



# OPEN Poor sleep quality was associated with increased plasma aldosterone concentration in community dwellers, a cross-sectional study

Xiufang Li<sup>1,2</sup>, Mulalibieke Heizhati<sup>1,2</sup>✉, Mei Li<sup>1</sup>, Ling Yao<sup>1</sup>, Ting Wu<sup>1</sup>, Wenbo Yang<sup>1</sup>, Lin Gan<sup>1</sup>, Hui Wang<sup>1</sup>, Miaomiao Liu<sup>1</sup>, Adalaiti Maitituersun<sup>1</sup>, Mengyue Lin<sup>1</sup>, Jing Hong<sup>1</sup> & Nanfang Li<sup>1</sup>✉

Sleep is implicated in circulating aldosterone, whereas effects of overall sleep quality are not characterized. Therefore, we explored relationship of sleep quality with plasma aldosterone concentration (PAC) in general population. We evaluated sleep quality using Pittsburgh sleep quality index (PSQI) and measured PAC in adults cross-sectionally. We divided participants into very good, fairly good, fairly bad and very bad sleepers, compared PAC and log-PAC, and applied linear regression to examine association of PSQI score with log-PAC, in total, gender- and age-stratified (young, middle-aged and old) participants. Sensitivity analysis were performed by excluding hypertension, sleep disordered breathing (SDB), or both. Among 29,499 participants, PAC showed significant increase from very good to very bad sleepers in total (14.3 vs. 14.4 vs. 14.7 vs. 15.8ng/dL), and in male participants (13.1 vs. 13.6 vs. 14.1 vs. 14.9ng/dL), consistent in the young and the middle-aged ( $P$  for all  $< 0.001$ ) and in log PAC of total, in male and in different age groups ( $P$  for trend  $< 0.001$ ). PSQI score showed significant positive association with log-PAC in total (B, 95%CI: 0.007, 0.003–0.010,  $P < 0.001$ ) in male participants (0.013, 0.008–0.018,  $P < 0.001$ ), consistent in the young and the middle-aged and in adjusted models. In female, PSQI score showed significant positive association with log-PAC in the old-aged. Sensitivity analysis yielded consistent observation with main analysis. Poor sleep quality is associated with elevated PAC, in young and middle-aged male and in elder female, independent of SDB and hypertension, indicating potential involvement of sleep quality on regulation of circulating aldosterone.

**Keywords** Sleep quality, Plasma aldosterone concentration, General population, Hypertension, Sleep disordered breathing, Disease prevention

Aldosterone, primary mineralocorticoid, is synthesized in the outer zone of the adrenal cortex called the zona glomerulosa, and plays a key role in the maintenance of intravascular volume, electrolyte balance, and blood pressure (BP), physiologically<sup>1</sup>. Autonomous secretion of aldosterone, independent of main regulators, is known as primary aldosteronism, the most common secondary hypertension and a well-known risk factor for cardiovascular (CV) morbidity and mortality<sup>2</sup>.

Recent studies have also shown that, chronic increase in circulating aldosterone, in addition to primary aldosteronism, contributes to elevation in BP or development of hypertension<sup>3,4</sup>, development of diabetes<sup>5</sup>, renal dysfunction<sup>5</sup>, aortic dissection<sup>6</sup>, changes in cognition<sup>7</sup>, and to CV morbidity, and mortality<sup>8–10</sup>, independent of BP<sup>8–10</sup>. Therefore, background reasons for elevation in circulating aldosterone have begun to acquire rising attention.

Normally, physiological regulators of aldosterone production include angiotensin II, potassium, and adrenocorticotrophic hormone, which increase aldosterone secretion both acutely, as well as chronically<sup>11</sup>. In

<sup>1</sup>Hypertension Center of People's Hospital of Xinjiang Uygur Autonomous Region, Xinjiang Hypertension Institute, HC Key Laboratory of Hypertension Clinical Research, Key Laboratory of Xinjiang Uygur Autonomous Region "Hypertension Research Laboratory", Xinjiang Clinical Medical Research Center for Hypertension (Cardio-Cerebrovascular) Disease, No. 91 Tianchi Road, Urumqi 830001, Xinjiang, China. <sup>2</sup>Xiufang Li and Mulalibieke Heizhati have contributed equally to this work and share first authorship. ✉email: 1017663289@qq.com; lnanfang2016@sina.com

addition, hormones, such as serotonin, estrogen, parathyroid hormone, and vasopressin have been proposed to modulate aldosterone production<sup>1</sup>. Furthermore, emerging evidence show that, life style-related factors are associated with circulating aldosterone<sup>12</sup>.

In addition to the above, changes in sleep quality may affect renin angiotensin aldosterone system by changing excretion of aldosterone<sup>13,14</sup>. Experimental studies show that circulating aldosterone may rise in condition of sleep deprivation or of disrupted circadian system<sup>13,15</sup>. Therefore, it might be reasonable to speculate that sleep quality is in negative association with circulating aldosterone, since the plausibility may be supported by the fact that endocrine is one of the two axes, through which the impact of sleep on organ functions is principally mediated<sup>16</sup>. However, the association between chronic changes in overall sleep quality towards poor and circulating aldosterone has not been characterized. It might be critical to investigate the relationship of sleep quality with aldosterone, given the fact that poor sleep quality is highly prevalent, 31–67.3% in adults<sup>16–18</sup>, and a well-known risk factor for incident hypertension<sup>19,20</sup>, incident diabetes<sup>21</sup>, obesity, renal dysfunction<sup>22</sup>, low cognitive performance<sup>23</sup>, and CV morbidity and mortality<sup>24,25</sup> with mechanisms incompletely understood<sup>14,26</sup>.

Therefore, we intended to explore the relationship between overall sleep quality, assessed using Pittsburgh sleep quality index (PSQI), and plasma aldosterone concentration (PAC) in community based population by considering age, and gender, known modulators or confounders of sleep and or aldosterone using a previous cross-sectional survey data conducted in Northwest China<sup>20,23,27–30</sup>. Clarifying this relationship could lead to sleep quality optimization programs at the population level, shown to be feasible and result in disease prevention<sup>31</sup>.

