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ORIGINAL RESEARCH

Associations Between Complement C4, Habitual Constipation, and Sleep Disturbance in Oldest-Old and Centenarian Chinese Adults

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Background: Sleep disturbance is an immune-related disease, and the gut–brain axis is an important regulatory pathway. This cross-sectional study was designed to address these associations between complement C4, habitual constipation, and sleep disturbance and presents a reference for prevention and treatment of sleep disturbance.

Methods: Based on the China Hainan Centenarian Cohort Study, Pittsburgh Sleep Quality Index (PSQI) was used to evaluate sleep disturbance following standard procedure. Complement C4 and habitual constipation were assessed between groups with sleep disturbance and without sleep disturbance by enzyme colorimetry and Intestinal Health Questionnaire, respectively.

Results: A total of 1621 participants were included with the prevalence of sleep disturbance being 30.41%. Complement C4 was significantly lower (24 mg/dL versus 25 mg/dL, $P < 0.05$) and habitual constipation was significantly higher (19.88% versus 14.27%, $P < 0.05$) in the group with sleep disturbance than in the group without sleep disturbance. Multiple linear regression models detected a negative association between complement C4 and PSQI (β: −0.030, 95% confidence interval [CI]: −0.052–-0.008, $P < 0.05$) and a positive association between habitual constipation and PSQI (β: 0.610, 95% CI: 0.145–1.074, $P < 0.05$). In the multiple logistic regression models, complement C4 was negatively associated with sleep disturbance (odds ratio: 0.978, 95% CI: 0.963–0.993, $P < 0.05$), and habitual constipation was positively associated with sleep disturbance (odds ratio: 1.609, 95% CI: 1.194–2.168, $P < 0.05$).

Conclusion: The present study provides epidemiological evidence that sleep disturbance is negatively associated with complement C4 and positively associated with habitual constipation in oldest-old and centenarian Chinese adults, which expands the knowledge for the associations between complement C4, habitual constipation, and sleep disturbance in the elderly population and provides new insights and pathways on the treatment of sleep disturbance by regulating immune factors and intestinal function.

Keywords: centenarian, complement C4, habitual constipation, oldest-old, sleep disturbance

Introduction

Sleep disturbance, characterized by difficulty falling asleep, decreased sleep duration, and abnormal daytime function, is becoming increasingly common worldwide. Currently, the prevalence of sleep disturbance in the elderly population

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exceeds 17%.[1] Studies have found that sleep disturbance is an important cause of physical and mental diseases; therefore, its prevention and treatment are essential for improving the quality of life and expectancy of the elderly population.[2–4] Modern researches have found that immunity is an important factor affecting sleep state.[5,6] Complement C4 regulates the body's immunity through the classical and lectin pathways of complement activation.[7,8] Furthermore, with the exploration of the gut–brain axis, it has been gradually recognized that intestinal dysfunction has an important regulatory effect on the central nervous system.[9] Habitual constipation is an important factor affecting the homeostasis of intestinal and multiple organs.[10] Previous studies have found that digestive symptoms are significantly associated with sleep disturbance.[11]

Complement C4 and habitual constipation have been realized to have close physiological connections through a variety of complex mechanisms.[12,13] Bacteria accumulate in patients with habitual constipation, affecting the immune system and inflammatory cytokines, including complement C4, and disrupts sleep quality through the gut–brain axis.[14,15] Previous studies have found that complement C4 are closely related to sleep quality of young males, and studies have also shown that individuals with habitual constipation have poorer sleep quality and more daytime dysfunction than those with normal bowel movements.[16–20] However, few studies have analyzed the relationships between complement C4, habitual constipation, and sleep disturbance in the elderly population, and there is a blank for epidemiological data and lacks research support on large samples in oldest-old and centenarian adults.[21–24] Therefore, based on the China Hainan Centenarian Cohort Study (CHCCS), the present study was designed to address the associations between complement C4, habitual constipation, and sleep disturbance in oldest-old and centenarian Chinese adults. This study filled the gap in the elderly population, provided the support with large sample data and presented a reference for prevention and treatment of sleep disturbance.

