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The association between restless legs syndrome, cardiovascular and metabolic diseases: hypotheses and evidence from the literature

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ABSTRACT

The association Restless Legs Syndrome (RLS) and both cardiovascular risk factors (CVRFs), such as hypertension and diabetes, and cardiovascular diseases (CVDs) still remains elusive. Although several shared physiophatological causes could explain these possible relationships, the emerging body of literature focusing on these disorders remains controversial. The reasons for these inconsistent findings are mainly due to the different methodologies applied.
First, considering that RLS, CVRFs and CVDs are influenced by age and sex, many clinical and population-based studies performed a selection bias by restricting the sample collection to these covariates. Second, assessments of covariates are often incomparable and the methods applied for diseases assessment are often affected by low sensitivity and specificity. Only few population-based studies collected data by means of face-to-face interview or physical examination in order to limit the false positive rate compared to questionnaires administered by mail or telephone. The assessment of RLS was not always performed according to International RLS Study Group (IRLSSG) criteria and anyway the four diagnostic criteria did not allow the exclusion of other disorders that may act as mimics (Hening et al., 2009; Allen et al., 2014). Disease assessment ranged from a self-reported diagnosis, information on the use of specific medications, or a direct measurement of BP and blood glucose levels. Moreover, some anti-hypertensive medications, such as beta-blockers and certain calcium channel blockers, could both ameliorate and aggravate RLS symptoms (Innes et al., 2012) and therefore it would be important to consider medications as confounding factors. In addition, the co-occurrence of several CVRFs is frequent and they may influence each other. Therefore, the cross-sectional nature of most studies cannot assess the causal relationship between them and the variables of interest (i.e., RLS and/or CVDs). Finally, only few studies adjusted their analyses for other cardiovascular risk factors, such as diabetes mellitus, history of myocardial infarction, Body Mass Index (BMI), dyslipidemia, and smoking status, that might act as confounders or mediators.
In summary, longitudinal population-based studies and meta-analyses will be necessary in order to build a sufficiently robust body of evidence on this topic.

Key Words
Restless Legs Syndrome • Hypertension • Cardio-vascular risk factors • Cardio-vascular diseases • Diabetes

Restless legs syndrome, cardiovascular risk and the pathophysiological link

Restless Legs Syndrome (RLS) is a sensori-motor disorder characterized by an urge to move the legs usually accompanied by unpleasant sensations, such as paresthesia and/or dysesthesia, that usually appears or worsens at rest, especially in the evening-night and that ameliorates with movement (Allen et al., 2003; American Academy of Sleep Medicine, 2014). In Western countries about

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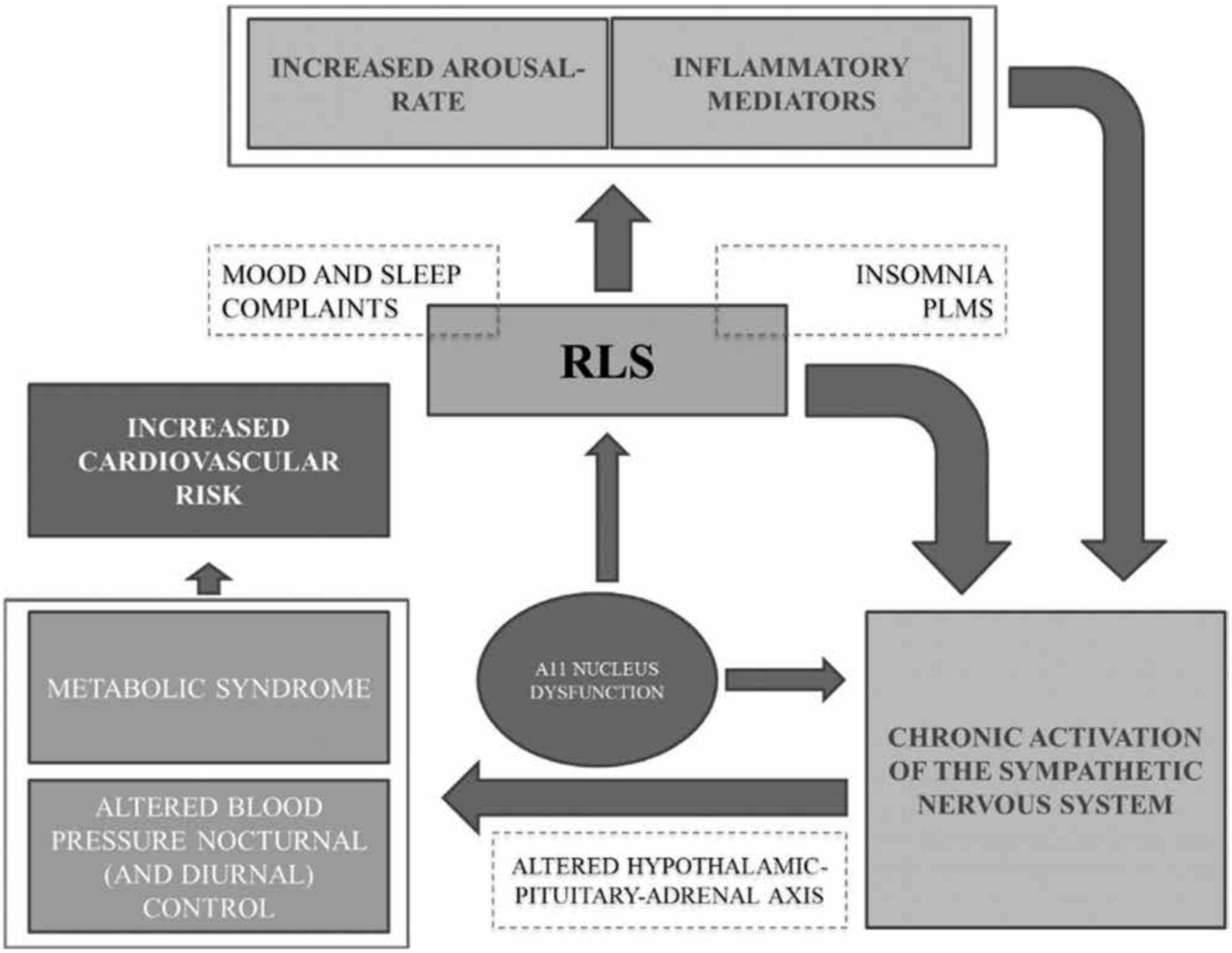

Figure 1. - Schematic representation of the main pathophysiological hypotheses underpinning the association between Restless Legs Syndrome and Cardiovascular Diseases. RLS: Restless Legs Syndrome; PLMS: Periodic Limb Movements during Sleep.

