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Relationship between circadian syndrome and stroke: A cross-sectional study of the national health and nutrition examination survey

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Aim: The aim of this study was to assess the relationship of circadian syndrome and stroke.

Methods: We performed a cross-sectional analysis of 11,855 participants from the National Health and Nutrition Examination Survey (NHANES) database between 2005 and 2018, and collected the baseline characteristics. Multivariate logistic regression models were developed to explore the association between circadian syndrome and stroke. Simultaneously, subgroup analyses based on the difference of gender, race, and components associated with circadian syndrome also were performed. The odds ratio (OR) and 95% CI were calculated in this study.

Results: All the participants were divided into the non-stroke group and the stroke group. There were approximately 3.48% patients exclusively with stroke and 19.03% patients exclusively with circadian syndrome in our study. The results suggested that the risk of stroke in patients with circadian syndrome was higher than that in patients without circadian syndrome (OR = 1.322, 95% CI: 1.020–1.713). Similar associations were found in women with circadian syndrome (OR = 1.515, 95% CI: 1.086–2.114), non-Hispanic whites with circadian syndrome (OR = 1.544, 95% CI: 1.124–2.122), participants with circadian syndrome who had elevated waist circumference (OR = 1.395, 95% CI: 1.070–1.819) or short sleep (OR = 1.763, 95% CI: 1.033–3.009).

Conclusion: Circadian syndrome was associated with the risk of stroke. Particularly, we should pay more close attention to the risk of stroke in those populations who were female, non-Hispanic whites, had the symptoms of elevated waist circumference or short sleep.

KEYWORDS

circadian syndrome, stroke, correlation, (NHANES) database, symptom

Introduction

Stroke is the leading cause of mortality and serious long-term disability worldwide and has been considered one of the most prevalent and devastating diseases affecting humanity today (1, 2). According to the report of the Global Burden of Disease, the number of patients who were diagnosed with stroke has continued to increase in recent years, resulting in a significant economic burden (3). Existing evidence suggested the risk factors related to stroke, such as arterial hypertension, dyslipidemia, diabetes mellitus, obesity, sleep disorders (4, 5). A better understanding of the contribution of risk factors to stroke burden is important for effective prevention strategies.

The circadian system plays an important role in human health and metabolism (6). Some poor lifestyles, including sleep disturbances, the use of artificial light, and shift work, have been reported to cause the circadian rhythm disturbances, which have adverse effects on human health (7). Recently, a growing number of studies have focused on the relationship between the circadian system and chronic diseases (8–10). Circadian dysfunction has been proposed and defined as the presence of any four of the following seven traits, including elevated waist circumference, elevated triglycerides, reduced high-density lipoprotein (HDL)-cholesterol, elevated blood pressure, elevated fasting glucose, short sleep duration (<6 h/day), and the depression symptom (7). Shi et al. (11) assessed the association between circadian syndrome and cardiovascular disease (CVD), and the result also suggested that the circadian syndrome was a strong predictor for CVD occurrence. However, to the best of our knowledge, there has been no study that examined the association between circadian syndrome and stroke so far.

Herein, the aim of this study was to explore the correlation between circadian syndrome and the occurrence of stroke, and focusing on the number of symptoms in circadian syndrome. In addition, we performed subgroup analyses based on gender, race, and components associated with circadian syndrome.

Methods

Data sources and study design

All data in this study were derived from the National Health and Nutrition Examination Survey (NHANES) database between 2005 and 2018. NHANES, as a major program of the National Center for Health Statistics (NCHS), aims to evaluate the health and nutrition of adults and children in the United States (12, 13). The survey adopts a complex multistage sampling method every year to extract nationally representative data of ~5,000 people (14). The data collection process in NHANES contained two parts, an in-person interview (including demographic, socioeconomic, dietary, and health-related questions) and a physical examination (including

medical, dental, and physiological measurements, as well as laboratory tests) performed in the Mobile Examination Center (MEC) (14, 15). https://www.cdc.gov/nchs/nhanes/about_nhanes.htm.