## Materials and methods

### Study population

In this cross-sectional study, we used multi-stage stratified sampling method to enroll participants aged  $\geq 18$  years from Emin Xinjiang between March to November 2019, as described in previous studies<sup>20,23,27–30</sup>. Inclusion criteria encompassed (1) local inhabitants, (2) residence at current address for 6 months or longer, and (3) informed consent was obtained from all participants. Those unable to cooperate due to mental and/or cognitive problems, confirmed secondary hypertension including primary aldosteronism, pheochromocytoma, renovascular hypertension, renal hypertension, Cushing's syndrome, chronic kidney disease (stage 3–5), hepatic dysfunction, and pregnant female were excluded. The study was approved by Ethics Committee of People's Hospital of Xinjiang Uygur Autonomous Region, including any relevant details and all experiments were performed in accordance with relevant guidelines and regulations.

### Data collection

As described in previous studies, standardized questionnaire were completed for each participant by face-to-face interview with trained investigators including socio-demographic characteristics, lifestyle, PSQI, No-SAS scale, and medical histories, and history of CV disease (CVD), with demographic data and blood sample collection<sup>23</sup>.

BP, height, weight, and abdominal circumference were measured which described in previous studies also<sup>20,23,28</sup>. BP was measured using with OMRON HBP-1300 Professional Portable BP Monitor (OMRON, Kyoto, Japan) three times on the right arm positioned at heart level with participant sitting at rest for five minutes, with 30 s between each measurement with an observer present. Average of three readings was used for analysis. Height and weight were measured to the nearest 0.1 cm and 0.1 kg, respectively, with participants in lightweight clothing and without shoes. Body mass index (BMI) was calculated by dividing weight by height squared ( $\text{kg}/\text{m}^2$ ). Abdominal circumference was measured at the midpoint between the lower rib and upper margin of the iliac crest to the nearest 0.1 cm at the end of a normal expiration<sup>20,23,28</sup>.

### Blood sample collection and PAC measurement

All participants were asked to arrive fasting on the morning for venous blood collection by experienced nurses. Within 30 min, the blood sample was centrifuged at 3000 rpm for 20 min at 4 °C to separate serum and preserved in the refrigerators. One sample was transported to local hospital to measure serum fasting blood glucose (FBG), lipid profiles, glutamic-pyruvic transaminase (ALT), glutamic oxalacetic transaminase (AST) and creatinine.

The other samples were sent to Xinjiang Hypertension Institute (located in the above mentioned hospital in Urumqi city), stored in portable refrigerators with temperature as low as -20 °C during delivery and the time on the road was about 6–7 h. Upon arrival, we stored samples at -80 °C until PAC measurement. PAC was measured by automatic biochemical analyzer (Zhengzhou Antu Biological Engineering Co., LTD, model AutoLumo A2000), by chemiluminescence using a commercially available kit (Autobio Diagnostics Co., Ltd, Zheng zhou City, China) and following the manufacturer's instruction, and the assay coefficients of variation were not greater than 15%.

### Sleep quality assessment

Sleep quality was assessed using Chinese version of PSQI<sup>32</sup>. PSQI is an accepted instrument due to its moderate structural validity identifying patients with poor sleep quality<sup>33</sup>. PSQI consists of 19 items that are coded on a four-point scale (0–3) to obtain seven elements: subjective sleep quality, sleep disturbance, daytime dysfunction, sleep onset latency, habitual sleep efficiency, sleep duration, and use of sleep medication<sup>33</sup>. The sum of all sub-scale scores represents the total sleep quality score ranging between 0 and 21, with higher scores representing poorer sleep quality. Sleep quality was categorized into four groups as very good (PSQI score  $\leq 4$ ), fairly good (5–9), fairly bad (10–14) and very bad sleep ( $\geq 15$ )<sup>20,23,34</sup>.

## Definitions of co-variables

Hypertension was defined as systolic BP  $\geq 140$  mmHg, and/or diastolic BP (DBP)  $\geq 90$  mmHg, and/or use of anti-hypertensive medicine within 2 weeks<sup>28,35</sup>. Alcohol consumption was defined as consuming alcoholic beverage at least once per week in the past month<sup>20,36</sup>. Cigarette consumption was defined as participants who have smoked at least 20 packets of cigarettes in their lifetime and currently smoke cigarettes<sup>20,36</sup>. Abdominal obesity was defined as having an abdominal circumference  $\geq 90$  cm for males and  $\geq 85$  cm for females<sup>20,37</sup>. Education attainment status was categorized into lower senior high, and senior high and higher (9 year education). CVD was defined as self-reported medical history of coronary heart disease and stroke. SDB was identified using a threshold of 8 points or more of the NoSAS score as given in Sup Table 1<sup>23,38</sup>.

## Statistical analysis

Participants were divided into four groups as very good, fairly good, fairly bad and very bad sleepers. Analysis were performed in total population and in stratified population by age (<45, 45–60 and  $\geq 60$  years) and gender (male and female).

Continuous variables with normal distribution were presented as means  $\pm$  standard deviations and analyzed using ANOVA test; otherwise, presented as median and 25th–75th percentiles and analyzed using Kruskal–Wallis H test. Categorical variables were expressed as proportion (%) and analyzed using Chi-square test.

Distribution of PAC among different sleep quality groups were characterized using Kruskal–Wallis H test. Log-transformed PAC analysis, due to skewed distribution, was also performed in order to explore its trend from very good to very bad sleepers.

Restricted cubic spline was plotted between PQSI score as continuous variable as parameter for sleep quality and log-PAC before and after adjusting for relevant confounders. Linear regression analysis was used to estimate unadjusted and adjusted B values and 95% confidence intervals (95% CIs) for the association between PSQI score and log-PAC. Variables to be adjusted were selected using univariate linear regression. Tolerance and variance inflation factor of multiple linear regression were used to evaluate collinearity among variables. Collinearity was considered when tolerance was  $< 0.1$  or variance inflation factor was  $> 10$ . Age and or gender were removed from the model when it was the stratification variable.

Sensitivity analysis was conducted for comparison of PAC among different sleep quality groups by exclusion of participants with hypertension, SDB or any one of the both, and for linear regression analysis of PSQI score and log PAC by exclusion of participants with hypertension or SDB with adjusted models consistent with main analysis.

Results were considered statistically significant for two-tailed value of  $P < 0.05$ . RCS was performed with R package (version 4.0.3) and others were performed with SPSS statistical software, version 24.0.

