Association between cardiovascular health metrics and restless legs syndrome: A population-based study

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Abstract

Background Cardiovascular diseases is increasingly identified to be related to the restless legs syndrome (RLS). However, the relationship between Cardiovascular Health Metric (CVH) and RLS need to be further confirmed. The present study aimed to assess the association of overall CVH metric and 7 Simple's Life (LS7) with the RLS risk.

Methods In a cross-sectional population-based study, 3,772 adults (57.6 ± 5.11 years of age) were recruited and completed the structured questionnaire between January 2 and May 21, 2022. Blood sample and other body measurements were obtained by trained nurses. The definition and score of CVH metric was determined by the attendance of LS7, and the RLS was diagnosed by the International Restless Legs Syndrome Study Group (IRLSSG) criteria. Multivariate logistic regression models were applied to examine the associations of overall CVH metric and its SL7 profiles with prevalence of RLS.

Results Overall, 301 (7.98%) were diagnosed with RLS. Multivariable logistic regression analysis showed that, in comparison to inadequate scores, higher scores of overall CVH metric and body mass index (BMI), physical activity, blood pressure and total cholesterol (TC) metric were negatively associated with the prevalence of RLS (multi-adjusted odd ratios [ORs] ranged from 0.32 to 0.67, all *P* for trend < 0.05). Per 1-SD increase in over CVH metric and each SL7 profile yielded the similar results (ORs ranged from 0.65 to 0.85, all *P* for trend < 0.05). Significant differences in the association of RLS with smoke profile and overall CVH metric were detected with females (*P* for interaction = 0.005) and older participants (*P* for interaction = 0.013), respectively.

Conclusion To be at an ideal behavioural CVH may be benefit in RLS, especially for women and older people. Interventions concerning to promote and preserve favourable CVH should be regarded in the prevention and treatment of RLS.

Background

Restless Legs syndrome (RLS), also called "Willis-Ekbom disease", is a common neurological sensor-motor disorder which is characterized by sensory symptom (restlessness and unpleasant sensations) and motor symptoms (periodic limb movements) [1]. This disease presents among 2–3% of adult population, and the prevalence of RLS increase with age and higher among women [2]. Although dysfunction of the dopaminergic system and brain iron deficiency might be contributing factors of RLS, the pathophysiological pathways resulting in RLS remain unsolved.

An increasing number of heterogeneous publications suggested that RLS exists in the comorbidities of a series of diseases, such as polyneuropathy [3], Parkinson disease [4], multiple sclerosis [5], iron deficiency anaemia [6], obesity [7] and particularly cardiovascular diseases (CVDs). Even though some studies failed to provide supporting evidence for the relationship between RLS and CVDs [8–11], a study positive association between RLS and coronary artery disease (CAD) (Odd ratio [OR] = 2.05; 95% confidence interval [CI] 1.38–3.04) and CVDs (OR = 2.07; 95% CI 1.43-3.00) [12]. A more recent study also found relationships between RLS and marginally elevated risk of coronary heart disease (CHD) (hazard ratio [HR] = 1.46; 95%CI, 0.97–2.18) and myocardial infarction (MI) (HR = 1.80; 95%CI 1.07–3.01) [13]. Furthermore, several cardiovascular risk factors, including female sex, smoking, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), total cholesterol (TC), have been demonstrated to be significantly associated with RLS [14]. Taken together, the association between cardiovascular health and RLS need to be further confirmed.

In 2010, the American Heart Association (AHA) developed the concept of ideal cardiovascular health (CVH) metrics by classifying the seven modifiable health behaviours and factors into “poor”, “intermediate” and “ideal” levels [15]. The seven ideal CVH metrics (also known as Life's Simple 7, LS7) comprehensively defines ideal cardiovascular health as presence of four ideal health behaviours (body mass index [BMI] < 25kg/cm^2; quit smoking 12 months ago; physical activity reach a goal level; healthy diet allied with current dietary recommendations) and three ideal metabolic measures (untreated systolic blood pressure [SBP]/ untreated diastolic blood pressure [DBP] < 120/80 mm Hg; untreated TC < 200 mg/dL; and untreated fasting blood glucose (FBG) < 100 mg/dL [15].

An ideal CVH metric has been demonstrated to exert protective effect against the risk of premature mortality not matter in general population or in cardiometabolic disease patients [16]. Moreover, there are accumulating evidence suggesting that a higher score of ideal DVH metric is not only associated with decreased risk of CVDs [17], but also associated with lower risk of neurobiological events like stroke [18] and dementia [19], higher white matter hyperintensity (WMH) volume and brain volume (BV) [20], but reduced burden of biomarkers of brain aging [21]. Similarly, increasing evidence suggested negative associations of LS7 with the risks of dementia [22, 23] and Alzheimer’s disease (AD) [23]. However, there are sparse studies that directly concerned to the impact of ideal CVH metrics on the RLS risk. A study performed in Amerindians aged ≥ 40 years in South America reported null association between ideal DVH metric and RLS[24]. Furthermore, this study was limited by their small sample size (665 participants). Available evidence now describing relationship between CVH metrics and risk of RLS need to be further confirmed.

Thereby, we performed the current cross-sectional study with a larger sample size in order to understand the association between ideal CVH metrics and the RLS. We hypothesized that higher CVH metrics might be related with a lower prevalence of RLS.

