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ORIGINAL RESEARCH

Sleep Duration and Cardiometabolic-Kidney-Metabolic Syndrome: The Role of Depressive Symptoms in a Longitudinal Study

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Background: Sleep disturbances are increasingly recognized as modifiable risk factors for metabolic and cardiovascular diseases. However, the relationship between sleep duration patterns and Cardiometabolic-Kidney-Metabolic (CKM) syndrome remains under-explored, particularly regarding the mediating role of mental health factors. This study investigates the longitudinal association between sleep duration and CKM risk, examining whether depressive symptoms mediate this relationship.

Methods: We analyzed data from 6462 participants (aged ≥45 years) from the China Health and Retirement Longitudinal Study. Sleep duration was self-reported and categorized as short (<7 hours), optimal (7–9 hours), or long (>9 hours), with 2-year sleep trajectories also defined. CKM syndrome was classified per American Heart Association guidelines, and depressive symptoms were assessed via the 10-item Center for Epidemiologic Studies Depression Scale. Associations were examined using multivariable logistic regression, restricted cubic splines, and causal mediation analysis.

Results: Baseline short sleep duration was independently associated with increased CKM risk (adjusted OR = 1.148; 95% CI: 1.014–1.299). Persistently abnormal sleep over two years further elevated this risk (OR = 1.259; 95% CI: 1.077–1.471). We observed a significant non-linear dose-response relationship between sleep duration and CKM risk (P = 0.031). Causal mediation analysis showed that depressive symptoms partially mediated this association (ACME = −0.002; P < 0.001). Subgroup analyses revealed stronger associations among women, individuals with lower education, and urban residents.

Conclusion: Both short and persistently abnormal sleep independently increase CKM syndrome risk, with depressive symptoms acting as a key mediator. These findings highlight the importance of integrated interventions targeting sleep optimization and mental health management, particularly for high-risk demographic subgroups. Sleep assessment should be incorporated into CKM risk stratification and prevention strategies.

Keywords: sleep duration, cardiometabolic-kidney-metabolic syndrome, depressive symptoms, longitudinal study, mediation analysis

Introduction

Cardiometabolic-Kidney Metabolic Syndrome (CKM) is a systemic disorder characterized by complex interactions among the metabolic, renal, and cardiovascular systems, leading to multi-organ dysfunction and a significantly increased risk of adverse cardiovascular events. This syndrome places a substantial economic burden on both individuals and society.[1,2] Therefore, early identification and intervention of CKM-related risk factors are essential for its prevention.

Sleep, as a fundamental physiological process, plays a crucial role in both physical and mental health through its duration and quality.[3] Research has shown that sleep deprivation can lead to endothelial dysfunction, disrupt glucose metabolism, and impair appetite regulation, thus accelerating cognitive decline.[4–6] Abnormal sleep duration is closely associated with an increased risk of obesity, cardiovascular disease, and all-cause mortality.[7–10] However, most studies have relied on sleep duration measured at a single time point to investigate its association with disease, neglecting the dynamic changes in sleep behavior and potentially underestimating or distorting the true impact of sleep on health.[11]

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Moreover, the potential effects of sleep on metabolic health may be mediated indirectly through psychopathological mechanisms. Depressive symptoms and sleep disturbances exhibit a bidirectional relationship. On one hand, insufficient sleep may exacerbate depressive moods by overactivating the hypothalamic–pituitary–adrenal (HPA) axis and triggering neuroinflammatory responses; on the other hand, the negative cognitive bias and circadian rhythm disruption associated with depressive symptoms may further impair sleep quality.[12,13] Additionally, depressive symptoms can directly increase the risk of metabolic syndrome and cardiovascular–renal damage by promoting unhealthy behaviors, such as prolonged sedentary behavior and high-fat diets, and by activating chronic low-grade inflammation.[14]

Collectively, these findings suggest that sleep patterns may be closely linked to the development of CKM, with depression potentially acting as a key mediator in the sleep–CKM relationship. However, research in this area remains limited. Therefore, this study uses data from the China Health and Retirement Longitudinal Study (CHARLS) to: (1) examine the association between sleep duration (and its trajectory) and CKM syndrome; and (2) apply a causal mediation analysis framework to explore whether depressive symptoms mediate the relationship between sleep and CKM. The ultimate goal of this research is to identify potential targets for multidimensional interventions in CKM and to assess whether the synergistic effects of improving sleep quality and managing depressive symptoms can reduce the risk of CKM.

Methods

Study Population

This study used three-wave follow-up data (2011, 2013, and 2015) from CHARLS. CHARLS is a nationally representative cohort study designed to systematically evaluate dynamic changes in health and socioeconomic status among middle-aged and older adults in China. The original CHARLS study was approved by the Ethics Review Board of Peking University (IRB00001052-11015), and all participants provided written informed consent prior to their involvement. The protocol for the present secondary analysis was reviewed and approved by the Ethics Committee of Beijing Anzhen Hospital, Capital Medical University (Approval No. 2025142x). This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. During data collection, researchers received standardized training and administered questionnaires through face-to-face interviews to ensure data quality.[15]

The participant selection process is illustrated in Figure 1. Participants were included if they met the following criteria: (1) were aged 45 years or older at baseline; and (2) completed all three follow-up waves with complete data for