Materials and Methods

Study Population

Based on the China Hainan Centenarian Cohort Study (CHCCS), a home visit survey was conducted on all centenarians and oldest-old adults (1800 participants) residing in 18 cities and counties of Hainan Province from June 2014 to December 2016 based on a demographic list provided by the Civil Affairs Bureau. All researchers in different disciplines were well trained in a unified standard and implemented data enter, recheck and storage in a professional pattern. Questionnaire surveys and physical examinations were conducted in the form of face-to-face household surveys by strictly trained investigators using standardized protocols.[25,26] The age of 80 years and above as the standard of recruitment was determined according to the second-generation identification card and verified by the local Civil Affairs Bureau. After excluding participants with incomplete data [five participants without Pittsburgh Sleep Quality Index (PSQI), 42 participants without defecation habits, and 132 participants without complement C4], a total of 1621 participants, including 909 centenarians and 712 oldest-old adults aged 80–99 years were included in the final analysis. The protocol was approved by the Ethics Committee of Hainan Hospital of Chinese People's Liberation Army General Hospital (Sanya, Hainan; 301HNLL-2016-01), and all participants provided informed consent.

Sleep Disturbance

PSQI is a commonly used scale for sleep research both domestically and abroad, with good reliability and validity in assessing sleep quality.[27] PSQI, which consists of 18 items, was used to evaluate seven components, such as subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disorder, use of sleep medication, and daytime dysfunction.[28] Each component was divided into four levels, scored 0–3 points, and the total score of the seven components was 0–21. The reverse score was used for subjective sleep quality. Scores >7 were identified as sleep disturbance, and a higher score indicated poorer sleep quality. This study used a binary classification method and defined the corresponding cutoff value, which not only conforms to the recognized cutoff value but also comprehensively covers sleep disturbance in the elderly population.[29,30]

Habitual Constipation

Defecation habits were obtained using the National Health and Nutrition Examination Survey Intestinal Health Questionnaire in consistent with the recognized descriptions of defecation frequency and characteristics. Defecation frequency was assessed with the following question: "Are you often constipated?" and "How often have bowel movements?". Participants who had difficulty in bowel movements exerted force for each time and the interval between defecation >3 days was determined as habitual constipation.[31] Bristol Stool Form Scale with color picture cards and written descriptions of seven stool types were used to assess defecation characteristics. Based on the following questions: "What shape is your stool?", participants were considered constipated with a stool of type 1 (like a nut separated into hard lumps) or type 2 (like a sausage but lumpy).[32]

Adjusting Covariates

The investigators measured the systolic and diastolic blood pressure of the participants in a sitting position using a calibrated desktop sphygmomanometer (Yuwell Medical Equipment and Supply Co., Ltd., Jiangsu, China). Each parameter was measured twice and averaged, with at least a one-minute interval between two measurements. Venous blood samples were obtained from all participants by our professional nurses and transported within 4 h of cold storage (4°C) to the clinical laboratory. Total cholesterol, triglyceride, fasting blood glucose, immunoglobulin A, immunoglobulin G, immunoglobulin M, immunoglobulin E, complement C3, and complement C4 levels were determined by enzyme colorimetry (Roche Products Ltd., Basel, Switzerland) on a fully automatic biochemical autoanalyzer (COBAS c702; Roche Products Ltd).

Statistical Analyses

Continuous variables were described as median (interquartile range), and categorical variables were described as number (percentage). Characteristics were compared using the *t*-test for continuous variables and chi-square test for categorical variables. Multiple linear regression analyses were firstly performed with PSQI as dependent variable and with complement C4 as independent variable adjusting for age, sex, ethnicity, systolic and diastolic blood pressure, total cholesterol, triglyceride, fasting blood glucose, immunoglobulin A, immunoglobulin G, immunoglobulin M, immunoglobulin E, and complement C3, and then performed with PSQI as dependent variable and with habitual constipation as independent variable adjusting for age, sex, ethnicity, systolic and diastolic blood pressure, total cholesterol, triglyceride, and fasting blood glucose. Multiple logistic regression analyses were firstly performed with sleep disturbance as dependent variable and with complement C4 as independent variable adjusting for age, sex, ethnicity, systolic and diastolic blood pressure, total cholesterol, triglyceride, fasting blood glucose, immunoglobulin A, immunoglobulin G, immunoglobulin M, immunoglobulin E, and complement C3, and then performed with sleep disturbance as dependent variable and with habitual constipation as independent variable adjusting for age, sex, ethnicity, systolic and diastolic blood pressure, total cholesterol, triglyceride, and fasting blood glucose. There was no multicollinearity (Durbin–Watson ≈ 2) in the multiple linear regression analyses, and each variable was independent of each other (variance inflation factor < 10 for all). Model fit (Hosmer and Lemeshow test) was good ($P > 0.05$) in the multiple logistic regression analyses. Statistical analyses were conducted using Statistical Package for Social Science software (version 17.0; Chicago, IL, USA). Statistical significance was set at $P < 0.05$, and confidence interval (CI) was computed at the 95% level.

