechanisms, limited evidence supports the link between sleep duration and all-cause mortality rate. Nevertheless, current epidemiological evidence supports that longer sleep is linked to higher mortality rates from cardiovascular and diabetes causes than shorter sleep.[7] Among accumulating evidence, a recent study using the National Health and Aging Trends Study (NHATS) data from 2011 to 2018 showed that, sleep disruptions such as difficulty initiating sleep (HR, 1.44; 95% CI,1.20–1.72), difficulty falling back asleep (HR, 1.56; 95% CI,1.29–1.89), and concurrent sleep difficulties (HR, 1.80; 95% CI, 1.44–2.24) were associated with greater risk of all-cause mortality.[62] Another study using the same data and analytical approach from NHATS showed increased all-cause mortality in relation to difficulty maintaining alertness ("Some Days": HR = 1.49, 95% CI: 1.13–1.94 and "Most/Every Day": HR = 1.65, 95% CI: 1.17–2.32), napping ("Some days": HR = 1.38, 95% CI: 1.03–1.85; "Most/Every Day": HR = 1.73, 95% CI: 1.29–2.32), sleep quality ("Poor/Very Poor": HR = 1.75, 95% CI: 1.17–2.61), and very short sleep duration (≤5 h: HR = 2.38, 95% CI: 1.44–3.92).[63] A 2018 Japanese prospective cohort (Hisayama Study) of community-dwelling older adults (≥ 60 years) without dementia had a significantly greater risk of all-cause mortality from short sleep duration (<5.0 h: hazard ratio HR = 2.29, 95% CI = 1.15–4.56) and long sleep duration (≥10.0 h: HR = 1.67, 95% CI = 1.07–2.60).[64] Data from a population-based male cohort and various sleep complaints showed that older male adults reporting poor sleep and daytime 48% higher chance of dying than subjects who were not affected by any of the chosen sleep complaints.[65] Self-reported long sleep duration was associated with 58% increased risk of dementia-specific mortality in a cohort of elders without dementia.[6] A prospective study using data from the Singapore Chinese Health Study has shown that compared to normal sleep duration (7 h), both short sleep (≤5 h) (hazard ratio [HR] 1.27, 95% confidence interval [CI] 1.06–1.53) and long sleep (≥9 h) (HR 1.47, 95% CI 1.24–1.73) had increased risk of all-cause mortality.[66] Interventions for sleep disorders, such as long-term continuous positive airway pressure use, may lower mortality rates in this population.

According to recent studies, sleep quality and duration may influence cognitive function. Individuals with poor sleep quality were more likely to experience subjective cognitive decline compared to individuals with good sleep quality.[29] In another study, sleep disturbances were negatively correlated with memory recall and processing speed.[30] Sleep duration has also been shown to be related to cognitive function. Hua et al. (2020) found that a change from short sleep duration (less than 6 h) to moderate sleep duration (between 6–8 h) was associated with better global cognition scores.[31] Joo et al. (2021) and Ma et al. (2020) both observed U-shaped associations between sleep duration and cognitive decline.[29,32] Furthermore, Lucey et al. (2021) found that longitudinal changes in cognitive function decreased at low and high values of total sleep time.[33] There are further effects of sleep on cognitive function depending on subgroup status.[33] In a study of older adults with hypertension, Chen et al. (2023) found that sleep quality was negatively associated with depression and cognitive function.[34] Furthermore, Troxel et al. (2022) found that higher sleep efficiency and less wakefulness after sleep onset (WASO) were associated with greater attention, executive function, and visuospatial ability in a predominantly African American sample.[35] Additionally, increases in WASO over a 5-year span were associated with poorer attention, executive function, and visuospatial ability.[35] Taken together, these findings suggest an important role of sleep quality and sleep duration on numerous cognitive domains for individuals across a wide range of backgrounds.

Other studies have indicated that sleep and cognition interacted in relation to mortality risk. For instance, data from the Chinese Longitudinal Healthy Longevity Surveys show that self-reported short sleep duration was associated with greater risk of mortality (HR: 1.03 (0.98–1.09)) as well as long sleep duration (HR: 1.13 (1.08–1.18)).[67] In stratified analysis by cognitive impairment, physical disability, and chronic conditions, the risk of mortality was present only among people with MMSE scores ≤24.[67] There was a statistically significant interaction between long sleep and cognitive impairment in relation to mortality (p for interaction = 0.002).[67] A population-based, in-lab, longitudinal study from the Penn State Adult Cohort showed that the risk of all-cause mortality and mortality associated with possible vascular cognitive impairment (n = 122) was significantly increased in those who slept <6 h at first-visit (hazards ratio [HR] = 1.79, 95% confidence interval [CI] = 1.28–2.51 and HR = 4.01, 95% CI = 2.66–6.05, respectively).[68] Those findings are in contrast with our present study, the latter showing that the association between poor sleep quality and mortality risk was mostly observed among individuals with above median global mental status.

