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Abstract. Shi Z, Tuomilehto J, Kronfeld-Schor N, Alberti KG, Stern N, El-Osta A, Bilu C, Einat H, Zimmet P (QU Health, Qatar University, Doha, Qatar; University of Helsinki, Helsinki, Finland; Tel Aviv University, Tel Aviv, Israel; College London, London, UK; Tel Aviv Medical Center, Tel Aviv, Israel; Monash University, Melbourne, Vic., Australia; The Chinese University of Hong Kong, Hong Kong SAR, China; Tel Aviv-Yaffo Academic College, Tel Aviv, Israel; Monash University, Melbourne, Vic., Australia). The circadian syndrome predicts cardiovascular disease better than metabolic syndrome in Chinese adults. *J. Intern. Med.* 2021; **289**: 851–860. https://doi.org/10.1111/joim.13204

Background. To compare the predictive value of the circadian syndrome (CircS) and Metabolic syndrome (MetS) for cardiovascular disease.

Method. We used the data of 9360 Chinese adults aged ≥40 years from the 2011 China Health and Retirement Longitudinal Study (CHARLS). Of the participants, 8253 people were followed in the 2015 survey. MetS was defined using the harmonized criteria. CircS was based on the components of the International Diabetes Federation (IDF) MetS plus short sleep and depression. The cut-off for CircS was set as ≥4. Multivariable logistic regression analysis was used to examine the associations.

Results. The prevalence of CircS and MetS was 39.0% and 44.7%. Both MetS and CircS were directly associated with prevalent CVD. The odds ratios for prevalent CVD comparing CircS with MetS, respectively, were 2.83 (95%CI 2.33–3.43) and 2.34 (1.93–2.83) in men, and 2.33 (1.98–2.73) and 1.79 (1.53–2.10) in women. Similar associations were found for incident CVD. The five-year incidence of CVD was 15.1% in CircS and 14.0% in MetS. The number of CircS components has a better predictive power for both prevalent and incident CVD than those of Mets components as indicated by the area under the ROC (AUC). AUC values for CVD in 2011 were higher for CircS than MetS in both men (0.659 (95%CI 0.634–0.684) vs 0.635 (95%CI 0.610–0.661)) and women (0.652 (95%CI 0.632–0.672) vs 0.619 (95%CI 0.599–0.640)).

Conclusion. The circadian syndrome is a strong and better predictor for CVD than the metabolic syndrome in Chinese adults.

Keywords: adults, cardiovascular disease, Chinese, circadian syndrome, metabolic syndrome.

Introduction

Cardiovascular disease is a major threat to human health globally [1]. Identifying the risk factors for CVD is vital for its prevention. A variety of factors have been found to be associated with CVD in China, mostly related to sedentary lifestyles and high consumption of an unhealthy diet [2].

Metabolic syndrome (MetS) is defined by a cluster of risk factors for cardiovascular disease and includes raised blood pressure, dyslipidaemia (raised triglycerides and lowed high-density lipoprotein cholesterol), raised fasting glucose and central obesity [3]. It is well recognized that MetS is associated with an increased risk of CVDs and the prevalence of MetS is increasing worldwide [4, 5]. In China, the prevalence of MetS was 33.9% in

2010 [6]. However, there is debate about the underline mechanism of MetS and suggested mechanisms include insulin resistance [7], central obesity-related inflammation [8] and genetics [9].

Recently, circadian dysfunction has been proposed as an important underlying aetiological factor for the metabolic syndrome [10]. The concept of CircS is built on the fact that several chronic disorders including obesity, hypertension, dyslipidaemia, type 2 diabetes, depression, sleep disorder and nonalcoholic fatty liver disease (NAFLD) have a strong link with circadian rhythms. Modern lifestyle (e.g. sleep deprivation, high-energy diet and shift work) and the use of artificial light can cause circadian rhythm disruption, with different health outcomes [10]. Disturbances in sleep patterns and depressive symptoms have a negative effect on the circadian rhythm of numerous body functions that increase the risk of CVD. Therefore, it has been suggested that the circadian syndrome (CircS) should be considered as a novel CVD risk cluster [10]. Despite the concept of CircS, no definition of CircS has been proposed so far.

There is no study yet that has examined the association between the circadian syndrome and cardiovascular disease so it is not known whether it is a better predictor for CVD than the metabolic syndrome. The aim of this study was to answer the question using data from China Health and Retirement Longitudinal Study (CHARLS).