Our cross-sectional study included 12,826 participants whose surveys included information on stroke history and characteristics of circadian syndrome. Meanwhile, the exclusion criteria were as follows: (1) subjects without the information of height, weight, marital status, the educational level, household income, smoking, and sleep disorders ($n = 518$); (2) the participants had missing information on heart failure, coronary heart disease (CHD), hypertension, and diabetes mellitus ($n = 453$). All the participants provided written consent to participate in the NHANES survey, and data collection was approved by the NCHS Research Ethics Review Committee.

Data collection

We collected the following information in the current study: age (years), gender, body mass index (BMI, kg/m^2), race, marital status, the educational level, household income, smoking, sleep disorders, type of dietary intake [dietary fiber, fat, protein, fruit, vegetables, vitamin A (mcg), vitamin C (mg), vitamin D (mg), vitamin E (mg)], the history of diseases [heart failure, CHD, angina, heart disease, hypertension, high cholesterol, diabetes mellitus], biomarkers [total cholesterol (TC, mg/dL), glycosylated hemoglobin (HbA1c, %), LDL (mg/dL), C-reactive protein (CRP, mg/dL)], and circadian syndrome. Sleep duration was assessed by the question, “How much sleep do you usually get at night on weekdays or workdays?” (16). Sleep disorders were identified by the question “Have you ever been told by a doctor or other health professional that you have a sleep disorder?”. The participants who answered “yes” were asked to say the type of sleep disorder (sleep apnea, insomnia, restless legs, and others) (17, 18). Hypertension was defined as systolic blood pressure of ≥ 140 mmHg and/or diastolic blood pressure of ≥ 90 mmHg or the using of antihypertensive medications (19).

Definition of circadian syndrome

Having ≥ 4 of the following components was defined as having circadian syndrome (11): elevated waist circumference (≥ 102 cm in men, ≥ 88 cm in women), elevated triglycerides (≥ 150 mg/dL) or the using of lipid-lowering medication, reduced high-density lipoprotein (HDL)-cholesterol (< 40 mg/dL in men and < 50 mg/dL in women) or the using of lipid-lowering medication, elevated blood pressure (systolic ≥ 130 and/or diastolic ≥ 85 mmHg) or the using of an anti-hypertensive drug, elevated fasting glucose (≥ 100 mg/dL) or the using of anti-diabetic medication, short sleep (<6 h/day),

depression symptoms [the patient health status questionnaire-9 (PHQ-9) score ≥ 10] (20, 21).

To estimate the association between the symptoms of circadian syndrome and stroke, we defined the circadian syndrome exposure numbers based on the number of components each participant experienced (elevated waist circumference, elevated triglycerides, reduced HDL cholesterol, elevated blood pressure, elevated fasting glucose, short sleep, and depression symptoms): 4 indicated that an exposure of circadian syndrome was composed of four components; 5 indicated circadian syndrome consists of five components; ≥ 6 represented circadian syndrome had more than six factors. Noteworthy, <4 means that the participants were not defined as circadian syndrome.

Outcome

The primary outcome of our study was the occurrence of stroke. Stroke was defined as through the question: “Has a doctor or other health professional ever told you that you had a stroke?”. The participant was considered as a stroke victim when the response was “yes” of the question (5, 22).

Statistical analysis

After weighted analysis, all measurement data were approximately normal distribution. The measurement data were shown by mean \pm standard error (Mean \pm SE), and the independent-samples t-test was used for the comparison between two groups. The enumeration data were described as the number of cases and the composition ratio [n (%)], comparison between groups adopted χ^2 or the Fisher’s exact test. Additionally, we also interpolated the missing value by multiple Imputation (R: mice), and the sensitivity analysis after interpolation is shown in [Supplementary Table 1](#).

First of all, we performed the univariate difference analysis in the study. Then, variables with statistical significance in univariate difference analysis were included as covariables in the multivariate logistic regression model to explore the correlation between circadian syndrome and stroke, and assess the association between the number of symptoms of circadian syndrome and stroke. Three models were introduced: Model 1 was the coarse model; Model 2 adjusted age and BMI; Model 3 adjusted age, BMI, race, marital status, the educational level, household income, sleep disorders, heart failure, CHD, angina, heart disease, hypertension, high cholesterol, diabetes mellitus, smoking, the intake of dietary fiber, the intake of protein, the intake of fat, the intake of vitamin D, the intake of vitamin E, the intake of fruits, TC, HbA1c, and LDL. Simultaneously, we also conducted subgroup analyses based on the difference of gender, race, and components associated with circadian syndrome. The odds ratio (OR) and 95% confidence interval

(CI) were calculated. SAS (version 9.4) software was used for statistical analyses. All statistical tests were conducted by using bilateral tests. $p < 0.05$ was considered as statistically significant difference.

