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Association of restless legs syndrome and obesity: A sub-population of the MASHAD cohort study☆

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A B S T R A C T

Introduction: Restless Legs Syndrome (RLS), as a relatively unknown sleep disorder, often associated with obesity. The purpose of this study was to examine the relationship between RLS and different definitions of obesity within the Mashhad stroke and heart atherosclerotic disorder (MASHAD) cohort study population.

Methods: A total of 1006 subjects, with an average age of 57 (51.75–63.00) years old, were randomly selected from the MASHAD cohort study phase II. This sample included 449 males and 557 females, who were contacted by phone to inquire about RLS. Anthropometric measurements such as weight, height, waist circumference (WC), and hip circumference (HC) were taken. Central obesity was defined as a WC $>$ 90 cm for men and $>$85 cm for women, as well as a waist-to-hip ratio (WHR) greater than 0.90 for men and 0.85 for women. Statistical analyses were conducted using R version 4.3.2 for Windows, with a significance level set at a two-sided P-value$<$0.05. Chi-squared and Fisher's exact tests were used to compare the categorical variables between two study groups. Logistic models applied to evaluate the association between RLS and BMI while adjusting for age effects.

Results: The study found a significant relationship between RLS and employment status (p-value = 0.04), marital status (p-value = 0.05), and BMI (p-value$<$0.001). The results showed that in the total population, the OR of RLS in subjects having BMI$>$30 kg/m^2 increased to 1.50(1.10–2.03) after adjusting for confounding factors (p-value$<$0.01). A BMI$>$30 kg/m^2 increased odds of RLS by 1.72 times in males (95%CI: 1.03–2.84, p-value$<$0.05), however this association was diminished after adjustment (OR = 1.20, 95%CI: 0.64–2.17). There was no significant association between BMI and RLS in females. Moreover, there was no significant association between RLS and obesity based on WC and WHR in fully adjusted model respectively.

Conclusion: There was a significant association between BMI and RLS. A BMI$>$30 kg/m^2 increased the odds of RLS by 1.50 times in the study population.

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1. Introduction

Restless legs syndrome (RLS) is a nervous system disorder that causes patients to feel a strong urge to move their legs. This disease is also known as Willis-Ekbom's disease (Bose and Jacob, 2019).

RLS, a relatively unknown sleep disorder, can be classified as such because it typically occurs or worsens during periods of rest. Individuals with RLS may have trouble sleeping or sitting for long periods such as in a theater or car). If left untreated, this disease can worsen, over time, leading to problems at work or home (Guay et al., 2020). People with RLS experience unusual sensations in their legs such as itching, stretching, pain, burning or tingling, and constantly try to move their legs to relieve these sensations. While primarily affecting the legs, RLS can also impact the arms and other parts of the body when severe (Trenkwalder and Paulus, 2010).

RLS affects about 5–10% of the general population (Rothdach et al., 2000; Tison et al., 2005), and is more common in women and more likely to cause more severe symptoms in middle-aged individuals. Diagnosis can be challenging, especially if symptoms are mild and infrequent, but early treatment can help manage the condition (Braga-Neto et al., 2004).

RLS can be categorized into primary and secondary types with the latter resulting from underlying conditions like peripheral neuropathy, diabetes mellitus, spinal ataxia, cardiovascular disease, Parkinson's disease, kidney disease, and iron deficiency anemia (Allen et al., 2003; Schlesinger et al., 2009). RLS with sleep disorders is more prevalent in obese individuals (Baran et al., 2018; Gao et al., 2009).

Anthropometry is a method used to measure the human body in terms of bone, fat and muscle dimensions (Ehrampoush et al., 2017). Assessing adipose tissue is crucial, as high levels of fat and a high BMI have been linked to various health risks (Fontela et al., 2017; Hruby et al., 2016).

