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RESEARCH ARTICLE

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The circadian syndrome is a predictor for cognition impairment in middle-aged adults: Comparison with the metabolic syndrome

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Abstract

Aims: Circadian syndrome (CircS) is considered a better predictor for cardiovascular disease than the metabolic syndrome (MetS). We aim to examine the associations between CircS and MetS with cognition in Chinese adults.

Method: We used the data of 8546 Chinese adults aged ≥40 years from the 2011 China Health and Retirement Longitudinal Study. MetS was defined using harmonised criteria. CircS included the components of MetS plus short sleep and depression. The cut-off for CircS was set as ≥4. Global cognitive function was assessed during the face-to-face interview.

Results: CircS and MetS had opposite associations with the global cognition score and self-reported poor memory. Compared with individuals without the CircS and MetS, the regression coefficients (95%CI) for global cognition score were −1.02 (−1.71 to −0.34) for CircS alone and 0.52 (0.09 to 0.96) for MetS alone in men; −1.36 (−2.00 to −0.72) for CircS alone and 0.60 (0.15 to 1.06) for MetS alone in

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women. Having CircS alone was 2.53 times more likely to report poor memory in men (95%CI 1.80–3.55) and 2.08 times more likely in women (95%CI 1.54–2.81). In contrast, having MetS alone was less likely to report poor memory (OR 0.64 (0.49–0.84) in men and 0.65 (0.52–0.81) in women). People with CircS and MetS combined were more likely to have self-reported poor memory.

Conclusions: CircS is a strong and better predictor for cognition impairment than MetS in Chinese middle-aged adults. MetS without short sleep and depression is associated with better cognition.

KEYWORDS
adults, Chinese, circadian syndrome, cognition, memory, metabolic syndrome, sleep

1 | INTRODUCTION

The prevalence of dementia, a condition characterised by cognitive decline, has significantly increased globally. This is pertinent in low-income and middle-income countries due to population ageing and the heavy burden of modifiable risk factors.[1,2] It was estimated to affect 35.6 million individuals worldwide in 2010, and by 2050, that number is expected to rise to 115.4 million.[1] In China, it was reported that the prevalence of mild cognitive impairment, a precursor of dementia, among people aged 55 years and older, was 15.4%.[3] Furthermore, the overall prevalence of dementia in China was 4.22% in adults aged 60 years and older, with women having a 3-fold higher likelihood than men.[4] Cognitive function plays a critical role in daily life and is associated with various factors such as ageing, lifestyle, and health status. Cognitive decline is already evident in middle-aged adults.[5] Identifying modifiable risk factors for cognitive impairment is the key to the prevention of dementia.

The metabolic syndrome (MetS) is a cluster of conditions that increases the risk of cardiovascular diseases (CVD).[6] The components of the MetS include high blood pressure, elevated blood glucose, central obesity, and dyslipidaemia (raised triglycerides and reduced level of high-density lipoprotein (HDL) cholesterol); these conditions have been found to be associated with an increased risk of cognitive decline and dementia. The association between MetS and cognitive decline is however inconclusive.[7] Several studies have shown that people with MetS are more likely to experience cognitive impairment and an increased risk of developing dementia compared with those without MetS. MetS has been shown to be associated with poor self-reported health.[8] Findings from the Israel Diabetes and Cognitive Decline study suggested that self-reported poor health was associated with a faster decline in global cognition among older adults with type 2 diabetes.[9] A recent systematic review by Koutsonida et al. examined the association between MetS and cognitive decline in distinct cognitive domains.[10] The review found that most studies did not find statistically significant results for most cognitive domains and decline in specific cognitive domains was not consistently associated with the presence of MetS.

Like MetS, the circadian syndrome (CircS) was recently shown to contribute to the development of CVD. The concept of CircS was first proposed by Zimmet et al.[11] It relates to the disruption of circadian rhythm caused by modern lifestyle factors such as shift work, artificial light exposure, and physical inactivity.[11] Based on this concept, two additional components, short sleep and depression, have been added to the components of MetS to define CircS in epidemiological studies.[12,13] We have previously reported that CircS improves CVD prediction when compared to MetS in Chinese and US populations.[12,13] Furthermore, a recent study in China found that CircS mediates the association between air pollution and CVD.[14]

It is well known that CVD is a significant risk factor for cognitive decline and/or dementia.[15] Dementia and CVD share most common risk factors including high blood pressure, blood lipids, diabetes, obesity, smoking, and unhealthy lifestyle.[16,17] Short sleep and depression have been associated with poor cognitive function.[18–20] Thus far, no study has examined the association between CircS and cognitive function. Using data from China Health and Retirement Longitudinal Study (CHARLS), we examine whether CircS indices improved cognition prediction than MetS alone.