Results

Baseline characteristics

After excluding some participants who had the missing information ($n = 971$), a total of 11,855 eligible participants were enrolled eventually, and they were divided into the non-stroke group ($n = 11,443$) and the stroke group ($n = 412$). The incidence of stroke approximately was 3.48% in our study. Baseline characteristics of all the subjects were displayed in [Table 1](#). Overall, the average age was 47.45 ± 0.29 years. Approximately, 2,473 participants were identified as having circadian syndrome, of which 1,614 participants with circadian syndrome were identified by four features, and 711 participants were identified by five features. Moreover, [Table 1](#) also reveals that some variables had statistical significance between the non-stroke group and the stroke group ($p < 0.05$).

The association of circadian syndrome and stroke

As illustrated in [Table 2](#), the results suggested that the risk of stroke in the patients with circadian syndrome was higher than that in the patients without circadian syndrome (Model 1: OR = 2.050, 95 CI%: 1.587–2.648). After adjusting some covariates, the results of Model 2 (OR = 1.539, 95 CI%: 1.186–1.996) and Model 3 (OR = 1.322, 95 CI%: 1.020–1.713) were similar to those of Model 1. In addition, we also found when the patients with circadian syndrome composed of more than six components, the risk of stroke was 2.591-times higher than the patients with circadian syndrome composed of four components (OR = 3.591, 95 CI%: 1.972–6.538).

The association of circadian syndrome and stroke based on gender, race, and components associated with circadian syndrome

[Figure 1](#) indicates the result of subgroup analysis based on the gender. After adjusting covariates, we found that the risk of stroke in the female patients with circadian syndrome was 1.515 times higher than the patients without circadian syndrome (Model 3: OR = 1.515, 95 CI%: 1.086–2.114, $p < 0.05$). Nevertheless, there was not a statistical significance between male patients with circadian syndrome and stroke (Model 3,

TABLE 1 Baseline characteristics of all participants.