2-4% of adults suffer from RLS in its clinically significant form (Allen et al., 2010). RLS can be either idiopathic or secondary to medical or physiological conditions, such as iron deficiency, kidney failure, neuropathy or pregnancy. In 90% of patients, RLS is associated with Periodic Limb Movements during Sleep (PLMS), which are repetitive flexion movements of the lower limbs, usually appearing during non-REM sleep (NREM), lasting 0.5-10 seconds, presenting with a repetitive fashion and often causing arousals (Walters and Rye, 2009; Alessandria and Provini, 2013).

In the last years, many studies have evidenced a possible relationship between RLS and cardiovascular diseases (CVDs), in particular hypertension. In order to elucidate the physiopathogenetic basis of this association, different hypotheses have been proposed (Figure 1) (Portaluppi et al., 2009; Walters and Rye, 2009; Innes et al., 2012; Ferini-Strambi et al., 2014; Calandra-Buonaura et al., 2015).

1) RLS could increase the risk of CVDs and metabolic disorders through a chronic activation of the sympathetic nervous system and/or hypothalamic-pituitary-adrenal (HPA) axis. Many studies evidenced that RLS with/without PLMS is associated with increased arousal rate, nocturnal blood pressure (BP) and heart rate (HR) (Alessandria and Provini, 2013; Ferini-Strambi et al., 2014; Nannapaneni et al., 2014; Ferri et al., 2015; Silvani et al., 2015). Moreover, the sustained absence of sleep due to insomnia and/or the frequent recurrence of PLMS-related arousals could prevent the physiological decrease in BP during sleep causing a "non-dipping" profile, and an irregular BP pattern leading to autonomic imbal-

ance and therefore, to an increased cardiovascular risk (Innes et al., 2012; Ferini-Strambi et al., 2014; Nannapaneni et al., 2014). Augmented nocturnal cortisol excretion has been demonstrated in RLS independently from the presence of PLMS (Schilling et al., 2010). Consequently, sympathetic hyperactivity, parasympathetic hypoactivity and an increased cortisol release could underpin the development of a metabolic syndrome (Innes et al., 2012). Another complementary possible explanation is the association between mood and sleep complains related to RLS. It has been demonstrated that poor sleep quality and depression are associated with sympathetic-parasympathetic imbalance and therefore with autonomic dysregulation. Moreover, affective disorders have been linked to augmented cardiovascular risk and metabolic syndrome (Innes et al., 2012).

2) The second possible explanation is that CVDs and metabolic syndrome, characterized by sympathetic and HPA axis overflow with neuroendocrine dysregulation, pain generation and motor control impairment, may conversely increase the risk for RLS (Walters and Rye, 2009; Innes et al., 2012). Moreover, CVDs and metabolic syndrome are related to mood disorders and altered sleep, which may promote or exacerbate RLS symptoms.
3) Another possible hypothesis is that CVDs, metabolic diseases and RLS share common risk factors, including sleep disruption, obstructive sleep apnea, affective disorders, sympathetic hyperactivity, chronic stress, and inflammatory pathways (Innes et al., 2012; Ferini-Strambi et al., 2014). In particular, many epidemiological studies documented a strong association between depressive disorder and RLS suggesting a bidirectional relationship between the two disorders (Szentkiralyi et al., 2013b; Becker and Sharon, 2014; Mackie and Winkelman, 2015; Trautmann et al., 2015). Although the mechanism of this association is not fully understood, a common alteration of dopaminergic system has been proposed as possible substrate of this comorbidity (Becker and Sharon, 2014).
4) A dysfunction in the dopaminergic A11 hypothalamic nucleus has been hypothesized in RLS (Walters and Rye, 2009). This nucleus modulates sympathetic activity through projections to preganglionic sympathetic neurons and therefore its hypofunction could lead to hyperactivation of sympathetic outflow and cause hypertension (Walters and Rye, 2009; Ferini-Strambi et al., 2014).

Several clinical and population-based studies focused on the association between RLS and cardiovascular risk factors (CVRFs) and CVDs. Among the different pathophysiological hypotheses and study designs, some investigated the role of RLS as a risk factor for CVDs and others the risk of incident RLS in subjects with CVRFs at baseline (Walters and Rye, 2009; Innes et al., 2012). Apart from the epidemiological and pathophysiological importance of these studies, one major issue is related to the role of RLS as possible CVRF with a subsequent impact on quality of life and management of patients.

The aim of this narrative review is to describe current evidence regarding the association between RLS, CVRFs and CVDs, focusing *mainly* on general population-based studies.

A summary of the main methodological issues and results of the studies is reported in the Table I.

Association between RLS and hypertension

A significant amount of clinical and population-based studies focused on the relationship between RLS and hypertension showing contradictory results. Differences in the studies' design, in population characteristics and in the definition of RLS and hypertension may explain these conflicting results.

Population-based studies

Among the population-based studies assessing the relationship between RLS and hypertension, eight found a significant association, in six after adjustment for possible confounding factors. All studies but one applied the International Restless Legs Syndrome Study Group (IRLSSG) criteria (Walters, 1995; Allen et al., 2003) for RLS assessment.

In a study performed in Sweden, Ulfberg and colleagues (2001) evaluated the prevalence and comorbidities of RLS in a sample of males, aged 18-64 years, randomly selected from the general population. Out of the original sample, 2608 (66%) subjects responded to a mailed questionnaire including questions based on IRLSSG criteria for the diagnosis of RLS and items concerning self-reported disease diagnosis including hypertension. The authors

Table I. - Summary of the main studies regarding the association between Restless Legs Syndrome, hypertension and diabetes mellitus/glucose intolerance (studies are presented in chronological order).

Author, year	Study design	Sample size	Enrollment setting	Age range and gender	Disease assessment	Disease definition			
						IRLSSG criteria	Hypertension	DM	CVDs
Banno et al., 2000	Cross-sectional	1090	Clinical	11-90 ♀♂	Medical records	-	Medical records	Medical records	Medical records
Rothdach et al., 2000	Cross-sectional	369	General population	≥65 ♀♂	Face-to-face interview	+	Self-reported		
Skomro et al., 2001	Cross-sectional	106	Clinical	≥18 ♀♂	Questionnaires and interview	+	-	Chart review and self-reported	Chart review and self-reported
Ulfberg et al., 2001	Cross-sectional	2608	General population	18-64 ♂	Mailed questionnaire	+	Self-reported	-	-
Ohayon and Roth, 2002	Cross-sectional	18980	General population	15-100 ♀♂	Telephone interview	+	Self-reported	-	Self-reported
Berger et al., 2004	Cross-sectional	4107	General population	20-79 ♀♂	Face-to-face interview	+	Automatic measurement	Self-reported	Self-reported
Foley et al., 2004	Cross-sectional	1506	Community-dwelling	55-84 ♀♂	Self-administered questionnaire	-	-	Self-reported	Self-reported
Högl et al., 2005	Cross-sectional	701	General population	50-89 ♀♂	Face-to-face interview	+	Self-reported and/or measurement	Self-reported and/or measurement	Self-reported and/or measurement
Lopes et al., 2005	Cross-sectional	100	Clinical	≥18 ♀♂	Clinical visit	+	-	Medical assessment	-
Elwood et al., 2006	Longitudinal cohort study	1986	General population	55-69 ♂	Self-administered questionnaire	-	-	-	Exam, medical records
Lee et al., 2006	Cross-sectional	1071	General population	≥18 ♀♂	Face-to-face interview	+	-	Self-reported	Self-reported
Phillips et al., 2006	Cross-sectional	1506	General population	≥18 ♀♂	Telephone interview	+	Self-reported	Self-reported	Self-reported
Winkelman et al., 2006	Cross-sectional	2821	General population	30-60 ♀♂	Mailed questionnaire	-	Self-reported or reported physician-diagnosis	Self-reported	Self-reported
Alattar et al., 2007	Cross-sectional	1934	Primary care	≥18 ♀♂	Self-administered questionnaire	-	Self-reported	Self-reported	Self-reported
Merlino et al., 2007	Cross-sectional	211	Clinical	≥18 ♀♂	Clinical visit	+	-	Medical assessment	Laboratory and medical assessment