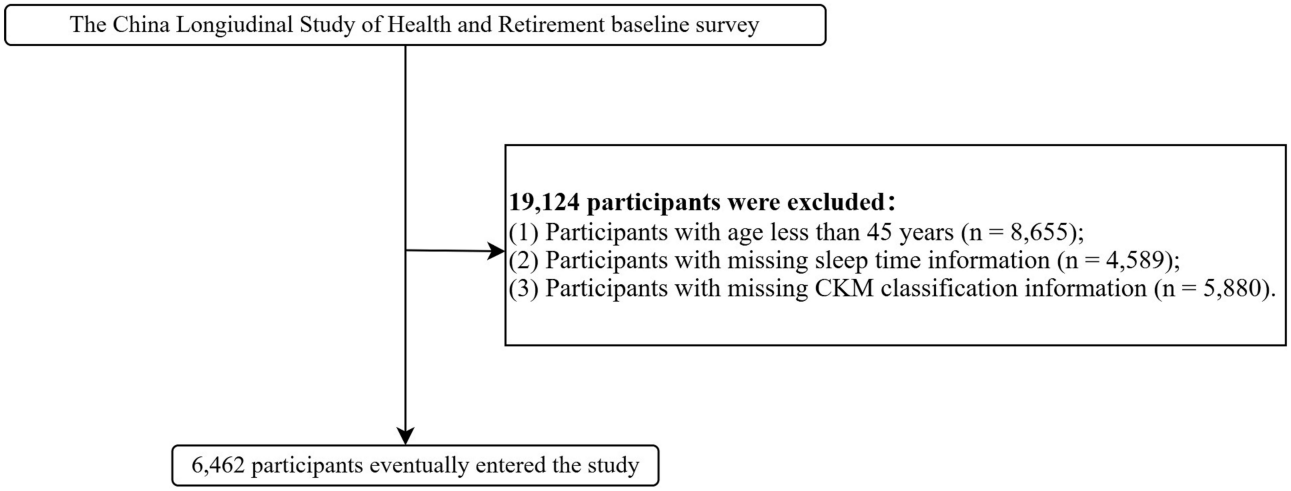

Figure 1 Inclusion and exclusion criteria flowchart of this study.
Abbreviation: CKM, Cardiometabolic-Kidney-Metabolic.

the key variables of sleep duration and CKM staging. After applying these criteria, a final sample of 6462 participants was included in the analysis.

Measurements

Measurement of Sleep Duration and Sleep Trend

Sleep duration data were obtained from the CHARLS questionnaire item: "During the past month, how many hours of actual sleep did you get per night on average?" Based on international consensus, participants were classified into three groups: optimal sleep (7–9 hours/day), short sleep (<7 hours/day), and long sleep (>9 hours/day).[16–18] Four longitudinal trajectories were further defined by integrating baseline (2011) and follow-up (2013) data: (1) stable optimal sleep (7–9 hours at both time points), (2) persistent abnormal sleep (<7 or >9 hours at both time points), (3) sleep deterioration (optimal → abnormal), and (4) sleep improvement (abnormal → optimal).

Definition of CKM Syndrome Stage

We defined CKM syndrome stages based on the American Heart Association classification and related studies.[2,19] Participants were categorized into two groups: early CKM (Stages 0, 1, 2, and 3) and advanced CKM (Stage 4). The staging process incorporated an elevated 10-year cardiovascular disease risk, predicted by the Framingham risk score, as a risk equivalent for subclinical cardiovascular disease.[20] The estimated glomerular filtration rate was calculated using the Chronic Kidney Disease (CKD) Epidemiology Collaboration equation, and CKD staging followed the Kidney Disease: Improving Global Outcomes guidelines.[21,22] The detailed classification criteria for CKM syndrome are provided in Supplementary Table 1.

Measurement of Depressive Symptoms

In CHARLS, depressive symptoms were assessed using the 10-item Center for Epidemiologic Studies Depression Scale (CESD-10).[23] The CESD-10 consists of 10 items, which are categorized into positively and negatively oriented questions. Each item has four response options: "rarely or none of the time" (0 points), "some of the time" (1 point), "occasionally" (2 points), and "most or all of the time" (3 points). For negatively oriented items (eg, "I felt depressed"), higher scores reflect greater symptom severity, while positively oriented items (eg, "I felt hopeful") are reverse-scored (3 points for "rarely or none of the time" to 0 points for "most or all of the time"). Total scores range from 0 to 30, with higher scores indicating greater depressive risk and severity. This scale has been widely used and has demonstrated good reliability and validity for assessing depressive symptoms in the general adult population in China.[24]

Data Collection

Data were collected through standardized questionnaires, physical examinations, and laboratory tests. We obtained information on demographic characteristics (age, sex, education level, marital status, residence), anthropometric measures, and lifestyle factors including smoking and drinking history. Physical activity was quantified as Metabolic Equivalent of Task (MET) hours, and functional status was evaluated using the Activities of Daily Living (ADL) scale. Laboratory parameters measured from blood samples included triglycerides, low-density lipoprotein, and fasting glucose, among others.

Statistical Analysis

Continuous variables were presented as the mean ± standard deviation (for normally distributed data) or median (interquartile range, IQR), while categorical variables were expressed as frequency (percentage). Group differences were assessed using analysis of variance, the Kruskal–Wallis test, or the chi-square test, as appropriate. There were no missing data for the primary independent variable (sleep duration) or the dependent variable (CKM syndrome). Missing values for covariates were handled using multiple imputation. The association between sleep duration and CKM syndrome was analyzed using multivariable logistic regression models. Model 1 was an unadjusted model. Model 2 was adjusted for age, sex, education, marital status, residence, smoking history, alcohol consumption, MET, and ADL. Results were reported as odds ratios (OR) with 95% confidence intervals (CI). To explore the mediating role of depressive symptoms (measured by CESD scores), a causal mediation analysis was conducted. This analysis involved

three models: (1) a total effect model to examine the overall impact of sleep duration on CKM syndrome; (2) a mediation model to analyze the association between sleep duration and CESD scores; and (3) a direct effect model to re-evaluate the sleep-CKM syndrome relationship after adjusting for CESD scores. The indirect effect was estimated using bootstrap resampling with 5000 iterations to calculate the 95% CI. Restricted cubic splines (RCS) with three knots were used to flexibly model and visualize the potential non-linear dose-response relationship between sleep duration and the incidence of CKM syndrome. Furthermore, subgroup and interaction analyses were conducted to explore potential effect modification by demographic characteristics, health behaviors, and anthropometric measures, with results visualized using forest plots. Two sensitivity analyses were performed to test the robustness of our findings: (1) excluding participants with CKD at baseline, and (2) excluding individuals reporting extreme sleep durations (<4 or >12 hours per night).All statistical analyses were performed using R version 4.4.2. A two-tailed $P < 0.05$ was considered statistically significant.