Our results regarding the sex differences in the association between cognition and mortality being mediated through sleep can be attributed to hormonal factors, whereby estrogen has been shown to be a potential protective factor against poor cardiovascular health among others.[69] Women in fact tend to have a different sleep architecture compared to men, tending towards deeper sleep.[70] Coping strategies against stress may differ between men and women, possibly leading to our current finding that sleep mediated the association between cognition and mortality to a greater extent among women.[71] In fact, sleep latency may be triggered by other mental health issues and psychosocial factors, including anxiety disorders and depression, both being more prevalent among women.[71] More generally, psychopathological conditions are strongly associated with disruptions in sleep patterns and deterioration of cognitive function.[72,73] In fact, women frequently experience heightened levels of stress as a result of their traditional caregiving role, heavy demands, and cultural expectations.[74] These factors can disturb their sleep patterns and contribute to compromising both their mental and physical well-being.[74] Biologically speaking, and more generally, hormonal influences, inflammatory responses, autonomic regulation, and metabolic pathways all contribute to the observed effects in our study, given that poor sleep is influenced by hormonal changes, can increase inflammatory responses, dysregulate the autonomic nervous system, and alter glucose metabolism.[69,75,76] There is recent evidence that the microglia, which are the immune cells of the central nervous system, can regulate sleep-wake cycles and responses to sleep alteration, with major implication for AD and other neurodegenerative disorders.[77] The influence of microglia on insomnia and sleep-disordered breathing among a number of sleep disorders is detailed elsewhere.[77] Furthermore, the impact of inadequate sleep on cognitive decline and mortality risk may be exacerbated by lifestyle behaviors, such as multitasking which is more prevalent pattern of behavior among women.[74] Social support networks, which are often more extensive and engaged among women, can impact the quality of sleep. Whereas men generally have smaller networks, women tend to lose those networks as they age.[74]

These biological influences may be different between men and women and can affect the way sleep increases mortality risk particularly among individuals with intact or normal cognition. Furthermore, from a clinical standpoint, our findings indicate that among women only, sleep latency and global score act as mediators in the association between cognition and mortality, indicating that women with higher mental status may have shorter sleep latency, therefore decreasing the risk for all-cause mortality. Therefore, the enhancement of sleep quality in general, as well as sleep latency in particular, has the potential to magnify the beneficial impact of improved mental health on survival outcomes in women. Consistent evaluation of mental health and sleep patterns may facilitate targeted therapy.

Our study has numerous strengths. First, this is the first study of middle-aged urban adults to examine whether sleep and cognitive performance interact with to determine all-cause mortality risk, while also exploring bi-directional mediational effects. It is also the first to do so by examining differences across sex and racial groups in a well-powered study with up to 10 years of follow-up. The HANDLS contains a wealth of data, allowing for the examination of various hypotheses while accounting for key confounders. Moreover, the PSQI was used, a standard scale for self-reported sleep quality, from which a global score and sub-domain scores were derived. Furthermore, advanced techniques were used, which included multiple imputations applied to covariates, Cox proportional hazards models on multiple imputed data, and 4-way decomposition of total effects into effects due to mediation only, interaction only, both or none. However, our study findings should be interpreted in light of notable limitations. First, although both date and cause of death were available, the sample was under-powered for cause-specific mortality analyses, thus precluding us from determining whether those associations were driven by cardiovascular or non-cardiovascular deaths. Second, poor sleep quality, while measured using a standard scale, did not encompass the entire PSQI by excluding sleep efficiency as a sub-domain in w3 of HANDLS. This reduced the comparability of our findings with those of other studies. Nevertheless, the PSQI was previously validated against more objective measures such as those obtained from an accelerometer.[78,79] Third, the lack