The RLS pathological mechanism is related to a disturbance in the dopaminergic system, suggesting that environmental factors that affect the central nervous system's dopaminergic status can contribute to the development of RLS. Investigating the relationship between dopamine-dependent factors and RLS risk is essential for understanding its pathogenesis and preventing the condition (Allen, 2007; Paulus and Trenkwalder, 2006). In obese individuals, reduced availability of D2 receptors in the brain leads to decreased dopamine levels, increasing the risk of RLS (Wang et al., 2001). Epidemiological studies have shown a correlation between increased BMI and RLS development (Kim et al., 2005; Ohayon and Roth, 2002), indicating that measuring anthropometric indicators can help assess the risk of RLS.

This study aims to determine the association between RLS and total and central obesity, defined by BMI, waist circumference (WC) and waist to hip ratio (WHR) in men and women aged 45–75 years participating in the Mashhad stroke and heart atherosclerotic disorder (MASHAD) cohort study. A large-scale investigation was conducted to explore the relationship between overall obesity (indicated by higher BMI) and abdominal obesity (indicated by greater WC or WHR) and the risk of RLS in both male and female participants. Detailed data were collected, reviewed and analyzed from the cohort in Mashhad to achieve the goal.

2. Methods

The current study was conducted on a sub-population of MASHAD cohort study. The inclusion/exclusion criteria were previously explained in details (Ghayour-Mobarhan et al., 2015). In the MASHAD study, participants were selected from three regions in the city, using a stratified cluster random sampling technique. Each region was then divided into nine sites centered around Healthcare Centers divisions. Through phase two MASHAD cohort study which was conducted between 2018 and 2021, total 9704 participants of phase one were recruited. In current study, total 1006 participants were randomly selected samples from the entire population covered by the Healthcare Centers divisions.

Demographic variables and physical level activity (PAL) as well as anthropometric measurements were recorded for all participants. Height, weight, WC and hip circumferences (HC) were measured according to standard protocols (Manual, 2007). BMI was calcualted using the formula of weight Kg/Height $(m)^2$. WHR was obtained by dividing the WC by the HC. Total obesity was defined as BMI$\geq$30 kg/m^2. Central obesity was calculatd according to both WC and WHR. WC $\geq$ 90 cm in men and $\geq$85 cm in women (Bao et al., 2008) or WHR$\geq$0.90 in men and $\geq$0.85 in women was considred as abdominal obesity (Organization WH, 2000).

All subjects then asked by phone about the Persian translation of a single question identified in English by the International RLS Study Group: "When you try to relax in the evening or sleep at night, do you ever have unpleasant, restless feelings in your legs that can be relieved by walking or movement?", (Ferri et al., 2007). They were then enterd into the analysis in two group: with and without RLS.

3. Ethics

Informed consent was obtained from all the participants. The study protocol was approved by Mashhad University of Medical Sciences ethics committee (ID = 991783; IR.MUMS.REC.1399.677).

4. Statistical analysis

Statistical analysis was performed separately according to sex. Categorical variables were represented by frequency and percentage. Continuous variables were expressed as median (interquartile range [IQR]) and mean (standard deviation). Due to the asymmetric nature of the variables, the median and IQR are more reliable. The normality of continuous variables distribution was assessed using histograms and Q-Q plots and tested using normality tests. The differences in continuous variables (age, PAL, BMI, WHR and WC) between two sexes and two groups (RLS group and Non-RLS group) examined by Mann-Whitney. The differences in categorical variables between two groups were tested by Chi-squared and Fisher's exact test separately according to sex. The linearity of the log-odds was assessed by the Box-Tidwell test. The collinearity of the variables was also checked. The association between RLS and BMI was tested by logistic models) Full model) by adjusting the effect of age. Odds ratios (ORs) and corresponding confidence intervals were calculated for all models. All statistical analyses were performed using R version 4.3.2 for Windows. A two-sided P-value of <0.05 was considered statistically significant.

5. Results

There were 449 men and 557 women in this study. The overall median age was 57 (IQR = 51.75–63.00) years, while the ages of the males and females were 58 (IQR = 52–64) and 57 (IQR = 51–61), respectively. In general, there was a significant relationship between having RLS and variables such as employment status, marriage, and diabetes, etc. The baseline characteristics of the study subjects according to sex are shown in Table 1.