Methods

Study design and participants

A cross-sectional population-based study was carried out between January 2 and May 21, 2022. Participants were recruited from three communities (Mashi, Sanjiaotang and Yueyingtang) of Xijiao Street in Meijiang District, Meizhou, China. Participants were recruited through community staff to publicize, issue recruitment advertisements and research objects to be introduced to each other. Eligible

Chinese adults should be aged ≥ 45 years. A total of 3772 individuals were left in our analysis after excluding those who met any of the following excluding criteria: i) those aged under 45 years (n = 24); ii) those with missing health data (n = 25); iii) those refused to participate(n = 175); iv) those had severely health conditions (e.g., cancers and heart failure) or difficulties in communication (n = 75).

It was voluntary to participate in the study, and the written informed consent was collected from all participants before the start of survey. The protocol of this study was approved by the Medical Ethics Committee of Meizhou People's Hospital, and all procedures involving human participants were conducted in accordance with the 1964 Helsinki declaration.

Data collection

All included participants underwent a face-to-face interview by specially trained professional interviewers. A structured questionnaire was adopted to obtain demographic information (age, sex, marital status, educational levels, annual family income), health-related behaviours (tobacco smoking, drinking status, tea consumption, physical activity level, and taste preference), the presence of comorbidities (diabetes, dyslipidemia, heart diseases, chronic renal insufficiency, and anemia), medication use (usage of anti-hypertension drugs, hypoglycemic agents, and lipid-lowering drugs), and dietary habits (daily or weekly consumptions of different foods).

Anthropometric and biochemical measurements

Height and weight were measured with participants wearing lightweight clothes and no shoes neither hats. SBP and DBP were obtained by using automated electronic device with participants had been sitting for at least 5 minutes. After an overnight fast, blood sample was collected and stored at 2°C to 8°C then sent to laboratory. Biochemical markers, including TC, total triglycerides (TG), HDL-C, LDL-C, and FBG were measured by using an auto-analyser (Hitachi 747; Hitachi, Tokyo, Japan). The BMI was calculated based on individual's weight and height.

CVH metrics

According to the guidance of the AHA, seven modifiable health behaviours and factors, the definitions of three classifications of seven CVH metric components are as follows: 1) BMI: poor (≥ 30.0 kg/cm^2), intermediate (25.0-29.9 kg/cm^2), ideal (< 25.0 kg/cm^2); 2) smoking: poor (current smoking), intermediate (quit smoking < 12 months prior), ideal (never smoked/ quit smoking for at least 12 months prior); 3) physical activity: poor (none activity), intermediate (1–149 minutes/week of moderate-intensity activities or 1–74 min/week of vigorous-intensity activities), ideal (≥ 150 minutes/week of moderate-intensity-activities, or ≥ 75 minutes/week of vigorous-intensity-activities or ≥ 150 minutes/week of conduct moderate- plus vigorous- intensity-activities); 4) diet: was defined by five dimensions: fruits and vegetables ≥ 4.5 cups/day; fishes ≥ 20 g/week; red meats < 75g/day; soybean and products ≥ 125 g/day;

and drink tea every day. poor (daily salty intake ≥ 10g), intermediate (daily salty intake 6-10g), ideal (daily salty intake < 6g); 5) blood pressure: poor (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg), intermediate (treated to goal or SBP: 120–139 mmHg or DBP: 80–89 mmHg), ideal (untreated SBP < 120 mmHg and untreated DBP < 80 mmHg); 6) TC: poor (TC ≥ 240 mg/dL), intermediate (TC: 200–239 mg/dL or treated to goal), ideal (untreated TC < 200 mg/dL); 7) FBG: poor (FBG ≥ 126 mg/dL), intermediate (FBG: 100–125 mg/dL or treated to goal), ideal (untreated FBG < 100 mg/dL). Each component of CVH metrics was assigned with a score of 0, 1, and 2 to present "poor", "intermediate", and "ideal" levels, respectively. The overall CVH metrics score is the summary of the 7-component CVH metrics scores [15], and the ideal CVH profile was defined by meeting 5–7 metrics in ideal range; 3–4 metrics in intermediate level; and 0–2 metrics in poor level, respectively.

RLS diagnosis

According to the criteria of the International Restless Legs Syndrome Study Group (IRLSSG), the RLS was defined if one met all four essential criteria: 1) have an urge to move legs, which is frequently accompanied or caused by uncomfortable and unpleasant sensations in the legs. Sometime, this urge to move occurs without the unpleasant feelings and other body parts are occasionally involved aside from the legs; 2) the urge to move or unpleasant sensations present or worsen during resting time, such as lying or sitting; 3) moving, such as walking or stretching, can partially or completely reduce the urge to move or unpleasant feelings, at least for the duration of the activity; 4) the urge to move or unpleasant sensations are stronger or exclusively present at night compared with day time (the night-time deterioration may not be apparent when symptoms are very severe, but it must have been previously presented) [25].

Statistical analysis

The categorical variables were presented as numbers (percentages) and the Chi-square test was used to determine differences between non-RLS and RLS groups. Continuous variables were descried as means ± standard deviations (SDs) and comparison between groups was performed by using student *t*-test.