Mallon et al., 2008	Cross-sectional	3496	General population	30-65 ♀♂	Mailed questionnaire	-	Self-reported	-	-
Wesstrom et al., 2008	Cross-sectional	3516	General population	18-64 ♀	Mailed questionnaire	+	Self-reported	Self-reported	Self-reported
Winkelman et al., 2008	Cross-sectional	3433	General population	44-98 ♀♂	Self-administered questionnaire	+	Self-reported and/or measurement	Self-reported	Self-reported and/or measurement
Bosco et al., 2009	Cross-sectional	260	Clinical	≥18 ♀♂	Clinical visit	+	-	Direct measurement of glucose intolerance	Medical assessment
Schlesinger et al., 2009	Cross-sectional	1537	Primary care	Around 50 ♀♂	Self-administered questionnaire + sleep-specialist assessment	+	Self-reported and/or measurement	Self-reported and/or measurement	Self-reported and/or measurement
Benediktsdottir et al., 2010	Cross-sectional	1370	General population	≥40 ♀♂	Face-to-face interview	+	Self-reported physician-diagnosis	Self-reported physician-diagnosis	Self-reported physician-diagnosis
Juuti et al., 2010	Cross-sectional	997	General population	57 ♀♂	Self-administered questionnaire	+	Self-reported and/or measurement	Self-reported	Self-reported
Celle et al., 2010	Cross-sectional	318	General population	68.6±0.8 ♀♂	Clinical assessment	+	Direct measurement	Laboratory testing	Measurement and self- reported
Keckeis et al., 2010	Cross-sectional	97 (18 RLS)	Clinical	≥18 ♀♂	Clinical visit	+	-	Direct measurement of glucose intolerance	Self-report and medical assessment
Möller et al., 2010	Cross-sectional	16531	Primary care	≥18 ♀♂	Self-administered questionnaire	+	Physician-reported	Physician-reported	Physician-reported
Batool-Anwar et al., 2011	Cross-sectional	65544	Health professionals	25-42 ♀	Self-administered questionnaire	+	Self-reported	-	-
Li et al., 2012	Longitudinal	70977	Health professionals (NHS)	30-55 ♀	Mailed questionnaire	+	Self-reported	Self-reported	Self-reported
Winter et al., 2012	Longitudinal	29756	Health professionals (WHS)	≥45 ♀	Mailed questionnaire	+	Self-reported	Self-reported	Self-reported
		19182	Health professionals (PHS)	≥40 ♂		+	Self-reported	Self-reported	Self-reported
Szentkirályi et al., 2013	Longitudinal	1312	General population (DHS)	25-75 ♀♂	Face-to-face interview + mailed questionnaire	+	Self-reported	Self-reported	Self-reported
		4308	General population (SHIP)	20-79 ♀♂		+	Self-reported	Self-reported	Self-reported

Winter et al., 2013a	Cross-sectional	30262	Health professionals (WHS)	≥45 ♀	Mailed questionnaire	+	Self-reported	Self-reported	Self-reported
Winter et al., 2013b	Cross-sectional	22786	Health professionals (PHS)	≥40 ♂	Mailed questionnaire	+	Self-reported	Self-reported	Self-reported
Giannini et al., 2014	Cross-sectional	1709	General population	≥18 ♀♂	Self-administered questionnaire	+	Self-reported	Self-reported	Self-reported
Zobeiri and Shokoohi, 2014	Cross-sectional	280	Clinical	≥18 ♀♂	Clinical visit	+	Medical assessment	Medical assessment	Medical assessment
Shi et al., 2015	Cross-sectional	2941	General population	≥18 ♀♂	Screening questionnaire + sleep-specialist phone interview	+	Self-reported physician-diagnosis	Self-reported physician-diagnosis	Self-reported physician-diagnosis

Legend. IRLSSG: International Restless Legs Syndrome Study Group; DM: Diabetes Mellitus; CVDs: Cardiovascular Diseases; CVRFs: Cardiovascular Risk Factors; PLMS: Periodic Limb Movements during Sleep; WHS: Women's Health Study; PHS: Physicians' Health Study; NHS: Nurses' Health Study; DHS: Dortmund Health Study; SHIP: Study of Health in Pomerania.

showed that patients suffering from RLS were more likely to report hypertension after adjustment for age, witnessed sleep apneas, smoking and alcohol consumption [odds ratio (OR) = 1.5; confidence interval (CI) = 0.9-2.4].

The same results were found in a European multicenter cross-sectional study of 18980 subjects who underwent a telephone interview conducted by means of a software application specifically designed for epidemiological studies (Ohayon et al., 2002). RLS diagnosis was based on the International Classification of Sleep Disorders (ICSD) criteria of 1990 (Diagnostic Classification Steering Committee, Thorpy M.J., 1990), while hypertension was self-reported. RLS sufferers had a higher prevalence of hypertension when compared with controls (21.8% vs. 11.1%, p< 0.001). The association remained statistically significant also after adjustment for age, sex, daytime work, body mass index (BMI), BP, musculoskeletal or heart disease, mental disorders, physical exercise, snoring, obstructive sleep apnea, cataplexy, coffee or alcohol consumption, smoking status, life stress and use of hypnotic medications (OR= 1.36; CI = 1.14-1.61, p< 0.001).

An increased prevalence of self-reported hypertension in participants suffering from RLS was shown in the cross-sectional study conducted in the U.S. by Batool-Anwar (2011) in 65544 middle-aged nurses. Participants completed a questionnaire investigating RLS diagnosis based on IRLSSG criteria and other questions investigating demographic characteristics, and hypertension. It was demonstrated that subjects with high-frequency RLS symptoms (> 15 times/month) had a statistically significant higher OR (OR= 1.41; CI= 1.24-1.61) of suffering from hypertension.