Method

Data source and analytical sample

CHARLS is a prospective study of adults aged ≥ 45 years conducted in 28 provinces in China, but some people aged 40–44 years attended the baseline examination [11]. Ethical approval for the CHARLS study was reviewed by the Peking University institutional review board (IRB). Informed consent was obtained from all the participants prior to their inclusion in the study. In the current study, the 2011 baseline and 2015 follow-up data were used.

At baseline, a total of 17 708 participants completed a face-to-face interview. Height, weight, waist circumference and blood pressure were measured by trained health workers. Fasting blood samples were measured for glucose and lipids. The response rate was 80.5%. All the baseline participants were invited to participate in the follow-up survey in 2015. In the current analysis, we used the data of 9360 Chinese adults (4258 men and 5102 women) aged ≥ 40 years from the 2011 CHARLS. Of the participants, 8253 participants were followed in the 2015 survey (Fig. 1).

Exposure measures: Metabolic syndrome and circadian syndrome

Fasting blood samples were collected and stored at −70°C at the Chinese Center for Disease Control and Prevention. Biomarkers including high-sensitivity C-reactive protein (CRP), total high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterols and triglycerides, glycated haemoglobin (HbA1c), fasting plasma glucose and haemoglobin were measured at the Younanmen Center for Clinical Laboratory of Capital Medical University [12]. Quality control samples were used daily during the testing period, and results were within the target range (two standard deviations of mean control concentrations).

Blood pressure was measured, whilst seated, by trained nurses using HEM-7200 electronic monitor (Omron, Dalian). The mean of three measurements was used. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or use of antihypertensive medications.

Depressive symptoms were assessed using the ten-question version of the Center for Epidemiologic Studies-Depression scale (CES-D). Participants with a CES-D score of ≥10 were defined as having depressive symptoms [13].

Metabolic syndrome was defined according to the definition in 'Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity' [3] (Table 1). Having ≥ 3 of the following components was defined as having MetS: elevated waist circumference (≥85 cm in men, ≥80 cm in women), high blood pressure (Systolic ≥ 130 and/or diastolic ≥ 85 mmHg) or drug treatment for hypertension, high LDL-cholesterol (≥130 mg dL^{-1}) or drug treatment for high LDL, low HDL cholesterol (<40 mg dL^{-1} in men and < 50 mg dL^{-1} in women) or drug treatment for low HDL, high TG (≥150 mg dL^{-1}) or drug treatment for high
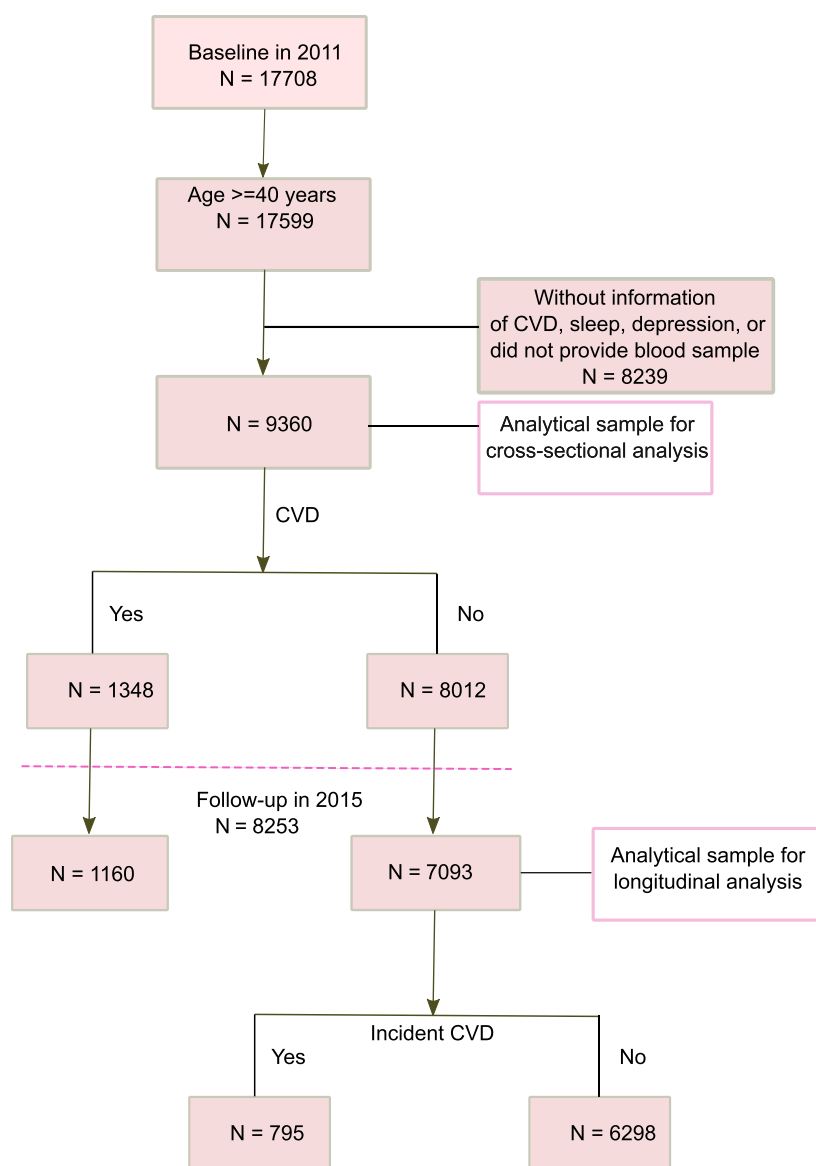
Fig. 1 *Sample flow chart.*