In the primary analysis, the total CVH metric and the seven-components metric were transferred into tertiles (T1-T3), with the lowest tertile (poor) using as reference. We used the logistic regression to estimate the odd ratios (ORs) and correspondence 95% CIs in order to investigate the cross-sectional association between CVH metrics and RLS. The total and seven-components of CVH metrics were analysed as continuous variables with the ORs expressed by teritles and per 1-SD increase. A test for trend was subsequently explored by treating CVH metric tertiles or per1-SD increase as continuous variable.

To assess the potential confounding effect, we performed multivariable models as follows: model 1 was adjusted for age and sex; model 2 was adjusted for age, sex, material status, educational level, annual income level, drinking status, tea consumption, heart diseases, chronic renal insufficiency, and anaemia;

model 3 included covariates in model 2 plus groups of those who had consumptions of vegetable and fruits > 500g/day, fishes ≥ 200g/week, soybean and its products ≥ 125g/week, red meats < 75g/day and sweeten beverages < 450 ml/day.

In the secondary analysis, we tested effect modification of sex (female *vs*. male) and age (45–60 *vs*. ≥60 years) on the associations of total and each component of the CVH metrics varies with RLS by generating stratum specific ORs and 95%CIs in the final model 3. All analyses were carried out using SPSS version 17.0 (version 17.0, SPSS, Inc., Chicago, Illinois, United States), and a *P*-value of < 0.05 was considered statistically significant.

Results

Demographics and measurements in participants

Table 1 shows the sociodemographic information and selected biochemical characteristics of participants according to the diagnosis of RLS. Of 3,772 participants approached, the mean age of them was 57.6 ± 5.11years and 301 (7.98%) were diagnosed with RLS. Our participants were more likely to report being females (71.42%), being married/had cohabitation (91.01%), having secondary and high schools of education (45.92%), having per capita family income at 2000 to 5000 yuan (44.41%), being non-smokers (85.66%), not drinking (94.43), not drinking tea (50.29%), almost not doing physical activity (37.22%), having a heavy taste (43.21%). As for comorbidities or medication history, most of them denied suffering diabetes (88.12%), dyslipidemia (74.95%), heart diseases (88.44%), chronic renal insufficiency (99.52%), anaemia (94.91%), and denied using anti-hypertension drugs (87.20%), hypoglycemic agents (99.36%), or lipid-lowering drugs (86.43%). In dietary habits, more than haft of our participants reported consuming vegetables or fruits ≥ 500g/day (50.80%), fishes ≥ 200g/week (68.29%), but less than 50% of them reported eating soybean and products ≥ 125g/week (49.42%), red meats < 75g/day (49.73%) and sweeten beverages < 450ml/day (17.39%). The mean values of BMI, SBP, DBP, TC, TG, HDL-C, LDL-C and FBG in overall population were 23.06 ± 3.80 km/cm^2, 122.79 ± 20.99 mmHg, 77.86 ± 11.86 mmHg, 5.44 ± 1.07 mmol/L, 1.59 ± 1.44 mmol/L, 1.41 ± 0.35 mmol/L, 3.63 ± 0.90 mmol/L, and 4.81 ± 1.14 mmol/L, respectively.

Table 1
Demographics of study population

Variables	Overall	Non-RLS	RLS	*P-value* [a]
	N = 3772	N = 3471	N = 301	
Age, $\bar{X}$ ± SD	57.6 ± 5.11	57.57 ± 5.07	57.92 ± 5.60	0.063
Sex, N (%)				0.897
Female	2694 (71.42)	2480 (71.45)	214 (71.10)	
Male	1078 (28.58)	991 (28.55)	87 (28.90)	
Marital status, N (%)				0.395
Married/cohabitation	3433 (91.01)	3155 (90.90)	278 (92.36)	
Single/divorced/widowed	339 (8.99)	316 (9.10)	23 (7.64)	
Educational levels, N (%)				0.532
Elementary school and below	1186 (31.44)	1087 (31.32)	99 (32.89)	
Secondary and high schools	1732 (45.92)	1603 (46.18)	129 (42.86)	
University and above	854 (22.64)	781 (22.5)	73 (24.25)	
Annual income levels, N (%)				0.846
< 1000 yuan	187 (4.96)	175 (5.04)	12 (3.99)	
1000 ~ 2000 yuan	1215 (32.21)	1114 (32.09)	101 (33.55)	
2000 ~ 5000 yuan	1675 (44.41)	1542 (44.43)	133 (44.19)	
> 5000 yuan	695 (18.43)	640 (18.44)	55 (18.27)	
Smoking status, N (%)				0.399
Never smoke	3231 (85.66)	2980 (85.85)	251 (83.39)	
Quit smoking	173 (4.59)	155 (4.47)	18 (5.98)	
Current smoking	368 (9.76)	336 (9.68)	32 (10.63)	
Drinking status, N (%)				0.224

[a] *P*-value was calculated by Chi-square for categorical variables and student t- test or *Mann-Whitney U* test for continuous variables;

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, total triglycerides; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; SD, standard deviation.