To examine the results in more detail, the variables were first examined as a univariate model for each of the models. Then the full model (adjusting the effect of age) was fitted to them. No nonlinear relationship was observed in different types of obesity. All of the Variance Inflation Factor (VIF) values were less than 5, indicating the absence of collinearity (Table 2).

As summarized in Table 3, in the total population, the OR of RLS in subjects with a BMI> 30 kg/m^2 increased to 1.77(CI: 1.35–2.32) and 1.50(1.10–2.03) before and after adjustment for confounding factors ($p < 0.001$ and $p < 0.01$, respectively). A BMI> 30 kg/m^2 increased the odds of RLS by 1.72 times in males (CI: 1.03–2.84, $p < 0.05$), however this association was diminished after adjustment (OR = 1.20, 95%CI:

Table 1
Baseline characteristics of the study population.

Variables	Total			Male			Female		
	RLS-	RLS+	p-value	RLS-	RLS+	p-value	RLS-	RLS+	p-value
Age (year)	57(52–63) 57.60 ± 7.96	57(51–62) 57.07 ± 7.51	0.42	58(52–65) 58.32 ± 8.28	59(53–64.50) 58.88 ± 8.06	0.56	56(51–61) 56.77 ± 7.50	57(50–61) 56.32 ± 7.15	0.73
PAL	1.68(1.45–1.96) 1.74 ± 0.43	1.69(1.47–1.97) 1.77 ± 0.44	0.61	1.56(1.33–1.89) 1.65 ± 0.45	1.55(1.35–1.85) 1.64 ± 0.44	0.91	1.80(1.59–2.03) 1.84 ± 0.37	1.72(1.52–2.02) 1.82 ± 0.44	0.08
BMI (kg/m^2)	27.65(24.87–30.81) 28.01 ± 4.74	29.05(25.91–32.47) 29.39 ± 5.01	<0.001	26.67(24.34–29.07) 26.89 ± 4.38	27.90(24.23–30.15) 27.75 ± 4.20	0.05	29.01(25.97–32.51) 29.29 ± 4.81	29.52(26.21–33.31) 30.07 ± 5.16	0.12
WHR	0.91(0.85–0.97) 0.91 ± 0.08	0.89(0.84–0.95) 0.90 ± 0.09	0.03	0.94(0.90–0.98) 0.94 ± 0.06	0.95(0.90–0.99) 0.95 ± 0.07	0.09	0.86(0.82–0.92) 0.87 ± 0.08	0.87(0.82–0.92) 0.87 ± 0.08	0.34
WC (cm)	92(86–98) 91.98 ± 10.30	93(85–100) 93.02 ± 11.21	0.22	93(87–99) 93.47 ± 9.64	96(87.75–102.25) 95.87 ± 10.56	0.04	90(83.00–97.87) 90.30 ± 10.77	91(84–99) 91.86 ± 11.28	0.15
Education; N(%)									
Illiterate	42(7.37)	31(8.73)	0.33[a]	17(5.67)	5(4.76)	0.98[a]	25(9.26)	26(10.40)	0.34[a]
Elementary	174(30.53)	125(35.21)		73(24.33)	29(27.62)		101(37.41)	96(38.40)	
Diploma or less	243(42.63)	150(42.25)		138(46.00)	48(45.71)		105(38.89)	102(40.80)	
Associated degree	33(5.79)	18(5.07)		22(7.33)	5(4.76)		11(4.07)	13(5.20)	
Bachelor	65(11.40)	27(7.61)		39(13.00)	14(13.33)		26(9.63)	13(5.20)	
Master	8(1.40)	3(0.85)		8(2.67)	3(2.86)		0(0.00)	0(0.00)	
PhD or more	5(0.88)	1(0.28)		3(1.00)	1(0.95)		2(0.74)	0(0.00)	
Smoking; N(%)									
No	116(55.77)	88(56.41)	0.90	71(52.21)	38(60.32)	0.29	45(62.50)	50(53.76)	0.26
Yes	92(44.23)	68(43.59)		65(47.79)	25(39.68)		27(37.50)	43(46.24)	
employment status; N(%)									
Employee	394(68.17)	274(74.86)	0.04	149(49.83)	44(41.51)	0.32	245(87.81)	230(88.46)	0.19