2 | METHOD

2.1 | Study sample

The study was conducted as part of the CHARLS, which surveyed adults aged 45 years and above across 28 provinces in China.[21,22] Some participants aged 40–44 years also took part in the baseline examination. The study was approved by the Peking University institutional review board and all participants provided informed consent. The current study used data from the 2011 baseline survey.

A total of 17,708 participants completed a face-to-face interview at baseline. Trained health workers measured height, weight, waist circumference, and blood pressure and collected fasting blood samples for glucose and lipid analysis. The response rate was 80.5%. The current analysis included data from 8546 participants aged 40 years and above, including 3952 men and 4594 women, as shown in Figure 1.

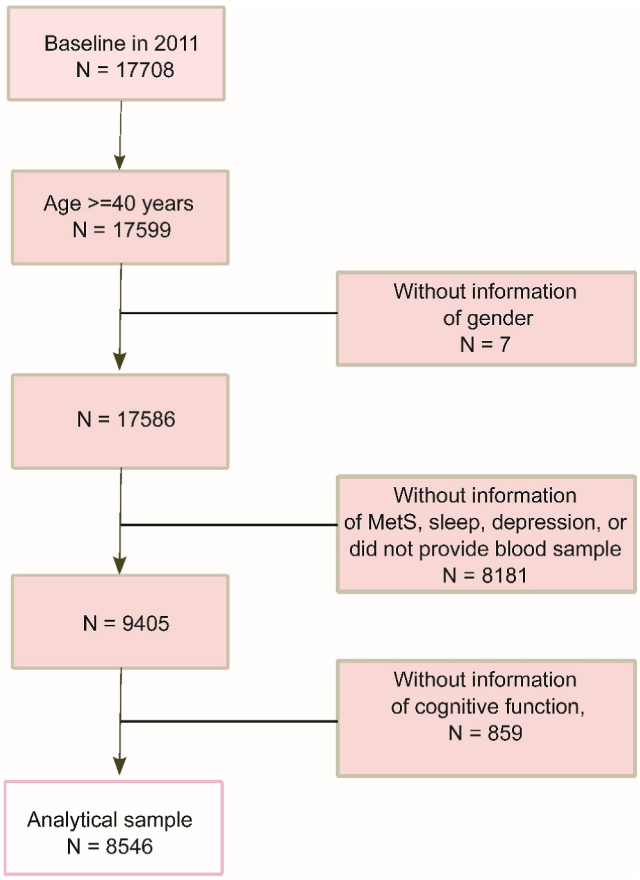

FIGURE 1 Flowchart of the study cohort.

2.2 | Exposure variables: Metabolic syndrome and circadian syndrome

Fasting blood samples were collected and stored at −70°C at the Chinese Centre for Disease Control and Prevention. Biomarkers including high-sensitivity C-reactive protein, total HDL and low-density lipoprotein (LDL) cholesterol, triglycerides, glycated haemoglobin (HbA1c), fasting plasma glucose, and haemoglobin were analysed at the Younanmen Centre for Clinical Laboratory of Capital Medical University. Quality control samples were used daily to ensure accurate results.

Blood pressure was measured by trained nurses using an HEM-7200 electronic monitor (Omron, Dalian) while the participant was seated. The average of three readings was used, and hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, or the use of antihypertensive medication.

Depressive symptoms were assessed using the ten-question version of the Centre for Epidemiologic Studies-Depression scale (CES-D). Participants with a CES-D score of ≥10 were defined as having depressive symptoms.

2.2.1 | Metabolic syndrome

MetS was defined based on the following index.[6] A participant was considered to have MetS if he/she had ≥3 of the following components: elevated waist circumference (≥85 cm in men, ≥80 cm in women), elevated blood pressure (systolic ≥130 and/or diastolic ≥85 mm Hg) or treatment for hypertension, elevated fasting glucose (≥100 mg/dL, or treatment for diabetes), high LDL cholesterol (≥130 mg/dL) or treatment for high LDL, low HDL cholesterol (<40 mg/dL in men, <50 mg/dL in women), and high triglycerides (≥150 mg/dL) or treatment for high triglycerides. Treatment for abnormal blood lipids was based on self-reported use of Western medication.