TG. Lipid-lowering medications were based on self-report use of western medication for the treatment of abnormal blood lipids.

CircS was based on 6 components including short sleep (<6 hours day^{-1}), depression and four components used to define MetS. A cut-off for CircS was set as ≥4 components (Table 1).

Outcome measure: Self-reported CVD

At baseline and follow-up, participants were asked whether they had been diagnosed by a doctor to have stroke or cardiac events (including heart attack, coronary heart disease, angina, congestive heart failure or other heart problems). A positive answer to the question was defined as having CVD.

Table 1. *Definition of metabolic syndrome and circadian syndrome*

Measure	Categorical cut points	Included in MetS	Included in CircS
Elevated waist circumference	Population- and country-specific definitions (≥85 cm in men, ≥80 in women)	√	√
Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator)	≥150 mg dL^{-1} (1.7 mmol L^{-1})	√	√
Reduced HDL-C (drug treatment for reduced HDL-C is an alternate indicator)	<40 mg dL^{-1} (1.0 mmol L^{-1}) in men; <50 mg dL^{-1} (1.3 mmol L^{-1}) in women	√	√
Elevated blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator)	Systolic ≥ 130 and/or diastolic ≥ 85 mmHg	√	√
Elevated fasting glucose (drug treatment of elevated glucose is an alternate indicator)	≥100 mg dL^{-1}	√	√
Short sleep	<6 hours day^{-1}		√
Depression symptom	10 item CES-D score ≥ 10		√
Definition criteria		≥3 components	≥4 components

Covariates

We included the following covariates in the current study: age, gender, education (low, medium, high), residence (urban, rural), physical activity (active, less active, sedentary) [12], smoking (current smokers, ex-smoker or nonsmoker) and alcohol consumption (nondrinker or drinker).

Kidney function was evaluated by the estimated glomerular filtration rate (eGFR) using serum creatinine. The CKD-EPI creatinine equation was used to estimate eGFR [14]. Chronic kidney disease (CKD) was defined as eGFR < 60 mL min^{-1}/1.73 m^2 [15].

Statistical analyses

Multivariable logistic regression analysis was used to examine the associations between MetS or CircS and CVD. The multivariable logistic model adjusted for age, education, smoking, alcohol drinking, physical activity and residence. The predictive power of the two indices (the number of Mets and CircS components were treated as continuous variables) for CVD was assessed using the receiver-operating characteristic (ROC) curve

analysis. We used *roccomp* command in Stata to compare the difference of AUCs between MetS and CircS. To assess the association between MetS/CircS with incident CVD in 2015, we excluded all those with CVD at baseline in 2011. Gender-specific analyses were conducted. Net reclassification improvement (NRI) was calculated using STATA NRI command [16]. In the NRI calculations, two risk levels were selected; >15% and <15% CVD. All analyses were conducted using STATA 16.1 (Stata Corporation, College Station, TX, USA). Statistical significance was considered when $P < 0.05$ (two sided).