Variables	Overall	Non-RLS	RLS	*P-value* [a]
	N = 3772	**N = 3471**	**N = 301**	
Never drink	3562 (94.43)	3275 (94.35)	287 (95.35)	
Quit drinking	39 (1.03)	34 (0.98)	5 (1.66)	
Current drinking	171 (4.53)	162 (4.67)	9 (2.99)	
Tea consumption, N (%)				0.753
No	1897 (50.29)	1743 (50.22)	154 (51.16)	
Yes	1875 (49.71)	1728 (49.78)	147 (48.84)	
Physical activity, N (%) [b]				**<0.001**
Almost not	1404 (37.22)	1259 (36.27)	145 (48.17)	
Intermediate level	1402 (37.17)	1302 (37.51)	100 (33.22)	
Ideal level	966 (25.61)	910 (26.22)	56 (18.60)	
Taste preference, N (%)				0.475
Light	894 (23.70)	828 (23.85)	66 (21.93)	
Intermediate	1248 (33.09)	1153 (33.22)	95 (31.56)	
Heavy	1630 (43.21)	1490 (42.93)	140 (46.51)	
Diabetes, N (%)				**0.037**
No	3324 (88.12)	3070 (88.45)	254 (84.39)	
Yes	448 (11.88)	401 (11.55)	47 (15.61)	
Dyslipidemia, N (%)				0.972
No	2827 (74.95)	2602 (74.96)	225 (74.75)	
Yes	863 (22.88)	794 (22.88)	69 (22.92)	
Heart diseases, N (%)				0.302
No	3336 (88.44)	3076 (88.62)	260 (86.38)	
Yes	399 (10.58)	362 (10.43)	37 (12.29)	

[a] *P*-value was calculated by Chi-square for categorical variables and student t- test or *Mann-Whitney U* test for continuous variables;

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, total triglycerides; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; SD, standard deviation.

Variables	Overall	Non-RLS	RLS	*P-value* [a]
	N = 3772	N = 3471	N = 301	
Chronic renal insufficiency, N (%)				0.210
No	3754 (99.52)	3456 (99.57)	298 (99.00)	
Yes	11 (0.29)	9 (0.26)	2 (0.66)	
Anaemia, N (%)				0.184
No	3580 (94.91)	3290 (94.79)	290 (96.35)	
Yes	140 (3.71)	133 (3.83)	7 (2.33)	
Usage of anti-hypertension drugs, N (%)				0.326
No	3289 (87.20)	3032 (87.35)	257 (85.38)	
Yes	483 (12.80)	439 (12.65)	44 (14.62)	
Usage of Hypoglycemic agents, N (%)				1.000
No	3748 (99.36)	3449 (99.37)	299 (99.34)	
Yes	24 (0.64)	22 (0.63)	2 (0.66)	
Usage of lipid-lowering drugs, N (%)				0.367
No	3260 (86.43)	3005 (86.57)	255 (84.72)	
Yes	512 (13.57)	466 (13.43)	46 (15.28)	
Consume vegetables and fruits ≥ 500g/day, N (%)				0.800
No	1856 (49.20)	1710 (49.27)	146 (48.50)	
Yes	1916 (50.80)	1761 (50.73)	155 (51.50)	
Consume fishes ≥ 200g/week, N (%)				0.173
No	1196 (31.71)	1090 (31.40)	106 (35.22)	
Yes	2576 (68.29)	2381 (68.60)	195 (64.78)	

[a] *P*-value was calculated by Chi-square for categorical variables and student t- test or *Mann-Whitney U* test for continuous variables;

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, total triglycerides; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; SD, standard deviation.

Variables	Overall	Non-RLS	RLS	*P-value* [a]
	N = 3772	N = 3471	N = 301	
Consume soybean and products ≥ 125g/week, N (%)				0.266
No	1908 (50.58)	1765 (50.85)	143 (47.51)	
Yes	1864 (49.42)	1706 (49.15)	158 (52.49)	
Consume red meats < 75g/day, N (%)				0.449
No	1896 (50.27)	1751 (50.45)	145 (48.17)	
Yes	1876 (49.73)	1720 (49.55)	156 (51.83)	
Drink beverages < 450ml/day, N (%)				0.370
No	3116 (82.61)	2873 (82.77)	243 (80.73)	
Yes	656 (17.39)	598 (17.23)	58 (19.27)	
BMI, kg/cm^2, $\bar{X}$ ± SD	23.06 ± 3.80	23.00 ± 3.79	23.7 ± 3.88	0.398
SBP, mmHg, $\bar{X}$ ± SD	122.79 ± 20.99	122.58 ± 20.78	125.28 ± 23.17	0.059
DBP, mmHg, $\bar{X}$ ± SD	77.86 ± 11.86	77.74 ± 11.77	79.22 ± 12.79	0.346
TC, mmol/L, $\bar{X}$ ± SD	5.44 ± 1.07	5.42 ± 1.07	5.58 ± 1.03	0.601
TG, mmol/L, $\bar{X}$ ± SD	1.59 ± 1.44	1.57 ± 1.40	1.79 ± 1.86	**0.003**
HDL-C, mmol/L, $\bar{X}$ ± SD	1.41 ± 0.35	1.41 ± 0.35	1.39 ± 0.36	0.395
LDL-C, mmol/L, $\bar{X}$ ± SD	3.63 ± 0.90	3.62 ± 0.90	3.69 ± 0.92	0.421
FBG, mmol/L, $\bar{X}$ ± SD	4.81 ± 1.14	4.81 ± 1.13	4.91 ± 1.28	**0.033**

[a] *P*-value was calculated by Chi-square for categorical variables and student t- test or *Mann-Whitney U* test for continuous variables;

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, total triglycerides; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; SD, standard deviation.

