Association of sleep quality and sleep duration with estimated Glomerular filtration rate (eGFR) in a secondary analysis based on a cross-sectional study

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Abstract

Background: Poor sleep conditions can cause many diseases. However, proof regarding the link of sleep status with renal function in general population is limited. This study was undertaken to investigate the association of sleep quality and sleep duration with estimated Glomerular filtration rate (eGFR) in Taiwanese participants.

Methods: The present study was a cross-sectional study. 5714 Taiwanese who visited a health center for a self-motivated general health assessment were collected in this study. The main outcome variables included Pittsburgh Sleep Quality Index (PSQI) and Self-reported sleep duration. The Independent variable is estimated glomerular filtration rate (eGFR). Multivariate linear regression model and two-piecewise linear model are employed to examine the association between outcomes and independent variables after adjusting for covariates involved in this study.

Results: After adjusting potential confounders, a non-linear relationship was detected between sleep quality and eGFR, which cut-point was 71. The effect sizes and the 95% confidence intervals on the right sides of inflection point were 0.982(0.967, 0.998) and 1.006 (1.001, 1.010).

Conclusion: The relationship between sleep quality and eGFR is non-linear. Sleep quality was negatively related to eGFR when eGFR is higher than 71 points.

Introduction

Sleep plays an important role in maintaining personal health¹. However, in today's society, short sleep duration, poor sleep quality, and even insomnia are common². Existing evidence has shown that short sleep duration or poor sleep quality is closely related to cardiovascular disease, obesity, hypertension, non-alcoholic liver disease, diabetes (DM), dyslipidemia, and even death^{3,4}. This suggests that sleep duration and quality may be a new and modifiable target for the treatment and prevention of various chronic diseases.

There are many evaluation indicators of renal function, including traditional indicators just as a bun, Cr, and so on. However, the most common indicator used in clinical is estimated glomerular filtration rate (eGFR)⁵. Previous studies have shown that sleep status (quality and length) is related to eGFR in Chronic kidney disease (CKD) patients⁶, but in the general population, evidence regarding eGFR and sleep status is limited. Therefore, we performed a secondary analysis based on a published dataset to investigate the true relationship between sleep status and eGFR in Taiwanese adults. If the true relationship in the general population is found, it will help doctors provide more health advice to medical examiners, and provide supporting pilot data for subsequent cascading studies.

Participants And Methods

Methods

Data source

We extracted data from the 'DATADRYAD' database([www. Datadryad.org](http://www.Datadryad.org)). Given the data, uploader has waived all copyright, therefore, a secondary analysis without infringing on the authors' rights. When data were used, Dryad data package (Dryad data package: Yu-Tsung Chou, Chung-Hao Li, Wei-Chen Shen, Yi-Ching Yang, FengHwa Lu, Jin-Shang Wu, Chih-Jen Chang (2020). Data from: Association of sleep quality and sleep duration with serum uric acid levels in adults. PLoS ONE. <https://doi.org/10.1371/journal.pone.0239185>) was noted. Variables included in the database file were listed as follows: age, sex, alanine aminotransferase (ALT), systolic blood pressure (SBP), fasting blood glucose(FBG), diastolic blood pressure (DBP), hypertension, body mass index (BMI), uric acid, triglyceride(TG), total cholesterol (TC),high-density lipoprotein cholesterol (HDL-C), eGFR, smoking status, exercise status, diabetes, alcohol consumption, use of uric acid lowering drug, use of hypoglycemic drugs, use of antihypertensive drug, use of lipid-lowering drugs, Pittsburgh Sleep Quality Index (PSQI) and Self-reported sleep duration.

Study population

Yu-Tsung Chou et al. ⁷ completed the entire study, and we just outlined the steps of the study here. More details have been described in the original literature. Yu-Tsung Chou et al.conducted a cross-sectional study at a health examination center at National Cheng Kung University Hospital in Tainan city, Taiwan from October 2001 to August 2009. A total of 5714 participants were recruited and selected according to exclusion standards. Exclusion standards: (1) participants were aged <18 years, (2) participants on medications for hyperuricemia, hypertension, DM, or dyslipidemia;(3) those with incomplete data were excluded. Researchers obtained information (values) of PSQI, Self-reported sleep duration, eGFR, and other covariants at baseline. In the previously published article, Yu-Tsung Chou, et al. has clearly stated that: the study was conducted by the Declaration of Helsinki. Informed consent was obtained from all participants.