Variables	Total (<i>n</i> = 11,855)	Groups		Statistics	<i>P</i>
		Stroke group (<i>n</i> = 412)	Non-stroke group (<i>n</i> = 11,443)		
Age, years, Mean ± SE	47.45 ± 0.29	63.9 ± 0.93	46.99 ± 0.28	<i>t</i> = -12.380	<0.001
Gender				$\chi^2 = 3.019$	0.086
Men	5,857 (49.51)	193 (46.84)	5,664 (49.50)		
Women	5,998 (50.49)	219 (53.16)	5,779 (50.50)		
BMI, kg/m ² , <i>n</i> (%)				$\chi^2 = 5.894$	0.125
<18.5	180 (1.51)	5 (1.21)	175 (1.53)		
18.5–	3,265 (28.16)	97 (23.54)	3,168 (27.69)		
25–	3,970 (33.56)	119 (28.88)	3,851 (33.65)		
≥30	4,440 (36.77)	191 (46.36)	4,249 (37.13)		
Race, <i>n</i> (%)				$\chi^2 = 40.471$	<0.001
Mexican American	1,814 (8.56)	35 (8.50)	1,779 (15.55)		
Other race	2,569 (12.87)	49 (11.89)	2,520 (22.02)		
Non-Hispanic white	5,142 (68.60)	207 (50.24)	4,935 (43.13)		
Non-Hispanic black	2,330 (9.98)	121 (29.37)	2,209 (19.30)		
Marital status, <i>n</i> (%)				$\chi^2 = 55.780$	<0.001
Married	6,149 (56.05)	216 (52.43)	5,933 (51.85)		
Widowed/divorced	2,532 (17.56)	147 (35.68)	2,385 (20.84)		
Unmarried	2,164 (17.89)	32 (7.77)	2,132 (18.63)		
Cohabitation	1,010 (8.50)	17 (4.13)	993 (8.68)		
Educational level, <i>n</i> (%)				$\chi^2 = 29.465$	<0.001
Junior high and below	2,766 (15.27)	140 (33.98)	2,626 (22.95)		
High school/GED	2,678 (22.63)	105 (25.49)	2,573 (22.49)		
Graduate and above	6,411 (62.10)	167 (40.53)	6,244 (54.57)		
Household income, <i>n</i> (%)				$\chi^2 = 12.705$	0.001
<20,000\$	2,794 (16.35)	135 (32.77)	2,659 (23.24)		
≥20,000\$	9,061 (83.65)	277 (67.23)	8,784 (76.76)		
Smoking, <i>n</i> (%)	5,294 (44.70)	253 (61.41)	5,041 (44.05)	$\chi^2 = 26.210$	<0.001
Sleep disorders, <i>n</i> (%)	1,702 (16.08)	99 (24.03)	1,603 (14.01)	$\chi^2 = 21.855$	<0.001
Heart failure, <i>n</i> (%)	336 (2.19)	71 (17.23)	265 (2.32)	$\chi^2 = 36.789$	<0.001
CHD, <i>n</i> (%)	473 (3.38)	69 (16.75)	404 (3.53)	$\chi^2 = 28.363$	<0.001
Angina, <i>n</i> (%)	273 (2.01)	43 (10.44)	230 (2.01)	$\chi^2 = 19.093$	<0.001
Heart disease, <i>n</i> (%)	475 (3.17)	84 (20.39)	391 (3.42)	$\chi^2 = 27.854$	<0.001
Hypertension, <i>n</i> (%)	4,239 (32.21)	305 (74.03)	3,934 (34.38)	$\chi^2 = 70.054$	<0.001
High cholesterol, <i>n</i> (%)	4,206 (34.38)	247 (59.95)	3,959 (34.60)	$\chi^2 = 42.532$	<0.001
Diabetes mellitus, <i>n</i> (%)	1,574 (9.89)	134 (32.52)	1,440 (12.58)	$\chi^2 = 44.722$	<0.001
Type of dietary intake, Mean ± SE					
Dietary fiber	17.06 ± 0.19	14.41 ± 0.49	17.13 ± 0.19	<i>t</i> = 5.340	<0.001
Fat	85.51 ± 0.59	74.49 ± 3.39	85.81 ± 0.59	<i>t</i> = 3.410	0.001
Protein	84.19 ± 0.54	68.92 ± 2.42	84.61 ± 0.53	<i>t</i> = 6.570	<0.001
Fruit	1.58 ± 0.02	1.41 ± 0.07	1.58 ± 0.02	<i>t</i> = 2.400	0.018
Vegetable	0.90 ± 0.02	0.82 ± 0.07	0.91 ± 0.02	<i>t</i> = 1.170	0.247
Vitamin A	605.44 ± 7.25	575.46 ± 30.94	606.26 ± 7.24	<i>t</i> = 1.010	0.313
Vitamin C	75.93 ± 1.15	69.35 ± 5.13	76.12 ± 1.15	<i>t</i> = 1.290	0.199
Vitamin E	8.77 ± 0.10	7.31 ± 0.36	8.81 ± 0.10	<i>t</i> = 4.160	<0.001
Vitamin D	4.46 ± 0.07	3.87 ± 0.23	4.48 ± 0.07	<i>t</i> = 2.630	0.010

(Continued)