## Results

### Population characteristics

Totally, 29,499 participants with complete data on PSQI and PAC comprised current analytical sample, aged 48 years and with 53.8% females. Among the total population, 14,391 (48.8%) were Han nationality (Table 1).

Participants in very bad sleep quality group were older, more likely to be female, to have lower education attainment, less likely to smoke and drink, and to have higher BMI, and abdominal circumference (Table 1).

### Distribution of PAC and trend of log PAC in different sleep quality groups

In total participants, median PAC showed significant increase from very good to very bad sleepers (14.3 vs. 14.4 vs. 14.7 vs. 15.8 ng/dL), consistent in young (14.8 vs. 15.8 vs. 15.9 vs. 16.9 ng/dL), middle-aged (14.2 vs. 14.3 vs. 14.6 vs. 16.2 ng/dL) and older participants (13.5 vs. 13.3 vs. 14.1 vs. 15.1 ng/dL), although with a decrease in elderly fairly good sleepers ( $P$  for all  $< 0.001$ , Table 2).

In male participants, PAC also showed significant increase from very good to very bad sleepers (13.1 vs. 13.6 vs. 14.1 vs. 14.9 ng/dL), consistent in the young (13.1 vs. 14.2 vs. 14.3 vs. 13.9 ng/dL) and the middle-aged (13.3 vs. 13.7 vs. 14.8 vs. 16.7 ng/dL) ( $P$  for all  $< 0.001$ , Table 2).

In female participants, in the aged  $\geq 60$  years, PAC was increased from very good to very bad sleepers although with a decrease in fairly good sleepers (14.2 vs. 13.6 vs. 14.6 vs. 15.7 ng/dL,  $P = 0.001$ ).

In Han nationality participants, PAC was increased from very good to very bad sleepers although with a decrease in fairly good sleepers (15.8 vs. 15.5 vs. 16.1 vs. 17.3 ng/dL,  $P = 0.001$ ). There were no statistical differences in other ethnic groups.

As in lower part of Table 2, log-transformed PAC showed significant increasing trend from very good to very bad sleepers in total (1.17 vs. 1.17 vs. 1.18 vs. 1.19), and in male (1.13 vs. 1.14 vs. 1.16 vs. 1.18) participants, consistent in different age groups ( $P$  for all  $< 0.001$ ,  $P$  for trend in all  $< 0.05$ ).

In male participants, log-transformed PAC also showed significant increase from very good to very bad sleepers in the young (1.13 vs. 1.15 vs. 1.16 vs. 1.16) and the middle-aged (1.13 vs. 1.14 vs. 1.18 vs. 1.21) ( $P$  for all  $< 0.001$ , Table 2).

In female participants, in the aged  $\geq 60$  years, log-transformed PAC was increased from very good to very bad sleepers although with a decrease in fairly good sleepers (1.16 vs. 1.15 vs. 1.17 vs. 1.19,  $P = 0.002$ ).

Log-transformed PAC showed significant increasing trend from very good to very bad sleepers in Han nationality participants (1.20 vs. 1.20 vs. 1.22 vs. 1.25,  $P < 0.001$ ). No statistical differences were found in other ethnic groups (Table 2).

### Relationship between PSQI score and log-PAC

As in Fig. 1, we verified the linear relationship between PSQI scale and log PAC by RCS method, and there was an obvious dose-response relationship.

	Total	Very Good	Fairly Good	Fairly Bad	Very Bad	F, X <sup>2</sup> ,H/P
N (n,%)	29,499	17,183 (58.2)	8807 (29.9)	2956 (10.0)	553 (1.9)	
Age (years)	48 (38,57)	45 (35,54)	50 (41,59)	54 (46,63)	56 (48,65)	1663.2/<0.001
≤ 45 years (n,%)	119,557(40.5)	8276 (48.2)	2925 (33.2)	658 (22.3)	98 (17.7)	1437.2/<0.001
45–60 years (n,%)	11,581 (39.3)	6303 (36.7)	3770 (42.8)	1272 (43.0)	236 (42.7)	
≥ 60 years (n,%)	5961 (20.2)	2604 (15.2)	2112 (24.0)	1026 (34.7)	219 (39.6)	
Gender (women, n,%)	15,883 (53.8)	8314 (48.4)	5056 (57.5)	2058 (69.6)	446 (80.7)	709.7/<0.001
Ethnicity						
Han (n,%)	14,391(48.8)	7979(55.4)	4593(31.9)	1553(10.8)	266(1.8)	109.2/<0.001
Others (n,%)	15,108(51.2)	9204(60.9)	4214(27.9)	1403(9.3)	287(1.9)	
Education (≥ senior high, n,%)	8787 (29.8)	5300 (30.9)	2583 (29.3)	787 (26.6)	117 (21.2)	45.4/<0.001
Current cigarette consumption (n,%)	7699 (26.1)	4996 (29.1)	2120 (24.1)	526 (17.8)	57 (10.3)	276.1/<0.001
Current alcohol intake (n,%)	9711 (33.0)	5928 (34.6)	2928 (33.3)	753 (25.5)	102 (18.5)	147.5/<0.001
Body mass index (kg/m <sup>2</sup> )	25.5 (22.8,28.3)	25.3 (22.6,28.2)	25.6 (23.1,28.5)	25.8 (23.2,28.7)	26.4 (23.5,29.4)	30.9/<0.001
24–28 kg/m <sup>2</sup> (n,%)	10,859 (36.8)	6217 (36.2)	3324 (37.8)	1123 (38.0)	195 (35.3)	75.5/<0.001
≥ 28 kg/m <sup>2</sup> (n,%)	8159 (27.7)	4551 (26.5)	2527 (28.7)	886 (30.0)	195 (35.3)	
Abdominal circumference (cm)	89.0 (81.0,97.0)	88.4 (80.2,96.4)	89.4 (81.5,97.2)	89.8 (82.2,98.1)	91.2 (84.0,99.5)	95.8/<0.001
Abdominal obesity (n,%)	16,376 (55.6)	9094 (53.0)	5099 (57.9)	1806 (61.1)	377 (68.2)	136.8/<0.001
Systolic blood pressure (mmHg)	123 (111,139)	122 (111,136)	125 (112,140)	128 (114,143)	128 (115,146)	191.8/<0.001
Diastolic blood pressure (mmHg)	79 (70,88)	79 (70,87)	80 (70,88)	80 (71,88)	80 (71,89)	33.0/<0.001
Hypertension (n,%)	10,792 (36.6)	5552 (32.3)	3526 (40.0)	1405 (47.5)	309 (55.9)	421.9/<0.001
Anti-hypertensive agent intake (n,%)	4518 (15.3)	1865 (10.9)	1644 (18.7)	508 (27.7)	204 (36.9)	862.1/<0.001
Sleep disordered breathing (n,%)	7231(26.2)	3868 (23.8)	2344 (28.8)	853 (31.7)	166 (32.5)	128.4/<0.001
No-SAS score	5 (2,7)	5 (2,7)	5 (2,8)	6 (3,9)	6 (3,9)	290.9/<0.001
Cardiovascular disease (n,%)	1327 (4.5)	435 (2.5)	515 (5.8)	305 (10.3)	73 (13.0)	518.0/<0.001
Fasting blood glucose (mmol/L)	5.3 (4.8,5.9)	5.3 (4.8,5.9)	5.4 (4.9,6.0)	5.4 (4.9,6.1)	5.4 (4.9,6.3)	46.8/<0.001
Serum creatinine (umol/L)	69.2 (58.7,82.0)	69.7 (59.0,82.0)	69.2 (58.3,82.6)	68.2 (57.5,82.2)	69.7 (57.6,79.9)	20.4/<0.001
Total cholesterol (mmol/L)	5.2 ± 1.3	4.8 ± 1.2	4.9 ± 1.3	5.0 ± 1.3	5.2 ± 1.3	35.1/<0.001
Glutamic-pyruvic transaminase (u/L)	21.0 (16.0,28.0)	21.0 (16.0,28.0)	21.0 (16.0,28.0)	20.0 (16.0,27.0)	20.0 (16.0,28.0)	0.8/0.500
Glutamic oxalacetic transaminase (u/L)	21.0 (18.0,26.0)	21.0 (18.0,26.0)	21.0 (18.0,26.0)	21.0 (18.0,26.0)	21.0 (18.0,26.0)	0.1/0.946
Plasma aldosterone concentration (ng/dL)	14.4 (10.3,20.5)	14.3 (10.2,20.4)	14.4 (10.3,20.5)	14.7 (10.6,21.0)	15.8 (11.2,21.9)	23.9/<0.001