Results

The mean age of the participants was 59.1 (SD 9.5) years in 2011 (Table 2). The prevalence of CircS and MetS was 39.0% and 44.7%, respectively. In total, 428 (4.6%) and 967 (10.3%) participants had either CircS or MetS alone and 3218 (34.4%) had both CircS and MetS. The CircS alone group was younger and had the highest prevalence of CKD (25%) but lower BMI than other groups. All the participants in the CircS alone group had depression and short sleep duration. Overall, depression

Table 2. *Sample characteristics by MetS and CircS status amongst participants attending China Health and Retirement Longitudinal Study (CHARLS) (N = 9360)*

	Total $N = 9360$	Normal $N = 4747$	CircS alone $N = 428$	MetS alone $N = 967$	Both MetS and CircS $N = 3218$	*P*-value
Age (years)	59.1 (9.5)	58.6 (9.6)	60.7 (9.7)	58.2 (9.3)	59.8 (9.3)	<0.001
Gender						<0.001
Male	4258 (45.5%)	2678 (56.4%)	175 (40.9%)	456 (47.2%)	949 (29.5%)	
Female	5102 (54.5%)	2069 (43.6%)	253 (59.1%)	511 (52.8%)	2269 (70.5%)	
Education						<0.001
Illiterate	4334 (46.3%)	2093 (44.1%)	260 (60.7%)	369 (38.2%)	1612 (50.1%)	
Primary school	2163 (23.1%)	1169 (24.6%)	84 (19.6%)	213 (22.0%)	697 (21.7%)	
Middle school	1909 (20.4%)	998 (21.0%)	66 (15.4%)	249 (25.7%)	596 (18.5%)	
High school or above	953 (10.2%)	487 (10.3%)	18 (4.2%)	136 (14.1%)	312 (9.7%)	
Residence						<0.001
Rural	5998 (64.1%)	3285 (69.2%)	320 (74.8%)	557 (57.6%)	1836 (57.1%)	
Urban	3362 (35.9%)	1462 (30.8%)	108 (25.2%)	410 (42.4%)	1382 (42.9%)	
Smoking						<0.001
Yes	3610 (38.6%)	2201 (46.4%)	167 (39.0%)	369 (38.2%)	873 (27.1%)	
No	5749 (61.4%)	2545 (53.6%)	261 (61.0%)	598 (61.8%)	2345 (72.9%)	
Drinking						<0.001
None drinker	5093 (54.4%)	2212 (46.6%)	244 (57.0%)	508 (52.5%)	2129 (66.2%)	
Ex-drinker	1274 (13.6%)	712 (15.0%)	58 (13.6%)	125 (12.9%)	379 (11.8%)	
Current drinker	2993 (32.0%)	1823 (38.4%)	126 (29.4%)	334 (34.5%)	710 (22.1%)	
Physical activity						<0.001
Active	2244 (24.0%)	1244 (26.2%)	102 (23.8%)	257 (26.6%)	641 (19.9%)	
Less active	5741 (61.3%)	2957 (62.3%)	262 (61.2%)	567 (58.6%)	1955 (60.8%)	
Sedentary	1375 (14.7%)	546 (11.5%)	64 (15.0%)	143 (14.8%)	622 (19.3%)	
BMI (kg m^{-2})	23.6 (3.9)	22.1 (3.3)	22.5 (3.5)	24.9 (3.6)	25.7 (3.8)	<0.001
Systolic BP	131 (22)	124 (20)	132 (22)	135 (21)	139 (22)	<0.001
Diastolic BP	76 (12)	738 (11)	76 (12)	79 (12)	80 (12)	<0.001
High-sensitivity CRP (mg dL^{-1})	1.06 (.56-2.2)	.82 (.47-1.74)	.91 (.52-2.165)	1.18 (.63-2.31)	1.41 (.75-2.83)	<0.001
CVD in 2011	1348 (14.4%)	445 (9.4%)	80 (18.7%)	98 (10.1%)	725 (22.5%)	<0.001
Hypertension	3749 (41.0%)	1108 (23.5%)	189 (45.1%)	455 (48.5%)	1997 (65.4%)	<0.001
CKD	1054 (14.9%)	480 (13.5%)	83 (25.3%)	87 (12.2%)	404 (16.5%)	<0.001
Anaemia	1188 (13.0%)	698 (15.1%)	67 (15.9%)	104 (10.9%)	319 (10.3%)	<0.001
Central obesity	4899 (52.3%)	1227 (25.8%)	198 (46.3%)	707 (73.1%)	2767 (86.0%)	<0.001
Heart Problems	1188 (12.7%)	393 (8.3%)	68 (15.9%)	88 (9.1%)	639 (19.9%)	<0.001
Stroke	215 (2.3%)	61 (1.3%)	14 (3.3%)	13 (1.3%)	127 (4.0%)	<0.001
Elevated plasma glucose	5536 (59.1%)	1862 (39.2%)	249 (58.2%)	705 (72.9%)	2720 (84.5%)	<0.001
Elevated serum triglycerides	2804 (30.0%)	264 (5.6%)	44 (10.3%)	314 (32.5%)	2182 (67.8%)	<0.001