Comparison between non-RLS and RLS groups

The study groups did not differ regarding to most variables, but the percentage of those who reached ideal level at physical activity was lower in RLS group than that of non-RLS group (18.60% *vs.* 26.22%, *P* < 0.001), and those with diabetes was more prevalent in RLS group than that of non-RLS group (15.61%

vs. 11.55%, *P* = 0.037). With regards to measurements, although no significant between-groups differences were found in BMI; SBP; DBP; TC; HDL-C and LDL-C between groups (all *P* > 0.05), significant differences in TG and FBG were seen between groups, with the higher levels of TG was observed in RLS group compared with non-RSL group (1.79 mg/dL *vs.* 1.57 mg/dL, *P* = 0.003), as well as the FBG (4.91 mg/dL *vs*. 4.81 mg/dL, *P* = 0.033). Compared with the non-RLS group, participants in RLS group were more likely to have poor overall CVH metric and physical activity metric, and to have poor or intermediate levels in BMI, blood pressure and TC metrics (each *P* < 0.05). For details of group differences, please see Tables1 and 2.

Table 2

The scores of total and seven profiles of CVH metrics in patients with RLS compared to health subjects [a]

CVH metric	Overall	Non-RLS	RLS	*P-value* [b]
Total CVH metric				**<0.001**
Poor	1255 (33.27)	1106 (31.86)	149 (49.50)	
Intermediate	1556 (41.25)	1444 (41.60)	112 (37.21)	
Ideal	961 (25.48)	921 (26.53)	40 (13.29)	
BMI metric				**<0.001**
Poor	106 (2.81)	92 (2.65)	14 (4.65)	
Intermediate	908 (24.07)	813 (23.42)	95 (31.56)	
Ideal	2757 (73.09)	2565 (73.90)	192 (63.79)	
Smoking metric				0.399
Poor	368 (9.76)	336 (9.68)	32 (10.63)	
Intermediate	173 (4.59)	155 (4.47)	18 (5.98)	
Ideal	3231 (85.66)	2980 (85.85)	251 (83.39)	
Physical activity metric				**<0.001**
Poor	1404 (37.22)	1259 (36.27)	145 (48.17)	
Intermediate	1402 (37.17)	1302 (37.51)	100 (33.22)	
Ideal	966 (25.61)	910 (26.22)	56 (18.60)	
Healthy diet metric				0.269
Poor	1632 (43.27)	1492 (42.98)	140 (46.51)	
Intermediate	2084 (55.25)	1925 (55.46)	159 (52.82)	
Ideal	56 (1.48)	54 (1.56)	2 (0.66)	
Blood pressure metric				**0.008**

[a] Seven profiles of CVH metric were defined at three levels according to the guidance of American Heart Association.

[b] *P*-value was calculated by Chi-square for categorical variables and student t- test or *Mann-Whitney U* test for continuous variables.

Abbreviations: CVH metric, Cardiovascular Health metric; RLS, Restless Legs Syndrome; SD, standard deviation; BMI, body mass index; TC, total cholesterol.

CVH metric	Overall	Non-RLS	RLS	*P-value* [b]
Poor	962 (25.50)	865 (24.92)	97 (32.23)	
Intermediate	1053 (27.92)	967 (27.86)	86 (28.57)	
Ideal	1757 (46.58)	1639 (47.22)	118 (39.20)	
TC metric				**0.001**
Poor	797 (21.13)	721 (20.77)	76 (25.25)	
Intermediate	1360 (36.06)	1234 (35.55)	126 (41.86)	
Ideal	1615 (42.82)	1516 (43.68)	99 (32.89)	
Fasting blood glucose metric				0.121
Poor	3296 (87.38)	3036 (87.47)	260 (86.38)	
Intermediate	370 (9.81)	343 (9.88)	27 (8.97)	
Ideal	106 (2.81)	92 (2.65)	14 (4.65)	

[a] Seven profiles of CVH metric were defined at three levels according to the guidance of American Heart Association.

[b] *P*-value was calculated by Chi-square for categorical variables and student t- test or *Mann-Whitney U* test for continuous variables.

Abbreviations: CVH metric, Cardiovascular Health metric; RLS, Restless Legs Syndrome; SD, standard deviation; BMI, body mass index; TC, total cholesterol.

Stratifications

The sex-stratified relationships of overall and individual CVH metrics scores with RLS were presented in Table 4. We observed a significantly decreased RLS risk among women in top tertile of smoking metric score (T3: OR = 0.38, 95%CI 0.17–0.84, *P* for trend = 0.003) compared with those in the bottom tertile. But this association lost significance in their male counterparts (T3: OR = 0.97, 95%CI 0.56–1.69, *P* for trend = 0.905), suggesting a significant sex-differences in risk of RLS across tertiles of smoking metric score (*P* for interaction = 0.005). No significant interaction of sex was found between overall or other six components of CVH metrics scores and RLS risk (*P* for interaction ranged from 0.229 to 0.854).

Table 4
The results of logistic regression analysis for association of total and seven profiles of CVH metrics scores with RLS by sexes.