Results

Baseline Characteristics

A total of 6462 participants were included in the final analysis and categorized based on their nocturnal sleep duration. Detailed baseline characteristics are presented in Table 1. Significant differences ($P < 0.05$) across sleep duration groups were observed for age, education level, marital status, residence, Body mass index, Waist circumference, DBP, ADL score, and depressive symptoms (CESD score).

Relationship Between Sleep Duration, Trends, and CKM Syndrome

As shown in the fully adjusted models in Table 2, baseline sleep duration remained a significant predictor of incident CKM syndrome. When analyzed continuously, each additional hour of sleep was associated with a 4.0% reduction in CKM risk (OR = 0.960, 95% CI: 0.930–0.992, $P = 0.013$). When analyzed categorically, participants with short sleep duration (<7 hours) at baseline had a 14.8% higher risk of developing CKM syndrome compared to those with optimal sleep (OR = 1.148, 95% CI: 1.014–1.299, $P = 0.030$). In contrast, long sleep duration at baseline was not significantly associated with CKM risk in the adjusted model.

We then examined the effect of 2-year sleep trajectories. The "Stable Abnormal" sleep group showed a significantly elevated risk of CKM syndrome compared to the "Stable Optimal" group in both the unadjusted model (OR = 1.453, 95% CI: 1.249–1.690, $P < 0.001$) and the fully adjusted model (OR = 1.259, 95% CI: 1.077–1.471, $P = 0.004$). Other sleep trajectories, such as improving or worsening sleep, were not significantly associated with CKM risk in the adjusted models.

The RCS regression model revealed a significant overall association between sleep duration and CKM risk (Wald test $P = 0.006$). The test for non-linearity was also significant (non-linearity test $P = 0.031$), indicating a J-shaped relationship between sleep duration and the risk of CKM (Figure 2). The dose-response curve suggests that the risk is lowest at longer sleep durations, becoming statistically significant for sleep durations exceeding approximately 7.5 hours.

Causal mediation analysis was performed to investigate whether depressive symptoms (CESD score) mediate the association between sleep duration and CKM syndrome (Table 3). The analysis revealed a significant indirect pathway. Specifically, each one-hour increase in sleep duration was associated with a decrease in depressive symptom scores (Path a: $\beta = -0.226$, $P < 0.001$), and higher depressive symptom scores were, in turn, associated with increased odds of CKM syndrome (Path b: OR = 1.035, $P < 0.001$). The bootstrap test confirmed a significant indirect effect, indicating that depressive symptoms partially mediate the relationship between sleep and CKM risk (Average Causal Mediation Effect [ACME] = −0.0015; $P < 0.001$). After accounting for this mediation, the direct effect of sleep duration on CKM was no longer statistically significant (Average Direct Effect [ADE] = −0.0057; $P = 0.060$).

We conducted stratified analyses to investigate whether the relationship between sleep duration and CKM syndrome varied across key demographic subgroups (Figure 3). The magnitude of the association appeared to differ by age and residence. Specifically, the protective effect of longer sleep was more pronounced in participants younger than 65 years (OR = 0.94, 95% CI: 0.90–0.98) compared to those aged 65 and older (OR = 0.98, 95% CI: 0.93–1.03). Similarly, the association was stronger among urban residents (OR = 0.95, 95% CI: 0.91–0.99) than rural residents (OR = 0.97, 95%

Table 1 Baseline Characteristics of Participants Stratified by Sleep Duration

Variable	Level	Normal Sleep	Less Sleep	More Sleep	*P*-value
Age (mean (SD))		57.32 (8.31)	59.06 (8.41)	59.27 (9.74)	<0.001
Gender, n (%)	Female	1532 (52.2)	1768 (54.5)	142 (51.1)	0.149
	Male	1405 (47.8)	1479 (45.5)	136 (48.9)	
Education, n (%)	Less than lower secondary education	2608 (88.8)	2918 (89.9)	263 (94.6)	0.008
	Secondary or above	329 (11.2)	329 (10.1)	15 (5.4)	
Marital status, n (%)	Married	2685 (91.4)	2863 (88.2)	232 (83.5)	<0.001
	Non-married	252 (8.6)	384 (11.8)	46 (16.5)	
Residence, n (%)	Rural	1945 (66.2)	2056 (63.3)	200 (71.9)	0.003
	Urban	992 (33.8)	1191 (36.7)	78 (28.1)	
Smoking, n (%)	No	1785 (60.8)	1998 (61.5)	164 (59.0)	0.636
	Yes	1152 (39.2)	1249 (38.5)	114 (41.0)	
Drinking, n (%)	No	1813 (61.8)	1970 (60.7)	163 (58.6)	0.491
	Yes	1123 (38.2)	1274 (39.3)	115 (41.4)	
BMI (median [IQR])		23.42 [21.19, 26.05]	23.14 [20.87, 25.78]	22.65 [20.71, 25.48]	0.001
WC (median [IQR])		85.00 [78.40, 93.00]	84.20 [78.00, 91.45]	84.20 [78.30, 91.75]	0.010
SBP (mean (SD))		128.84 (20.72)	128.68 (20.51)	130.23 (23.15)	0.526
DBP (mean (SD))		75.82 (12.14)	74.91 (12.01)	76.26 (14.13)	0.010
TG (median [IQR])		107.08 [74.34, 157.53]	106.20 [76.11, 154.88]	107.53 [75.22, 157.53]	0.962
LDL (median [IQR])		113.66 [93.94, 136.66]	114.05 [91.62, 136.86]	116.75 [91.24, 138.79]	0.754
MET (mean (SD))		7731.60 (7711.35)	7097.81 (7241.78)	7893.20 (6808.54)	0.074
ADL (mean (SD))		0.18 (0.66)	0.34 (0.88)	0.32 (0.86)	<0.001
Glucose (mean (SD))		110.39 (34.62)	109.77 (35.65)	109.05 (33.16)	0.781
CESD (median [IQR])		3.00 [0.00, 6.00]	4.00 [2.00, 9.00]	4.00 [1.00, 6.00]	<0.001