Results

A total of 1621 participants had 909 centenarians (56.08%). The median age of the study population was 100 years (range: 80–116). The prevalence of sleep disturbance was 30.41% (493 participants). As shown in Table 1, complement C4 was significantly lower (24 mg/dL versus 25 mg/dL, $P < 0.05$), and habitual constipation was significantly higher (19.88% versus 14.27%, $P < 0.05$) in the group with sleep disturbance than in the group without sleep disturbance (Figure 1).

In the multiple linear regression analyses without adjustment, complement C4 was negatively associated with PSQI (β: −0.018, 95% CI: −0.036–0.000, $P < 0.05$), and habitual constipation was positively associated with PSQI (β: 0.563,

Table 1 Basic Characteristics of Participants with and without Sleep Disturbance

Characteristics	Total Sample (n=1621)	With Sleep Disturbance (n=493)	Without Sleep Disturbance (n=1128)	P
Age (years)*	100 (85, 103)	100 (85, 103)	100 (85, 102)	0.889
Females, n %	1172 (72.30)	371 (75.25)	801 (71.01)	0.079
Ethnic Han, n %	1436 (88.59)	435 (88.24)	1001 (88.74)	0.768
Immunoglobulin A (g/dL)*	333 (253, 427)	333 (254, 428)	333 (252, 426)	0.747
Immunoglobulin G (g/dL)*	1550 (1350, 1780)	1560 (1350, 1770)	1540 (1350, 1790)	0.905
Immunoglobulin M (g/dL)*	104 (73, 142)	100 (73, 141)	104 (72, 142)	0.791
Immunoglobulin E (g/dL)*	236 (77, 757)	248 (77, 774)	235 (75, 753)	0.781
Complement C3 (mg/dL)*	102 (89, 118)	103 (89, 118)	102 (88, 119)	0.568
Complement C4 (mg/dL)*	24 (20, 30)	24 (19, 29)	25 (20, 30)	0.027
Habitual constipation, n %	259 (15.98)	98 (19.88)	161 (14.27)	0.005
Systolic blood pressure (mmHg)*	149 (133, 169)	149 (133, 170)	149 (133, 169)	0.732
Diastolic blood pressure (mmHg)*	76 (69, 86)	77 (70, 86)	76 (69, 86)	0.717
Total cholesterol (mmol/L)*	4.7 (4.2, 5.5)	4.8 (4.2, 5.5)	4.7 (4.2, 5.5)	0.457
Triglyceride (mmol/L)*	1.0 (0.8, 1.4)	1.0 (0.8, 1.4)	1.0 (0.8, 1.5)	0.826
Fasting blood glucose (mmol/L)*	4.6 (4.0, 5.6)	4.6 (4.0, 5.5)	4.6 (4.0, 5.6)	0.840

Notes *Median (interquartile range).

95% CI: 0.128–0.997, P < 0.05; Table 2). Moreover, a negative association between complement C4 and PSQI (β: −0.030, 95% CI: −0.052–-0.008, P < 0.05) and a positive association between habitual constipation and PSQI (β: 0.610, 95% CI: 0.145–1.074, P < 0.05) remained significant gradually adjusting for covariates in the multiple linear regression models.

In the multiple logistic regression analyses without adjustment, complement C4 was negatively associated with sleep disturbance [odds ratio (OR): 0.984, 95% CI 0.972–0.997, P < 0.05], and habitual constipation was positively associated with sleep disturbance (OR: 1.490, 95% CI 1.130–1.966, P < 0.05; Table 3). Moreover, a negative association between complement C4 and sleep disturbance (OR: 0.978, 95% CI: 0.963–0.993, P < 0.05) and a positive association between habitual constipation and sleep disturbance (OR: 1.609, 95% CI: 1.194–2.168, P < 0.05) remained in the same direction, gradually adjusting for covariates in the multiple logistic regression models.

