

Poor sleep quality is associated with altered cortisol levels in older adults with high anxiety levels: a moderation analysis of Midlife in United States study

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ABSTRACT

Objectives: While poor sleep predicts cortisol levels in older adults, the moderating influence of anxiety remains under-examined. This study evaluates whether anxiety alters the association between sleep quality and 12-hour creatinine-adjusted urinary cortisol in community-dwelling older adults.

Methods: Utilizing biomarker data from the MIDUS 3 study (2017–2022; N = 747, mean age = 66), we performed multiple linear regression-based moderation analysis with bias-corrected bootstrapping and heteroskedasticity-robust standard errors. Anxiety was measured via the STAI scale and sleep quality via the PSQI scale. The adjusted model controlled for mean-centered covariates: BMI, age, LDL, depression (CESD scale), smoking history, sex, and HbA1c.

Results: In the simple moderation model, anxiety significantly moderated the sleep-cortisol relationship (Beta = -0.022, 95% CI: [-0.036, -0.007]). Specifically, poorer sleep (higher PSQI score) was associated with lower cortisol levels only among individuals with higher relative anxiety score (Mean +1 SD; Beta = -0.34; 95% CI: [-0.57, -0.104]). Neither sleep quality nor anxiety exhibited significant main effects. In the adjusted model, the moderation effect remained significant. Significant covariate associations included age (Beta = 0.118, 95% CI: [0.038, 0.203]), BMI (Beta = -0.222, 95% CI: [-0.313, -0.129]), and LDL (Beta = 0.028, 95% CI: [0.006, 0.048]).

Conclusion: Anxiety significantly moderates the link between sleep quality and cortisol in community-dwelling older adults. These findings suggest that sleep-related endocrine responses may vary according to anxiety levels, highlighting the necessity of assessing anxiety when evaluating stress biomarkers in aging populations.

1. Introduction

Insomnia and poor sleep quality are significant health challenges in aging populations. A global meta-analysis of community-dwelling older adults reported poor sleep prevalence rates of 40% [1], with approximately 19.6% meeting the DSM criteria for insomnia disorder [2]. Beyond general wellbeing, poor sleep quality independently predicts

reduced health-related quality of life (HRQoL) in older adults [3]. These disruptions are increasingly linked to neuroendocrine dysregulation, specifically within the hypothalamic-pituitary-adrenal (HPA) axis, which governs cortisol secretion [4]. While sleep fragmentation in older adults is often associated with elevated daytime cortisol [5], recurrent short sleep cycles can lead to a flattened diurnal rhythm [6]. The nature of this dysregulation often depends on duration; acute sleep deprivation

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typically increases cortisol levels, whereas chronic deprivation has been linked to decreased or "blunted" levels [7].

Parallel to sleep disturbances, anxiety is a major contributor to disability worldwide, with a 12-month prevalence reaching up to 29.8% in older populations [8]. Factors such as chronic physical conditions and social isolation contribute to this burden [9], leading to increased medical service utilization and impaired short-term memory [10,11]. Like sleep, anxiety is deeply implicated in hormonal dysregulation in older adults. Evidence supports associations between anxiety and thyroid dysfunction [12], as well as significant cortisol dysregulation; notably, elevated cortisol levels in older adults with generalized anxiety disorder have been shown to decrease following successful clinical treatment [13]. Furthermore, anxiety has been shown to exacerbate sleep disturbances in individuals with existing mood disorders [14,15], suggesting that these two conditions often co-occur to strain the endocrine system.

Despite the established independent links between sleep, anxiety, and cortisol regulation, few studies have examined their interactive effects in older populations. Understanding whether anxiety acts as a moderator in the sleep-cortisol relationship is vital for explaining variability in HPA axis profiles. Therefore, the current study conducts an exploratory analysis of whether anxiety moderates the relationship between sleep quality and 12-hour urinary cortisol levels.

2. Materials and methods

2.1. Sample

The Midlife in the United States (MIDUS) study is a longitudinal investigation initiated in 1995, enrolling >7000 Americans aged 25–75 years, with oversampling from five metropolitan areas. The study examines the influence of psychological, behavioral, and social factors on age-related physical and mental health outcomes. Follow-up waves were conducted in 2009 (MIDUS 2) and 2013 (MIDUS 3), the latter of which incorporated comprehensive biomarker data collection.