Sex groups*	Odd ratios (95% Confident intervals)			*P* for trend	*P* for interaction
	T1 (ref)	T2	T3 (highest)		
Total CVH metric					0.645
Female	1.00	0.59 (0.43, 0.82)	0.31 (0.21, 0.47)	0.001	
Male	1.00	0.56 (0.33, 0.93)	0.38 (0.18, 0.78)	0.003	
BMI metric					0.532
Female	1.00	0.81 (0.41, 1.63)	0.50 (0.26, 0.97)	0.001	
Male	1.00	0.99 (0.22, 4.57)	0.68 (0.15, 3.08)	0.133	
Smoking metric					**0.005**
Female	1.00	1.76 (0.43, 7.23)	0.38 (0.17, 0.84)	0.003	
Male	1.00	1.02 (0.49, 2.12)	0.97 (0.56, 1.69)	0.905	
Physical activity metric					0.229
Female	1.00	0.70 (0.51, 0.97)	0.62 (0.43, 0.91)	0.008	
Male	1.00	0.59 (0.35, 0.99)	0.41 (0.22, 0.77)	0.003	
Healthy diet metric					0.854
Female	1.00	0.90 (0.68, 1.20)	0.28 (0.04, 2.10)	0.268	
Male	1.00	0.86 (0.54, 1.39)	0.80 (0.09, 6.87)	0.540	
Blood pressure metric					0.662
Female	1.00	0.68 (0.47, 1.00)	0.63 (0.45, 0.89)	0.011	
Male	1.00	1.09 (0.62, 1.90)	0.71 (0.40, 1.24)	0.216	
TC metric					0.624
Female	1.00	0.86 (0.60, 1.24)	0.62 (0.43, 0.91)	0.010	
Male	1.00	1.21 (0.68, 2.17)	0.59 (0.31, 1.10)	0.052	

Note:

The estimates were presented as Odd Ratios and their 95% confident intervals;

The analysis was conducted in Model 3;

Abbreviations: CVH metric, Cardiovascular Health metric; RLS, Restless Legs Syndrome; BMI, body mass index; TC, total cholesterol.

Sex groups*	Odd ratios (95% Confident intervals)			*P* for trend	*P* for interaction
	T1 (ref)	T2	T3 (highest)		
Fasting blood glucose metric					0.475
Female	1.00	0.65 (0.37, 1.14)	2.13 (1.09, 4.14)	0.496	
Male	1.00	1.93 (1.01, 3.70)	1.25 (0.37, 4.27)	0.136	
Note:					
The estimates were presented as Odd Ratios and their 95% confident intervals;					
The analysis was conducted in Model 3;					
Abbreviations: CVH metric, Cardiovascular Health metric; RLS, Restless Legs Syndrome; BMI, body mass index; TC, total cholesterol.					

When the population was stratified by age, the risk of progression to RLS in those with higher tertiles of overall CVH metric score was significantly lower among individuals with an age of ≥ 60 years (T2: OR = 0.40, 95% CI 0.23–0.69; T3: OR = 0.25, 95% CI 0.12–0.54; $P < 0.001$) than among individuals who aged 45–60 years (T2: OR = 0.67, 95% CI 0.49–0.92; T3: OR = 0.35, 95% CI 0.23–0.52; $P < 0.001$), indicating the modification effect of age on the relationship between overall CVH metric score and RLS (*P* for interaction = 0.013). However, no significant group by age was identified for all seven CVH metrics scores (*P* for interaction ranged from 0.078 to 0.668, in Table 5).

Table 5
The results of logistic regression analysis for association of total and seven profiles of CVH metrics scores with RLS by ages.

Age groups	Odd ratios (95% Confident intervals)			*P* for trend	*P* for interaction
	T1 (ref)	T2	T3 (highest)		
Total CVH metric					**0.013**
45–60 years old	1.00	0.67 (0.49, 0.92)	0.35 (0.23, 0.52)	0.001	
≥ 60 years old	1.00	0.4 (0.23, 0.69)	0.25 (0.12, 0.54)	0.001	
BMI metric					0.668
45–60 years old	1.00	0.75 (0.35, 1.59)	0.47 (0.23, 0.98)	0.001	
≥ 60 years old	1.00	0.87 (0.28, 2.73)	0.52 (0.17, 1.60)	0.043	
Smoking metric					0.509
45–60 years old	1.00	1.25 (0.58, 2.73)	0.82 (0.46, 1.45)	0.425	
≥ 60 years old	1.00	0.84 (0.28, 2.52)	0.62 (0.29, 1.34)	0.212	
Physical activity metric					0.078
45–60 years old	1.00	0.76 (0.55, 1.03)	0.64 (0.44, 0.92)	0.012	
≥ 60 years old	1.00	0.44 (0.25, 0.79)	0.41 (0.21, 0.79)	0.002	
Healthy diet metric					0.524
45–60 years old	1.00	0.91 (0.68, 1.20)	0.52 (0.12, 2.25)	0.361	
≥ 60 years old	1.00	0.82 (0.50, 1.34)	——	0.313	
Blood pressure metric					0.538
45–60 years old	1.00	0.89 (0.62, 1.29)	0.70 (0.50, 1.00)	0.040	
≥ 60 years old	1.00	0.52 (0.27, 1.02)	0.50 (0.29, 0.87)	0.015	
TC metric					0.378
45–60 years old	1.00	1.07 (0.74, 1.53)	0.67 (0.46, 0.97)	0.014	
≥ 60 years old	1.00	0.75 (0.41, 1.37)	0.50 (0.27, 0.92)	0.024	

Note:

The estimates were presented as Odd Ratios and their 95% confident intervals;

The analysis was conducted in Model 3;

Abbreviations: CVH metric, Cardiovascular Health metric; T, tertile; BMI, body mass index; TC, total cholesterol.