Unemployed	28(4.84)	20(5.46)		24(8.03)	11(10.38)		4(1.43)	9(3.46)	
Retired	156(26.99)	72(19.67)		126(42.14)	51(48.11)		30(10.75)	21(8.08)	
Marriage; N(%)									
Single	6(1.01)	4(1.08)	0.05	4(1.27)	1(0.92)	0.10[a]	2(0.72)	3(1.15)	0.81[a]
Married	553(93.10)	327(88.14)		310(98.41)	105(96.33)		243(87.10)	222(84.73)	
Divorced	8(1.35)	8(2.16)		1(0.32)	2(1.83)		7(2.51)	6(2.29)	
Widow	27(4.55)	32(8.63)		0(0.00)	1(0.92)		27(9.68)	31(11.83)	
Diabetes mellitus; N(%)									
No	436(74.28)	240(65.75)	<0.01	223(71.47)	77(71.96)	0.92	213(77.45)	163(63.18)	<0.001
Yes	151(25.72)	125(34.25)		89(28.53)	30(28.04)		62(22.55)	95(36.82)	
Hypertension; N(%)									
No	288(48.40)	170(45.82)	0.43	141(44.62)	58(53.21)	0.12	147(52.69)	112(42.75)	0.02
Yes	307(51.60)	201(54.18)		175(55.38)	51(46.79)		132(47.31)	150(57.25)	
BMI Categories; N(%)									
<30	421(71.11)	216(58.22)	<0.001	256(81.27)	78(71.56)	0.03	165(59.57)	138(52.67)	0.11
≥30	171(28.89)	155(41.78)		59(18.73)	31(28.44)		112(40.43)	124(47.33)	
WHR Categories; N(%)									
0	205(34.92)	120(32.70)	0.48	78(25.08)	21(19.81)	0.27	127(46.01)	99(37.93)	0.06
1	382(65.08)	247(67.30)		233(74.92)	85(80.19)		149(53.99)	162(62.07)	
WC Categories; N(%)									
0	174(29.59)	96(26.16)	0.25	96(30.77)	30(28.30)	0.63	78(28.26)	66(25.29)	0.44
1	414(70.41)	271(73.84)		216(69.23)	76(71.70)		198(71.74)	195(74.71)	
CVD; N(%)									
event	51(10.35)	52(16.51)	0.01	32(12.65)	17(19.54)	0.11	19(7.92)	35(15.35)	0.01
Healthy	442(89.65)	263(83.49)		221(87.35)	70(80.46)		221(92.08)	193(84.65)	

Abbreviations: physical activity level: PAL; body mass index: BMI; waist circumference: WC; waist to hip circumference: WHR; AOR: adjusted odd ratio, CI: Confidence Interval; cardiovascular disease: CVD.

[a] Fisher's exact test.

0.64–2.17). There was no significant association between BMI and RLS in females (OR = 1.20, 95%CI:0.82–1.75). The OR of RLS in obese subjects based on WC and WHR was 1.05(95%CI:0.76–1.47, P > 0.05) and 1.00(95%CI:0.72–1.38, p > 0.05), respectively, in the fully adjusted model. ORs and confidence intervals of different types of obesity are shown in Fig. 1.

6. Discussion

In this study, we investigated the relationship between RLS and obesity. In the total population, a BMI>30 kg/m^2 can increase the odds of RLS by 1.5 times after adjustment for confounding factors, significantly. A BMI>30 kg/m^2 can increase the odds of RLS by 1.72 times in males, significantly, which was not significant after adjustment. While there was no significant association between BMI and RLS in females. There were no significant associations between WC and WHR with RLS. However, a positive relationship was observed which was clinically valuable.