Instead, in another Swedish study based on mailed questionnaires administered to a cohort of 3496 subjects aged 30-65 years, the presence of RLS was not assessed according to IRLSSG criteria and hypertension diagnosis was self-reported (Mallon et al., 2008). Comparing participants with RLS and controls, an increased prevalence of hypertension was reported in males (12.8% vs. 7.9%, p = 0.02) but not in females (13.0% vs. 9.7%, p = 0.10).

A mailed questionnaire-based study of 70977 women without coronary heart disease and stroke at baseline showed a significant association between physician-diagnosed RLS and history of hypertension (RLS sufferers: 66.5%; controls: 55.7%; p < 0.05) (Li et al., 2012).

A longitudinal study performed on two large cohorts of adults and elderly subjects (Dortmund Health Study, DHS; n= 1312; Study of Health in Pomerania, SHIP; n = 4308) evaluated the incidence of RLS in subjects with CVRFs and CVDs and, conversely, the presence of RLS at baseline and the incidence of CVRFs (Szentkirályi et al., 2013a). Hypertension was related to incident RLS only in the SHIP cohort, after adjustment for age and sex (OR = 1.55; CI = 1.14-2.09; p < 0.01) and the association remained significant also after adjustment for CVRFs and CVDs. Conversely, prevalent RLS was not associated with an increased risk of incident hypertension.

A recent survey conducted on 2941 adults living in a rural Chinese community showed an increased risk of hypertension in subjects with RLS (OR = 4.10; CI = 1.88-8.92; p < 0.001, in a multivariate adjusted model) (Shi et al., 2015). RLS was assessed by means of a face-to-face interview using the four-items IRLSSG screening questionnaire and was confirmed by a phone-interview performed by a sleep-specialist, while hypertension was established by a self-reported medical-diagnosis. After stratification for gender, the significance of this association was found just in males (OR = 7.18; CI = 1.74-29.58; p = 0.006).

Winter and colleagues (2012) assessed the risk of incident cardiovascular diseases, in particular major events, such as non-fatal myocardial infarction, non-fatal stroke or death from CVD events, in a large cohort of health professionals: 29756 females aged ≥ 45 years and 19182 aged ≥ 40 years belonging to two cohort studies, namely the Women's Health Study (WHS) and the Physicians' Health Study (PHS), respectively. RLS was ascertained by using a validated three-items questionnaire based on IRLSSG criteria. Cardiovascular outcomes, such as stroke or myocardial infarction, and CVRFs, such as hypertension, were self-reported by participants and confirmed by a medical-records review during follow-up, according to current diagnostic criteria. Although RLS was not associated with incident vascular events, a cross-sectional analysis performed at baseline showed that RLS sufferers were more likely to report a history of hypertension compared with controls (WHS: 50.4% vs 46.7%, p < 0.01; PHS: 51.2% vs 48.3%, p = 0.04).

On the contrary, other studies found no significant association between RLS, generally assessed by using IRLSSG criteria (Walters, 1995; Allen et al., 2003), and hypertension.

A cross-sectional analysis of the association between RLS, CVRFs and prevalent CVDs in 30262 women from the WHS population demonstrated a significant association between RLS and history of hypertension, defined as blood pressure ≥ 140/90 mmHg or antihypertensive medication use, after age-adjustment (OR= 1.16; CI = 1.08-1.25) (Winter et al., 2013a). However, the significance of this association was not confirmed in the multivariable-adjusted analysis, including CVRFs, post-menopausal status and aspirin, hormone and/or oral contraceptives use. They also confirmed these results in 22786 men belonging to the PHS cohort, where age and multivariable-adjusted models (including CVRFs, and aspirin-assignment) did not show an increased risk of hypertension in RLS sufferers (Winter et al., 2013b).

In a study conducted in northeastern Germany, 4107 subjects aged 20-79 years were face-to-face interviewed in two central study facilities by trained interviewers (Berger et al., 2004). Hypertension diagnosis was established if BP values were ≥ 160 mmHg systolic or ≥ 95 mmHg diastolic during the three automatic measurements. RLS sufferers did not show an increased prevalence of hypertension compared with controls (19.9% vs. 17.8%, p= 0.31) after adjustment for age and sex.

Similar results were also evidenced in a study performed by Winkelman and colleagues (2006) in two large adult cohorts. In the first prospective study conducted on the Wisconsin Sleep Cohort sample, 2821 (67%) participants aged 30-60 years completed a mailed questionnaire investigating RLS symptoms. Considering symptoms frequency, the authors stratified participants as follows: 1- Daily RLS symptoms when the frequency was “daily/nightly”; 2- Frequent RLS symptoms when occurring “at least weekly” but not “daily/nightly”; 3- Monthly RLS symptoms when occurring “monthly”; 4- Absence of RLS symptoms if they were not reported or occurred less than once per month. Hypertension was self-reported or based on the report of a medical-diagnosis report. In this study, participants suffering from daily or frequent RLS symptoms did not show an increased risk of hypertension (daily RLS symptoms: OR =1.27, CI=0.85-1.91; frequent RLS symptoms: OR= 0.98, CI= 0.66-1.45).

This lack of association was also reported in a Swedish study based on mailed questionnaires conducted on 3516 women aged 18-64 years (Wesstrom et al., 2008). Participants with a diagnosis of RLS did not show an augmented risk of self-reported hypertension after adjustment for age, smoking status, alcohol and coffee consumption and use of sleeping pills (OR= 1.08; CI= 0.79-1.46).

Comparable results were reported by the same research group in 3433 participants of the Sleep Heart Health Study (Winkelman et al., 2008). RLS status was assessed according to IRLSSG criteria. Hypertension was determined by a systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg, or by the current use of antihypertensive medication. After adjustment for age, sex, race and BMI, only a weak association between RLS and hypertension was found (OR= 1.30; CI= 0.92-1.82).

In a Scandinavian multi-center study of randomly selected adults, subjects were invited to participate in an assessment including a structured interview, administration of questionnaires, blood samples collection and spirometry (Benediktsdottir et al., 2010). Hypertension was confirmed if participants had been diagnosed by a physician and were taking antihypertensive medication. The study evidenced no difference in the prevalence of hypertension between RLS patients and controls (35.2% vs. 30.1%, p= 0.15) also after adjustment for center, age, sex and smoking history (p = 0.19).

More recently, Giannini and colleagues (2014) have assessed the association between RLS and hypertension in 1709 South Tyrolean adults. All participants were face-to-face interviewed in one central study facility by a trained study nurse. RLS diagnosis was performed on the basis of the four IRLSSG criteria. Hypertension or antihypertensive medication use were self-reported. Data about sex, age, diabetes mellitus, smoking status, dyslipidemia, history of myocardial infarction, sleep quality and BMI were also collected. In this study, RLS sufferers were more likely to have hypertension when compared with controls (OR= 2.08, CI 95% 1.49-2.92, p < 0.001), but the multivariable regression model did not reveal any association after adjustment for well-known confounding CVRFs such as raised blood lipids, smoking status, diabetes mellitus, history of myocardial infarction and BMI (OR= 1.25, CI 95% 0.85 - 1.85, p = 0.252).