of objective sleep parameter measurements in our analysis left room for non-differential misclassification, which would have biased our research's association measures toward the null value. The PSQI test is unable to distinguish between those with and without sleep disorders such as insomnia and sleep apnea. However, rather than using a general measure of sleep, the PSQI instrument's use of subscales enables us to investigate specific elements of sleep. Fourth, both the PSQI scores and the MMSE total score were only measured at w3, and a future improvement would entail repeated measures on these metrics over time. Multiple repeated measurements of sleep and cognitive function would enhance the comprehensiveness and subtlety of our understanding of the interaction between these variables and mortality risk. This would provide valuable insights into temporal patterns, trajectories, and long-term associations that cannot be captured by a single time point analysis. Fifth, given the complexity of the analysis, we did not include domains of cognition in our present analyses. Nevertheless, future studies are needed to examine interaction between sleep patterns and various cognitive domains in relation to mortality status. In a similar vein, we must acknowledge that four-way decomposition models rely on a rigid set of assumptions (see Supplemental Material) and that exposure-induced mediator-outcome confounding may have occurred and, to our knowledge, there are no measures within *med4way* that account for this potential.[80] Finally, due to the observational nature of the study, both residual confounding and selection biases cannot be ruled out.

In summary, a complex relationship between sleep, global mental status and mortality was uncovered, whereby generally poor global mental status was associated with greater mortality risk at better sleep quality levels and vice versa, in a sex and race-specific manner. Pure mediation of the effect of poor global mental status on mortality risk through the global sleep score and sleep latency sub-score was detected among women. Further longitudinal studies with multiple sleep and cognitive performance repeats, including measures of global mental status, are needed to corroborate our current findings in comparable study samples, in addition to mechanistic studies aiming at explaining our key findings, intervention studies to increase longevity targeting sleep quality and cognition through behavioral therapies, pharmacological treatments, or lifestyle modifications, and integrating findings from various data sources with diverse populations.

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Declaration of conflicting interests

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Data availability

The study protocol (09-AG-N248) received approval from the National Institute on Environmental Health Sciences' Institutional Review Board (IRB) of the National Institutes of Health (NIH). Upon request, data can be made available to researchers with approved proposals, after they have agreed to confidentiality as required by our IRB. Policies are publicized on: https://handls.nih.gov. Data access request can be sent to principal investigators (PI) or the study manager, Jennifer Norbeck at norbeckje@mail.nih.gov. These data are owned by the National Institute on Aging at the NIH. The PIs have made those data restricted to the public

for two main reasons: "(1) The study collects medical, psychological, cognitive, and psychosocial information on racial and poverty differences that could be misconstrued or willfully manipulated to promote racial discrimination; and (2) Although the sample is fairly large, there are sufficient identifiers that the PIs cannot guarantee absolute confidentiality for every participant as we have stated in acquiring our confidentiality certificate."[81]

Supplemental material

Supplemental material for this article is available online.

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Supplemental Method 1: Description of cognitive tests, literacy and the 20-item CES-D

Mini-Mental State Examination (MMSE)

The MMSE[1] is used to assess global cognitive functioning and includes items spanning orientation, concentration, immediate and short-term memory, language and constructional praxis. Scores range from 0 to 30, with higher scores indicating better global mental status.

Wide Range Achievement Test – 3rd Edition: Word and Letter Reading Subtest (WRAT)

The WRAT Word and Letter Reading Subtest,[2] a test of reading ability, is often used as a proxy for literacy and quality of education. Participants were instructed to read a list of 50 words of increasing difficulty. If the first five words were not correctly pronounced, letter reading was also administered. Standard instructions were used with the tan form. The outcome variable used was the total number of correctly pronounced words.

Center for Epidemiological Studies Depression Scale (CES-D)

The CES-D[3] is a 20-item measure of depressive symptomatology. Participants are asked to consider the frequency and severity of their symptoms over the last week. Scores range from 0 to 60. Scores of $\geq$16 indicate significant depressive symptoms and scores of $\geq$20 indicate a clinically significant amount of depressive symptoms.