2.2. Procedures

This cross-sectional analysis utilized data exclusively from the MIDUS 3 Biomarker Project (2017–2022). For MIDUS 3, data were collected between 2017 and 2022 during a 24-hour research visit at one of three sites (University of California, Los Angeles; University of Wisconsin–Madison; and Georgetown University). Trained clinical staff conducted standardized assessments and collected biological specimens to evaluate the function of multiple physiological systems. The MIDUS 3 Biomarker Project sample included 747 participants: 644 from the longitudinal survey cohort and 103 from the Milwaukee oversample, yielding an overall adjusted response rate of 64.3% (747/1162). All participant data ($n = 747$) were included in the analysis.

2.2.1. Self-report measures

The primary variable tested for its association with cortisol regulation in this study was sleep quality, assessed using the Pittsburgh Sleep Quality Index (PSQI) in MIDUS 3. The total PSQI score was used in the analyses, with higher scores reflecting poorer sleep quality [16]. In the adjusted moderation model, covariates included two psychological measures (i.e., depression and anxiety). Depression was measured using the Center for Epidemiological Studies Depression Scale (CES-D) [17], anxiety was measured using State-Trait Anxiety Inventory (STAI), trait subscale (STAI-T) [18], and higher scores indicated greater depressive and anxiety levels, respectively.

2.2.2. Biological measures

In the adjusted model, covariates also included history of regular smoking (yes/no), body mass index (BMI), low-density lipoprotein cholesterol (LDL), sex, and hemoglobin A1c (HbA1c).

The outcome variable was 12-hour urinary cortisol. Overnight urine samples were collected between 19:00 and 07:00 by trained nursing staff, except during the early phase of the COVID-19 pandemic, when collection transitioned to overnight outpatient settings. Participants were instructed on proper use of collection devices (urinals for men, collection hats for women) and were asked to notify nursing staff after each void. Procedures for urine collection and refrigeration were thoroughly explained, and staff provided consistent reminders to ensure protocol adherence. Detailed procedures for urine, blood, and saliva collection are available in the MIDUS 3 Biomarker Project documentation [19].

Urinary cortisol concentrations were measured using liquid chromatography-tandem mass spectrometry (LC-MS/MS) with laboratory-developed methods. Quality control was ensured using three pooled urine samples [20]. All assays were conducted at the University of Wisconsin–Madison Institute for Clinical and Translational Research. Additional details regarding MIDUS 3 procedures and collection of other serum markers can be found on the study website [19].

2.3. Statistical analysis

Descriptive statistics were used to summarize sample characteristics, with means and standard deviations (SD) for continuous variables, medians and interquartile ranges (IQR) for skewed variables, and counts and percentages for categorical variables.

Moderation analysis was performed to examine whether anxiety modified the association between sleep quality and 12-h urinary cortisol (creatinine-adjusted). Bias-corrected bootstrapping with 5000 replications was used to calculate 95% confidence intervals (CIs). Simple slope analyses identified levels of anxiety at which moderation effects were significant. An adjusted moderation model controlled for age, sex, BMI, smoking history, LDL-C, HbA1c, and depressive symptoms using multiple linear regression. Covariates were mean-centered to address multicollinearity, and variance inflation factors (VIFs) were all < 4 . To meet analysis assumptions, heteroskedasticity was addressed using heteroskedasticity-consistent (HC3) standard error method, and bias-corrected bootstrapped 95% CIs – which handled the minor deviation in normality of residuals assumption – were also reported. Of the participants, at most, approximately 10% were excluded due to incomplete data on the primary study variables ($N = 668$). Consequently, listwise deletion was deemed suitable considering the large and suitable size of the final sample.

Bivariate associations between sleep quality and anxiety were examined using Pearson's correlation coefficients. A two-tailed p -value < 0.05 was considered statistically significant. All analyses were performed using Jamovi software (version 2.6.13; The jamovi project, 2024), a user-friendly freely available software [21].

Ethical approval

The MIDUS 3 biomarker project was approved from the Institutional Review Board at the University of Wisconsin–Madison. All participants provided informed consent prior to participation in MIDUS study. The current study is a secondary analysis of publicly available de-identifiable data and was conducted in accordance with the principles of the Declaration of Helsinki.

3. Results

The total number of participants in our study was 747, with 44.2% being males. Basic features of participants are displayed under Table 1. Pearson's correlation analysis revealed a significant positive association between poor sleep quality and anxiety ($r = 0.404$, $P < 0.001$).

Simple moderation analysis was conducted to examine the association between sleep quality and urinary cortisol levels, with anxiety levels entered as the moderator. The results revealed a significant

Table 1
Basic features of participants.