Juuti and colleagues (2010) evaluated 997 Finnish subjects aged 57 years by means of a structured mailed questionnaires, a clinical interview, a physical examination, and laboratory measurements. RLS was investigated by using self-administered questionnaires, while hypertension was diagnosed when the mean of two measurements was ≥90 mmHg for diastolic or ≥160 mmHg for systolic BP values, or when the participant reported a previous diagnosis or anti-hypertensive medications use. No statistically significant association between RLS and hypertension was found after adjustment for glucose tolerance, gender, smoking, CVDs, waist circumference, depression, use of antidepressant and hypnotic medication, daytime sleepiness, habitual snoring and arthropathies (OR= 0.88; CI= 0.56-1.40).

A study on 701 adult and elderly subjects from northern Italy showed no significant differences in hypertension prevalence in participants with and without RLS (56.8% vs. 56.0%, p= 0.92) (Högl et al., 2005). In this study, the diagnosis of RLS was established by face-to-face interview performed by a neurologist with expertise in sleep disorders and the diagnosis of hypertension was based on direct measurement (≥ 140/90 mmHg) or on the current use of anti-hypertensive medications.

Other population-based studies investigated this relationship on elderly subjects showing a reduced or equivalent incidence of hypertension in RLS sufferers when compared with controls. In a 7-year follow-up study conducted by Celle and colleagues (2010) on French elderly subjects (65 ± 1 years), the association between sleep-related breathing disorders and cardiovascular and cerebrovascular morbidity has been investigated. RLS status was evaluated according to the four IRLSSG criteria and also information about the frequency of RLS symptoms was collected (>1/week for the previous 6 months). Hypertension was assessed by means of clinical interview and measurements. In this study RLS sufferers reported lower incidence of hypertension compared with controls (38.7% vs. 43.1%, p< 0.01) also when only participants without sleep-related breathing disorders were considered (33.8% vs. 36.5%, p< 0.05). Arterial BP levels did not differ between the two groups.

A negative association between the two conditions was reported also by Rothdach and colleagues (2000) in 369 German elderly subjects. RLS was assessed, according to IRLSSG criteria, by means of a face-to-face interview conducted by two trained physicians, while hypertension diagnosis was self-reported. Hypertension incidence in subjects suffering from RLS was lower than in controls (5.6% vs. 23.4%, p<0.04).

Conversely, one telephone interview-based study conducted on 1506 adults compared subjects with and without hypertension reporting that the first group was more likely to have RLS after adjustment for age, gender, and diagnosis of sleep disorders (p< 0.05) (Phillips et al., 2006).

Clinical-based studies

Among the studies assessing the increased prevalence of hypertension in patients with RLS in a clinical setting, four found a significant association, while one did not. In all studies but one, using ICD-9 classification, RLS was assessed on the basis of IRLSSG criteria (Walters, 1995; Allen et al., 2003).

A survey conducted on 16531 adults enrolled in German primary care practices, revealed that RLS sufferers were more likely to report hypertension (Möller et al., 2010). In subjects who had answered affirmatively to a previous screening questionnaire investigating the presence of unpleasant sensations in the legs, RLS was assessed by a questionnaire filled in by a physician according to IRLSSG criteria. The clinical criteria for identifying hypertension were not reported, but the diagnosis was based on the knowledge of the physician. Hypertension was significantly more prevalent in participants with RLS when compared to controls (55.8% vs. 45.1%, p<0.0001), particularly in subjects younger than 60 years.

Similar results were reported in a survey conducted in primary care sites in North Carolina on 1934 adults who responded to a self-reported health questionnaire (Alattar et al., 2007). A question about tingling, creeping, or restless feelings in the legs while trying to fall asleep was used to screen RLS. Subjects suffering from symptoms suggesting RLS showed an increase risk of having a self-reported hypertension (OR=1.35, p< 0.01) after adjustment for age, race and sex.

In a Canadian study performed in a Sleep Disorders Center, patients with an ICSD diagnosis of RLS were enrolled and compared with controls belonging to the Manitoba Health Database (Banno et al., 2000). Comorbidities were assessed on the basis of physician ICD-9CM diagnosis performed in the 5-years prior to RLS onset. In this study, males with RLS showed an augmented risk of having essential hypertension compared to controls (26.2% vs. 14.8%, OR=2.1, p< 0.05), while information about hypertension in females was not reported.

A case-control study performed on 140 consecutive patients with diabetes and 140 non diabetic controls, a higher prevalence of hypertension, assessed by medical check-list based interview, was found in RLS sufferers compared with controls (36% vs 17.3%; p = 0.003) (Zobeiri and Shokoohi, 2014).
Schlesinger and colleagues (2009) conducted a survey on 1537 individuals attending their annual check-up at the Rambam Center of Preventive Medicine in Israel. Participants filled in a questionnaire designed according to IRLSSG-criteria and underwent a face-to-face interview with a senior neurologist to confirm or disprove the diagnosis of RLS. Hypertension was confirmed in case of a physician diagnosis, anti-hypertensive medications use or when BP was above 140/90 mmHg at direct measurement. RLS sufferers did not show a statistically significant increase in the prevalence of hypertension compared with controls.

Association between RLS, cardiovascular diseases and diabetes

Many studies evaluated the comorbidity between RLS and cardiac diseases, in particular acute coronary syndrome, showing a possible association.