TABLE 1 Continued

Variables	Total (<i>n</i> = 11,855)	Groups		Statistics	<i>P</i>
		Stroke group (<i>n</i> = 412)	Non-stroke group (<i>n</i> = 11,443)		
Biomarkers, Mean ± SE					
TC	192.47 ± 0.65	184.5 ± 2.68	192.69 ± 0.67	<i>t</i> = 2.820	0.006
GHb	5.63 ± 0.01	6.11 ± 0.09	5.62 ± 0.01	<i>t</i> = −5.580	<0.001
LDL	113.55 ± 0.47	104.56 ± 2.33	113.8 ± 0.48	<i>t</i> = 3.750	<0.001
CRP	1.90 ± 0.06	2.38 ± 0.34	1.89 ± 0.06	<i>t</i> = −1.460	0.149
Circadian syndrome, <i>n</i> (%)				$\chi^2 = 23.680$	<0.001
No	9,382 (80.97)	271 (65.78)	9,111 (79.62)		
Yes	2,473 (19.03)	141 (34.22)	2,332 (20.38)		
Components of circadian syndrome				<i>Z</i> = 7.179	<0.001
<4	9,382 (79.14)	271 (65.78)	9,111 (79.62)		
4	1,614 (13.61)	79 (19.17)	1,535 (13.41)		
5	711 (6.00)	41 (9.95)	670 (5.86)		
≥6	133 (1.12)	17 (4.13)	116 (1.01)		

BMI, body mass index; GED, General Equivalent Diploma; CHD, coronary heart disease; TC, total cholesterol; GHb, glycosylated hemoglobin; LDL, low-density lipoprotein; CRP, C-reactive protein.

TABLE 2 The influence of circadian syndrome on stroke.

Variables	Model 1		Model 2		Model 3	
	OR (95%CI)	<i>P</i>	OR (95%CI)	<i>P</i>	OR (95%CI)	<i>P</i>
Circadian syndrome						
No						
Yes	2.050 (1.587–2.648)	<0.001	1.539 (1.186–1.996)	0.001	1.322 (1.020–1.713)	0.033
Components of circadian syndrome						
4	Ref		Ref		Ref	
5	1.282 (0.770–2.133)	0.336	1.287 (0.757–2.189)	0.358	1.318 (0.757–2.294)	0.325
≥6	3.365 (1.883–6.015)	<0.001	3.916 (2.123–7.223)	<0.001	3.591 (1.972–6.538)	<0.001

OR, odds ratio; CI, confidence interval.

Model 1: coarse model.

Model 2: adjusted age and body mass index (BMI).