RLS is a common movement disorder in which the patient tends to move her legs a lot and has a significant impact on sleep, daily activities and quality of life (Garcia-Borreguero et al., 2004; Kushida, 2007). It is divided into two primary or idiopathic and secondary types. The cause of idiopathic is unknown, which may be caused by genetics and family history (Walters et al., 2003). While secondary RLS is caused by environmental factors such as iron deficiency, anemia, pregnancy, diabetes and rheumatoid arthritis (Beladi-Mousavi et al., 2015; Turk et al., 2018). Furthermore, it has been shown that effective lifestyle factors such as lack of physical activity, obesity, smoking, alcohol consumption and stress can increase the incidence of RLS (Phillips et al., 2000). In the current study, socio-economic factors were investigated and a significant relationship between RLS and employment status and marriage was found. Studies have shown a relationship between depression, anxiety and insomnia with RLS (Lee et al., 2008; Winkelmann et al., 2005). Exposure to stressful life events can increase the risk of RLS (Didato et al., 2020).

Most studies have shown a relationship between obesity and a high risk of RLS prevalence (Kim et al., 2005; Ohayon and Roth, 2002; Phillips et al., 2000). Our results also indicate that a BMI greater than 30

Table 2
The collinearity of the significant variables in study groups.

Variables	Total			Male			Female		
	Univariate P-value	Full Model P-value	VIF	Univariate P-value	Full Model P-value	VIF	Univariate P-value	Full Model P-value	VIF
Model 1									
Age, years	0.31	0.75	1.23	0.54	0.91	1.48	0.47	0.51	1.08
BMI Categories			1.03			1.02			1.03
<30 (kg/m^2)									
>=30 (kg/m^2)	<0.001	<0.01		0.03	0.56		0.11	0.35	
Diabetes			1.06			1.09			1.04
0									
1	<0.01	0.02		0.92	0.63		<0.001	<0.001	
CVD			1.07			1.10			1.03
0									
1	0.01	0.02		0.12	0.35		0.01	0.03	
Employment status			1.20			1.41			1.06
Employee									
Unemployed	0.93	0.48		0.27	0.09		0.15	0.17	
Retired	0.01	0.14		0.19	0.08		0.33	0.61	
Model 2									
Age, years	0.31	0.54	1.23	0.54	0.99	1.47	0.47	0.39	1.08
Central obesity according to WC			1.02			1.01			1.03
0									
1	0.25	0.76		0.63	0.99		0.44	0.94	
Diabetes			1.06			1.09			1.04
0									
1	<0.01	0.01		0.92	0.55		<0.001	<0.001	
CVD			1.07			1.11			1.03
0									
1	0.01	0.01		0.12	0.30		0.01	0.02	
Employment status			1.18			1.41			1.05
Employee									
Unemployed	0.93	0.56		0.27	0.09		0.15	0.18	
Retired	0.01	0.08		0.19	0.06		0.33	0.57	
Model 3									
Age, years	0.31	0.54	1.27	0.54	0.97	1.50	0.47	0.26	1.15
Central obesity according to WHR			1.11			1.06			1.13
0									
1	0.48	0.98		0.27	0.99		0.06	0.21	
Diabetes			1.09			1.11			1.07
0									
1	<0.01	0.01		0.92	0.55		<0.001	<0.01	
CVD			1.08			1.10			1.04
0									
1	0.01	0.01		0.12	0.29		0.01	0.01	
Employment status			1.19			1.41			1.05
Employee									
Unemployed	0.93	0.57		0.27	0.09		0.15	0.23	
Retired	0.01	0.08		0.19	0.06		0.33	0.62	

Full Model: Fully adjusted for age, Diabetes, CVD and Employment status.
Abbreviations: body mass index: BMI; waist circumference: WC; waist to hip circumference: WHR; AOR: adjusted odd ratio, CI: Confidence Interval, VIF: Variance Inflation Factor.