Discussion

In the present study, there was a negative association between complement C4 and sleep disturbance and a positive association between habitual constipation and sleep disturbance in oldest-old and centenarian Chinese adults. Participants

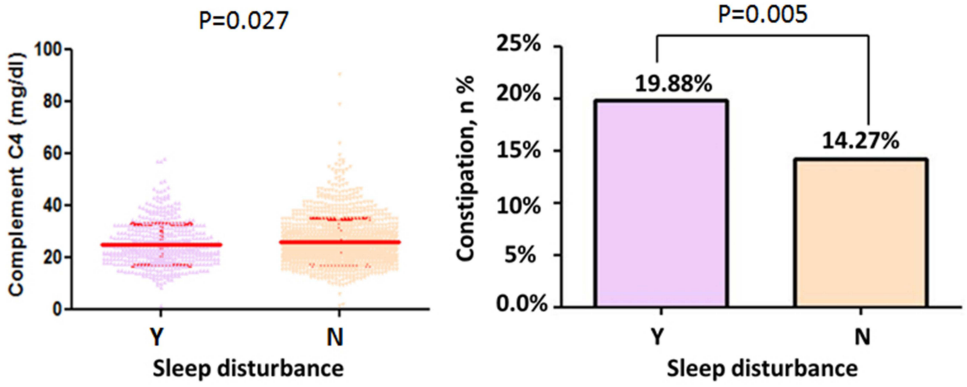

Figure 1 Complement C4 and habitual constipation of participants with and without sleep disturbance.

Table 2 Multiple Linear Regression Analyses Between Complement C4, Habitual Constipation and Pittsburgh Sleep Quality Index

Variables	Beta	95% Confidence Interval	P
Model 1			
Complement C4 (mg/dL)*	−0.018	−0.036–0.000	0.046
Habitual constipation#	0.563	0.128–0.997	0.011
Model 2			
Complement C4 (mg/dL)**	−0.020	−0.039–-0.002	0.032
Habitual constipation##	0.593	0.149–1.037	0.009
Model 3			
Complement C4 (mg/dL)***	−0.030	−0.052–-0.008	0.007
Habitual constipation###	0.610	0.145–1.074	0.010

Notes: Model 1: *With Pittsburgh Sleep Quality Index as dependent variable and with complement C4 as independent variable; #with Pittsburgh Sleep Quality Index as dependent variable and with habitual constipation as independent variable; Model 2: **With Pittsburgh Sleep Quality Index as dependent variable and with complement C4 as independent variable adjusting for age, sex, and ethnicity; ##with Pittsburgh Sleep Quality Index as dependent variable and with habitual constipation as independent variable adjusting for age, sex, and ethnicity; Model 3: ***With Pittsburgh Sleep Quality Index as dependent variable and with complement C4 as independent variable adjusting for age, sex, ethnicity, systolic and diastolic blood pressure, total cholesterol, triglyceride, fasting blood glucose, immunoglobulin A, immunoglobulin G, immunoglobulin M, immunoglobulin E, and complement C3; ###With Pittsburgh Sleep Quality Index as dependent variable and with habitual constipation as independent variable adjusting for age, sex, ethnicity, systolic and diastolic blood pressure, total cholesterol, triglyceride, and fasting blood glucose.

Table 3 Multiple Logistic Regression Analyses Between Complement C4, Habitual Constipation and Sleep Disturbance

Variables	Odds Ratio	95% Confidence Interval	P
Model 1			
Complement C4 (mg/dL)*	0.984	0.972–0.997	0.013
Habitual constipation#	1.490	1.130–1.966	0.005
Model 2			
Complement C4 (mg/dL)**	0.983	0.970–0.995	0.008
Habitual constipation##	1.555	1.170–2.067	0.002
Model 3			
Complement C4 (mg/dL)***	0.978	0.963–0.993	0.004
Habitual constipation###	1.609	1.194–2.168	0.002