2.2.2 | Circadian syndrome

CircS was defined based on seven components, including short sleep (<6 h/day), depression, and five components used to define MetS.[12,13] A person with a score of ≥4 components was considered as having CircS. For each person, a third variable based on MetS and CircS was created with the following potential values: normal, MetS alone, CircS alone, or both MetS and CircS combined.

2.3 | Outcome variables: Cognitive function

Cognitive function consisted of both global cognition score and self-reported memory.

Global cognition was measured using components of the Telephone Interview of Cognitive Status (TICS) battery during a face-to-face interview.[22] The interview covers several components of cognition function, including memory, orientation, mental intactness, and attention. Memory was tested through immediate and delayed word recall tests. In the tests, participants were asked to repeat 10 Chinese nouns without order and then again after a 5-min interval (0–10 scores). Orientation was assessed by examining the participants' recognition of the date, month, year and day of the week (0–4 scores). Visuoconstruction was evaluated by having individuals redraw an overlapping pentagon picture (0–1 score). Numeric ability was measured through serial subtraction of 7 from 100 (0–5 scores). The total cognitive function score ranged from 0 to 30, with higher scores indicating improved cognitive function. Of the TICS has an excellent sensitivity (>99%) and specificity (86%) in the screening and detection of Alzheimer's disease (AD).[23] The Chinese version of TICS has been reported in our previous studies[24,25] and other studies.[26–28]

Self-rated memory was assessed based on the following question: "How would you rate your memory at the present time? Would you say it is excellent, very good, good, fair or poor?" Individuals who reported 'poor' were defined as having a self-reported poor memory.

2.4 | Statistical analyses

Multivariable linear regression and logistic regression analyses were used to examine the associations between MetS and CircS or individual components of CircS and cognitive function/self-reported poor memory. In the multivariable models, age, education, smoking, alcohol

TABLE 1 Sample characteristics by MetS and CircS status among adults aged above 40 years attending the China Health and Retirement Longitudinal Study in 2011 (n = 8456).

	Total N = 8546	Normal N = 4327	CircS alone N = 366	MetS alone N = 904	MetS and CircS N = 2949	p-value
Age (years)	58.8 (9.3)	58.4 (9.4)	60.2 (9.5)	58.0 (9.1)	59.5 (9.2)	<0.001
Gender						<0.001
Male	3952 (46.2%)	2477 (57.2%)	156 (42.6%)	432 (47.8%)	887 (30.1%)	
Female	4594 (53.8%)	1850 (42.8%)	210 (57.4%)	472 (52.2%)	2062 (69.9%)	
Education						<0.001
Illiterate	3819 (44.7%)	1838 (42.5%)	219 (59.8%)	334 (36.9%)	1428 (48.4%)	
Primary school	1994 (23.3%)	1072 (24.8%)	67 (18.3%)	201 (22.2%)	654 (22.2%)	
Middle school	1810 (21.2%)	951 (22.0%)	63 (17.2%)	235 (26.0%)	561 (19.0%)	
High school or above	922 (10.8%)	466 (10.8%)	17 (4.6%)	134 (14.8%)	305 (10.3%)	
Residence						<0.001
Rural	5409 (63.3%)	2965 (68.5%)	271 (74.0%)	516 (57.1%)	1657 (56.2%)	
Urban	3137 (36.7%)	1362 (31.5%)	95 (26.0%)	388 (42.9%)	1292 (43.8%)	
Smoking						<0.001
Yes	3337 (39.1%)	2030 (46.9%)	146 (39.9%)	352 (38.9%)	809 (27.4%)	
No	5208 (60.9%)	2296 (53.1%)	220 (60.1%)	552 (61.1%)	2140 (72.6%)	
Drinking						<0.001
None drinker	4603 (53.9%)	1985 (45.9%)	206 (56.3%)	471 (52.1%)	1941 (65.8%)	
Ex-drinker	1161 (13.6%)	647 (15.0%)	47 (12.8%)	118 (13.1%)	349 (11.8%)	
Current drinker	2782 (32.6%)	1695 (39.2%)	113 (30.9%)	315 (34.8%)	659 (22.3%)	
Physical activity						<0.001
Active	2072 (24.2%)	1157 (26.7%)	89 (24.3%)	240 (26.5%)	586 (19.9%)	
Less active	5236 (61.3%)	2685 (62.1%)	222 (60.7%)	530 (58.6%)	1799 (61.0%)	
Sedentary	1238 (14.5%)	485 (11.2%)	55 (15.0%)	134 (14.8%)	564 (19.1%)	
BMI (kg/m^2)	23.6 (3.9)	22.1 (3.3)	22.6 (3.2)	24.9 (3.6)	25.7 (3.8)	<0.001
Systolic BP (mmHg)	130.5 (21.4)	124.3 (19.4)	131.3 (21.8)	135.0 (20.5)	138.4 (21.6)	<0.001
Diastolic BP (mmHg)	76.0 (12.2)	72.9 (11.3)	75.5 (11.8)	78.6 (11.8)	80.0 (12.2)	<0.001
High sensitivity CRP (mg/dL)	1.05 (0.55–2.18)	0.82 (0.47–1.73)	0.92 (0.51–2.2)	1.15 (0.62–2.265)	1.39 (0.75–2.81)	<0.001
CVD	1219 (14.3%)	400 (9.3%)	67 (18.4%)	90 (10.0%)	662 (22.5%)	<0.001
Hypertension	3426 (41.0%)	1007 (23.4%)	159 (44.3%)	428 (48.6%)	1832 (65.2%)	<0.001
CKD	929 (14.5%)	430 (13.3%)	72 (26.1%)	76 (11.5%)	351 (15.8%)	<0.001
Anaemia	1049 (12.6%)	623 (14.7%)	54 (14.9%)	93 (10.4%)	279 (9.8%)	<0.001
Central obesity	4494 (52.6%)	1118 (25.8%)	173 (47.3%)	658 (72.8%)	2545 (86.3%)	<0.001
Heart problems	1080 (12.7%)	354 (8.2%)	56 (15.3%)	82 (9.1%)	588 (20.0%)	<0.001
Stroke	189 (2.2%)	53 (1.2%)	12 (3.3%)	10 (1.1%)	114 (3.9%)	<0.001
Elevated glucose	5068 (59.3%)	1696 (39.2%)	211 (57.7%)	660 (73.0%)	2501 (84.8%)	<0.001
Elevated triglycerides	2602 (30.4%)	255 (5.9%)	37 (10.1%)	295 (32.6%)	2015 (68.3%)	<0.001
Elevated blood pressure	4652 (54.4%)	1464 (33.8%)	209 (57.1%)	618 (68.4%)	2361 (80.1%)	<0.001
Reduced HDL-C	3623 (42.4%)	638 (14.7%)	102 (27.9%)	481 (53.2%)	2402 (81.5%)	<0.001
Depression	3201 (37.5%)	1406 (32.5%)	366 (100.0%)	0 (0.0%)	1429 (48.5%)	<0.001