Table 3
Association of Restless Legs Syndrome with body mass index (BMI), waist circumference (WC) and waist to hip circumference (WHR) using Logistic regression.

Variables	Total		Male		Female	
	Univariate OR (95% CI)	Full Model AOR (95% CI)	Univariate OR (95% CI)	Full Model AOR (95% CI)	Univariate OR (95% CI)	Full Model AOR (95% CI)
BMI Categories						
<30 (kg/m^2)	1.00	1.00	1.00	1.00	1.00	1.00
>=30 (kg/ m^2)	1.77 (1.35–2.32) ***	1.00	1.00	1.00	1.00	1.00
Central obesity according to WC						
0	1.00	1.00	1.00	1.00	1.00	1.00
1	1.19(0.89–1.59)	1.05(0.76–1.47)	1.13(0.70–1.85)	1.00(0.57–1.79)	1.16(0.79–1.71)	1.02(0.66–1.57)
Central obesity according to WHR						
0	1.00	1.00	1.00	1.00	1.00	1.00
1	1.10(0.84–1.46)	1.00(0.72–1.38)	1.35(0.80–2.37)	1.00(0.53–1.95)	1.39(0.99–1.97)	1.29(0.86–1.95)

Full Model: Fully adjusted for age, Diabetes, CVD and Employment status.
Significance level, ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$.
Abbreviations: body mass index: BMI; waist circumference: WC; waist to hip circumference: WHR; AOR: adjusted odd ratio, CI: Confidence Interval.

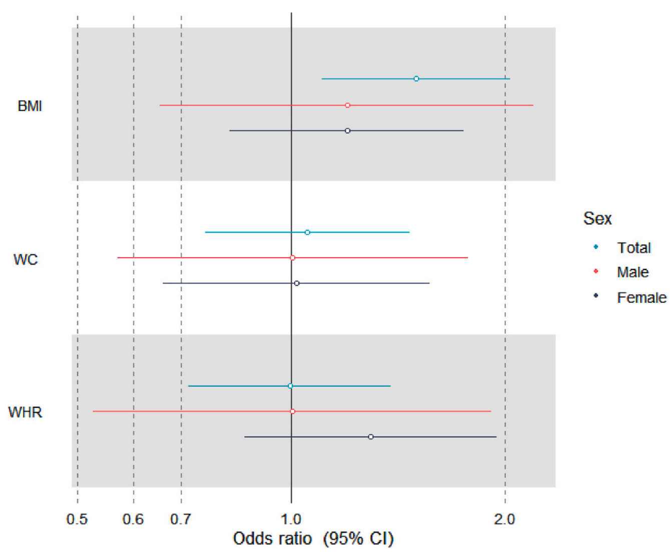

Fig. 1. Forest plot summarizing multivariable logistic regression models for the BMI, WC and WHR. The dependent variable was RLS. There were 9 separate regression models by adjusting the effect of age, Diabetes, CVD and Employment status.

kg/m^2 can increase the risk of RLS in the study population. Several studies have demonstrated a significant relationship between obesity and RLS (Baran et al., 2018; Phillips et al., 2000). Previous epidemiological studies have suggested that BMI is associated with an increase in RLS regardless of other confounders such as WHR index and WC index (Gao et al., 2009; Kim et al., 2005). However, our study revealed that men with a higher BMI are more likely to be affected by RLS than women.

The mechanism by which obesity and increased BMI are associated with RLS is complex. Results from several studies suggest that the dopaminergic system in the central nervous system may influence both obesity and RLS. Obese people have lower numbers of dopamine D2 receptors, and the number of dopamine receptors is broadly inversely related to BMI (Wang et al., 2001). Reduction of dopamine receptors increases appetite and obesity. These results are consistent with observations from animal studies in obese rats that had fewer dopamine D2 receptors (Hamdi et al., 1992; Huang et al., 2006). Genetic studies showed that there is a relationship between obesity and various genes related to dopamine metabolism such as MAOA and MAOB (Need et al., 2006). Studies have also shown that genetic variants of human obesity genes that predict BMI interact with the dopamine D2 receptor (Comings et al., 1996). However, according to previous studies and our results, obesity increases the risk of RLS.