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Supplemental Methods

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1 Four-Way Decomposition Models

1.1 *Background*

Let Y denote the response, A the exposure (in this case sleep quality (continuous), a its realized value (Pittsburgh Sleep Quality Index [PSQI] score), M the mediator (global mental status–continuous), m its realized value (Mini-Mental State Examination [MMSE] total score), and $\boldsymbol{c}$ the vector of confounders. Under the assumption of no confounding, namely:

$$\text{i. } Y_{am} \coprod A|C$$

$$\text{ii. } Y_{am} \coprod M|(A,C)$$

$$\text{iii. } M_a \coprod A|C$$

$$\text{iv. } Y_{am} \coprod A*|C$$

that the effect of A on Y is unconfounded conditional on C (i), that the effect of M on Y is unconfounded conditional on (A, C), (ii), the effect of A on M is unconfounded conditional on C (iii), and that any mediator outcome confounders are not affected by the exposure (iv), we can partition the sources of total effect of the model into four components (Equation 1).[1]

$$TE = CDE + INT_{ref} + INT_{med} + PIE \tag{1}$$

We interpret this model to reflect that the total effect of the exposure, A, on the outcome, Y, is a sum of the *controlled direct effect* (CDE–i.e., the effect of A on Y not due to any interaction or mediation), *the reference interaction* (INT_{ref}–i.e., the effect of interaction only), *the mediated interaction* (INT_{med}–i.e., the

effect of interaction and mediation), and *the purely indirect effect* (PIE–i.e., the indirect effect only). In lay terms, we conceptialize these components in the following manner[1]:

- *controlled direct effect*: the effect of the exposure on the outcome without the presence of the mediator.
- *the reference interaction*: the exposure affects the outcome in the presence of the mediator and the presence of the exposure is not required for the presence of the mediator.
- *the mediated interaction*: the exposure affects the outcome in the presence of the mediator and the presence of the exposure is required for the presence of the mediator.
- *the purely indirect effect*: also called the "mediated main effect" and reflects that the mediator causes the outcome in the absence of the exposure but the exposure is required for the mediator to become present.

Additional details on the four-way decomposition model are provided in an original publication that we refer the readers to.[1]

1.2 *Four-Way Decomposition: Implementation*

The process of estimating the components of the partitioned model in Equation 1 requires the fitting of two regression models and then using the parameter estimates for the final computation of the components. A robust summary of the *med4way* command in Stata is described elsewhere and we refer the reviewers to that commentary though we provide a succinct summary of the implementation and estimation of the effects.[3] Under the assumption of no unmeasured confounding (as detailed above in **1.1**) we can estimate, on average, the four components of the model on a population but not the individual-level effects. The two regression models required are provided and include a model for the expectation of Y conditioned on the exposure, mediator, and confounders (Equation 2) and a model for the expectation of M conditioned on the exposure and confounders (Equation 3):

$$\mathrm{E}[Y|(a,m,\boldsymbol{c})] = \theta_0 + \theta_1 a + \theta_2 m + \theta_3 a * m + \boldsymbol{\theta}_c c \tag{2}$$

$$\mathrm{E}[M|(a,\boldsymbol{c})] = \beta_0 + \beta_1 a + \boldsymbol{\beta}_c^T \boldsymbol{c} \tag{3}$$

Estimates of these parameters therefore facilitate the direct computation of estimates of the four component sources of variation for the total effect (TE):

$$\mathrm{E}[CDE|c] = \theta_1(a - a')$$

$$\mathrm{E}[INT_{ref}|c] = \theta_3(\beta_0 + \beta_1 a' + \boldsymbol{\beta}_c^T \boldsymbol{c})(a - a')$$

$$\mathrm{E}[INT_{med}|c] = \theta_3\beta_1(a - a')(a - a')$$

$$\mathrm{E}[PIE|c] = (\theta_2\beta_1 + \theta_3\beta_1 a')(a - a')$$

where a and a' are arbitrary values of the exposure such that $a - a'$ reflects a one-unit difference (or some other meaningful difference) in the exposure.[4] The models we describe are generalizable and *Med4way* can handle outcome variables from several distributions (e.g., binomial, log-binomial, Poisson, negative binomial, Weibull, Cox, etc.).[3] In our analysis, $\mathrm{E}[Y|(a, m, c)]$ and $\mathrm{E}[M|(a, c)]$ are specified as follows:

$$\lambda(t|x, v, \boldsymbol{z}) = \lambda_0(t) + \theta_1 x + \theta_2 v + \theta_3 x * v + \boldsymbol{\theta}_z^T \boldsymbol{z} \tag{4}$$

$$\mathrm{E}[V|(x, \boldsymbol{z})] = \beta_0 + \beta_1 x + \boldsymbol{\beta}_z^T \boldsymbol{z} \tag{5}$$

where, in Equation 4, we model the log hazard at time t as a function of x, PSQI, v, MMSE total score, and $\boldsymbol{z}$, the vector of confounders/covariates discussed in the manuscript. In Equation 5, we model the expectation of the mediator, V, as a function of sleep quality and the other covariates using ordinary least squares.

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