**Table 1.** Characteristics of study participants by sleep quality.

As in Table 3, PSQI score showed significant positive association with log-PAC in total (B, 95%CI: 0.007, 0.003–0.010,  $P < 0.001$ ) and young (0.017, 0.010–0.023,  $P < 0.001$ ), middle-aged (0.010, 0.006–0.015,  $P < 0.001$ ) and in elderly participants (0.011, 0.005–0.017,  $P < 0.001$ ), consistent in adjusted model 1 and 2.

In males, PSQI score was in significant positive association with log-PAC in total (B, 95%CI 0.013, 0.008–0.018,  $P < 0.001$ ), young (0.019, 0.010–0.027,  $P < 0.001$ ), and middle-aged (0.019, 0.010–0.027,  $P < 0.001$ ) participants, consistent in adjusted model 1 and 2. In females, PSQI score showed significant positive association with log-PAC in the aged ≥ 60 years (0.008, 0.000–0.015,  $P = 0.039$ ), consistent in adjusted model 1 and 2.

PSQI score showed significant positive association with log-PAC Han nationality participants (B, 95%CI 0.005, 0.001–0.010,  $P = 0.025$ ), consistent in adjusted model 1 and 2. In other ethnic groups, PSQI score was in significant positive association with log-PAC in model 1 (B, 95%CI: 0.006, 0.001–0.010,  $P = 0.025$ ).

Model 1 was adjusted for age, gender, BMI, abdominal circumference, alcohol and cigarette consumption status, education status, SBP, DBP, FBG, ALT, AST, TC, SDB, CVD and ethnic. Model 2 was further adjusted for serum creatinine. Selection of variables to be adjusted was given in Sup Table 2.

### Sensitivity analysis

Given in Table 4, when participants with SDB were excluded, log PAC showed an increasing trend from very good to very bad sleepers in total, male, female, young, middle-aged and in elder participants ( $P$  for trend for all  $< 0.05$ ).

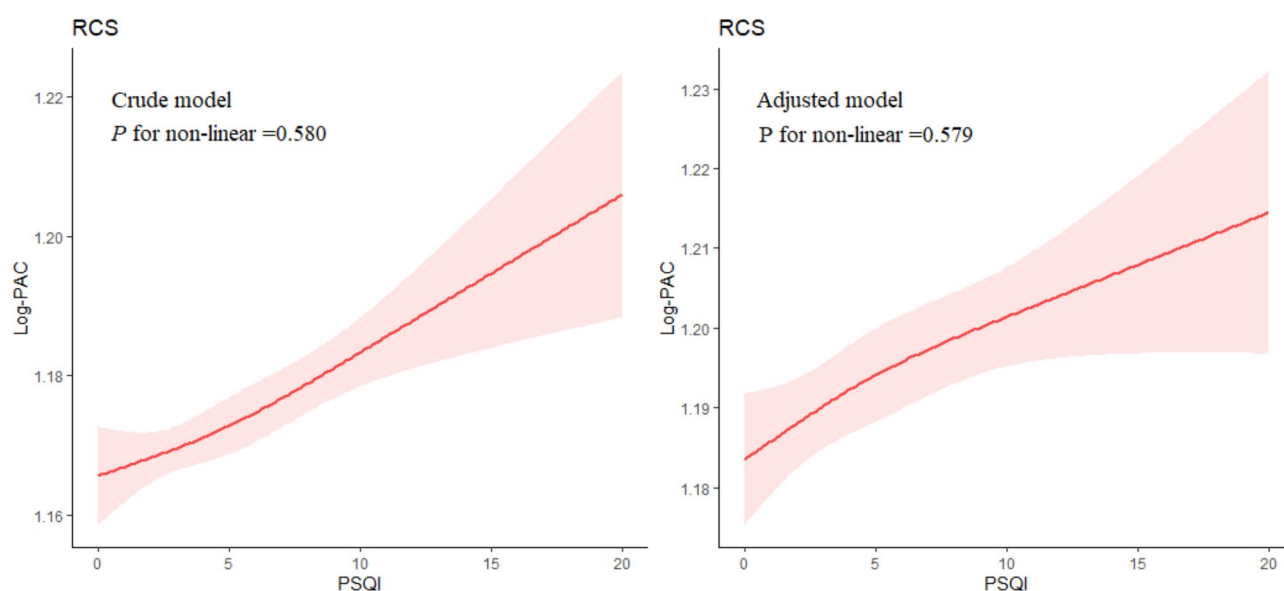
When participants with hypertension were excluded, log PAC showed an increasing trend from very good to very bad sleepers in total ( $P$  for trend  $< 0.001$ ), male ( $P$  for trend  $< 0.001$ ), female (marginally), young ( $P$  for trend  $< 0.001$ ), middle-aged ( $P$  for trend = 0.001) and in elder (marginally) participants.