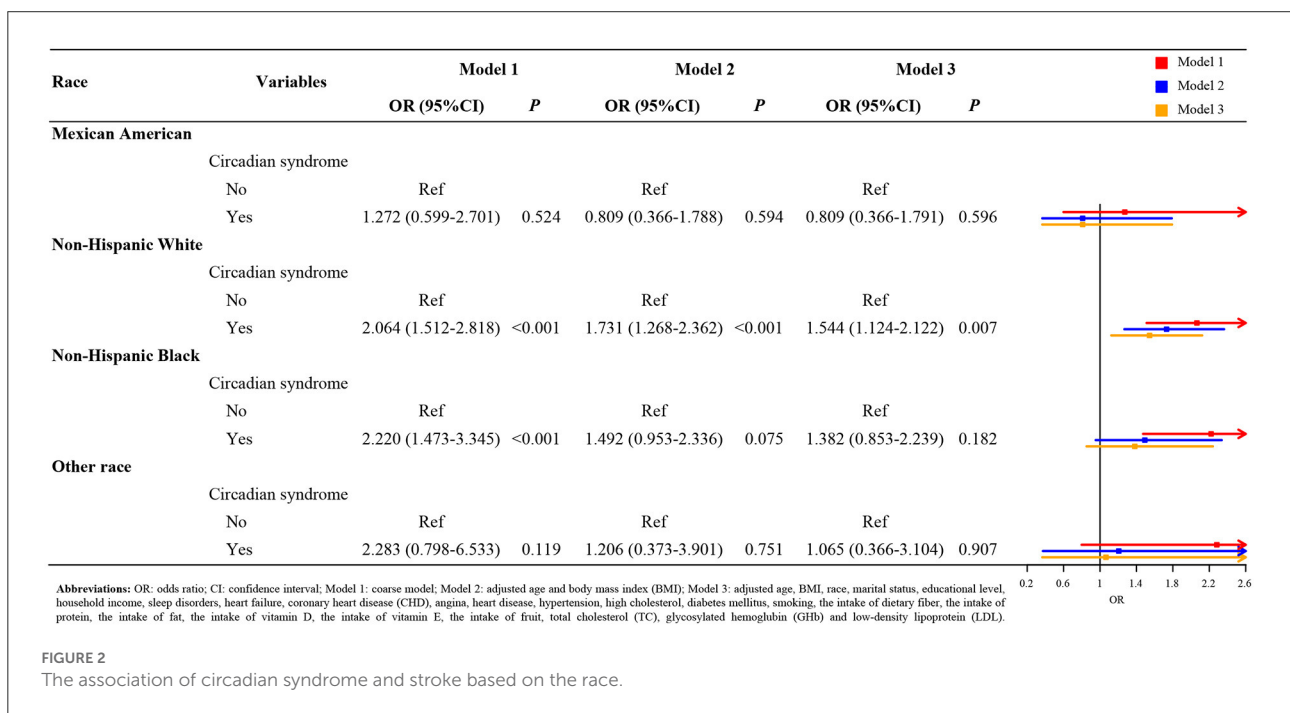
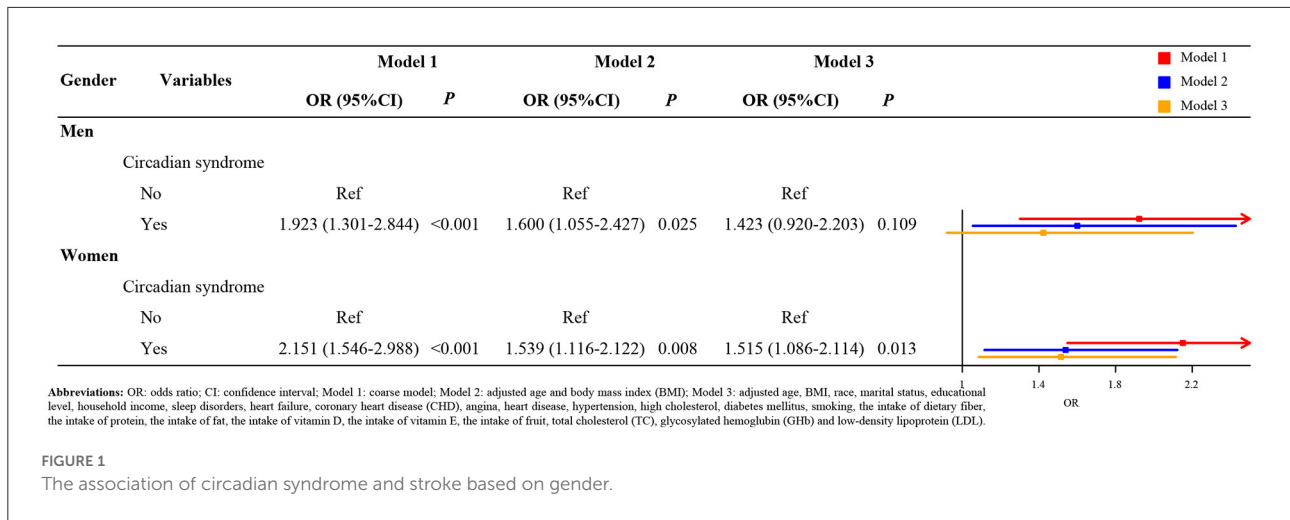
Model 3: adjusted age, BMI, race, marital status, the educational level, household income, sleep disorders, heart failure, coronary heart disease (CHD), angina, heart disease, hypertension, high cholesterol, diabetes mellitus, smoking, the intake of dietary fiber, the intake of protein, the intake of fat, the intake of vitamin D, the intake of vitamin E, the intake of fruit, total cholesterol (TC), glycosylated hemoglobin (GHb), and low-density lipoprotein (LDL).

$p > 0.05$). Similarly, from the results of the racial subgroup analysis (Figure 2), the patients with circadian syndrome had a higher risk of stroke than those without circadian syndrome only for non-Hispanic whites (Model 3: OR = 1.544, 95 CI%: 1.124–2.122, $p < 0.05$). It is worth noting that we also investigated the correlation between stroke and components associated with circadian syndrome. As shown in Figure 3, the results illustrated that the patients with circadian syndrome with the characteristic of elevated waist circumference had higher risk of stroke compared to the normal waist circumference (Model 3: OR = 1.395, 95 CI%: 1.070–1.819, $p < 0.05$); the patients with circadian syndrome with the characteristic of having short

sleep were associated with the higher risk of stroke than those without short sleep (Model 3: OR = 1.763, 95 CI%: 1.033–3.009, $p < 0.05$).