Notes: Data are presented as mean (standard deviation, SD) for normally distributed continuous variables, median [interquartile range, IQR] for non-normally distributed continuous variables, and n (%) for categorical variables. Comparisons were made using one-way analysis of variance (ANOVA) for normally distributed data, the Kruskal–Wallis test for non-normally distributed data, and the Chi-square test for categorical data. Statistical significance was defined as a two-tailed $P < 0.05$. Sleep duration categories were defined as: Normal sleep (7–9 hours/night), Less sleep (<7 hours/night), and More sleep (>9 hours/night).

Abbreviations: ADL, Activities of Daily Living; BMI, Body Mass Index; CESD, Center for Epidemiologic Studies Depression Scale; DBP, Diastolic Blood Pressure; IQR, Interquartile Range; LDL, Low-Density Lipoprotein; MET, Metabolic Equivalent of Task; SD, Standard Deviation; SBP, Systolic Blood Pressure; TG, Triglycerides; WC, Waist Circumference.

CI: 0.92–1.02). The association was comparable between males and females. However, despite these observed differences in point estimates, formal tests for interaction did not reach statistical significance for any of the subgroups (all P for interaction > 0.05).

To confirm the robustness of our primary findings, we conducted two sensitivity analyses. First, we repeated the analysis after excluding participants who had chronic kidney disease (CKD) at baseline. Second, we re-analyzed the data after excluding individuals who reported extreme sleep durations (<4 hours or >12 hours per night). As detailed in Supplementary Table 2 and Supplementary Table 3, the association between sleep duration and the risk of incident CKM syndrome remained consistent and significant in both scenarios, supporting the stability of our results.

Discussion

In this longitudinal study based on the CHARLS cohort, we identified several key findings. First, baseline short sleep duration (<7 hours) emerged as an independent risk factor for incident CKM syndrome, with a 14.8% increased risk. Second, persistent abnormal sleep patterns over a 2-year period were associated with elevated CKM risk even after full adjustment, highlighting the importance of sustained sleep quality. Third, our causal mediation analysis revealed that depressive symptoms partially explained the sleep-CKM relationship, suggesting an important psychobiological pathway. Finally, the protective association of adequate sleep was particularly evident among women, individuals with lower education, and urban residents.

Table 2 Association of Baseline Sleep Duration and 2-Year Sleep Trajectories with Incident CKM Syndrome

	Model 1	*P*	Model 2	*P*
Sleep Duration	0.926 (0.898, 0.956)	<0.001	0.960 (0.930, 0.992)	0.013
Sleep Category				
Optimal Sleep	Ref		Ref	
Short Sleep	1.287 (1.141, 1.451)	<0.001	1.148 (1.014, 1.299)	0.030
Long Sleep	0.919 (0.673, 1.257)	0.598	0.851 (0.618, 1.172)	0.324
Sleep Trajectories				
Stable_norm	Ref		Ref	
Abnormal→Normal	0.988 (0.811, 1.203)	0.901	0.899 (0.735, 1.100)	0.301
Normal→Abnormal	1.096 (0.915, 1.312)	0.320	1.049 (0.873, 1.262)	0.608
Stable_Abnorm	1.453 (1.249, 1.690)	<0.001	1.259 (1.077, 1.471)	0.004

Notes: Data are presented as odds ratios (OR) with 95% confidence intervals (CI). Model 1 represents unadjusted estimates. Model 2 is adjusted for age, sex, education level, marital status, residence, smoking, drinking, MET, and ADL. "Ref" denotes the reference group. Statistical significance is defined as P < 0.05. Sleep Trajectories are defined as follows: "Abnormal → Optimal" indicates improvement, "Optimal → Abnormal" indicates deterioration, and "Stable Abnormal" reflects persistent abnormal sleep patterns (<7 or >9 hours).

Abbreviations: ADL, Activities of Daily Living; CKM, Cardio-Kidney-Metabolic; MET, Metabolic Equivalent of Task.

The contrast between our baseline and trajectory findings provides important clinical insights. While a single baseline measure of short sleep showed independent predictive value, the persistence of abnormal sleep patterns over time emerged as an even more robust risk factor (OR = 1.259, 95% CI: 1.077–1.471). The sustained elevation in risk observed