In similar studies conducted in Iran, the prevalence of RLS has been observed more in overweight women, especially in diabetic patients who are obese, as well as in pregnant women and women with iron deficiency. This is contrary to the results of our study (Gheshlagh et al., 2016; Modarresnia et al., 2018; Meharaban et al., 2015). In our study, we did not take pregnancy and diabetes in women into account, and the age of the women in our study was older, showing no difference compared to another study (Batool-Anwar et al., 2016). Additionally, another study indicated that obese men have a higher chance of developing RLS compared to women, which aligns with our study (Kageyama et al., 2000; Wali and Abaalkhail, 2015). Generally, women tend to have a higher BMI than men, increasing the likelihood of RLS among obese men. However, strategies to reduce weight and enhance dopaminergic function can involve behavioral interventions such as exercise. Studies on animal models have shown that can boost dopamine release and increase D2 receptor activity (Hattori et al., 1994; MacRae et al., 1987). Weight loss and maintaining a low BMI can decrease the risk of RLS in both men and women.

On the other hand, the results regarding the prevalence of RLS based on geographical regions show that the highest prevalence is in the east of Iran and the lowest is in the north, indicating that gender, geographic and racial factors all play a role in the prevalence of this disease (Sorbi et al., 2020).

Therefore, early diagnosis of RLS disorder and providing appropriate prevention and treatment strategies to reduce its impact on Iranian adults, particularly focusing on maintaining a healthy weight, proper nutrition, adequate physical activity and reducing exposure to stressful life events, is necessary.

7. Study strengths and limitations

This study had strengths and limitations. The cohort study included a community from Mashhad city that was randomly conducted through telephone calls and not through face-to-face interviews, but the results obtained were analyzed in a very detailed and in-depth manner. Moreover, ddefinition of RLS based on one question could be another limitation for this study.

8. Conclusion

In summary, the present study showed a significant association between BMI, employment status, marital status, CVD and diabetes with RLS. Having a BMI≥30 kg/m^2 can increase the RLS risk by 1.50 times compared to having a BMI of<30 kg/m^2 in the study population. Given the high prevalence of RLS as a relatively unknown sleep disorder, prioritizing prevention as the initial step and treatment as the subsequent step is crucial. It appears that managing obesity could be beneficial in both preventing and treating RLS. However, more research particularly in the physiopathology of this relationship, is recommended.

CRediT authorship contribution statement

Azam Vafaei: Writing – review & editing, Writing – original draft, Supervision, Investigation, Conceptualization. **Fatemeh Khorashadizadeh:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Conceptualization. **Maryam Saberi-Karimian:** Writing – review & editing, Writing – original draft, Investigation. **Sara Saffar Soflaei:** Writing – review & editing, Writing – original draft, Investigation. **Mahnaz Amini:** Writing – review & editing, Investigation. **Abolfazl Rashid:** Investigation. **Sara Yousefian:** Investigation. **Gordon A. Ferns:** Writing – review & editing. **Habibollah Esmaily:** Software, Methodology, Formal analysis, Data curation. **Majid Ghayour-Mobarhan:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Funding acquisition, Conceptualization. **Reza Salaran:** Investigation. **Fatemeh Taherian:** Investigation, Conceptualization.

Declarations

There is no conflict of interest. The study approval code form MUMS ethics committee is IR.MUMS.REC.1399.677 which was given approval according to Helsinki ethical principles in medical research. The data belongs to MUMS and could be shared upon a reasonable request by the corresponding author. All the authors have reviewed and approved the final version of the manuscript. They also agreed to be responsible for all aspects of the work.

Declaration of competing interest

The authors confirm no conflicts of interest.

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