When participants with SDB or hypertension were excluded, log PAC showed a significant increasing trend from very good to very bad sleepers in total, male, young, middle-aged and in elder participants ( $P$  for trend for all  $< 0.05$ ), except for female participants.

In sensitivity analysis for linear regression (Table 5), when participants with SDB were excluded, PSQI score showed positive association with log PAC in total (significant in all models), male (significant in all models), female (marginally in adjusted models), young (marginally in adjusted models), and middle-aged (marginally in

	Total	Very Good	Fairly Good	Fairly Bad	Very Bad	H/F/P	P for trend
N,%	29,499	17,183 (58.2)	8807 (29.9)	2956 (10)	553 (1.9)		
PAC							
Total	14.4 (10.3,20.5)	14.3 (10.2,20.4)	14.4 (10.3,20.5)	14.7 (10.6,21.0)	15.8 (11.2,21.9)	23.9/<0.001	–
< 45 years	15.1 (10.5,21.7)	14.8 (10.4,21.3)	15.8 (10.7,22.6)	15.9 (11.1,22.2)	16.9 (11.1,26.7)	28.3/<0.001	–
45–60 years	14.3 (10.4,20.1)	14.2 (10.2,19.9)	14.3 (10.4,20.1)	14.6 (10.8,21.1)	16.2 (11.5,21.4)	19.8/<0.001	–
≥ 60 years	13.6 (9.9,18.8)	13.5 (9.8,18.5)	13.3 (9.6,18.5)	14.1 (10.3,19.7)	15.1 (11.0,20.9)	23.6/<0.001	–
Male	13.5 (9.4,19.1)	13.1 (9.4,18.8)	13.6 (9.4,19.4)	14.1 (10.0,20.0)	14.9 (10.7,22.2)	24.0/<0.001	–
< 45 years	13.4 (9.4,19.2)	13.1 (9.3,18.8)	14.2 (9.6,20.1)	14.3 (11.1,20.5)	13.9 (9.3,21.5)	19.3/<0.001	–
45–60 years	13.5 (9.6,19.3)	13.3 (9.5,19.3)	13.7 (9.5,19.3)	14.8 (10.2,21.5)	16.7 (11.9,23.5)	20.9/<0.001	–
≥ 60 years	12.9 (9.2,18.2)	12.9 (9.2,18.2)	12.8 (9.1,18.2)	12.6 (9.3,18.4)	14.1 (10.8,17.1)	2.1/0.560	–
Female	15.4 (11.0,21.9)	15.6 (11.2,22.3)	15.1 (10.8,21.4)	14.9 (10.8,21.4)	16.0 (11.3,21.8)	21.0/<0.001	–
< 45 years	16.7 (11.6,24.3)	16.5 (11.6,24.0)	17.2 (11.6,24.8)	16.5 (11.2,24.9)	17.7 (11.7,26.8)	2.3/0.506	–
45–60 years	14.9 (11.0,20.8)	15.1 (11.1,2.1)	14.7 (10.9,20.4)	14.6 (10.9,21.0)	16.1 (11.5,20.7)	4.7/0.193	–
≥ 60 years	14.1 (10.5,19.4)	14.2 (10.7,18.8)	13.6 (10.0,18.8)	14.6 (10.6,20.1)	15.7 (11.0,21.2)	15.4/0.002	–
Han ethnic	15.8 (11.3,22.1)	15.8 (11.3,22.1)	15.5 (11.1,21.7)	16.1 (11.7,23.1)	17.3 (12.7,23.5)	5.5/0.001	–
Other ethnic	13.3 (9.4,19.0)	13.3 (9.4,18.9)	13.4 (9.5,19.1)	13.3 (9.7,18.9)	14.5 (10.5,19.5)	0.6/0.626	–
Log-PAC							
Total	1.19 (0.22)	1.17 (0.21)	1.17 (0.21)	1.18 (0.21)	1.19 (0.21)	7.2/<0.001	< 0.001
< 45 years	1.19 (0.23)	1.18 (0.22)	1.20 (0.23)	1.21 (0.23)	1.23 (0.24)	9.2/<0.001	< 0.001
45–60 years	1.16 (0.20)	1.16 (0.20)	1.16 (0.20)	1.18 (0.21)	1.20 (0.19)	7.3/<0.001	< 0.001
≥ 60 years	1.14 (0.20)	1.14 (0.20)	1.13 (0.20)	1.16 (0.20)	1.18 (0.20)	8.1/<0.001	< 0.001
Male	1.13 (0.20)	1.13 (0.20)	1.14 (0.21)	1.16 (0.21)	1.18 (0.20)	8.4/<0.001	< 0.001
< 45 years	1.13 (0.20)	1.13 (0.20)	1.15 (0.21)	1.16 (0.19)	1.16 (0.23)	8.1/<0.001	< 0.001
45–60 years	1.14 (0.21)	1.13 (0.20)	1.14 (0.21)	1.18 (0.22)	1.21 (0.20)	5.9/<0.001	< 0.001
≥ 60 years	1.12 (0.20)	1.12 (0.20)	1.12 (0.20)	1.13 (0.22)	1.15 (0.17)	0.6/0.597	0.496
Female	1.20 (0.21)	1.21 (0.22)	1.19 (0.21)	1.19 (0.21)	1.20 (0.21)	7.8/<0.001	0.001
< 45 years	1.24 (0.23)	1.23 (0.23)	1.24 (0.24)	1.24 (0.25)	1.25 (0.24)	1.4/0.247	0.077
45–60 years	1.18 (0.20)	1.19 (0.20)	1.18 (0.19)	1.19 (0.20)	1.19 (0.18)	2.9/0.077	0.620
≥ 60 years	1.16 (0.19)	1.16 (0.19)	1.15 (0.19)	1.17 (0.20)	1.19 (0.21)	4.8/0.002	0.028
Han ethnic	1.20(0.21)	1.20(0.21)	1.20(0.20)	1.22(0.21)	1.25(0.20)	6.6/<0.001	0.025
Other ethnic	1.14(0.21)	1.14(0.21)	1.14(0.22)	1.14(0.21)	1.17(0.20)	1.8/0.151	0.063

**Table 2.** Plasma aldosterone concentration (PAC) and log-PAC by sleep quality in total, male and female participants and by age (ng/dL).