Table 2 (*Continued*)

	Total N = 9360	Normal N = 4747	CircS alone N = 428	MetS alone N = 967	Both MetS and CircS N = 3218	P-value
Elevated blood pressure	5117 (54.7%)	1619 (34.1%)	251 (58.6%)	661 (68.4%)	2586 (80.4%)	<0.001
Reduced serum HDL-C	3942 (42.1%)	695 (14.6%)	114 (26.6%)	514 (53.2%)	2619 (81.4%)	<0.001
Depression	3596 (38.4%)	1574 (33.2%)	428 (100.0%)	0 (0.0%)	1594 (49.5%)	<0.001
Short sleep	2822 (30.1%)	1150 (24.2%)	428 (100.0%)	0 (0.0%)	1244 (38.7%)	<0.001
Circadian syndrome	3646 (39.0%)	0 (0.0%)	428 (100.0%)	0 (0.0%)	3218 (100.0%)	<0.001
Metabolic syndrome	4185 (44.7%)	0 (0.0%)	0 (0.0%)	967 (100.0%)	3218 (100.0%)	<0.001
CVD in 2015	1954 (23.7%)	726 (17.1%)	111 (30.2%)	172 (20.2%)	945 (33.9%)	<0.001

Data are presented as mean (SD) or median (IQR) for continuous measures, and n (%) for categorical measures.

Table 3. *Association (odds ratio; 95% confidence interval, CI) between metabolic syndrome (MetS) and circadian syndrome (CircS) and CVD amongst adults attending China Health and Retirement Longitudinal Study (CHARLS)*

	MetS		CircS	
	Per one of MetS components (continuous)	MetS (yes vs no)	Per one of CircS components (continuous)	CircS (yes vs no)
Prevalent CVD in 2011				
Men (n = 4258)				
Model 1	1.45 (1.36–1.55)	2.42 (2.01–2.93)	1.47 (1.38–1.57)	2.87 (2.37–3.48)
Model 2	1.40 (1.31–1.50)	2.21 (1.82–2.69)	1.45 (1.36–1.54)	2.69 (2.21–3.27)
Women (n = 5102)				
Model 1	1.33 (1.26–1.41)	1.84 (1.57–2.16)	1.39 (1.32–1.46)	2.34 (2.00–2.74)
Model 2	1.30 (1.23–1.37)	1.71 (1.46–2.01)	1.38 (1.31–1.45)	2.23 (1.90–2.62)
Incident CVD in 2015				
Men (n = 3293)				
Model 1	1.22 (1.12–1.32)	1.57 (1.24–1.98)	1.24 (1.15–1.34)	1.67 (1.31–2.14)
Model 2	1.21 (1.11–1.31)	1.53 (1.21–1.94)	1.24 (1.15–1.34)	1.66 (1.30–2.13)
Women (n = 3800)				
Model 1	1.19 (1.11–1.28)	1.57 (1.28–1.92)	1.23 (1.15–1.31)	1.73 (1.42–2.12)
Model 2	1.19 (1.11–1.28)	1.54 (1.26–1.90)	1.23 (1.15–1.31)	1.72 (1.41–2.11)

Values are odds ratio (95%CI) derived from multivariable logistic regression models.
Model 1 adjusted for age.
Model 2 further adjusted for education, smoking, alcohol drinking, physical activity and residence (urban/rural).

was more common than short sleep amongst those with CircS (55.5% vs 45.9%).