TABLE 1 (Continued)

	Total N = 8546	Normal N = 4327	CircS alone N = 366	MetS alone N = 904	MetS and CircS N = 2949	p-value
Short sleep	2541 (29.7%)	1044 (24.1%)	366 (100.0%)	0 (0.0%)	1131 (38.4%)	<0.001
Circadian syndrome	3315 (38.8%)	0 (0.0%)	366 (100.0%)	0 (0.0%)	2949 (100.0%)	<0.001
Metabolic syndrome	3853 (45.1%)	0 (0.0%)	0 (0.0%)	904 (100.0%)	2949 (100.0%)	<0.001
Self-reported poor memory	3028 (35.4%)	1432 (33.1%)	208 (56.8%)	211 (23.4%)	1177 (39.9%)	<0.001
Global cognition score	13.5 (5.3)	13.7 (5.1)	11.4 (5.2)	14.7 (5.2)	13.1 (5.3)	<0.001

Note: Values are mean (SD), median (inter quartile range) or *n* (%).

Abbreviations: BMI, body mass index; CircS, circadian syndrome; CKD, chronic kidney disease; CVD, cardiovascular diseases; MetS, metabolic syndrome.

drinking, physical activity and residence (urban/rural) were adjusted as confounding factors. Considering that anaemia and CVD could be potential confounding factors, we further adjusted for them in another multivariate model. Gender-specific analyses were conducted. All analyses were conducted using STATA 17.0 (Stata Corporation). Statistical significance was considered when $p < 0.05$ (two sided).

3 | RESULTS

The mean age of the participants was 58.8 (SD 9.3) years (Table 1). The prevalence of CircS and MetS was 38.8% and 45.1%, respectively. In total, 366 (4.3%) and 904 (10.6%) individuals had the CircS or the MetS alone, respectively, while 2949 (34.5%) had the CircS and MetS combined. The MetS alone group was younger than the other categories and had the lowest prevalence of self-reported poor memory reported at 23.4% and the highest global cognition score (14.7 (5.2)).