Sex	Counts	% of Total
Male	330	44.20%
Female	417	55.80%
Having history of regular smoking		
Yes	329	44.00%
No	418	56.00%
Descriptives of continuous covariates		
	Mean	SD
Age	65.96	9.64
PSQI Global score (sleep quality)	6.30	3.49
BMI (kg/m ²)	29.92	6.63
LDL Cholesterol (mg/dL)	101.08	34.36
	Median	Q1 Q3
HbA1c (%)*	5.6	5.3 5.93
12-h Urinary Cortisol (adjusted for Creatinine) (µg/g)*	7.38	4.39 12.42
STAI Score (Anxiety)*	32	27 39
CESD Score (Depression)*	7	3 13

*Not normally distributed

moderation effect (Beta = −0.022; 95% CI: [−0.036, −0.007]), whereas the direct effects of sleep quality and anxiety levels were not significant (see Table 2). Simple slope analysis further demonstrated that poor sleep quality (higher PSQI scores) had a significant negative effect on cortisol levels specifically at higher relative anxiety levels (Mean +1 SD; Beta = −0.34; 95% CI: [−0.57, −0.104]). These results are summarized in Table 2 and illustrated in Fig. 1.

After adjustment for covariates, the moderation effect of anxiety remained statistically significant. Among the covariates, age (Beta = 0.118, 95% CI [0.038, 0.203]), BMI (Beta = −0.222, 95% CI [−0.313, −0.129]), and LDL (Beta = 0.028, 95% CI [0.006, 0.048]) were significantly associated with 12-hour urinary cortisol. In this model, higher age and LDL levels were associated with higher cortisol levels, whereas BMI showed a negative association. The application of robust standard error estimation effectively addressed heteroskedasticity, and mean-centering of covariates mitigated multicollinearity, with all variance inflation factor (VIF) values remaining below 4. Overall, the model demonstrated acceptable fit, with an acceptable R² value of 0.08 (see Table 3).

4. Discussion

Our analysis revealed a significant positive correlation between poor sleep quality and anxiety in this cohort of community-dwelling older adults. Existing literature suggests a bidirectional relationship between these variables, with some studies demonstrating that anxiety predicts poor sleep quality [22], while others indicate that poor sleep quality

Table 2
Simple moderation analysis for association between sleep quality and 12-hour urinary cortisol while considering Anxiety as a moderator in older adults.

Moderation Estimates					
	Estimate	SE	95% CI*		p
			Lower	Upper	
PSQI score	−0.154	0.105	−0.357	0.055	0.143
STAI score	0.02	0.039	−0.058	0.096	0.618
STAI (Anxiety) * PSQI (sleep quality) Interaction	−0.022	0.008	−0.036	−0.007	0.005
Simple Slope Estimates					
	Estimate	SE	95% CI		p
			Lower	Upper	
STAI Score (Anxiety)					
Low (−1 SD)	0.033	0.13	−0.216	0.301	0.797
Average	−0.153	0.105	−0.357	0.058	0.143
High (+1 SD)	−0.34	0.118	−0.57	−0.104	0.004

Note. shows the effect of the predictor on the dependent variable at different levels of the moderator (Anxiety)

*based on bias-corrected bootstrapping (5000 repl.).

predicts anxiety [23]. Importantly, our study provides novel evidence that anxiety moderates the association between sleep quality and cortisol levels. Specifically, poorer sleep quality was associated with significantly lower 12-hour urinary cortisol levels in community-dwelling older adults with higher relative anxiety (+1 SD), whereas neither anxiety nor sleep quality alone showed a significant main effect on cortisol. Utilizing the total continuous score maximized statistical power and illustrated a dose-response relationship across the full spectrum of this healthy cohort—an approach widely validated in community-based epidemiological research. Crucially, our study cohort comprised community-dwelling older adults with a generally low baseline burden of anxiety. The median STAI-T score was 32, and the subgroup utilized for slope analysis (+1 SD) represents a low-to-moderate boundary rather than clinically elevated trait anxiety. Consequently, our findings reflect the nuances of sub-clinical variations in anxiety within a healthy population. Although these constitute novel and important findings, caution is needed when generalizing these results to clinical populations.

Our findings may be consistent with a recent study by Yap et al. [24], which reported that higher wake after sleep onset (WASO), but not total sleep time (TST) or sleep efficiency (SE), were associated with lower awakening cortisol levels the following day. Yap et al. attributed this to temporary inhibition of cortisol secretion following nocturnal elevations associated with recurrent nighttime awakenings, a marker closely linked to poor sleep quality [25], as hypothesized by Backhaus et al. [26]. While our use of the global PSQI score precludes us from isolating specific sleep architecture components (such as fragmentation or duration) driving this effect, it is worth noting that subjective sleep quality ratings are heavily influenced by nighttime awakenings and sleep disruptions. Therefore, our results offer converging, albeit more generalized, evidence supporting the link between disrupted sleep and altered cortisol regulation in older adults. Although we used different method for sleep quality assessment in comparison to Yap et al., our results may extend their findings by suggesting that elevated anxiety—a factor not controlled for in many previous studies—is associated with poor sleep quality, commonly manifesting as recurrent nighttime awakenings, potentially resulting in lower 12-hour urinary cortisol. These results highlight the importance of including anxiety as a covariate in future research and underscore the need for adjusted analyses to account for its moderating effects. Clinically, anxiety should be recognized as a key associated factor with the alterations in neuroendocrine function, particularly cortisol regulation, in older adults.