Both MetS and CircS were directly associated with prevalent CVD. The prevalence of CVD at the baseline was 22.1% amongst those with CircS and 19.7% in those with MetS. The odds ratios

for prevalent CVD in fully adjusted multivariable analysis (Model 2) were 2.69 (95%CI 2.21–3.27) and 2.21 (1.82–2.69) in men for the CircS and MetS, respectively (Table 3), and 2.23 (1.90–2.62) and 1.71 (1.46–2.01), respectively, in women. The five-year incidence of CVD was 15.1% in CircS and 14.0% in MetS. The odds ratios for incident CVD

Table 4. *Association between metabolic syndrome (MetS) and circadian syndrome (CircS) status and CVD amongst adults attending China Health and Retirement Longitudinal Study (CHARLS)*

	Health status			
	Normal	CircS alone	Mets alone	CircS and MetS
Prevalent CVD in 2011				
Men (*n* = 4258)				
Model 1	1.00	1.88 (1.22–2.90)	1.32 (0.94–1.83)	3.25 (2.64–4.01)
Model 2	1.00	1.98 (1.28–3.06)	1.22 (0.87–1.71)	2.95 (2.38–3.65)
Women (*n* = 5102)				
Model 1	1.00	2.07 (1.48–2.90)	0.92 (0.66–1.27)	2.34 (1.97–2.78)
Model 2	1.00	2.13 (1.52–3.00)	0.86 (0.62–1.20)	2.18 (1.83–2.60)
Incident CVD in 2011–2015				
Men (*n* = 3293)				
Model 1	1.00	1.77 (1.20–2.60)	1.34 (1.02–1.75)	2.71 (2.25–3.27)
Model 2	1.00	1.87 (1.26–2.76)	1.27 (0.97–1.67)	2.55 (2.11–3.09)
Women (*n* = 3800)				
Model 1	1.00	2.05 (1.50–2.79)	1.12 (0.87–1.46)	2.20 (1.89–2.57)
Model 2	1.00	2.10 (1.54–2.87)	1.06 (0.82–1.38)	2.11 (1.81–2.46)

Values are odds ratio (95%CI) derived from multivariable logistic regression models.
Model 1 adjusted for age.
Model 2 further adjusted for education, smoking, alcohol drinking, physical activity and residence (urban/rural).

were 1.66 (1.30–2.13) and 1.53 (1.21–1.94) in men; 1.72 (1.41–2.11) and 1.54 (1.26–1.90) in women for CircS and MetS, respectively.

Having both MetS and CircS was associated with more than twice the risk of developing CVD in both men and women. CircS only was associated with 87% and 110% increased risk of developing CVD in men and women, respectively. MetS by itself was not statistically associated with CVD (Table 4).

The number of CircS components had a better predictive power for both prevalent and incident CVD than the number of MetS components as indicated by the area under the ROC (AUC) (Fig. 2). AUC values for CVD in 2011 were higher for CircS than MetS in both men (0.659 95%CI (0.634–0.684) vs 0.635 (95%CI (0.610–0.661)) and women (0.652 (95%CI 0.632–0.672) vs 0.619 (95%CI 0.599–0.640)). CircS had a higher specificity but a lower sensitivity for CVD than MetS (Table S1). Both MetS and CircS had a higher sensitivity for CVD in men than in women.

Net reclassification improvement after adding the risk score (short sleep and depression) to components of MetS for improved risk classification (CVD

risk above 15% or below 15%) was 0.040 for prevalent CVD in 2011 (*P* = 0.003) and 0.038 for incident CVD in 2011–2015 (*P* = 0.035).

Discussion

In this large population-based study of Chinese adults, we found that the CircS is a better predictor for both prevalent and incident CVD than the MetS. Having both MetS and CircS was associated with a doubled risk of CVD compared with people without any of these syndromes. Having CircS alone without MetS was associated with prevalent and incident CVD in both men and women, but in participants with MetS alone no statistically significant association with prevalent CVD was observed. Assessing the effect of the exposure on the incidence provides information of the time sequence that the exposure preceded the outcome, whilst the cross-sectional analysis at baseline cannot do it.