**Fig. 1.** The linear relationship between sleep quality by PSQI scale with log-PAC by RCS method.

PAC	Crude model	Model 1	Model 2
Total	0.007 (0.003,0.010), <0.001	0.006 (0.002,0.009), 0.001	0.005 (0.001,0.009), 0.007
<45 years	0.017 (0.010,0.023), <0.001	0.011 (0.004,0.017), 0.001	0.010 (0.003,0.018), 0.005
45–60 years	0.010 (0.006,0.015), <0.001	0.006 (0.001,0.011), 0.014	0.005 (0.001,0.012), 0.024
≥60 years	0.011 (0.005,0.017), <0.001	0.006 (0.000,0.013), 0.040	0.004 (-0.003,0.010), 0.241
Male	0.013 (0.008,0.018), <0.001	0.009 (0.004,0.014), 0.001	0.007 (0.001,0.013), 0.021
<45 years	0.020 (0.011,0.029), <0.001	0.016 (0.006,0.025), 0.002	0.014 (0.003,0.025), 0.010
45–60 years	0.019 (0.010,0.027), <0.001	0.015 (0.007,0.024), <0.001	0.014 (0.005,0.023), 0.002
≥60 years	0.002 (-0.009,0.012), 0.744	-0.004 (-0.014,0.007), 0.490	-0.008 (-0.019,0.003), 0.135
Female	-0.008 (-0.012,-0.004), <0.001	0.006 (0.002,0.011), 0.005	0.006 (0.002,0.011), 0.008
<45 years	0.004 (-0.004,0.013), 0.313	0.008 (-0.001,0.017), 0.076	0.008 (-0.001,0.018), 0.088
45–60 years	-0.002 (-0.008,0.004), 0.449	0.002 (-0.004,0.008), 0.457	0.003 (-0.003,0.010), 0.351
≥60 years	0.008 (0.000,0.015), 0.039	0.013 (0.005,0.020), 0.001	0.011 (0.003,0.019), 0.007
Ethnic			
Han ethnic	0.005 (0.001,0.010), 0.025	0.006 (0.001,0.010), 0.019	0.006 (0.001,0.011), 0.019
Other ethnic	0.004 (0.000,0.009), 0.063	0.006 (0.001,0.010), 0.025	0.005 (-0.001,0.010), 0.089

**Table 3.** Liner regression for relationship of PSQI score with log PAC in total, male and female participants and by age groups (B, 95%CI, P). Model 1 adjusted for variables: age, gender, BMI, abdominal circumference, alcohol and cigarette consumption status, education status, SBP, DBP, FBG, ALT, AST, total cholesterol, SDB, CVD and ethnic. Model 2 further adjusted for serum creatinine, on the basis of model 1. Abbreviation: PSQI: Pittsburgh Sleep Quality Index PAC, plasma aldosterone concentration; SDB, sleep disordered breathing; CVD, cardiovascular disease; ALT, glutamic-pyruvic transaminase; AST, glutamic oxalacetic transaminase; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose.

	Total	Very Good	Fairly Good	Fairly Bad	Very Bad	F/P	P for trend
Participants without SDB							
N (n,%)	20,367	12,379 (60.8)	5806 (28.5)	1838 (9.0)	344 (1.7)		
Total	1.18 (0.22)	1.17 (0.22)	1.18 (0.22)	1.19 (0.22)	1.21 (0.21)	5.6/0.001	<0.001
Male	1.12 (0.20)	1.12 (0.20)	1.12 (0.21)	1.14 (0.20)	1.19 (0.22)	3.6/0.014	0.005
Female	1.21 (0.22)	1.21 (0.22)	1.20 (0.22)	1.20 (0.22)	1.21 (0.21)	2.3/0.071	0.041
<45 years	1.19 (0.23)	1.19 (0.23)	1.21 (0.23)	1.21 (0.24)	1.23 (0.25)	5.9/0.001	<0.001
45–60 years	1.17 (0.20)	1.16 (0.20)	1.16 (0.20)	1.18 (0.20)	1.21 (0.19)	6.6/<0.001	<0.001
≥60 years	1.14 (0.20)	1.13 (0.19)	1.15 (0.21)	1.16 (0.20)	1.19 (0.20)	4.2/0.005	<0.001
Participants without hypertension							
N (n,%)	18,707	11,631 (62.2)	5281 (28.2)	1551 (8.3)	244 (1.3)		
Total	1.78 (0.22)	1.17 (0.22)	1.18 (0.21)	1.19 (0.21)	1.21 (0.21)	5.7/0.001	<0.001
Male	1.14 (0.20)	1.13 (0.20)	1.14 (0.20)	1.17 (0.20)	1.19 (0.19)	7.7/<0.001	<0.001
Female	1.21 (0.22)	1.21 (0.22)	1.21 (0.22)	1.20 (0.22)	1.21 (0.21)	1.5/0.216	0.078
<45 years	1.20 (0.23)	1.19 (0.23)	1.21 (0.23)	1.22 (0.23)	1.24 (0.28)	10.3/<0.001	<0.001
45–60 years	1.17 (0.20)	1.16 (0.20)	0.17 (0.20)	1.19 (0.20)	1.20 (0.18)	4.9/0.002	0.001
≥60 years	1.14 (0.19)	1.14 (0.19)	1.13 (0.19)	1.15 (0.0 19)	1.19 (0.18)	2.1/0.095	0.073
Participants without SDB or hypertension							
N (n,%)	14,867	9407 (63.3)	4089 (27.5)	1185 (8.0)	186 (1.3)		
Total participants	1.19 (0.22)	1.18 (0.22)	1.19 (0.22)	1.20 (0.22)	1.22 (0.22)	5.4/<0.001	<0.001
Male	1.13 (0.20)	1.12 (0.20)	1.13 (0.20)	1.15 (0.20)	1.19 (0.24)	3.7/0.011	0.001
Female	1.22 (0.22)	1.22 (0.22)	1.22 (0.22)	1.21 (0.22)	1.22 (0.22)	0.4/0.736	0.455
<45 years	1.20 (0.23)	1.19 (0.23)	1.21 (0.23)	1.22 (0.25)	1.24 (0.25)	7.6/<0.001	<0.001
45–60 years	1.17 (0.20)	1.16 (0.20)	1.17 (0.20)	1.19 (0.20)	1.20 (0.19)	3.7/0.011	0.002
≥60 years	1.15 (0.19)	1.13 (0.18)	1.16 (0.20)	1.16 (0.19)	1.20 (0.22)	2.5/0.062	0.020