Discussion

Stroke is recognized as one of the most devastating diseases affecting human civilization, which produced a high effect on the health and quality of life for humans (23). At present, the concept of circadian syndrome has been proposed, which might bring some risk for diseases. However, there were few studies to



investigate the association of circadian syndrome and the risk of stroke to date. In this cross-sectional study, the findings showed that circadian syndrome might be associated with the incidence of stroke, especially for female patients with circadian syndrome, non-Hispanic white patients with circadian syndrome, patients with circadian syndrome, who had the characteristic of elevated waist circumference or having short sleep.

To the best of our knowledge, this is the first study conducted to explore the association of circadian syndrome and stroke. Previous studies have only focused on the impact of metabolic syndrome on the risk of stroke (24, 25). However, compared to metabolic syndrome, the circadian syndrome

included two components of short sleep and depression symptom. Several reports have illustrated that short sleep and depression symptom could increase the risk of stroke (26, 27). As expected, circadian syndrome was related to the risk of stroke in our study. Because circadian syndrome was defined as meeting at least four characteristics, we discussed the association between the number of characteristics and stroke risk. Interestingly, our study results displayed who patients with circadian syndrome composed of more than six components had a higher risk of stroke compared to the patients with circadian syndrome composed of four components (OR = 3.591, 95 CI%: 1.972–6.538). Although we obtained no significant