Measurement of PSQI, Self-reported sleep duration, eGFR, and other covariants

Sleep duration and quality were assessed using the Chinese version of the PSQI, Participants with a PSQI score of >5 were defined as poor sleepers. The eGFR was calculated by using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. The measurement and assessment of PSQI and other covariants were described in detail in the original.

Statistical analysis

Continuous variables are represented by median (quartile) (skew distribution) or mean $\pm$ standard deviation (normal distribution), and categorical variables are represented by frequency or percentage. The differences between the mean and proportion of the groups were analyzed by Kruskal Wallis H (skew distribution) test, one-way analysis of variance (normal distribution), and chi-square test (categorical variable). (For outcome=sleep time) and binary logistic regression (for outcome=sleep quality (PSQI $\leq$ 5, PSQI $>$ 5) models are used for univariate and multiple linear analysis. According to the suggestion of STROBE statement, we also show unadjusted the result of the minimum adjustment and the adjustment in the fully adjusted model. Whether the covariances were adjusted determined by the following principle: when added to this model, changed the matched odds ratio by at least 10% ⁸.

We also use the Generalized Additive Model (GAM) to solve nonlinear problems. First, we use a smoothing graph (penalty method) to fit the relationship between eGFR and sleep status. Second, if a non-linear correlation was observed, we use a recursive method to automatically calculate the inflection point that will use the maximum model likelihood⁹. Third, to further explain the nonlinearity, we use a two-part linear model to fit the size of the effect on both sides of the inflection point. All analyses used statistical software packages R (<http://www.R-project.org>, R Foundation) and EmpowerStats (<http://www.empowerstats.com>, X&Y Solutions, Inc., Boston, Massachusetts). A P value of less than 0.05 (two-sided) is considered statistically significant.

Results

Baseline characteristics of participants

Baseline characteristics were listed in Table 1. In terms of self-reported sleep duration, no statistically significant differences are detected among different eGFR groups. Compared with high level (Q4) of eGFR group, participants are older in Q1, Q2, and Q3 groups. In addition, higher levels of ALT, SBP, FBG, uric acid, DBP, BMI, TC, TG, and HDL-C are observed in Q1, Q2, and Q3 eGFR groups compared with Q4 group.

Table 1

Baseline Characteristics of participants

eGFR	Q1	Q2	Q3	Q4	P-value
N	1427	1423	1435	1429	
Age, mean±SD, year	52.07 ± 10.95	47.38 ± 13.54	46.35 ± 9.61	36.92 ± 8.53	<0.001
ALT, median[P25, P75], U/L	28.00 [21.00 40.00]	26.00 [19.00 38.00]	26.00 [18.00 39.00]	19.00 [13.00 28.00]	<0.001*
SBP, mean±SD, mmHg	121.41 ± 16.69	118.62 ± 16.38	116.52 ± 16.05	108.44 ± 13.58	<0.001
FBG, mean±SD, mg/dL	94.52 ± 20.57	93.62 ± 24.58	93.55 ± 27.14	88.93 ± 23.69	<0.001
uric acid, mean±SD, mg/dL	7.11 ± 1.45	6.26 ± 1.39	5.82 ± 1.33	5.14 ± 1.33	<0.001
DBP, mean±SD, mmHg	73.41 ± 10.71	70.29 ± 24.58	68.91 ± 10.35	63.27 ± 9.07	<0.001
body mass index, mean±SD, kg/m ²	25.24 ± 3.06	24.47 ± 3.35	24.10 ± 3.33	23.01 ± 3.99	<0.001
TC, mean±SD, mg/dL	201.40 ± 36.04	199.46 ± 36.50	197.73 ± 36.73	182.73 ± 34.81	<0.001
TG, mean±SD, mg/dL	150.13 ± 97.32	132.70 ± 80.62	132.28 ± 101.09	104.65 ± 80.42	<0.001
HDL-C, mean±SD, mg/dL	44.59 ± 11.18	48.33 ± 13.02	49.51 ± 14.15	53.44 ± 13.77	<0.001
Self-reported sleep duration, mean±SD, h/day	6.42 ± 1.11	6.51 ± 1.12	6.46 ± 1.04	6.53 ± 1.17	0.059
Sex (n, %)					<0.001
female	53 (3.71%)	418 (29.37%)	627 (43.69%)	1113 (77.89%)	
male	1374 (96.29%)	1005 (70.63%)	808 (56.31%)	316 (22.11%)	
Uric acid-lowering drug use (n, %)					<0.001
No	1228 (86.05%)	1334 (93.75%)	1357 (94.56%)	1414 (98.95%)	
Yes	199 (13.95%)	89 (6.25%)	78 (5.44%)	15 (1.05%)	
DM (n, %)					<0.001
No	1309 (91.73%)	1328 (93.32%)	1336 (93.10%)	1383 (96.78%)	