In our study, the MetS was associated with a doubled risk of CVD. The finding is in line with previous studies. In a meta-analysis of 87 studies, MetS had an RR of 2.35 (95%CI 2.02–2.73) for CVD [5]. To the best of our knowledge, no study has assessed the prevalence of CircS and the
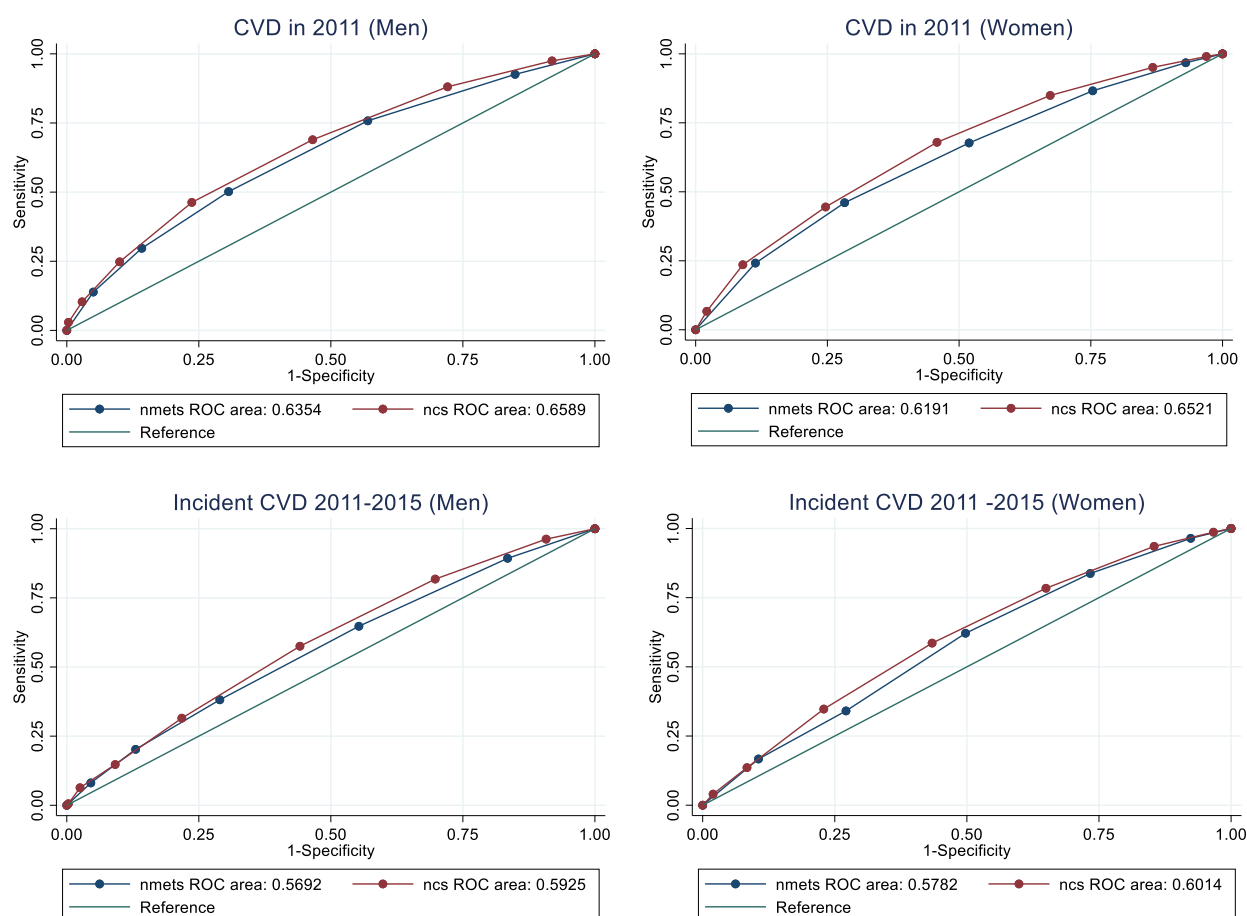
Fig. 2 *ROC for prevalent and incident CVD based on number of components of metabolic syndrome and circadian syndrome. There was a significant difference in AUC between the number of metabolic syndrome components and number of circadian syndrome components in both genders. nmets: number of metabolic syndrome components. ncs: number of circadian syndrome components.*

association between CircS and CVD. Two additional components, short sleep and depression, were added into the components of MetS to construct the CircS. Existing evidence suggests that both short sleep and depression are associated with increased risk of CVD [17, 18]. As expected, CircS was associated with CVD in our study. In fact, CircS has a better predictive value than MetS as indicated by AUC.