3.1 | Global cognition score

CircS and MetS had opposite associations with global cognition scores (Table 2). CircS was associated with a lower global cognition score compared with those without the condition. CircS had a regression coefficient (β) of −0.43 (95%CI −0.63 to −0.23) in men and women. However, MetS was directly associated with the global cognition score with a β of 0.49 (95%CI 0.28 to 0.71) after adjusting for age. Compared with individuals without CircS and MetS, the regression coefficients for global cognition score in men were −1.02 (−1.71 to −0.34) for CircS alone and 0.52 (0.09 to 0.96) for MetS alone and in women −1.36 (−2.00 to −0.72) for CircS alone and 0.60 (0.15 to 1.06) for MetS alone (Table 3). Further adjustment for anaemia and CVD as potential confounders did not change the above associations.

3.2 | Memory

Having CircS alone was 2.53 times more likely to report poor memory in men (95%CI 1.80–3.55) and 2.08 times more likely to report poor memory in women (95%CI 1.54–2.81), as shown in Table 4. In contrast, having MetS alone was less likely to report poor memory in men (OR 0.64 (95%CI 0.49–0.84)) and in women (OR 0.65 (95%CI 0.52–0.81)). Having both CircS and MetS had a slightly higher likelihood of having self-reported poor memory in both sexes than the normal subjects. The above associations did not change after further adjustment for anaemia and CVD (model 3).

MetS alone and CircS alone were associated with memory score, especially in women (Supplemental Table S1). Specifically, MetS alone was directly associated but CircS alone was inversely associated with memory.

3.3 | Individual components of CircS and cognition

We further examined the association between individual components of CircS and cognitive function. Central obesity was directly associated with the global cognitive function score, that is, lean people had poorer cognitive function, but short sleep and depression were inversely associated with the score (Supplemental Table S2). People with short sleep and depression reported more often self-reported poor memory (Supplemental Table S3).

4 | DISCUSSION

In this large population-based study with middle-aged Chinese adults, we investigated the effects of both CircS and MetS on cognitive functions. The results suggested that the CircS and MetS had opposite associations with a global cognition score and self-reported poor memory in Chinese adults. Compared with people without CircS or MetS, those having CircS alone were more likely (>2*X*) to report a poor memory in both genders. In contrast, those having MetS alone were less likely to report poor memory. People having both CircS and MetS combined had the highest likelihood of having self-reported poor memory and a lower global cognition score. The association between individual components of CircS and cognition varied.

TABLE 2 Association (regression coefficient; 95% confidence interval) between MetS and CircS with the global cognitive function score among adults attending the China Health and Retirement Longitudinal Study.

	MetS	*p* value	CircS	*p* value
Both genders				
Model 1[a]	**0.49 (0.28 to 0.71)**	<0.001	−0.31 (−0.53 to −0.08)	<0.001
Model 2[b]	0.07 (−0.12 to 0.27)	0.462	−0.43 (−0.63 to −0.23)	<0.001
Model 3[c]	0.09 (−0.11 to 0.29)	0.377	−0.43 (−0.63 to −0.22)	<0.001
Men				
Model 1[a]	**0.79 (0.48 to 1.09)**	<0.001	0.06 (−0.27 to 0.38)	0.730
Model 2[b]	**0.35 (0.07 to 0.64)**	0.016	−0.09 (−0.39 to 0.21)	0.565
Model 3[c]	**0.38 (0.09 to 0.67)**	0.011	−0.08 (−0.39 to 0.24)	0.630
Women				
Model 1[a]	**0.31 (0.01 to 0.61)**	0.045	**−0.52 (-0.82 to -0.21)**	**<0.001**
Model 2[b]	−0.05 (−0.32 to 0.21)	0.688	**−0.61 (-0.87 to -0.34)**	**<0.001**
Model 3[c]	−0.04 (−0.32 to 0.23)	0.750	**−0.60 (-0.87 to -0.33)**	**<0.001**

Note: Values are regression coefficients (95%CI) derived from multivariable linear regression models. A positive regression coefficient means a better cognitive function. Bold values represent statistically significant values.

Abbreviations: CircS, circadian syndrome; CVD, cardiovascular diseases; MetS, metabolic syndrome.

[a]Model 1 adjusted for age, sex (except in specific analyses).

[b]Model 2 further adjusted for education, physical activity, smoking, and alcohol drinking and residence (urban or rural).

[c]Model 3 further adjusted for anaemia and CVD.

TABLE 3 Association between MetS and CircS status and global cognitive function among adults attending the China Health and Retirement Longitudinal Study.