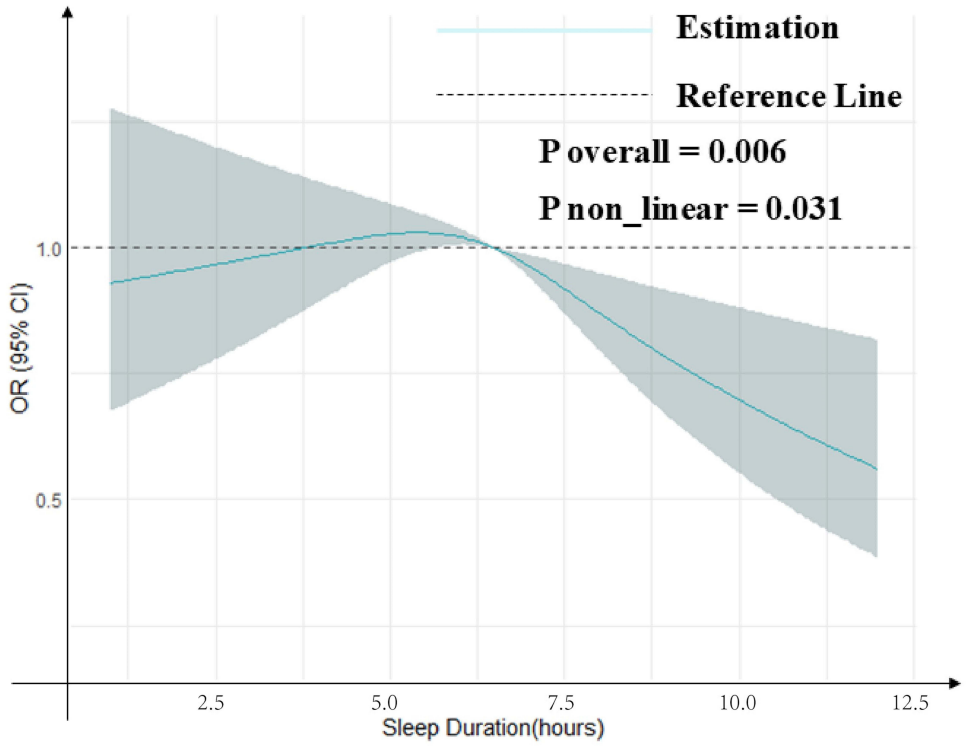

Figure 2 Dose-response relationship between sleep duration and the risk of CKM Syndrome.

Notes: The figure displays the dose-response relationship between sleep duration and the risk of CKM, based on a restricted cubic spline regression model. The solid line represents the estimated ORs, and the shaded area represents the corresponding 95% CIs. The dashed horizontal line indicates the reference line where the OR is 1.0. The overall association was statistically significant (*P*=0.006), with significant evidence of a non-linear relationship (*P*=0.031).

Abbreviations: CKM, Cardio-Kidney-Metabolic; CI, Confidence Interval; OR, Odds Ratio.

Table 3 Mediation Analysis Results

Path Analysis	Effect Size (OR/β)	95% CI	*P*
Total effect	−0.007	−0.013, 0	<0.001
Path a (Sleep→CESD)	−0.226	−0.301, −0.151	<0.001
Path b (CESD→CKM)	1.035	1.025, 1.045	<0.001
ACME	−0.002	−0.002, 0	<0.001
Direct effect	−0.006	−0.012, 0	0.06

Notes: Results are based on causal mediation analysis. The total, direct (ADE), and indirect (ACME) effects are presented on the risk difference scale. Path a coefficient (β) represents the change in the CESD score for each one-hour increase in sleep duration. Path b is presented as an odds ratio (OR) for CKM per one-unit increase in the CESD score. The negative signs for the total, direct, and indirect effects indicate that longer sleep duration is associated with a reduced risk of CKM syndrome.
Abbreviations: ACME, Average Causal Mediation Effect; ADE, Average Direct Effect; CI, Confidence Interval; CKM, Cardiometabolic-Kidney-Metabolic; CESD, Center for Epidemiologic Studies Depression Scale; OR, Odds Ratio.

with persistently abnormal sleep patterns underscores the clinical importance of addressing sleep disorders as a modifiable risk factor for CKM syndrome prevention.[25]

Exploring the Cascade Relationship "Sleep-Depression-Metabolism" at Epidemiological Level

Animal experiments indicate that chronic sleep deprivation initiates HPA axis overactivity via hypothalamic CRH neurons, disrupting cortisol rhythms and triggering insulin resistance. Concurrently, the NF-κB pathway-mediated IL-6/TNF-α release directly impairs endothelial function.[13,26,27] Controlled trials by Irwin et al demonstrate a 30% increase in IL-6 levels with sleep restricted to 6 hours per day, providing biological support for the observed CKM risk amplification in this study.[13]

Our mediation analysis provides compelling evidence for the psychobiological pathway linking sleep disturbance to metabolic dysfunction.Depression may exacerbate metabolic dysfunction through multiple mechanisms: first, activation of microglia-driven neuroinflammatory responses that promote insulin resistance, and second, behavioral changes

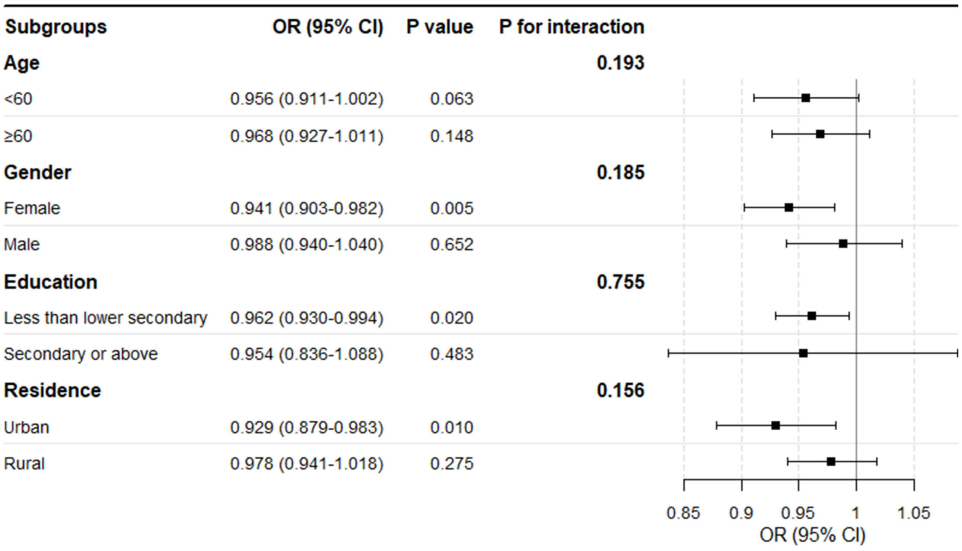

Figure 3 Subgroup Analysis of Sleep Duration and CKM Risk.
Notes: The forest plot displays the Odds Ratios (ORs) and 95% Confidence Intervals (CIs) for the association between a one-hour increase in sleep duration and the risk of CKM syndrome, stratified by age, gender, education, and residence. All models were adjusted for age, gender, education, marital status, residence, smoking, drinking, MET, and ADL, as appropriate. Bolded values represent the P-values for interaction, calculated to assess for effect modification across subgroups.
Abbreviations: ADL, Activities of Daily Living; CKM, Cardiometabolic-Kidney-Metabolic; CI, Confidence Interval; MET, Metabolic Equivalent of Task; OR, Odds Ratio.