Yes	118 (8.27%)	95 (6.68%)	99 (6.90%)	46 (3.22%)
Smoking status (n, %)	<0.001			
No	1131 (79.26%)	1160 (81.52%)	1181 (82.30%)	1298 (90.83%)
Yes	296 (20.74%)	263 (18.48%)	254 (17.70%)	131 (9.17%)
Alcoholic consumption (n, %)	<0.001			
No	1088 (76.24%)	1175 (82.57%)	1196 (83.34%)	1281 (89.64%)
Yes	339 (23.76%)	248 (17.43%)	239 (16.66%)	148 (10.36%)
Hypertension (n, %)	<0.001			
No	1036 (72.60%)	1139 (80.04%)	1203 (83.83%)	1355 (94.82%)
Yes	391 (27.40%)	284 (19.96%)	232 (16.17%)	74 (5.18%)
Exercise > 3/wk (n, %)	<0.001			
No	1182 (82.83%)	1226 (86.16%)	1243 (86.62%)	1333 (93.28%)
Yes	245 (17.17%)	197 (13.84%)	192 (13.38%)	96 (6.72%)
Use of hypoglycemic drugs (n, %)	<0.001			
No	1358 (95.16%)	1367 (96.06%)	1389 (96.79%)	1410 (98.67%)
Yes	69 (4.84%)	56 (3.94%)	46 (3.21%)	19 (1.33%)
Antihypertensive drug use (n, %)	<0.001			
No	1219 (85.42%)	1269 (89.18%)	1324 (92.26%)	1400 (97.97%)
Yes	208 (14.58%)	154 (10.82%)	111 (7.74%)	29 (2.03%)
Use of lipid-lowering drugs (n, %)	<0.001			
No	1290 (90.40%)	1333 (93.68%)	1344 (93.66%)	1403 (98.18%)

Yes	137 (9.60%)	90 (6.32%)	91 (6.34%)	26 (1.82%)
PSQI	<0.001			
≤5	599 (42.21%)	584 (41.30%)	541 (38.10%)	463 (32.58%)
≥5	820 (57.79%)	830 (58.70%)	879 (61.90%)	958 (67.42%)

ALT alanine aminotransferase, SBP systolic blood pressure, FBG fasting blood glucose, DBP diastolic blood pressure, hypertension, BMI body mass index, uric acid, triglyceride(TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), estimated glomerular filtration rate (eGFR) Pittsburgh Sleep Quality Index(PSQI),

The univariate and multivariate results of relationship between sleep status and eGFR

We showed the non-adjusted and adjusted models in Table 2.

For sleep quality a result obtained from crude model suggests that a unit increase of eGFR is associated with 1% increase of probability of good sleep quality (OR = 1.006, 95% confidence interval (CI): 1.004 to 1.009, $P < 0.0001$). After adjusting for other confounders (Minimally- and Fully-adjusted models), however, we do not detect the association between sleep quality and eGFR.

Self-reported sleep duration showed no correlation with eGFR ($\beta = -0.001$, 95% confidence interval (CI): -0.003 to 0.001, $P = 0.2415$). In minimally adjusted model (adjusted age, sex), the result showed no correlation was detected ($\beta = 0.001$, 95%CI: -0.002 to 0.003, $P = 0.6057$). The same findings also observed in fully-adjusted model.

For the purpose of sensitivity analyses, we also transformed eGFR from a continuous variable to a categorical variable according to quartile. The results of P for trend are consistent with eGFR as a continuous variable.