	Health indicators			
	Normal	CircS alone	MetS alone	CircS and MetS
Both genders				
Model 1[a]	0.00	**−1.71 (-2.23 to -1.19)**	**1.09 (0.74 to 1.44)**	0.10 (−0.14 to 0.34)
Model 2[b]	0.00	**−1.19 (-1.66 to -0.72)**	**0.55 (0.23 to 0.86)**	**−0.22 (-0.43 to -0.00)**
Model 3[c]	0.00	−1.17 (−1.64 to −0.70)	0.54 (0.22 to 0.86)	−0.21 (−0.43 to 0.01)
Men				
Model 1[a]	0.00	**−1.60 (-2.34 to -0.86)**	**1.03 (0.56 to 1.50)**	0.53 (0.18 to 0.88)
Model 2[b]	0.00	**−1.02 (-1.71 to -0.34)**	**0.52 (0.09 to 0.96)**	0.18 (−0.15 to 0.51)
Model 3[c]	0.00	−1.01 (−1.70 to −0.32)	0.54 (0.10 to 0.98)	0.21 (−0.14 to 0.55)
Women				
Model 1[a]	0.00	**−1.85 (-2.58 to -1.11)**	**1.12 (0.61 to 1.64)**	−0.12 (−0.45 to 0.20)
Model 2[b]	0.00	**−1.36 (-2.00 to -0.72)**	**0.60 (0.15 to 1.06)**	**−0.39 (-0.68 to -0.10)**
Model 3[c]	0.00	**−1.33 (-1.98 to -0.69)**	**0.58 (0.12 to 1.04)**	**−0.38 (-0.68 to -0.09)**

Note: Values are regression coefficients (95%CI) derived from multivariable linear regression models. A positive regression coefficient means a better cognitive function. Bold values represent statistically significant values.

Abbreviations: CircS, circadian syndrome; CVD, cardiovascular diseases; MetS, metabolic syndrome.

[a]Model 1 adjusted for age, sex (except in specific analyses).

[b]Model 2 further adjusted for education, physical activity, smoking, and alcohol drinking and residence (urban or rural).

[c]Model 3 further adjusted for anaemia and CVD.

TABLE 4 Association between MetS and CircS status and self-reported poor memory among adults attending the China Health and Retirement Longitudinal Study.

	Health indicators			
	Normal	CircS alone	MetS alone	CircS and MetS
Both genders				
Model 1[a]	1.00	**2.44 (1.96 to 3.04)**	**0.59 (0.50 to 0.70)**	**1.17 (1.05 to 1.29)**
Model 2[b]	1.00	**2.28 (1.82 to 2.85)**	**0.65 (0.55 to 0.77)**	**1.27 (1.15 to 1.42)**
Model 3[c]	1.00	**2.23 (1.78 to 2.79)**	**0.66 (0.55 to 0.78)**	**1.21 (1.09 to 1.35)**
Men				
Model 1[a]	1.00	**2.75 (1.98 to 3.83)**	**0.56 (0.43 to 0.72)**	**1.31 (1.11 to 1.54)**
Model 2[b]	1.00	**2.53 (1.80 to 3.55)**	**0.64 (0.49 to 0.84)**	**1.54 (1.30 to 1.83)**
Model 3[c]	1.00	**2.50 (1.78 to 3.52)**	**0.64 (0.49 to 0.84)**	**1.45 (1.21 to 1.74)**
Women				
Model 1[a]	1.00	**2.20 (1.65 to 2.95)**	**0.61 (0.49 to 0.76)**	1.11 (0.97 to 1.26)
Model 2[b]	1.00	**2.08 (1.54 to 2.81)**	**0.65 (0.52 to 0.81)**	**1.16 (1.01 to 1.33)**
Model 3[c]	1.00	**2.01 (1.49 to 2.72)**	**0.66 (0.53 to 0.83)**	**1.11 (0.96 to 1.27)**

Note: Values are odds ratios (95%CI) derived from multivariable logistic regression models. Bold values represent statistically significant values.

Abbreviations: CircS, circadian syndrome; CVD, cardiovascular diseases; MetS, metabolic syndrome.

[a]Model 1 adjusted for age, sex (except in specific analyses).

[b]Model 2 further adjusted for education, physical activity, smoking, and alcohol drinking and residence (urban or rural).

[c]Model 3 further adjusted for anaemia and CVD.