Population-based studies

Eleven out of eighteen population-based studies found a significant association between RLS and CVDs. In fourteen of the total number of studies, RLS was assessed by using IRLSSG criteria (Walters, 1995; Allen et al., 2003) and in most studies a multivariable-adjusted model was applied.
In a cross-sectional analysis performed by Ulfberg et colleagues (2001) in a males cohort, subjects with RLS showed an increased risk of self-reported heart problems (OR = 2.5; CI = 1.4-4.3; adjusted for age, witnessed apneas, smoking status and alcohol consumption).
Also in a multicenter European study, RLS sufferers were more likely to report heart diseases (6.5% vs 2.7%; p < 0.001) and diabetes (2.3% vs. 1.0%; p < 0.001) compared with controls (Ohayon et al., 2002).
A population-based study conducted on 4107 German adults, comparing participants with RLS and controls, showed that the first group was more likely to report a history of both myocardial infarction and diabetes mellitus after adjustment for age and sex (2.7% vs. 1.2%, p<0.01 and 7.4% vs. 4.8%, p = 0.004) (Berger et al., 2004). Diabetes mellitus was defined as self-reported physician-diagnosed plus treatment or as non-fasting glucose level ≥ 200 mg/dL. The logistic regression model restricted to age range of 20-59 and 60-79 years revealed an increased risk of diabetes mellitus only in the older group (OR= 1.57; CI= 1.05-2.35) after adjustment for sex, education, renal dysfunction, anemia, thyroid disease, and smoking status.
A community-based study performed on 1506 subjects aged 55-84 years assessed the presence of heart diseases, CVRFs such as hypertension or diabetes and symptoms suggesting RLS ("unpleasant feelings in the legs, like creepy, crawly or tingly feelings when lying down at night") by using a telephone-interview (Foley et al., 2004). The authors found a significantly higher OR of having symptoms suggesting RLS in people with heart diseases and diabetes compared to people without RLS symptoms, after a stepwise adjustment for significantly associated medical condition, as well as for age and gender (OR = 1.68; CI = 1.09-2.57 and OR= 1.81; CI = 1.17-2.81, respectively).
In a study published by Winkelman and colleagues (2006), a significant association between RLS with daily symptoms and self-reported history of heart attack, coronary artery disease, coronary by-pass or angioplasty and pace-maker was reported. In particular, the risk was higher in subjects with more frequent RLS symptoms (OR = 2.58; CI = 1.38-4.84). Taking into consideration the self-reported medical diagnosis of diabetes, authors did not reveal an increased risk of this condition in RLS sufferers.
A positive association between RLS and self-reported heart problems was also reported in a survey on 3516 Swedish women, after adjustment for age, smoking status, alcohol and coffee consumption and use of sleeping pills (OR = 2.13; CI =1.18-3.86) (Wesstrom et al., 2008). A lack of association between RLS and self-reported diabetes was also evidenced.
Winkelman and colleagues (2008) evaluated the association between RLS and prevalent CVDs/coronary disease in a population-based cross-sectional analysis on middle-aged and elderly subjects belonging to the Sleep Heart Health Study. RLS assessment was performed by using a self-administered questionnaire based on IRLSSG criteria, and subjects with moderate-severe distress and

frequency of symptoms higher than five times per month were included. Coronary disease was self-reported by participants on the basis of a clinical diagnosis. The results showed higher ORs for coronary diseases and CVDs in RLS sufferers compared with controls, after adjustment for CVRFs (OR = 2.05; C.I. = 1.38-3.04 and OR = 2.07; CI =1.43-3.00, respectively), with a stronger association with more severe and frequent RLS symptoms.

The study conducted by Juuti and colleagues (2010) on 997 subjects aged 57 years also investigated the relationship between RLS and coronary heart disease. The condition was diagnosed if participants self-reported previous myocardial infarction, reported a medical doctor diagnosis of angina pectoris or coronary heart disease, had visited a physician for chest pain, or had been hospitalized because of a myocardial infarction. A significant association between RLS and coronary heart disease was found after adjustment for glucose tolerance, gender, smoking status, cardiovascular health study, waist circumference, depression, use of antidepressant and hypnotic medications, daytime sleepiness, habitual snoring and arthropathies (OR= 2.92; CI= 1.18-7.23). Insufficient evidence of an association with type 2 diabetes or impaired glucose regulation was found.

A previous study evaluated the presence of physician-diagnosed RLS via questionnaire in 70977 women without coronary heart disease and stroke at baseline (Li et al., 2012). Over a six-years follow-up, a higher risk of developing coronary heart disease for women with at least three years of RLS symptoms was evidenced (OR = 1.72; CI = 1.09-2.73, p = 0.03).

In the study performed by Szentkirályi and colleagues (2013a) on two large population cohorts, a significant association between CVRFs and incident RLS was found, although a role of prevalent RLS in the incidence of CVRFs or CVDs was not demonstrated.

Mallon and colleagues (2008) reported a higher prevalence of self-reported heart disease among males suffering from RLS compared with controls (10.1% vs. 4.2%, p < 0.001), but this association was not found in females. No significant increased prevalence of self-reported history of diabetes was reported in either male or female RLS sufferers.

Elwood et al. (2006) evaluated 1986 men aged 55-69 years by using a questionnaire on sleep patterns, comprising snoring, RLS, obstructive sleep apnea, daytime sleepiness and insomnia. The participants underwent a 10-year follow-up. An increase in OR for incident stroke in RLS sufferers was found (OR = 1.67; CI = 1.07-2.60; p = 0.024), while the association between RLS and ischemic heart disease was not statistically significant.

Instead Lee and colleagues (2006) found no significant increase in the OR of having RLS in subjects with heart diseases when evaluating the prevalence of the risk factors for RLS in 1071 adults by using a questionnaire based on IRLSSG criteria. Also Benediktsdottir and colleagues (2010) found no significant association between RLS and self-reported cardiovascular diseases, while RLS sufferers showed a higher prevalence of a reported medical diagnosis of diabetes or use of therapies for diabetes compared with controls (7.4% vs 4.2%; p = 0.04 adjusted for center, age, sex and smoking history).

In the longitudinal study performed by Winter and colleagues (2012) on WHS and PHS cohorts, no significant association between RLS and incident major CVD events was demonstrated either in females or in males, also after adjustment for comorbidities.

The cross-sectional analysis performed on women belonging to WHS cohort evidenced a significant association between RLS and CVRFs, such as hypercholesterolemia (OR = 1.17; CI = 1.09-1.26), diabetes (OR = 1.19; CI = 1.04-1.35) and BMI higher than 35 (OR = 1.35; CI = 1.17-1.56), while no association with prevalent CVDs was found (Winter et al., 2013a).

Analyses conducted on male population of the PHS found a higher OR of RLS in subjects with diabetes (OR = 1.41; CI = 1.21-1.65), raised blood cholesterol (OR = 1.11; CI = 1.01-1.23) and prevalent stroke (OR = 1.40; CI = 1.05-1.86), while prevalent myocardial infarction was related to a decrease in OR for RLS (OR = 0.73; CI = 0.55-0.97) (Winter et al., 2013b).

Shi and colleagues (2015) have recently reported the absence of increased ORs for diabetes and heart problems in RLS sufferers, assessed by a self-reported diagnosis. Also Philips and colleagues (2006) found no link between RLS and heart problems in their evaluation of the association between RLS, heart diseases, hypertension, and diabetes by means of a telephone-interview based on self-reported diagnosis and IRLSSG criteria.

Finally, some population-based studies focused on diabetes and its association with RLS finding controversial results (Innes et al., 2012; Zobeiri and Shokoohi, 2014).

Clinical-based studies

Two studies focusing on primary care settings found a significant positive association between RLS and both diabetes and CVDs. In the study by Attalar and colleagues (2007), RLS patients had an increased risk of self-reported heart diseases and medical diagnosis of diabetes (OR= 2.06; $p \leq 0.001$ and OR = 1.95; $p \leq 0.001$, respectively, after adjustment for age, race and sex). Möller and colleagues (2010) evidenced similar results reporting that RLS sufferers had a higher prevalence of heart diseases (21.3% vs 16.5%; $p < 0.0001$) and diabetes (22.5% vs 16.8%; $p < 0.0001$) compared with controls. Other two clinical studies assessed the risk of having diabetes in RLS patients showing a lack of association (Banno et al., 2000; Schlesinger et al., 2009), while other studies focused on the risk of having RLS in diabetic patients but with conflicting results (Skomro et al., 2001; Lopes et al., 2005; Merlino et al., 2007). Two studies demonstrated an increased prevalence of glucose-metabolism abnormalities in RLS patients with and without PLMs (Bosco et al., 2007; Keckeis et al., 2010).