**Table 4.** Sensitivity analysis for Log-transformed PAC by sleep quality in total, male, female, and different age groups.



	Crude model	Model 1	Model 2
Participants without SDB			
Total	0.008 (0.004,0.012), <0.001	0.006 (0.002,0.011), 0.006	0.005 (0.001,0.010), 0.019
Male	0.011 (0.003,0.019), 0.005	0.011 (0.002,0.019), 0.013	0.010 (0.001,0.018), 0.022
Female	-0.005 (-0.010,0.000), 0.041	0.006 (0.001,0.011), 0.028	0.005 (0.000,0.010), 0.070
< 45 years	0.016 (0.008,0.023), <0.001	0.007 (0.000,0.015), 0.061	0.007 (0.000,0.015), 0.057
45–60 years	0.012 (0.006,0.017), <0.001	0.006 (0.000,0.013), 0.057	0.006 (-0.001,0.012), 0.076
≥ 60 years	0.017 (0.008,0.027), <0.001	0.010 (-0.000,0.020), 0.062	0.006 (-0.005,0.016), 0.269
Participants without hypertension			
Total	0.009 (1.158,1.173), <0.001	0.008 (0.003,0.012), 0.001	0.008 (0.003,0.013), 0.002
Male	0.017 (0.010,0.024), <0.001	0.013 (0.006,0.020), <0.001	0.012 (0.004,0.020), 0.004
Female	-0.005 (-0.011,0.001), 0.078	0.003 (0.002,0.013), 0.009	0.009 (0.002,0.015), 0.007
< 45 years	0.020 (0.013,0.027), <0.001	0.004 (0.005,0.020), 0.001	0.012 (0.004,0.020), 0.004
45–60 years	0.011 (0.005,0.018), 0.011	0.008 (0.001,0.014), 0.021	0.009 (0.002,0.016), 0.013
≥ 60 years	0.010 (-0.001,0.020), 0.073	0.008 (-0.002,0.019), 0.119	0.007 (-0.005,0.018), 0.245

**Table 5.** Sensitivity analysis for liner regression for relationship of PSQI score with log-transformed PAC by excluding SDB or hypertensive participants (B, 95%CI, P). Model 1 adjusted for variables: age, gender, BMI, abdominal circumference, alcohol and cigarette consumption status, education status, SBP, DBP, FBG, ALT, AST, total cholesterol, SDB, CVD and ethnic. Model 2 further adjusted for serum creatinine, on the basis of model 1. Abbreviation: PSQI: Pittsburgh Sleep Quality Index PAC, plasma aldosterone concentration; SDB, sleep disordered breathing; CVD, cardiovascular disease; ALT, glutamic-pyruvic transaminase; AST, glutamic oxalacetic transaminase; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose.

adjusted models) participants. When participants with hypertension were excluded, PSQI score showed positive association with log PAC in total (significant in all models), male (significant in all models), female (significant in adjusted models), young (significant in all models), and middle-aged (significant in all models) participants.

Discussion

Elevation in PAC even within physiological range is a cardio-renal-metabolic risk factor<sup>3,39</sup> without clear understanding for its elevation. In this population based cross-sectional survey, we explored the association of subjective sleep quality with circulating aldosterone.

Main results encompass the following. First, in total participants, PAC showed significant increasing trend from very good to very bad sleepers in total, and male participants, consistent in different age and Han nationality groups. Second, PSQI score showed significant positive association with log-PAC in total, male and Han nationality participants, consistent in young and middle-aged participants. In female, PSQI score showed a significant positive association with log-PAC in total and elder participants. Third, sensitivity analysis by excluding SDB, hypertension or the both in total, male, and in female participants and in age stratification largely yielded consistent results with the main analysis.

Observations from the current study may add some evidence on on-going uncertainty between sleep quality and PAC. Supportive of current results, Rubin et al. reported that mean aldosterone levels were 24% higher during REM sleep than during all other sleep stages combined<sup>40</sup>. Similar studies showed that, changes in the timing or duration of sleep affect the RAAS, either by altering the 24-h periodicity of the RAAS or by changing total 24-h aldosterone excretion<sup>41</sup>. The morning increase in aldosterone is due to effects of the circadian system plus increased morning activities<sup>12</sup>. Patients with sleep apnea experience nocturnal sleep disturbances and sleep fragmentation, which affect physiological fluctuations in aldosterone and renin<sup>42</sup>. On the other hand, sleep may also be affected by aldosterone levels. During sleep deprivation, aldosterone displayed lower plasma levels and PRA levels in the 23.00-07.00-hour period than during sleep. This study shows that sleep deprivation prevents the increase in aldosterone release during the night, thereby altering 24-hour aldosterone levels<sup>13</sup>. It has also been found that REM sleep usually begins at peak level or in the descending phases of aldosterone pulses<sup>43</sup>. In a recent study, cigarette consumption, BMI, cholesterol, BP, and FBG are positively associated with serum aldosterone in a group of community dwellers<sup>12</sup>. It is not difficult to observe that some of the above parameters are also risk factors for and or clinical characteristics of poor sleep quality<sup>21,27</sup>. These may suggest that poor sleep quality and these factors may share some patho-physiology in terms of increase in circulating aldosterone, and indicate the potential role of aldosterone as a mediator for the association of lifestyle risk factors with CVD, and as a target for prevention<sup>12</sup>. Studies on sleep quality and circulating aldosterone are scarce and thus it is difficult for provide more mechanistic analysis.