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including reduced physical activity and preference for high-fat diets that further aggravate energy metabolism imbalance.[28–30] These findings suggest that sleep regulation not only directly impacts metabolic homeostasis but may also cascade through psychopathological mechanisms, offering potential targets for multidimensional CKM interventions.

Demographic and Socioeconomic Disparities in Sleep-CKM Associations

While our formal tests for interaction did not reach statistical significance—a finding that may be due to limited statistical power—the subgroup analyses revealed several trends that merit discussion. These observations, though exploratory, can help generate hypotheses for future research.

For instance, the association appeared stronger in women, a trend that may be related to sex-specific differences in sleep architecture, hormonal influences on both sleep and metabolism, and differential stress responses.[31] Women often experience greater sleep disruption due to reproductive life stages and caregiving responsibilities, potentially making them more susceptible to the metabolic consequences of sleep disturbance.[32] Sleep disturbances during menopause and hormonal fluctuations throughout the reproductive years may contribute to increased metabolic vulnerability in women.[33] Additionally, women demonstrate different circadian rhythm patterns and sleep-wake regulation compared to men, which may influence their susceptibility to metabolic disorders when sleep is disrupted.[34]

Likewise, the effect seemed more pronounced among individuals with lower education, suggesting that socioeconomic factors may modulate the sleep-health relationship.[35] Lower socioeconomic status is often associated with increased exposure to sleep-disrupting environmental factors, limited access to healthcare for sleep disorders, and higher baseline metabolic risk, potentially amplifying the impact of sleep disturbance on CKM development.[36] Additionally, work-related factors such as shift work, multiple jobs, and job insecurity are more prevalent in lower socioeconomic groups and contribute to irregular sleep patterns.[37]

The urban-rural difference may reflect varying lifestyle patterns, environmental exposures, and healthcare access. Urban residents may face distinct sleep challenges related to light pollution, noise, and shift work, while also having better access to healthcare resources for managing sleep disorders and metabolic conditions.[38] However, they may also experience higher stress levels, more sedentary lifestyles, and different dietary patterns that could interact with sleep patterns to influence CKM risk.[39] Rural populations, conversely, may have more regular circadian rhythms due to reduced artificial light exposure but face barriers in accessing specialized sleep medicine services.[40]

Taken together, these observations underscore the importance of considering demographic and socioeconomic context in sleep research. Although our findings are not definitive enough to recommend targeted interventions at this stage, they provide a strong rationale for future, larger-scale studies.

Methodological Limitations and Future Directions

This study has several methodological limitations. First, reliance on self-reported sleep duration data may introduce recall bias and social desirability effects; future studies should incorporate objective sleep monitoring using wearable devices or actigraphy to capture sleep efficiency, fragmentation, and circadian rhythm parameters. Second, the temporal associations observed may be influenced by unobserved time-dependent confounding factors. Third, despite comprehensive adjustment for major confounders, residual confounding from unmeasured variables is still possible; specifically, our study could not account for underlying clinical conditions such as Obstructive Sleep Apnea or Restless Legs Syndrome, nor for other unmeasured factors like detailed sleep hygiene, dietary patterns, or specific genetic polymorphisms.

Our causal mediation analysis, while providing valuable insights into potential pathways, relies on strong assumptions including correct temporal sequencing and adequate control for confounding. For instance, our analysis could not adjust for the use of newer cardiometabolic agents (eg, SGLT2 inhibitors or GLP-1 RAs), whose utilization has rapidly increased since our study period and which profoundly impact CKM outcomes.[41] Given these constraints, our mediation results should be interpreted as highlighting potential pathways rather than establishing definitive causal mechanisms. Future research using instrumental variable approaches or Mendelian randomization could provide stronger causal evidence for the sleep-depression-CKM pathway by leveraging genetic variants as natural experiments. The J-shaped dose-response relationship observed in our restricted cubic spline analysis suggests that both insufficient and excessive

sleep may be associated with increased CKM risk, though the protective effect appears most pronounced at longer sleep durations. This non-linear relationship warrants further investigation to identify optimal sleep duration ranges and understand the mechanisms underlying potential risks associated with long sleep.

Future research directions should include: 1) Integration of multi-omics data (inflammatory biomarkers, cortisol profiles, epigenetic markers) to systematically validate the "sleep-depression-metabolism" pathway; 2) Cross-cultural validation using diverse cohorts to examine the generalizability of findings across different populations and healthcare systems; 3) Randomized controlled trials testing combined sleep optimization and depression management interventions, with assessment of their effects on CKM biomarkers and long-term cardiovascular outcomes.

Conclusions

This longitudinal study demonstrates that both baseline short sleep duration and persistent abnormal sleep patterns are independently associated with increased CKM syndrome risk. Depressive symptoms serve as important mediators in this relationship, with demographic and socioeconomic factors modifying the strength of associations. The findings highlight the clinical importance of comprehensive sleep assessment and the potential benefits of integrated interventions targeting both sleep optimization and mental health. These results support the inclusion of sleep evaluation in CKM risk stratification and prevention strategies, particularly for high-risk demographic subgroups.