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References

Alattar M., Harrington J.J., Mitchell C.M., Sloane P. Sleep problems in primary care: a North Carolina Family Practice Research Network (NC-FP-RN) study. *J. Am. Board Fam. Med.,* **20**: 365-374, 2007.

Alessandria M., Provini F. Periodic Limb Movements during Sleep: A New Sleep-Related Cardiovascular Risk Factor? *Front Neurol.,* **4**: 116, 2013.

Allen R.P., Picchietti D., Hening W.A., Trenkwalder C., Walters A.S., Montplaisir J. Restless Legs Syndrome Diagnosis and Epidemiology workshop at the National Institutes of Health; International Restless Legs Syndrome Study Group. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. *Sleep Med.,* **4**: 101-119, 2003.

Allen R.P., Stillman P., Myers A.J. Physician-diagnosed restless legs syndrome in a large sample of primary medical care patients in western Europe: Prevalence and characteristics. *Sleep Med.,* **11**: 31-37, 2010.

Allen R.P., Picchietti D.L., Garcia-Borreguero D., Ondo W.G., Walters A.S., Winkelman J.W., Zucconi M., Ferri R., Trenkwalder C., Lee H.B. International Restless Legs Syndrome Study Group. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria-history, rationale, description, and significance. *Sleep Med.,* **15**: 860-873, 2014.

American Academy of Sleep Medicine. *The International classification of sleep disorders, Third Edition*. 2014, Darien, IL: American Academy of Sleep Medicine.

Banno K., Delaive K., Walld R., Kryger M.H. Restless legs syndrome in 218 patients: associated disorders. *Sleep Med.,* **1**: 221-229, 2000.

Batool-Anwar S., Malhotra A., Forman J., Winkelman J., Li Y., Gao X. Restless legs syndrome and hypertension in middle-aged women. *Hypertension,* **58**: 791-796, 2011.

Becker P.M., Sharon D. Mood disorders in restless legs syndrome (Willis-Ekbom disease). *J. Clin. Psychiatry,* **75**: e679-694, 2014.

Benediktsdottir B., Janson C., Lindberg E., Arnardóttir E.S., Olafsson I., Cook E., Thorarinsdottir E.H., Gislason T. Prevalence of restless legs syndrome among adults in Iceland and Sweden: Lung function, comorbidity, ferritin, biomarkers and quality of life. *Sleep Med.,* **11**: 1043-1048, 2010.

Berger K., Luedemann J., Trenkwalder C., John U., Kessler C. Sex and the risk of restless legs syndrome in the general population. *Arch. Intern. Med.,* **164**: 196-202, 2004.

Bosco D., Plastino M., Fava A., Ettore M., Bosco F., Ermio C., Tallarigo F., Pirritano D., Consoli D. Role of the Oral Glucose Tolerance Test (OGTT) in the idiopathic restless legs syndrome. *J. Neurol. Sci.,* **287**: 60-63, 2009.

Calandra-Buonaura G., Provini F., Guaraldi P., Plazzi G., Cortelli P. Cardiovascular autonomic dysfunctions and sleep disorders. *Sleep Med. Rev.,* **26**: 43-56, 2015.

Celle S., Roche F., Kerleroux J., Thomas-Anterion C., Laurent B., Rouch I., Pichot V., Barthélémy J.C., Sforza E. Prevalence and clinical correlates of restless legs syndrome in an elderly French population: the synapse study. *J. Gerontol.,* **65**: 167-173, 2010.

Diagnostic Classification Steering Committee, Thorpy M.J. International classification of sleep disorders: diagnostic and coding manual (ICSD). 1990, Rochester, MN: American Sleep Disorders Association.

Elwood P., Hack M., Pickering J., Hughes J., Gallacher J. Sleep disturbance, stroke, and heart disease events: evidence from the Caerphilly cohort. *J. Epidemiol. Community Health,* **60**: 69-73, 2006.

Ferini-Strambi L., Walters A.S., Sica D. The relationship among restless legs syndrome (Willis-Ekbom Disease), hypertension, cardiovascular disease, and cerebrovascular disease. *J. Neurol.,* **261**: 1051-1068, 2014.

Ferri R., Rundo F., Zucconi M., Manconi M., Bruni O., Ferini-Strambi L., Fulda S. An Evidence-based Analysis of the Association between Periodic Leg Movements during Sleep and Arousals in Restless Legs Syndrome. *Sleep,* **38**: 919-924, 2015.

Foley D., Ancoli-Israel S., Britz P., Walsh J. Sleep disturbances and chronic disease in older adults: results of the 2003 National Sleep Foundation Sleep in America Survey. *J. Psychosom. Res.,* **56**: 497-502, 2004.

Giannini G., Zanigni S., Melotti R., Gögele M., Provini F., Facheris M.F., Cortelli P., Pramstaller P.P. Association between restless legs syndrome and hypertension: a preliminary population-based study in South Tyrol, Italy. *Eur. J. Neurol.,* **21**: 72-78, 2014.

Hening W.A., Allen R.P., Washburn M., Lesage S.R., Earley C.J. The four diagnostic criteria for Restless Legs Syndrome are unable to exclude confounding conditions ("mimics"). *Sleep Med.,* **10**: 976-981, 2009.

Högl B., Kiechl S., Willeit J., Saletu M., Frauscher B., Seppi K., Müller J., Rungger G., Gasperi A., Wenning G., Poewe W. Restless legs syndrome: a community-based study of prevalence, severity, and risk factors. *Neurology,* **64**: 1920-1924, 2005.

Innes K.E., Selfe T.K., Agarwal P. Restless legs syndrome and conditions associated with metabolic dysregulation, sympathoadrenal dysfunction, and cardiovascular disease risk: a systematic review. *Sleep Med. Rev.,* **16**: 309-339, 2012.

Juuti A.K., Läär E., Rajala U., Laakso M., Härkönen P., Keinänen-Kiukaanniemi S., Hiltunen L. Prevalence and associated factors of restless legs in a 57-year-old urban population in northern Finland. *Acta Neurol. Scand.,* **122**: 63-69, 2010.

Keckeis M., Lattova Z., Maurovich-Horvat E., Beitinger P.A., Birkmann S., Lauer C.J., Wetter T.C., Wilde-Frenz J., Pollmächer T. Impaired glucose tolerance in sleep disorders. *PLoS One,* **5**: e9444, 2010.