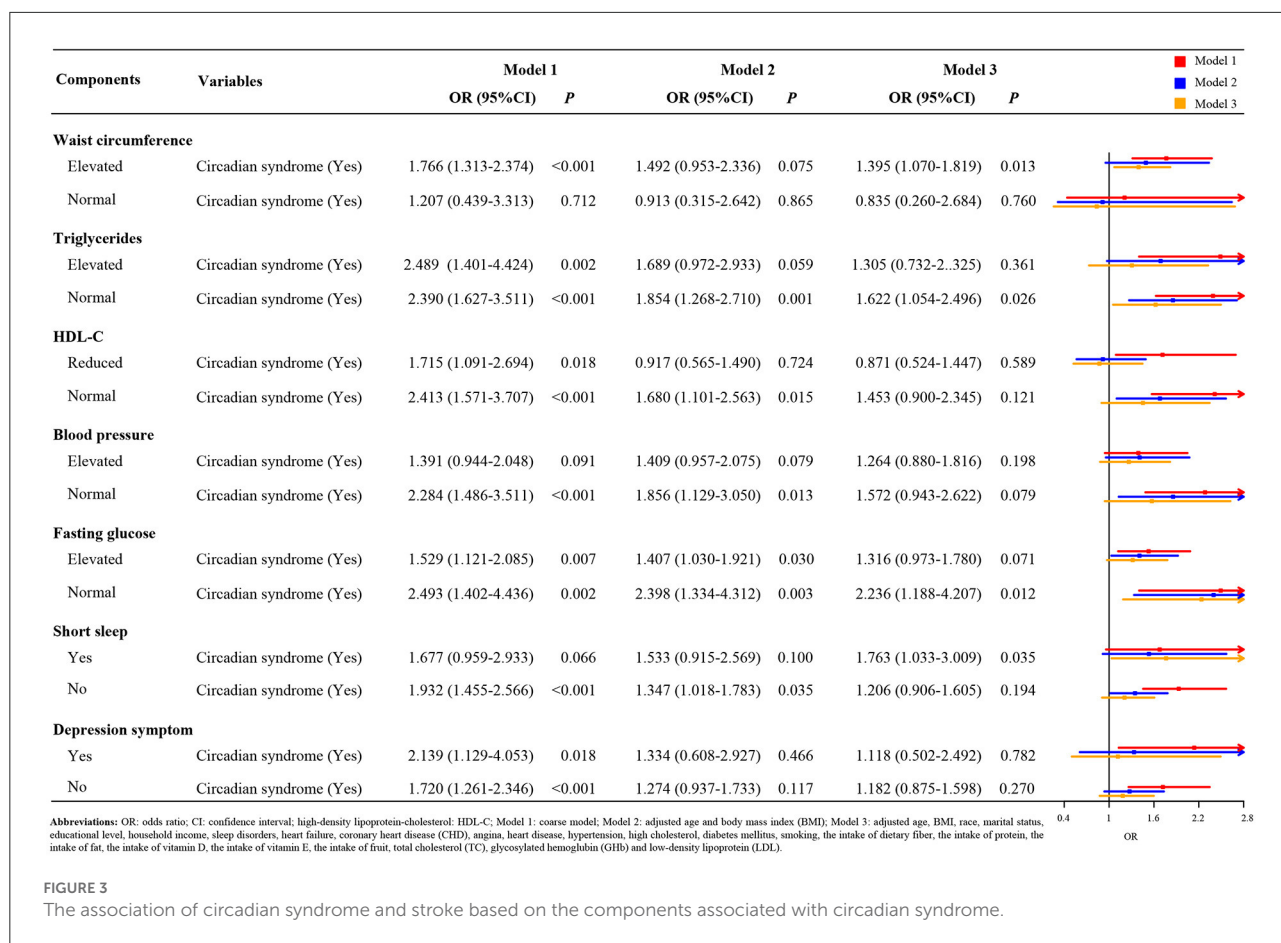


FIGURE 3 The association of circadian syndrome and stroke based on the components associated with circadian syndrome.

correlation between patients with circadian syndrome composed of five components and the prevalence of stroke ($p > 0.05$), the OR suggested that stroke risk in patients with circadian syndrome composed of five components may be higher than the circadian syndrome of four components, lower than the circadian syndrome of six components. This suggests that there might be a positive correlation between the number of components each participant with circadian syndrome and stroke experienced. In other words, the greater the number of matching characteristics in patients with circadian syndrome, the higher the risk of stroke may be. However, more prospective studies are still needed to confirm this positive association.

Additionally, the gender and race differences in the association between circadian syndrome and the risk of stroke were observed in this study. The result indicated that the association was more significant in female patients with circadian syndrome. This may be related to gender differences in arterial structure and function (28). In a stratified analysis of the seven features composed the circadian syndrome, we found that not all factors were associated with the risk of stroke; we guessed that the reason may be related to

our sample size. It is important to note that patients with circadian syndrome who had the characteristic of elevated waist circumference or short sleep seem to have higher risk on the occurrence of stroke. These findings indicated that future stroke prevention for patients with circadian syndrome may benefit from improving the sleep duration and shrinking the waist circumference, such as increase physical activity, adhere to a regular schedule, reduce the intake of high-calorie foods, and reduce sedentary time.

This study has some advantages. Firstly, our study included a relatively large sample size, which was sufficient to support our conclusion. Also, gender, race, and components were selected for subgroup analysis to provide a more detailed analysis of the impact of different populations diagnosed with circadian syndrome on the risk of stroke. However, our study has some limitations. Firstly, since this was a cross-sectional study, the causal relationship between circadian syndrome and the risk of stroke cannot be determined in this study. Secondly, we excluded some participants who had the missing information; we are not sure whether these missing cases affected the result of this study. Thirdly, the assessment of sleep duration and stroke relied on the participants' self-reported, which might

cause an information bias. Lastly, although our study has a relatively large sample size, it does not support the conclusion which factors constitute a stronger association between circadian syndrome and the risk of stroke. Thus, future studies should investigate the causal relationship between circadian syndrome and the risk of stroke in a large-scale population-based cohort study.

Conclusion

In short, circadian syndrome was associated with the risk of stroke. Of note, we should pay more close attention to the risk of stroke in those populations who are female patients with circadian syndrome, non-Hispanic white patients with circadian syndrome, and patients with circadian syndrome who had the characteristic of elevated waist circumference or having short sleep.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: <https://www.cdc.gov/nchs/nhanes/index.htm>.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the patients/participants or patients/participants legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

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Author contributions

YW and JL: designed the study. YW: wrote the manuscript. LY and YZ: collected, analyzed, and interpreted the data. JL: critically reviewed, edited, and approved the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fneur.2022.946172/full#supplementary-material>

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