Table 2

Results of univariate and multivariate analysis

Exposure	Non-adjusted model Effect size, 95%CI, P-value	Minimally-adjusted model Effect size, 95%CI, P-value	Fully-adjusted model Effect size, 95%CI, P-value
Sleep Quality Index(PSQI≤5,5)			
eGFR	1.006 (1.004, 1.009) <0.0001	1.002(0.999, 1.006) 0.1467	1.002 (0.998, 1.005) 0.3276
eGFR(quantile)			
Q1	Ref	Ref	Ref
Q2	1.038 (0.894, 1.205) 0.6228	0.972(0.831, 1.137) 0.7195	0.966 (0.822, 1.134) 0.6718
Q3	1.187 (1.021, 1.379) 0.0254	1.079(0.915, 1.273) 0.3663	1.054(0.888, 1.252) 0.5454
Q4	1.511 (1.297, 1.761) <0.0001	1.238(1.003, 1.528) 0.0469	1.184 (0.950, 1.476) 0.1323
P for trend	<0.0001	0.0341	0.1040
Self-reported sleep duration			
eGFR	-0.001 (-0.003, 0.001) 0.2415	0.001 (-0.002, 0.003) 0.6057	0.001(-0.002, 0.004) 0.4415
eGFR (quantile)			
Q1	Ref	Ref	Ref
Q2	0.005 (-0.121, 0.131) 0.9425	0.042 (-0.089, 0.174) 0.5282	0.059 (-0.075, 0.193) 0.3866
Q3	-0.030 (-0.156, 0.096) 0.64103	0.044 (-0.093, 0.182) 0.52662	0.066 (-0.076, 0.208) 0.3622
Q4	-0.066 (-0.191, 0.060) 0.30713	0.027 (-0.146, 0.200) 0.7568	0.060 (-0.120, 0.240) 0.5152
P for trend	0.0399	0.8861	0.9870

Non-adjusted model: we do not adjust for any covariates

Minimally-adjusted model: only sex and age are adjusted for.

Fully-adjusted model: all covariates presented in table 1 are adjusted for.

The analyses of non-linear relationship

Nonlinearity addressing is necessary because eGFR is a continuous variable. In the present study (Fig. 1), By smooth curve fitting, we found that the relationship between sleep quality and eGFR was non-linear (after adjusting other covariants in Table 1), We calculated the inflection point was 71. On the left of inflection point, there is no relationship between eGFR and sleep quality (OR:0.989, 95%CI 0.977to1.002, P=0.0907), respectively, we also observed a relationship between eGFR and sleep quality on the right of inflection point (OR:1.006, 95%CI 1.001to1.01, P=0.0189) (Table 3).PSQI scores of >5 were defined as poor sleepers, when eGFR is higher than 71points, the sleep quality decreases as the value of eGFR rises.

Table 3

nonlinearity of eGFR on sleeping quality

Outcome:	PSQI β ,95%,P-value
Fitting model using standard linear regression	1.003 (0.999, 1.007) 0.1994
Fitting model using two-piece wise linear model	
Inflection point	71
≤ 71	0.989 (0.977, 1.002) 0.0907
> 71	1.006 (1.001, 1.011) 0.0189
P for Log-likelihood ratio test	0.025
The adjustment strategy was the same as fully-adjusted model	

Discussion

This study conducted a secondary data analysis based on a published cross-sectional study to predict and investigate the relationship between eGFR and sleep status. Although no linear relationship between eGFR and sleep state was observed. However, a nonlinear relationship between them was detected. Our results also found that eGFR is negatively correlated with sleep quality in the interval where the eGFR value is higher than 71 points. This result shows that within a certain range as eGRF increases, the sleep quality becomes worse. This result is similar to the study of Kim et al ¹⁰. The results of Kim and our study indicate that excessive eGFR impairs sleep quality, which suggests that poor subjective sleep quality was associated with glomerular hyperfiltration in general population. The possible mechanism for the