4.1 | CircS, MetS, and cognition

This is the first study that examined the association between CircS and cognition. We found that CircS alone has a negative impact on global cognitive function and that people with CircS alone were more than twice more likely to report poor memory compared to individuals with normal health status. On the other hand, individuals with MetS alone did not show a decrease in the global cognitive function and they reported approximately 50% less poor memory compared to individuals with normal health status. Direct comparison of our results with those from other studies is not possible, but findings on the association between components of CircS and MetS with cognition can be found in the literature.[10,29,30] In 2014, a meta-analysis of 13 longitudinal studies found that age modified the association between MetS and cognitive decline.[29] In the older age group (>70 years), there was no significant association between MetS and cognitive decline, whereas a marginal significant association between MetS and cognitive decline was observed in the younger age group (≤70 years). The latest systematic review in 2022 which included 30 studies reported that most of the studies did not find a significant association between MetS and individual cognitive domains.[10] Results of studies in China examining the association between MetS and cognitive function remain inconsistent, with some studies finding a direct association[30] but other studies showing inverse[31] or no association.[32]

Although no previous study has reported a relationship between CircS and cognition, the individual components of CircS have been implicated to predict cognitive function. Sleep disturbances, such as insomnia and sleep apnea, have been associated with cognitive decline in middle-aged and older adults.[19,33] Furthermore, an association between sleep disorder and cognitive impairment was found in a meta-analysis which included 18 cohort studies with 246,786 individuals.[34] Moreover, depression is a risk factor for dementia and cognitive decline.[35] Indeed, depression was found to predict cognitive decline specifically in individuals with an above average allostatic load.[36] Furthermore, the direct association between obesity and global cognition score is consistent with other studies in China[37–39] and elsewhere. For example, in Finland, it was shown that obesity at midlife increases the risk of dementia and AD at late-life.[40] Furthermore, the clustering of vascular risk factors has an additive effect on the risk of AD.[16]

4.2 | Potential mechanisms

The exact biological and physiological mechanisms driving both CircS and MetS association with cognition are not clear. However, individual components of CircS and MetS may contribute directly or synergistically to impaired cognitive function.

4.2.1 | CircS and cognition

In our study, the main drivers of the positive association between CircS and poor cognition were short sleep duration and depression. As an additional key component of CircS, sleep is essential for

consolidating memory and regulating multiple aspects of cognition,[41] as well as normal brain functioning, and sleep disturbance could interfere with the function of neuronal pathways, which can lead to alternated neurotransmitter activity and impaired synaptic plasticity.[42] Laboratory controlled sleep study showed that two nights of recovery sleep after total sleep deprivation, although found to restore hippocampal connectivity, was still not able to recover episodic memory.[43] Other potential mechanisms linking sleep disturbances and dementia in older adults include increased sleep fragmentation and hypoxia, which may raise the level of several biomarkers of AD, including amyloid-β concentrations, amyloid plaques in the brain, and tau phosphorylation.[44,45] Furthermore, depression is associated with an increased risk of dementia incidence. Based on a meta-analysis of 32 cohort studies from high income countries with 62,598 participants being followed from 2 to 17 years (median 5 years), depression was identified as a risk factor for dementia (pooled effect size 1.97, 95%CI 1.67–2.32).[20] Both structural and functional brain abnormalities of depression have contributed to cognitive deficits in patients with depression, including biased attention, processing, rumination, and memory.[46] Additionally, inflammation and insulin resistance, the common risk factors for obesity and depression,[47] are associated with cognitive impairment.[48,49] It is worth noting that both depression and sleep disorders independently contribute to cognitive decline.[50,51] Hence, the predicting performance of sleep, depression alone, and their combination could be compared against that of CircS to further dissect the roles each component plays in cognitive decline. In addition, preclinical dementia can also cause depressed mental status and sleep conditions and mental health and sleep, leading to a potential bidirectional link between sleep, depression, and dementia.[52,53] While cross-sectional studies may be unable to tease out the complex interplay among these variables, future research with longitudinal design holds promise in further delineating their relationships.

4.2.2 | MetS and cognition

The main driver of the positive association between MetS and cognitive function in our study was obesity. Although overnutrition may lead to the MetS and other physical disorders such as diabetes mellitus, it does not necessarily have negative effects on cognition because good quality fat and protein are brain food.