Age groups	Odd ratios (95% Confident intervals)			*P* for trend	*P* for interaction
	T1 (ref)	T2	T3 (highest)		
Fasting blood glucose metric					0.306
45–60 years old	1.00	0.76 (0.45, 1.26)	1.77 (0.92, 3.40)	0.540	
≥ 60 years old	1.00	1.67 (0.81, 3.43)	2.41 (0.67, 8.68)	0.062	
Note:					
The estimates were presented as Odd Ratios and their 95% confident intervals;					
The analysis was conducted in Model 3;					
Abbreviations: CVH metric, Cardiovascular Health metric; T, tertile; BMI, body mass index; TC, total cholesterol.					

Discussion

In this cross-sectional study involving participants ages 45 years and above, we found a lower odd of RLS associated with a higher score of overall ideal CVH metric or its individual metrics in BMI, physical activity, blood pressure and TC. Consistently, a greater proportion of RLS was observed in those who rarely conducted physical activity, who had diabetes, who had higher levels of TG and FBG, who got poor level of total and specific LS7 metrics (e.g., BMI, physical activity, blood pressure, and TC) than non-RLS. The pattern of the association was largely robust to confounder adjustment but was significantly modified by sex and age stratifications.

An increasing number of studies have reported the associations between CVDs and RLS. For instance, a prior cross-sectional study in 3,433 middle-aged and elderly people observed independently association between RLS and CAD (OR = 2.05; 95% CI 1.38–3.04) and CVDs (OR = 2.07; 95% CI 1.43-3.00) [12]. The similar pattern of association of RLS with MI (HR = 1.80; 95%CI 1.07–3.01) and CHD (HR = 1.46; 95% CI 0.97–2.18) was also reported in another cross-sectional study based on 70,977 women in the Nurses' Health Study [13]. Of note, our study captured the beneficial effect of a favorable CVH metric score against the RLS. However, a study by Dredla BK *et al*. [24] did not observe a significant association between CVH metric and RLS, being contradict with our findings. Given that their study [24] was basically performed among adults Amerindians aged ≥ 40 years in South America, the variability in racial or ethnic factors across study populations may be responsible for the controversial findings as inheritance has been known to play a potential role in the etiology of RLS[26]. Furthermore, the relatively small sample size (665) in their study [24], might have led to underestimation of their results due to the insufficient testing power, thus contributing to the discrepancies between our study and their report. Although the mechanisms underlying the association between the CVDs and RLS are not fully understood, the periodic limb movement burden during sleep (PLMS) is related to incident CVDs [27] and increased blood pressure [28] due to the sympathetic activation accompanying PLMS. Autonomic dysregulation is a hallmark of

RLS, and the presence of PLMS is commonly found in patients with RLS [24], and this means that cardiovascular health might be worse in those had RLS coexisting PLMS [28].

The CVH metric was defined by SL7, so it may be assumed that different prevalence and incidence of RLS could be attributed to different health profiles. Common risk factors (e.g., female sex, smoking, HDL-C, LDL-C, TC) were found to be significantly associated with RLS [14], and our study reinforce the idea that the percentages of those who attaining ideal metrics for the overall CVH metric and specific LS7 (BMI, physical activity, blood pressure and TC) was higher in non-RLS group than in RLS group. These suggest that ideal adherence to these healthy life recommendations might be negatively associated with RLS. Even though there are limited studies directly concerning the relationship of each LS7 profile with RLS, prior studies have found the association between higher scores of ideal LS7 and better brain or neurological health. For instance, a study based on 1,987 subjects from the Washington Heights-Inwood Columbia Aging Project (WHICAP) found that a higher the LS7 components of physical activity was associated with lower risk of dementia among elder population [29]. Another study based on UK-biobank also suggested that adherence to ideal metrices of blood pressure, TC and FBG might offset the risk of dementia [30]. Higher scores of SL7 components (blood pressure, TC and FBG) might alleviate the pathology of AD by reducing pathological biomarkers in cerebrospinal fluid [31]. Therefore, understanding the effect of total CVH metric or LS7 on RLS is of great value for recognizing risk factors or helping patients to improve the prognosis.

It is in line with the studies by Xiang Gao *et al.*, [7] and K De Vito *et al.*, [32] which state that obesity was associated with increased risk of developing RLS, we found that individuals with RLS were more prone to have higher BMI level (presented as poor BMI metric). The increased RLS risk by high BMI could be explained by the reductions in dopamine D2 receptor. On one hand, dopamine deficiency could lead to obesity because dopamine is a neurotransmitter modulating motivation or reward circuits of foods [33]. On the other hand, low doses of dopamine agonists or α2δ ligands are uniquely recommended in clinical therapy of RLS [34] because a variety of cognitive, behavioral, and sensory-motor functions are regulated by the dopaminergic system[35]. In addition, iron deficiency, a common known risk factor of RLS, is also positively associated with obesity or overweight [36]. As for physical activity, one of the common cardiovascular related factors, Philips *et al.*, [37] found a significantly lower prevalence of RLS in subjects exercising more than three hours a month compared with subjects exercising less than three hours a month. Conversely, insufficient physical activity close to bedtime was associated with increased prevalence of RLS [38]. Moreover, undertaking moderate exercises, particularly light physical activity, in the evening could alleviate the symptoms of RLS[39], which further confirm the beneficial effect of physical activity against RLS. There is still a lack of knowledge about the mechanism(s) through which exercise might relieve RLS symptoms. One explanation is the positive effect of physical activity on the β-endorphin system. The β-endorphin is an endogenous opioid that promotes feelings of well-being and pain relief, while a defective opioid system might be part of the pathophysiology of RLS [40]. Besides, aerobic exercise may improve RLS symptoms by increasing blood flow to the brain and HD efficiency [41]