Abbreviations

ADL, Activities of Daily Living; CESD, Center for Epidemiologic Studies Depression Scale; CHARLS, China Health and Retirement Longitudinal Study, CI, Confidence Interval; CKD, Chronic Kidney Disease; CKM, Cardiometabolic-Kidney-Metabolic; HPA, Hypothalamic-Pituitary-Adrenal; IQR, Interquartile Range; MET, Metabolic Equivalent of Task; OR, Odds Ratio; RCS, Restricted Cubic Splines; SD, Standard Deviation.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

The original CHARLS study was approved by the Ethics Review Board of Peking University (IRB00001052-11015), and all participants provided written informed consent prior to their involvement. The current study protocol was separately reviewed and approved by the Ethics Committee of Beijing Anzhen Hospital, Capital Medical University (Approval No. 2025142x). The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

Author Contributions

Yilin Pan: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing - original draft. Jingru Bi: Visualization, Validation, Writing - review & editing. Long Feng: Validation, Data curation, Writing - review & editing. Xiaoyun Li: Conceptualization, Supervision, Project administration, Writing - review & editing.

All authors made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND drafted the work or revised it critically for important intellectual content; AND provided final approval of the version to be published; AND agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors have reviewed the manuscript and agree to its submission to *Nature and Science of Sleep*.

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References

1. Ndumele CE, Rangaswami J, Chow SL, et al. Cardiovascular-Kidney-Metabolic Health: a Presidential Advisory From the American Heart Association. *Circulation*. 2023;148(20):1606–1635. doi:10.1161/CIR.0000000000001184
2. Ndumele CE, Neeland IJ, Tuttle KR, et al. A Synopsis of the Evidence for the Science and Clinical Management of Cardiovascular-Kidney-Metabolic (CKM) Syndrome: a Scientific Statement From the American Heart Association. *Circulation*. 2023;148(20):1636–1664. doi:10.1161/CIR.0000000000001186
3. Watson NF, Badr MS, Belenky G, et al. Recommended Amount of Sleep for a Healthy Adult: a Joint Consensus Statement of the American Academy of Sleep Medicine and Sleep Research Society. *Sleep*. 2015;38(6):843–844. doi:10.5665/sleep.4716
4. Buxton OM, Pavlova M, Reid EW, Wang W, Simonson DC, Adler GK. Sleep restriction for 1 week reduces insulin sensitivity in healthy men. *Diabetes*. 2010;59(9):2126–2133. doi:10.2337/db09-0699
5. Buxton OM, Cain SW, O'Connor SP, et al. Adverse metabolic consequences in humans of prolonged sleep restriction combined with circadian disruption. *Sci Transl Med*. 2012;4(129):129ra43. doi:10.1126/scitranslmed.3003200
6. Dettoni JL, Consolim-Colombo FM, Drager LF, et al. Cardiovascular effects of partial sleep deprivation in healthy volunteers. *J Appl Physiol*. 2012;113(2):232–236. doi:10.1152/japplphysiol.01604.2011
7. Badran M, Yassin BA, Fox N, Laher I, Ayas N. Epidemiology of Sleep Disturbances and Cardiovascular Consequences. *Can J Cardiol*. 2015;31(7):873–879. doi:10.1016/j.cjca.2015.03.011
8. Cappuccio FP, Taggart FM, Kandala NB, et al. Meta-analysis of short sleep duration and obesity in children and adults. *Sleep*. 2008;31(5):619–626. doi:10.1093/sleep/31.5.619
9. Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. Sleep duration and all-cause mortality: a systematic review and meta-analysis of prospective studies. *Sleep*. 2010;33(5):585–592. doi:10.1093/sleep/33.5.585
10. Wang YH, Wang J, Chen SH, et al. Association of Longitudinal Patterns of Habitual Sleep Duration With Risk of Cardiovascular Events and All-Cause Mortality. *JAMA Netw Open*. 2020;3(5):e205246.
11. Jike M, Itani O, Watanabe N, Buysse DJ, Kaneita Y. Long sleep duration and health outcomes: a systematic review, meta-analysis and meta-regression. *Sleep Med Rev*. 2018;39:25–36. doi:10.1016/j.smrv.2017.06.011
12. Alvaro PK, Roberts RM, Harris JK. A Systematic Review Assessing Bidirectionality between Sleep Disturbances, Anxiety, and Depression. *Sleep*. 2013;36(7):1059–1068. doi:10.5665/sleep.2810
13. Irwin MR, Olmstead R, Carroll JE. Sleep Disturbance, Sleep Duration, and Inflammation: a Systematic Review and Meta-Analysis of Cohort Studies and Experimental Sleep Deprivation. *Biol Psychiatry*. 2016;80(1):40–52. doi:10.1016/j.biopsych.2015.05.014
14. Penninx BW. Depression and cardiovascular disease: epidemiological evidence on their linking mechanisms. *Neurosci Biobehav Rev*. 2017;74(Pt B):277–286. doi:10.1016/j.neubiorev.2016.07.003
15. Zhao Y, Hu Y, Smith JP, Strauss J, Yang G. Cohort profile: the China Health and Retirement Longitudinal Study (CHARLS). *Int J Epidemiol*. 2014;43(1):61–68. doi:10.1093/ije/dys203
16. Hirshkowitz M, Whiton K, Albert SM, et al. National Sleep Foundation's sleep time duration recommendations: methodology and results summary. *Sleep Health*. 2015;1(1):40–43. doi:10.1016/j.sleh.2014.12.010
17. García-Perdomo HA, Zapata-Copete J, Rojas-Cerón CA. Sleep duration and risk of all-cause mortality: a systematic review and meta-analysis. *Epidemiol Psychiatr Sci*. 2019;28(5):578–588. doi:10.1017/S2045796018000379
18. Chaput JP, Bouchard C, Tremblay A. Change in sleep duration and visceral fat accumulation over 6 years in adults. *Obesity*. 2014;22(5):E9–12. doi:10.1002/oby.20701
19. Aggarwal R, Ostrominski JW, Vaduganathan M. Prevalence of Cardiovascular-Kidney-Metabolic Syndrome Stages in US Adults, 2011-2020. *JAMA*. 2024;331(21):1858–1860. doi:10.1001/jama.2024.6892
20. D'Agostino Sr RB, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation*. 2008;117(6):743–753. doi:10.1161/CIRCULATIONAHA.107.699579
21. Ma YC, Zuo L, Chen JH, et al. Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. *J Am Soc Nephrol*. 2006;17(10):2937–2944. doi:10.1681/ASN.2006040368
22. CE Ndumele, J Rangaswami, SL Chow, et al. Correction to: cardiovascular-Kidney-Metabolic Health: a Presidential Advisory From the American Heart Association. *Circulation*. 2024;149(13):e1023. doi:10.1161/CIR.0000000000001241
23. Andresen EM, Malmgren JA, Carter WB, Patrick DL. Screening for depression in well older adults: evaluation of a short form of the CES-D (Center for Epidemiologic Studies Depression Scale). *Am J Prev Med*. 1994;10(2):77–84. doi:10.1016/S0749-3797(18)30622-6
24. Fu H, Si L, Guo R. What Is the Optimal Cut-Off Point of the 10-Item Center for Epidemiologic Studies Depression Scale for Screening Depression Among Chinese Individuals Aged 45 and Over? An Exploration Using Latent Profile Analysis. *Front Psychiatry*. 2022;13:820777. doi:10.3389/fpsyt.2022.820777
25. St-Onge MP, Grandner MA, Brown D, et al. Sleep Duration and Quality: impact on Lifestyle Behaviors and Cardiometabolic Health: a Scientific Statement From the American Heart Association. *Circulation*. 2016;134(18):e367–e86. doi:10.1161/CIR.0000000000000444
26. Besedovsky L, Lange T, Haack M. The Sleep-Immune Crosstalk in Health and Disease. *Physiol Rev*. 2019;99(3):1325–1380. doi:10.1152/physrev.00010.2018
27. Leproult R, Holmbäck U, Van Cauter E. Circadian misalignment augments markers of insulin resistance and inflammation, independently of sleep loss. *Diabetes*. 2014;63(6):1860–1869. doi:10.2337/db13-1546
28. de Wit L, Luppino F, van Straten A, Penninx B, Zitman F, Cuijpers P. Depression and obesity: a meta-analysis of community-based studies. *Psychiatry Res*. 2010;178(2):230–235. doi:10.1016/j.psychres.2009.04.015
29. Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nat Rev Immunol*. 2016;16(1):22–34. doi:10.1038/nri.2015.5