The interesting finding of this study is that MetS alone was not associated with the risk of CVD, but CircS alone was. Our findings emphasize the rationale and importance of incorporating short sleep and depression into the MetS risk factor cluster and construct the CircS. The prevalence of CircS alone was 4.6%. If we only use MetS to

prevent and predict CVD, this group will be missed. One of the important clinical features of this group is the high prevalence of CKD. Around 25% of the participants in this group had CKD. The significant association between CircS and CVD in this group may be partly due to CKD, but further adjusting for CKD did not attenuate the association between CircS and CVD. Daily rhythmicity is required for proper kidney function, which is the site of one of the most active peripheral clocks. Disrupted circadian rhythms have been associated with the development of CKD in both humans and animal models [19]. Therefore, it is not surprising that there was a significant association between CircS and CKD in our study and strengthens the hypothesis that disturbance of circadian rhythms is an important underlying etiological factor.

CircS alone group had lower BMI than other groups. High BMI is associated with increased risk of MetS, but not all overweight or obese people have MetS, and vice versa [20]. It is possible that in this group, circadian disruption is an even more central underlying etiological factor.

The rationale for the concept of CircS has been provided in its initial publication [10]. There is a strong link between circadian rhythms and MetS [21]. We found that CircS is a better substitute for the MetS. Similarly, all of the components of CircS have been shown to be related to circadian disruption [10]. Thus, circadian disruption could underline the common aetiology of MetS and CircS. Several factors have been proposed to be responsible for the disruption of circadian rhythm in our modern life, including the extensive use of artificial light, controlled ambient temperature and constant food availability, shift work, jet travel with different time zones [10]. All these factors have been shown to be related to the components of CircS used in the current study as well as CVD. For example, findings from a review of 85 studies suggest that artificial light at night had negative effects on psychological, cardiovascular and metabolic functions [22]. Mounting evidence suggests that sleep deprivation has metabolic consequences and increases the risk of type 2 diabetes and/or obesity [23]. Furthermore, a high fat diet, common in modern society, affects sleep quality [24]. In a clinical laboratory, Sheer *et al* found there is a causal link between circadian misalignment and metabolic homeostasis [25].

The limitation of this study is the short follow-up duration. We only have self-reported sleep duration rather than objectively measured sleep parameters. The original proposed CircS includes nonalcoholic fatty liver disease (NAFLD). It is known that the prevalence of NAFLD is high in China (~20%) [26]. However, we do not have information on NAFLD. The use of self-reported CVD is another limitation. However, self-reported CVD has been shown to be reliable to ascertain nonfatal events [27, 28], but fatal events remain undetected. The strength of the study is the large sample size and representative of the general population. This is the first study to assess the association between CircS and CVD risk. More studies are needed to validate our findings in other populations, and using more objective measurements of disturbances of the circadian rhythm. As the assessment of short sleep and depression is relatively easy and cheap, they should be routinely measured in combination of MetS in clinical settings to prevent CVD.

In conclusion, both MetS and CircS can predict CVD in the Chinese population and the use of CircS can predict CVD better. Adding sleep quality and depression to the MetS construct to create the CircS might be both a cost- and health effective approach to prevention of CVD.

Conflict of interest

All the authors report no conflicts.

Author contribution

Zumin Shi: Conceptualization (equal); Data curation (lead); Formal analysis (lead); Methodology (equal); Project administration (lead); Resources (equal); Software (equal); Visualization (equal); Writing-original draft (lead); Writing-review & editing (equal). **Jaakko Tuomilehto:** Methodology (equal); Writing-review & editing (equal). **Noga Kronfeld-Schor:** Conceptualization (equal); Writing-review & editing (equal). **George Alberti:** Writing-review & editing (equal). **Naftali Stern:** Writing-review & editing (equal). **Sam El-Osta:** Writing-review & editing (equal). **Carmel Bilu:** Writing-review & editing (equal). **Haim Einat:** Writing-review & editing (equal). **Paul Zimmet:** Conceptualization (equal); Investigation (equal); Methodology (equal); Project administration

(equal); Supervision (lead); Writing-review & editing (equal).

Data and resource availability

The data are available from the CHARLS website.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Sensitivity, specificity and AUC by metabolic syndrome and circadian syndrome in predicting CVD risk among adults in China.◼