Lee H.B., Hening W.A., Allen R.P., Earley C.J., Eaton W.W., Lyketsos C.G. Race and restless legs syndrome symptoms in an adult community sample in east Baltimore. *Sleep Med.,* **7**: 642-645, 2006.

Li Y., Walters A.S., Chiuve S.E., Rimm E.B., Winkelman J.W., Gao X. Prospective study of restless legs syndrome and coronary heart disease among women. *Circulation,* **126**: 1689-1694, 2012.

Lopes L.A., Lins Cde M., Adeodato V.G., Quental D.P., de Bruin P.F., Montenegro R.M. Jr., de Bruin V.M. Restless legs syndrome and quality of sleep in type 2 diabetes. *Diabetes Care,* **28**: 2633-2636, 2005.

Mackie S., Winkelman JW. Restless Legs Syndrome and Psychiatric Disorders. *Sleep Med. Clin.,* **10**: 351-357, 2015.

Mallon L., Broman J.E., Hetta J. Restless legs symptoms with sleepiness in relation to mortality: 20-year follow-up study of a middle-aged Swedish population. *Psychiatry Clin. Neurosci.,* **62**: 457-463, 2008.

Merlino G., Fratticci L., Valente M., Del Giudice A., Noacco C., Dolso P., Cancelli I., Scalise A., Gigli G.L. Association of restless legs syndrome in type 2 diabetes: a case-control study. *Sleep,* **30**: 866-871, 2007.

Möller C., Wetter T.C., Köster J., Stiasny-Kolster K. Differential diagnosis of unpleasant sensations in the legs: prevalence of restless legs syndrome in a primary care population. *Sleep Med.,* **11**: 161-166, 2010.

Nannapaneni S., Ramar K. Periodic limb movements during sleep and their effect on the cardiovascular system: is there a final answer? *Sleep Med.,* **15**: 379-384, 2014.

Ohayon M.M. and Roth T. Prevalence of restless legs syndrome and periodic limb movement disorder in the general population. *J. Psychosom. Res.,* **53**: 547-554, 2002.

Phillips B., Hening W., Britz P., Mannino D. Prevalence and correlates of restless legs syndrome: results from the 2005 National Sleep Foundation Poll. *Chest*, **129**: 76-80, 2006.

Portaluppi F., Cortelli P., Calandra-Buonaura G., Smolensky M.H., Fabbian F. Do restless legs syndrome (RLS) and periodic limbs movements of sleep (PLMS) play a role in nocturnal hypertension and increased cardiovascular risk of renally impaired patients? *Chronobiol. Int.,* **26**: 1206-1221, 2009.

Rothdach A.J., Trenkwalder C., Haberstock J., Keil U., Berger K. Prevalence and risk factors of RLS in an elderly population: the MEMO study. Memory and Morbidity in Augsburg Elderly. *Neurology,* **54**: 1064-1068, 2000.

Schilling C., Schredl M., Strobl P., Deuschle M. Restless legs syndrome: evidence for nocturnal hypothalamic-pituitary-adrenal system activation. *Mov. Disord.,* **25**:1047-1052, 2010.

Schlesinger I., Erikh I., Avizohar O., Sprecher E., Yarnitsky D. Cardiovascular risk factors in restless legs syndrome. *Mov. Disord.,* **24**: 1587-1592, 2009.

Shi Y., Yu H., Ding D., Yu P., Wu D., Hong Z. Prevalence and Risk Factors of Restless Legs Syndrome among Chinese Adults in a Rural Community of Shanghai in China. *PLoS One*, **10**: e0121215, 2015.

Silvani A., Calandra-Buonaura G., Benarroch E.E., Dampney R.A., Cortelli P. Bidirectional interactions between the baroreceptor reflex and arousal: an update. *Sleep Med.,* **16**: 210-216, 2015.

Skomro R.P., Ludwig S., Salamon E., Kryger M.H. Sleep complaints and restless legs syndrome in adult type 2 diabetics. *Sleep Med.,* **2**: 417-422, 2001.

Szentkiralyi A., Völzke H., Hoffmann W., Happe S., Berger K. A time sequence analysis of the relationship between cardiovascular risk factors, vascular diseases and restless legs syndrome in the general population. *J. Sleep Res.,* **22**: 434-442, 2013a.

Szentkiralyi A., Völzke H., Hoffmann W., Baune B.T., Berger K. The relationship between depressive symptoms and restless legs syndrome in two prospective cohort studies. *Psychosom. Med.,* **75**: 359-365, 2013b.

Trautmann E., Barke A., Frisch J.U., Schmidt A.L., Kunert F., Canelo M., Sixel-Döring F., Trenkwalder C. Restless Legs Syndrome: Psychiatric Comorbidities Are More Important Than Neuroticism. *Behav. Sleep Med.,* **13**: 375-386, 2015.

Ulfberg J., Nystrom B., Carter N., Edling C. Prevalence of restless legs syndrome among men aged 18 to 64 years: an association with somatic disease and neuropsychiatric symptoms. *Mov. Disord.,* **16**: 1159-1163, 2001.

Walters A.S. Toward a better definition of the restless legs syndrome. The International Restless Legs Syndrome Study Group. *Mov. Disord.,* **10**: 634-642, 1995.

Walters A.S. and Rye D.B. Review of the relationship of restless legs syndrome and periodic limb movements in sleep to hypertension, heart disease, and stroke. *Sleep*, **32**: 589-597, 2009.

Wesstrom J., Nilsson S., Sundstrom-Poromaa I., Ulfberg J. Restless legs syndrome among women: prevalence, co-morbidity and possible relationship to menopause. *Climacteric,* **11**: 422-428, 2008.

Winkelman J.W., Finn L., Young T. Prevalence and correlates of restless legs syndrome symptoms in the Wisconsin Sleep Cohort. *Sleep Med.,* **7**: 545-552, 2006.

Winkelman J.W., Shahar E., Sharief I., Gottlieb D.J. Association of restless legs syndrome and cardiovascular disease in the Sleep Heart Health Study. *Neurology,* **70**: 35-42, 2008.

Winter A.C., Schürks M., Glynn R.J., Buring J.E., Gaziano J.M., Berger K., Kurth T. Restless legs syndrome and risk of incident cardiovascular disease in women and men: prospective cohort study. *BMJ Open,* **2**: e000866, 2012.

Winter A.C., Schürks M., Glynn R.J., Buring J.E., Gaziano J.M., Berger K., Kurth T. Vascular risk factors, cardiovascular disease, and restless legs syndrome in women. *Am. J. Med.,* **126**: 220-227, 2013a.

Winter A.C., Berger K., Glynn R.J., Buring J.E., Gaziano J.M., Schürks M., Kurth T. Vascular risk factors, cardiovascular disease, and restless legs syndrome in men. *Am. J. Med.,* **126**: 228-235, 2013b.

Zobeiri M. and Shokoohi A. Restless leg syndrome in diabetics compared with normal controls. *Sleep Disord.,* **2014**: 871751, 2014.