30. Kiecolt-Glaser JK, Derry HM, Fagundes CP. Inflammation: depression fans the flames and feasts on the heat. *Am J Psychiatry*. 2015;172 (11):1075–1091. doi:10.1176/appi.ajp.2015.15020152
31. Baker FC, de Zambotti M, Colrain IM, Bei B. Sleep problems during the menopausal transition: prevalence, impact, and management challenges. *Nat Sci Sleep*. 2018;10:73–95. doi:10.2147/NSS.S125807
32. Kravitz HM, Ganz PA, Bromberger J, Powell LH, Sutton-Tyrrell K, Meyer PM. Sleep difficulty in women at midlife: a community survey of sleep and the menopausal transition. *Menopause*. 2003;10(1):19–28. doi:10.1097/00042192-200310010-00005
33. Polo-Kantola P. Sleep problems in midlife and beyond. *Maturitas*. 2011;68(3):224–232. doi:10.1016/j.maturitas.2010.12.009
34. Santhi N, Lazar AS, McCabe PJ, Lo JC, Groeger JA, Dijk DJ. Sex differences in the circadian regulation of sleep and waking cognition in humans. *Proc Natl Acad Sci U S A*. 2016;113(19):E2730–9. doi:10.1073/pnas.1521637113
35. Hale L, Do DP. Racial differences in self-reports of sleep duration in a population-based study. *Sleep*. 2007;30(9):1096–1103. doi:10.1093/sleep/30.9.1096
36. Johnson DA, Lisabeth L, Lewis TT, et al. The Contribution of Psychosocial Stressors to Sleep among African Americans in the Jackson Heart Study. *Sleep*. 2016;39(7):1411–1419. doi:10.5665/sleep.5974
37. Knutsson A, Kempe A. Shift work and diabetes--a systematic review. *Chronobiol Int*. 2014;31(10):1146–1151. doi:10.3109/07420528.2014.957308
38. Hale L, Troxel W, Buysse DJ. Sleep Health: an Opportunity for Public Health to Address Health Equity. *Annu Rev Public Health*. 2020;41:81–99. doi:10.1146/annurev-publhealth-040119-094412
39. Shan Z, Ma H, Xie M, et al. Sleep duration and risk of type 2 diabetes: a meta-analysis of prospective studies. *Diabetes Care*. 2015;38(3):529–537. doi:10.2337/dc14-2073
40. Singh GK, Kenney MK. Rising Prevalence and Neighborhood, Social, and Behavioral Determinants of Sleep Problems in US Children and Adolescents, 2003-2012. *Sleep Disord*. 2013;2013:394320. doi:10.1155/2013/394320
41. Karakasis P, Sagris M, Patoulias D, et al. Mitigating Increased Cardiovascular Risk in Patients with Obstructive Sleep Apnea Using GLP-1 Receptor Agonists and SGLT2 Inhibitors: hype or Hope? *Biomedicines*. 2024;12(11):2503. doi:10.3390/biomedicines12112503