Additionally, our results showed that higher LDL levels were associated with significantly higher 12-hour urinary cortisol in community-dwelling older adults. While prior studies have reported similar associations in other populations, such as obese pediatric patients and individuals with Cushing's disease [27,28], Whitworth et al. suggested that prolonged periods of cortisol excess may be required to induce dyslipidemia in healthy individuals [29]. Our findings support this concept and provide novel data on the relationship between cortisol and LDL in general community older adults, a population in which this association has been underexplored.

Interestingly, higher BMI in our study cohort was significantly associated with lower 12-hour urinary cortisol levels. This observation may align with previous research suggesting a negative association between BMI and various HPA axis markers. For instance, a large cross-sectional study of 394 men and 375 women reported an inverse relationship between BMI and the cortisol awakening response (CAR) in women [30]. Similarly, a seven-year longitudinal study of 1685 older adults found that a 1% annual increase in BMI was associated with lower waking cortisol levels [31]. While waking cortisol and 12-hour urinary cortisol capture different physiological aspects of HPA regulation, both findings suggest that obesity may be associated with a blunted cortisol profile and overall HPA axis dysregulation in older populations. Mechanistically, a recent meta-analysis concluded that aging in obese individuals is generally accompanied by reduced HPA axis activity,

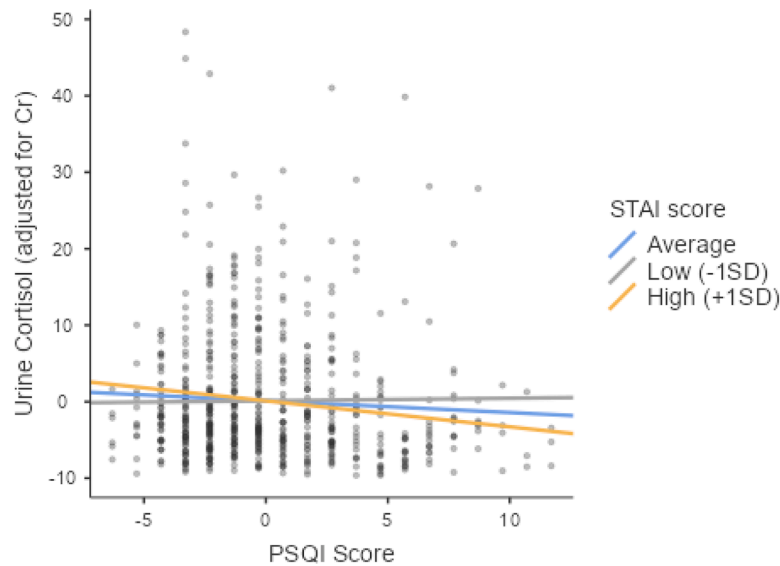


Fig. 1. Simple slope plot for moderation effect of anxiety on association between sleep quality and 12-hour urine cortisol level in older adults.

Table 3
multiple linear regression model for variables associated with 12-h urine cortisol in elderly.

Names	Effect	Estimate	SE	95% CI		β	p
				Lower	Upper		
(Intercept)	(Intercept)	10.208	0.345	9.525	10.894	0.019	<0.001
Sex	FEMALE - MALE	1.229	0.665	-0.108	2.505	0.145	0.065
Smoking	NO - YES	0.387	0.647	-0.875	1.646	0.046	0.55
PSQI score (Sleep quality)		-0.126	0.112	-0.334	0.094	-0.053	0.259
HbA1c		0.658	0.437	-0.167	1.435	0.08	0.133
LDL		0.028	0.011	0.006	0.048	0.111	0.014
STAI score (Anxiety level)		0.048	0.054	-0.058	0.151	0.049	0.374
Age		0.118	0.042	0.038	0.203	0.133	0.006
BMI		-0.22	0.049	-0.313	-0.129	-0.169	<0.001
CESD (Depression level)		-0.007	0.061	-0.126	0.116	-0.007	0.906
Sleep quality * Anxiety level		-0.02	0.008	-0.035	-0.005	-0.073	0.009

Note. Inferential tests and p-values of the effects are adjusted for heteroscedasticity. Robust SE (using HC3 method) and Bias-corrected Bootstrapping (5000 repl.) were used. Covariates scaling: centered.

resulting in decreased peripheral cortisol secretion. This age-related decline in HPA function may, in turn, attenuate the progression of obesity-related metabolic disorders, including type 2 diabetes and hypertension [32].