Interestingly, according to the findings of a German study based on two cohort studies (the Dortmund Health Study [n = 1312] and the Study of Health in Pomerania [n = 4308]), hypercholesterolaemia and hypertension have both been known as independent predictors of RLS incidence [42]. Our results reconfirmed these conclusions. Regarding to hypercholesterolaemia, prior studies conducted in US [32], in Israel [14], or in China [8] have demonstrated that RLS patients were more likely to have a disorder of lipid metabolism than those non-RLS. Although there is no consensus on the potential mechanisms causing RLS, it is well known that RLS patients tended to feel uncomfortable sensations and urge to stretch, move their legs and even walk during sleeping, thus contributing to sleep fragmentation, and sleep disorders are associated with hypercholesterolaemia and hypertension[43]. For instance, a Korean study showed that RLS patients were prone to have lower quality of sleep, and RLS patients suffering from insufficient or low quality of sleep tended to have worse serum lipid profile (higher LDL-C and TC) [44]. Furthermore, most prospective studies have reported significant elevations in nocturnal blood pressure in adults with RLS[28, 45]. Among them, the blood pressure and heart rate during sleeping could concomitantly rise after periodic limb movements indicating autonomic activation [43, 45]. Another possible explanation is that RLS symptoms may be attenuated by a wide range of common antihypertensive drugs, including certain alpha-2 agonists and beta-blockers, supporting a possible role of autonomic dysfunction in RLS aetiology [46].

Our stratified analysis pointed out that sex of female exerted significant modification effect on the association between smoking metric and RLS, and female with low score of smoking metric was more likely to develop RLS compared with the males. A prior epidemiologic literature in France also observed a higher prevalence of RLS in women rather than in men (10.8% *vs.* 5.8%, $P < 0.001$) [47]. This female-specific vulnerability of RLS might be partly ascribed to the sleep initiation insomnia, which is more prevalent in females than males [48]. In addition, as a not uncommon risk factor of RLS since the physiological bleeding during menstruation in women, dysfunction in iron metabolism [48], as well as other hormonal factors[49], contributes to the pathophysiology of RLS in women. Thus, the relationship between smoking and RLS was aggregated by female sex in our study. Similarly, significant interaction of age was found in the negative association between overall CVH metric and RLS, and the benefit of CVH metric to RLS was more evident in elderly participants aged ≥ 60 years. Although RLS can appear at any age, the vulnerability of RLS increases with age [34]. The prevalence of high CVH was lower at older ages as aging is a significant risk factor in the development of CVDs [50]. Physiological risk factors like blood pressure, cholesterol, and glucose were higher among older adults compared with younger adults, whereas ideal behavioural factors like physical activity and diet were less prevalent among them [50]. Thus it is interesting to consider that maintaining high CVH in elderly adults may result in markedly lower rate of RLS.

Our study also has limitations. First, we enrolled our participants by using stratified cluster random sampling method, and this might result in enrolment and selection bias and limit the generalizability of our findings. Second, the recall bias can not be ruled out in our results because the self-reported data was collected based on memory. Third, our findings could not be directly generalized to other populations.

Finally, the nature of cross-sectional study does not enable us to draw any causal conclusions between CVH metric and risk of RLS.

Conclusions

Our study provides evidence that better overall ideal CVH metrics and adherence to ideal LS7 profile may have favourable effects on RLS. This suggests that policies aimed at prevent or improve RLS symptoms should focus on lifestyle changes or metabolic risk profiles.

Abbreviations

AD	Alzheimer's disease
AHA	American Heart Association
BMI	Body mass index
CAD	Coronary artery disease
CHD	Coronary heart disease
CI	Confidence interval
CVDs	Cardiovascular diseases
CVH	Cardiovascular Health Metric
DBP	Diastolic blood pressure
FBG	Fasting blood glucose
HDL-C	High density lipoprotein cholesterol
HR	Hazard ratio
IRLSSG	International Restless Legs Syndrome Study Group
LDL-C	Low density lipoprotein cholesterol
LS7	7 Simple's Life
MI	Myocardial infarction
OR	Odd ratio
RLS	Restless Legs syndrome
SBP	Systolic blood pressure
SDs	Standard deviations
TC	Total cholesterol
TG	Total triglycerides
WMH	White matter hyperintensity

Declarations

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Author contributions

L.R.: study concepts and design. W.D., L.J., L.Q., M.X., Z.X., L.S.: investigation and data acquisition. W.D.: data analysis and manuscript preparation. L.R.: manuscript editing and review. All authors have read and agreed to the published version of the manuscript.

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Data availability statement

The original contributions presented in this study are included in the article, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Meizhou People's Hospital’s Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

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.

Consent for publication

Not applicable.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the insti-tutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Medical Ethics Committee of Meizhou People's Hospital (MPH-2021-034).

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