relationship between sleep quality and eGFR remains unclear. The common view is that poor sleep is considered part of normal aging. But a study showed that adult sleep quality is affected by age, self-reported sleep quality improves with age¹¹. In addition, a previous study has pointed out that eGFR declines with aging¹². Our research results found that sleep quality deteriorates as eGFR increases when eGFR is higher than 71 points (OR:1.006, 95%CI 1.001 to 1.01, P=0.0189), the normal value of eGFR was 80 ~ 120 ml / min. The possible mechanism is that young adults have normal eGFR and poor sleep quality. In addition, poor sleep quality will exacerbate inflammation and oxidative stress^{13,14}, and the exacerbation of inflammation and oxidative stress are associated with obesity and diabetes¹⁵. A previous study found that high eGFR is associated with early stages of kidney disease in the setting of various conditions such as obesity and diabetes¹⁶. Therefore, the sleep quality of patients in the early stage of kidney diseases deteriorates, and this may also be one of the reasons why the sleep quality deteriorates with the eGFR increase within a certain range in our study. Our research found that there is no relationship between eGFR and sleep quality when the eGFR value is lower than 71 (OR:0.989, 95%CI 0.977 to 1.002, P=0.0907). This shows that sleep quality has not changed with the eGFR decline. This result is different from the study of Chang et al¹⁷. The study of Chang shows that good kidney function within a certain range has a positive effect on the improvement of sleep quality. The reason for the different results between the two studies may be that our study population is normal, while Chang's study population is CKD. Our research shows that sleep time has nothing to do with eGFR. This result is different from previous studies¹⁸. The population of other studies and data analysis methods is different from this study, and we speculate that this is the reason for the different results. The eGFR is an important indicator for evaluating renal function, the normal range of eGFR was 80 ~ 120 ml / min, eGFR decreases in chronic kidney disease¹⁹, and increases in hypertensive diseases¹⁶. Our study found that high eGFR values cause a decline in sleep quality. This suggests that we should detect and intervene in the sleep quality of the patients with abnormal eGFR, to reduce the damage to the body caused by the decline in sleep quality. Our research found that the relationship between eGFR and sleep quality changes when the eGFR value is equal to 71. Since no previous studies have reported similar results, we cannot explain the specific reasons. However, this value can provide more health advice to medical examiners, and provide supporting pilot data for subsequent cascading studies. The methods and content of our research have some advantages. First, we not only use the generalized linear model to evaluate the linear relationship between sleep quality, sleep duration, and eGFR but also use the generalized additive model to clarify the nonlinear relationship. GAM has obvious advantages in dealing with nonlinear relationships. It can deal with non-parametric smoothing and fit regression splines to the data. The use of GAM will help us better discover the true relationship between exposure and results. Second, this study is an observational study that includes unavoidable potential confounders, so we use strict statistical adjustments to minimize residual confounders. Although previous studies have reported a relationship between sleep status and chronic kidney disease^{20,21}, there are no studies on sleep quality and eGFR. In our research, we found the relationship between sleep quality and eGFR. There are still some limitations to our research. First of all, this study is an analytical cross-sectional study, so it only provides evidence between exposure and outcome, and the credibility of the evidence is weak, and the cause and outcome

are difficult to distinguish. Secondly, because the study population only includes Chinese, it may not be able to improve references for other ethnic groups. Third, due to the limitation of the original data, we could not observe the correlation between the average night blood oxygen saturation and sleep quality and sleep duration, and eGFR. Similarly, we cannot study the level of hypoxia-inducible and inflammatory factors in plasma that reflect the body's hypoxia and its possible relationship with sleep status and eGFR.

Conclusion

The relationship between sleep quality and eGFR is non-linear. Sleep quality is negatively related to eGFR when eGFR was higher than 71.

Declarations

Ethics approval and consent to participate

In the previously published article⁷, Chou YT, et al. has clearly stated that: the study was approved by the Institutional Review Board of National Health and Nutrition Examination Survey(NCKUH) in Taiwan (IRB number: A-ER-107-285). Informed consent was obtained from all participants.

Consent for publication

Not applicable.

Availability of data and materials

Data can be downloaded from 'DATADRYAD' database ([www. Datadryad.org](http://www.datadryad.org)).

Competing interests

The authors declare no competing financial or non-financial interests.

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Author's contributions

RXC contributed to the drafting of the manuscript. CW, contributed to the conception and critical revision of the manuscript, analysis, and interpretation of the data, and YDC, contributed to approve the final

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Figures

Figure 1

The relationship between PSQI and eGFR. A nonlinear relationship between them was detected after adjusting for other covariants in Table 1