Different from the Western countries, in China, people with a high socioeconomic status (SES) were more likely to be overweight/obese. This association was previously observed in all age groups in China.[54,55] Low SES is a risk factor for dementia in different populations.[2,56] In a systematic review, midlife obesity was associated with an increased risk of dementia in late life.[57] However, most of the 19 included studies were from Western countries. In China, several population studies found that a high body mass index (BMI) was associated with better cognitive function.[37–39] For example, in CHARLS 2011–2015, BMI ≥28 kg/m^2 was associated with a slow cognitive decline (OR 0.70, 95%CI 0.60–0.81).[39] In contrast, large weight loss (more than 10%) was associated with an increased risk of cognitive impairment.[38] A similar 'obesity paradox' has also been observed in South Korea.[58] This may be due to reverse causation, that is, cognitive decline resulting in a decrease in weight. However, in the Singapore Chinese Health Study, obesity, weight loss and excessive weight gain in middle age (~50 years) were all found to be associated with the risk of cognitive impairment in older age (~70 years).[59] Reasons for the lack of the effect of the MetS on cognitive decline in our study as well as in the previous meta-analysis[10] despite the fact that individual components of the MetS have been found to increase the risk of dementia need to be addressed in the future.

4.3 | Study limitations and strengths

The strengths of this study include having a large sample of both genders, utilising objective measurements such as biospecimen in addition to face-to-face interviews. However, the study also has several limitations. First, a cross-sectional design makes it impossible to establish a causal relationship between CircS and cognition, with a possible reverse causality, where poor cognition leads to depression and sleep disturbances. It is also limited to adults in a specific region and the results may not be generalisable to other populations. Furthermore, a relatively low response rate (67%) for the participation in blood test, especially in young men, may cause some selection bias. This study also employed self-reported memory test, which may not fully reflect the cognitive function of participants. Further research with longitudinal design employing more objective measures of cognitive function is needed to confirm these findings and determine the generalisability of these results.

4.4 | Implications and conclusion

In this paper, we are not endorsing the MetS as a main risk factor for cognitive decline. Rather, we are identifying factors that may contribute to cognitive decline in patients with the MetS. In our study, short sleep duration and depression were considered the most important factors contributing to cognition impairment among those with CircS. The results of this study suggest that both MetS and CircS are associated with cognitive outcomes and highlight the importance of considering both in the evaluation of cognitive health. The prevention of cognition decline is important, especially using a multidomain intervention approach, which has been successfully implemented in the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability trial.[60] Incorporating the assessment of sleep and depression may provide additional value in the prevention of cognition decline. However, while in our study CircS shows stronger association with cognitive decline compared with MetS, it remains unclear whether CircS precedes or is a

consequence of cognitive impairment. Further research is needed to establish the causal relationship between CircS and cognition, and the potential implications of these findings for public health. Despite the known influence of environmental exposure on disease risk, research into gene-by-environment interactions will be important to understand the regulatory determinants associated with the development and progression of disease.

In conclusion, we found that the CircS is a strong and better predictor candidate for cognition impairment than the MetS in Chinese adults. Having the MetS without the short sleep and depression components is associated with better cognition. Epidemiological research suggests that action towards the prevention of dementia needs to be implemented earlier in life, since research has demonstrated that middle-aged adults are already showing signs of cognitive decline, which are associated with later dementia.[5] Our study showed that CircS predicts cognitive function and memory in middle-aged adults, highlighting the importance of targeted preventive strategies including promotion of sleep hygiene, and maintenance of mentally and physically active lifestyles during middle age and later in life to delay and prevent dementia. Our results clearly show that risk factors other than traditional CVD risk factors may be more relevant for the prevention of cognition decline in this population. Addressing sleep disorder and depression in addition to the MetS should be considered in the prevention of cognition impairment. Longitudinal studies that track the development of MetS, CircS, and cognitive function over time would provide valuable information on the direction of causality. Additionally, it would be important to consider the effect of other factors such as education, physical activity, smoking, alcohol consumption, stress and residence (urban or rural) on this association.

AUTHOR CONTRIBUTIONS

Zumin Shi, Naftali Stern, Jianghong Liu, Jaakko Tuomilehto, Noga Kronfeld-Schor, George Alberti, Assam El-Osta, Carmel Bilu, Yonit Marcus and Paul Zimmet contributed to the design and conduct of the study and the interpretation of the data. Zumin Shi, Naftali Stern, Jianghong Liu and Paul Zimmet contributed to the analysis and interpretation of data. Zumin Shi wrote the first draft of the manuscript and all authors contributed to subsequent draughts and approved the final version for submission. Zumin Shi has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data is available from the CHARLS website.

ETHICS STATEMENT

The survey was approved by the institutional review committee of Peking University. All participants provided informed consent.

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SUPPORTING INFORMATION

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