One interesting observation is that association of sleep quality or PSQI with PAC or log-PAC is not consistent in different age groups of male and female. Circulating aldosterone decrease with ageing and is modulated by different factors and or exposures such as estrogen in female and more cigarette consumption in male<sup>12</sup>. Therefore, we performed age and gender stratified analysis, but not in some due to smaller sample of very poor sleepers. In male participants of different age groups, sleep quality is negatively associated with PAC in the young

and the middle-aged, but not in the elderly. However, in the female, PSQI score shows a significant positive association with log-PAC only in the aged  $\geq 60$  years, consistent after adjustments. Based on current existing evidence, older age is associated with greater autonomous aldosterone secretion and less physiologic aldosterone secretion<sup>1</sup>. A cross-sectional analysis demonstrated difference in aldosterone levels between premenopausal and postmenopausal female, suggesting that estrogen may have a powerful reverse regulatory effect on aldosterone, and estrogen treatment reduces adrenal and circulating aldosterone levels<sup>44,45</sup>. Therefore, effects of other modulators, such as sleep quality, on aldosterone may become more prominent after menopause<sup>46</sup>.

Another point worthy of mention is that, we performed sensitivity analysis for most results by exclusion of total hypertensive and/or SDB participants with following considerations. First, we were not able to exclude effects on the current results of primary aldosteronism. Second, population-based studies show that hypertensives are characterized by elevated circulating aldosterone even with or without anti-hypertensive treatment<sup>47</sup>. Third, obstructive sleep apnea, the most common form of SDB, is one of main risk factors for poor sleep quality and characterized by elevation in circulating aldosterone<sup>48,49</sup>. Results on the association of sleep quality with PAC before and after sensitivity analyses remain consistent, suggesting that the association may still exist in population without hypertension and/or SDB. Thus, current results might be more credible, and may extend previous results to general population from community.

One distinct point of current study with previous ones is that, we performed plasma sample collection for aldosterone measurement with no strict requirements as in clinical setting. For example, changing or stopping antihypertensive medications before measurement are not possible in the studies like current one. However, all the blood samples were collected in the morning between 8:00 am to 11:00 am at local time (local work time) on the fasting condition (at least for 8 h) in the seated position, and the procedure might be  $< 30$  min for most participants. Consistent with previous studies<sup>4,50</sup>, PAC appear to be higher in female than in male and decreases with age in total, male and female participants, although we did not perform statistical comparison on this part. Therefore, circulating aldosterone levels like this may reflect one's real physiological levels for a certain duration of time, whereas not determined. Furthermore, current results may have some significance for disease treatment at clinical level and for disease prevention at population level, since emerging studies show that statin treatment can lower circulating aldosterone in high risk population such as hypertensive and diabetic patients<sup>51</sup> and even in general healthy population<sup>52</sup>.

In our study, it can be found that sleep quality is more closely related to serum aldosterone in the Han population compared with other ethnic minorities. Previous studies have shown that different ethnic groups have different dietary habits, such as excessive fat intake, variety of diet, high sodium, low potassium and other factors have a significant impact on sleep quality and aldosterone levels. Studies have shown that greater fat intake close to sleep may be associated with greater sleep disruption<sup>53</sup>. Meanwhile there was a positive correlation between higher dietary diversity with better sleep quality. Therefore, ensuring a diverse diet may be beneficial for maintaining good sleep quality among middle-aged and older adults<sup>54</sup>. On the other hand, it is certain that plasma aldosterone levels are easily affected by a small amount of changes in angiotensin, ACTH, potassium and sodium<sup>55</sup>. Potassium (K), acting synergistically with angiotensin-II, stimulates aldosterone production, which then promotes secretion of K in distal nephron. On the other hand, there are differences in serum aldosterone levels and sleep quality between different ethnic groups, and this relationship is related to the increase in specific diseases and also exists in stroke patients<sup>55–57</sup>. Studies on the association between dietary habits and sleep quality and circulating aldosterone in different ethnic populations are also scarce.

This study contains some limitations. First, due to the cross-sectional nature, we fail to establish a causal relationship between sleep quality with PAC. Second, PSQI survey, rather than the golden standard of polysomnography, was used for sleep quality assessment. However, PSQI contains high internal consistency ( $\alpha = 0.83$ ), test-retest reliability ( $r = 0.85$ )<sup>33</sup>. Third, influence of body position and time of blood drawing was not taken into account in the measurement of plasma aldosterone level, whereas participants had blood drawn in the morning while seated position. Fourth, we assessed SDB using the NoSAS scale, a subjective method. However, No-SAS scale has a sensitivity of 79% and specificity of 69% for SDB assessment<sup>38,58</sup>. Fifth, we failed to collect data on serum potassium and salt intake, which may have brought some bias to our results. However, population in Xinjiang is characterized high sodium and low potassium intake, and current results might be useful in places with similar situations.

In conclusion, poor sleep quality is associated with elevated PAC, especially in young and middle-aged male and in elder female, independent of SDB and hypertension, indicating the potential involvement of sleep quality on regulation of circulating aldosterone.

## Data availability

The data analyzed in this study is subject to the following licenses/restrictions: The data that support the findings of this study are available upon request from the corresponding author. Requests to access these datasets should be directed to lnanfang2016@sina.com.

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## Author contributions

Study concepts/study design were performed by Nanfang Li Mulalibieke Heizhati and Xiufang Li. Data acquisition was performed by Xiufang Li, Mulalibieke Heizhati, Mei Li, Ling Yao, Ting Wu, Wenbo Yang, Lin Gan, Hui Wang, Miaomiao Liu, Adalaiti Maitituersun, Mengyue Lin, and Jing Hong. Data analysis/interpretation was performed by Xiufang Li, and Mulalibieke Heizhati. Manuscript drafting or manuscript revision for important intellectual content was performed by Xiufang Li, Mulalibieke Heizhati Lin Gan, and Mengyue Lin. Nanfang Li gave important suggestions and did significant changes. All authors contributed to writing-review, editing and approved the final version of the paper. Xiufang Li and Mulalibieke Heizhati contributed equally to this work.

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## Declarations

## Competing interests

The authors declare no competing interests.

## Ethics statement

The study was approved by Ethics Committee of People's Hospital of Xinjiang Uygur Autonomous Region.

## Additional information

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**Correspondence** and requests for materials should be addressed to M.H. or N.L.

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