We observed no association between depression and 12-hour urinary cortisol after controlling for potential confounders. While prior studies have reported variable findings regarding depression and cortisol—often influenced by comorbidities and other factors [33,34]—our results suggest that, within this cohort, depression itself is not associated with altered cortisol levels when robust statistical adjustments are applied. From another point of view, it is highly probable that this null finding is attributable to the floor effect and low depressive burden observed in our community-dwelling sample of older adults (median CESD score of 7). While the use of continuous total scores is valid for assessing dose-response gradients, the lack of sufficient variance and absence of moderate-to-severe depressive symptoms potentially limited our ability to detect associations that might exist in populations with a higher depressive burden.

Clinical implications

Our findings emphasize the importance of considering anxiety in community-dwelling older adults, particularly those with poor sleep quality. Nevertheless, the generalization to clinical populations with elevated psychiatry burden cannot be assumed.

Non-pharmacological approaches should remain first-line strategies in community-dwelling older adults with Anxiety. Cognitive behavioral therapy (CBT) has demonstrated efficacy in reducing anxiety symptoms in older adults, especially when comorbid with insomnia [35]. Regular physical activity may also serve as an effective non-pharmacological intervention, alleviating sleep-related anxiety and reducing daytime sleepiness [36]. This implication is particularly relevant as a preventive strategy for anxiety in community-dwelling cohort.

When non-pharmacological strategies are insufficient, carefully selected pharmacological interventions may be considered under medical supervision, with attention to potential drug interactions. However, these pharmacologic options should generally be reserved for short-term use and as a last-line therapy to minimize side effects and interactions.

Limitations

One of the limitations in our study was the use of urinary cortisol levels as an indicator for cortisol regulation. The use of salivary cortisol would be a better indicator, however there was no such available variable in the data we used. It's important to mention that urinary cortisol and salivary cortisol capture different aspects of HPA-axis activity. In our analysis, urinary cortisol was the best indicator to be used. Of note, the use of 12-hour urinary cortisol remains a well-recognized and scientifically valid approach for the assessment of hypothalamic-pituitary-adrenal axis activity and cortisol regulation [37,38].

It should also be acknowledged that the use of cross-sectional design in our analysis cannot establish causation. Furthermore, residual confounding cannot be completely excluded despite adjustment for several covariates. Finally, our sample consists of community-dwelling older adults, making generalization of our findings to clinical populations with elevated psychiatry burden potentially inapplicable.

5. Conclusion

In conclusion, our study highlights a novel association between anxiety and poor sleep quality that is related to altered 12-hour urinary cortisol levels in community-dwelling older adults. Moreover, we identified additional relevant covariates, including LDL and BMI, that influence this association. These findings provide valuable insights to guide future research on neuroendocrine dysregulation and emphasize the importance of integrating anxiety assessment and management in both clinical practice and research involving older adults.

Article information and declarations

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Data availability statement

Data analyzed in the current study is publicly available at MIDUS study webpage: <https://www.icpsr.umich.edu/web/NACDA/studies/38837>

Generative AI use statement

AI tools (ChatGPT and Gemini Pro) utilized solely for language enhancement and readability. Authors reviewed, edited, and retain full responsibility for the final content.

CRediT authorship contribution statement

Laith Ashour: Writing – review & editing, Supervision, Project administration, Formal analysis, Data curation, Conceptualization. **Kamal Abo Zenha:** Investigation, Validation, Resources, Writing – original draft. **Zaid Alomari:** Investigation, Resources, Writing – original draft, Conceptualization. **Noura F. Al-Nawaiseh:** Investigation, Validation, Resources, Writing – original draft. **Mouna Hassan Alallan:** Investigation, Resources, Writing – original draft, Conceptualization. **Abeer Kalbounah:** Investigation, Validation, Resources, Writing – original draft. **Bashar Quteishat:** Investigation, Resources, Writing – original draft, Conceptualization. **Arar Alhawwari:** Investigation, Validation, Resources, Writing – original draft. **Abdelhadi Okasha:** Investigation, Validation, Resources, Writing – original draft. **Rima Heramas:** Investigation, Validation, Resources, Writing – original draft. **Abdelmajid A Alsarhan:** Investigation, Resources, Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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