Notes: Model 1: *With sleep disturbance as dependent variable and with complement C4 as independent variable; #With sleep disturbance as dependent variable and with habitual constipation as independent variable; Model 2: **With sleep disturbance as dependent variable and with complement C4 as independent variable adjusting for age, sex, and ethnicity; ##with sleep disturbance as dependent variable and with habitual constipation as independent variable adjusting for age, sex, and ethnicity; Model 3: ***With sleep disturbance as dependent variable and with complement C4 as independent variable adjusting for age, sex, ethnicity, systolic and diastolic blood pressure, total cholesterol, triglyceride, fasting blood glucose, immunoglobulin A, immunoglobulin G, immunoglobulin M, immunoglobulin E, and complement C3; ###With sleep disturbance as dependent variable and with habitual constipation as independent variable adjusting for age, sex, ethnicity, systolic and diastolic blood pressure, total cholesterol, triglyceride, and fasting blood glucose.

with lower complement C4 levels and a higher prevalence of habitual constipation were more prone to sleep disturbance in the elderly population.

Complement C4 is an important immune mediator. Inflammatory cytokines have been reported to be associated with sleep quality.[33,34] However, the relationship between complement C4 and sleep quality remains controversial. A previous study has found that proinflammatory complement C4 was associated with poor sleep quality and short sleep duration.[35] In contrast, other studies have concluded that sleep is associated with increased complement activation at night, reflected in elevated complement C3, and sleep deprivation prevents this activation.[16] In addition, a study of male college students

has shown that higher complement C4 and C3 levels could predict longer sleep duration.[36] The present study with large sample demonstrated a negative association between complement C4 and sleep disturbance in oldest-old and centenarian Chinese adults. The discrepancies for these results might be related to the divergence in study samples from different regions and populations and functional roles of complement C4 and C3.

In addition, we confirmed that habitual constipation was an important factor associated with sleep quality in oldest-old and centenarian Chinese adults. A previous study has found that people with normal stool had better sleep quality, whereas those with defecation difficulty had higher PQSI, suggesting poorer sleep quality.[17] Another study has realized that sleep disturbance group had significantly higher rate of habitual constipation compared with normal sleep group.[18] At the same time, several studies have found that constipation and insomnia often co-occur.[19] A study of elderly women has shown that poor sleep quality is a significant factor associated with habitual constipation.[20] Also studies have found that probiotic bacteria could improve brain function and life quality in the elderly population through neural regulation mechanisms of the gut–brain axis.[37–40]

The mechanisms of associations between complement C4, habitual constipation, and sleep disturbance are still unclear, but some studies have shown that they might be related to inflammatory reactions and gut–brain axis.[14,15] Previous study has shown that complement components including complement C4 and C3 contribute to slow-wave sleep, one of the deepest forms of sleep.[41] A study has found that intestinal flora such as Prevotella leads to the damage of sleep structure through the microbial-gut–brain axis.[42] Intestinal flora affects immune and inflammatory reactions of the body and intervenes in sleep function through the gut-brain axis. Animal experiments have shown that intestinal probiotics could restore the resting state of microglia, promote neuroinflammation normalization and improve brain dysfunction.[43]

While highlighting the findings of the present study, there was one limitation. This study was based on the elderly Chinese population (oldest-old and centenarian adults), so the popularization of research conclusion needs to be further demonstrated in other populations.

Conclusions

The present study provides epidemiological evidence that sleep disturbance is negatively associated with complement C4 and positively associated with habitual constipation in oldest-old and centenarian Chinese adults, which expands the knowledge for the associations between complement C4, habitual constipation, and sleep disturbance in the elderly population and provides new insights and pathways on the treatment of sleep disturbance by regulating immune factors and intestinal function. Future research should explore the interventions involving complement C4 and intestinal health to improve sleep disturbance and focus on the beneficial effects of probiotic bacteria on intestinal, immune and sleep functions in the elderly population.

Data Sharing Statement

All data and material are available under the requirements of the corresponding authors.

Ethics Approval and Consent to Participate

The current study was approved by the Ethics Committee of Hainan Hospital of Chinese People's Liberation Army General Hospital (Sanya, Hainan; Number: 301HNLL-2016-01). Prior to the current study, written informed consent was obtained from all participants. The current study complied with the Declaration of Helsinki.

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Disclosure

The authors declare no conflicts of interest in this work.

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