Exploring the Relationship of Sleep-Related Movement Disorders with Cerebrovascular Disease

by

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Institute of Medical Science
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Abstract

INTRODUCTION: The association of Sleep-Related Movement Disorders (SRMDs) such as Restless Legs Syndrome (RLS) and Periodic Limb Movements (PLMs) with cerebrovascular disease is underexplored. Emerging evidence links them to vascular disease, for which white matter hyperintensities (WMHs) are a well-recognized biomarker.

METHODS: We conducted a cross-sectional hospital-based observational study in which high-risk TIA and minor stroke patients were assessed for vascular risk factors, WMHs and polysomnography-determined sleep variables.

RESULTS: Ninety-seven patients were enrolled, of whom 44 completed polysomnography. Twenty-five percent had RLS, which was associated with lower quality of life. Independent of the effect of classical vascular risk factors, PLMs (but not RLS) were associated with WMHs on linear regression analyses (p=0.016).

CONCLUSIONS: SRMDs are prevalent after minor stroke/TIA. RLS is associated with poor quality of life, while PLMs are associated with WMHs. Whether PLMs are
implicated in the pathogenesis of WMHs or whether WMHs exacerbate PLMs remains uncertain.
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Abstract

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List of Abbreviations

AHI = apnea-hypopnea index
ARWMC = Age Related White Matter Changes scale
BP = blood pressure
CESD = Centre for Epidemiological Studies Depression Scale
CI = confidence interval
CPAP = continuous positive airway pressure
CRP = C-reactive protein
CT = computer tomography
DWI = diffusion weighted imaging
EEG = electroencephalogram
EMG = electromyogram
FLAIR = fluid-attenuated inversion recovery
HR = hazards ratio
ICC = Intra-class correlation coefficient
IL-6 = interleukin-6
IRLS = International Restless Legs Scale score
IRLSSG = International Restless Legs Syndrome Study Group
LDL = Low-density lipoprotein
MoCA = Montreal Cognitive Assessment
MRI = magnetic resonance imaging
MRS = magnetic resonance spectroscopy
NIHSS = National Institutes of Health Stroke Scale
OR = odds ratio
OS = oxidative stress
OSA = obstructive sleep apnea
PET = positron emission tomography
PLMD = periodic limb movement disorder
PLMs = periodic limb movements
PLMW = periodic limb movements in wake
RBD = REM sleep behavior disorder
RLS = restless legs syndrome
SBI = silent brain infarction
SD = standard deviation
SE = standard error
sICAM-1 = soluble intercellular adhesion molecule-1
SPECT = single-photon emission computed tomography
SSQoL = Stroke Specific Quality of Life Scale
SSRI = selective serotonin reuptake inhibitors
SVD = small vessel disease
TIA = transient ischemic attack
VBLSM = voxel-based lesion-symptom mapping
VCAM-1 = vascular cell adhesion molecule-1
WMD = white matter disease
WMHs = white matter hyperintensities
Chapter 1

Literature review

0 Introduction

Stroke is a leading cause of permanent disability in adults and one of the most frequent causes of death.\textsuperscript{1,2} In addition to substantial individual suffering, stroke results in enormous costs to society.\textsuperscript{3,4} While strong evidence exists to support the management of traditional vascular risk factors,\textsuperscript{5} these co-morbidities only partly address the full range of options available to improve outcomes and prevent future cerebrovascular events.

Recent attention has been directed to the association of sleep disorders with cerebrovascular disease.\textsuperscript{6,7} In particular, obstructive sleep apnea (OSA) has been demonstrated to be an independent risk factor for stroke and mortality,\textsuperscript{8} and treatment with continuous positive airway pressure (CPAP) has been shown to be safe\textsuperscript{9} and to improve outcomes\textsuperscript{10} post-stroke. Nonetheless, compliance with CPAP after stroke is a major impediment to routine utilization;\textsuperscript{11} in addition, sleep-disordered breathing alone does not explain the full spectrum of pathophysiological changes occurring at night that may modulate a patient’s risk for cerebrovascular disease.

Despite sharing common underlying pathophysiological mechanisms with sleep-disordered breathing,\textsuperscript{7} sleep-related movement disorders (SRMDs) such as Restless Legs Syndrome (RLS) and the closely related nocturnal Periodic Limb Movements (PLMs) have been relatively unexplored in the context of cerebrovascular disease. These are common treatable conditions\textsuperscript{12} that can arise after stroke,\textsuperscript{13,14} and preliminary evidence suggests an association with vascular risk factors and vascular events.\textsuperscript{15,16} The goal of this study was to investigate the potentially clinically-relevant but under-explored relationship of the sleep-related movement disorders RLS and PLMs with cerebrovascular disease.

The next two sections of this chapter provide an overview of RLS and PLMs. Afterwards, white matter hyperintensities (WMHs) and their role as a marker of vascular disease is
examined. Next, we discuss the rationale for studying patients with minor stroke and transient ischemic attack (TIA) in the present work. Finally, we conclude the chapter by reviewing the postulated mechanisms and literature to date that examines a link between the sleep-related movement disorders of interest and vascular disease. Each section will conclude by briefly discussing current gaps in the literature relevant to the current investigation.
1 Sleep-Related Movement Disorder #1: Restless Legs Syndrome

Movement disorders and sleep are closely related. Some abnormal movements are at least partially suppressed by sleep, including tremor and tics, while others are unmasked by sleep, such as PLMs, rhythmic movement disorder, bruxism, sleep-related leg cramps and REM sleep behavior disorder. The focus of this project will be on RLS and the intimately related PLMs, since these conditions are relatively common and have been the most explored in the context of vascular disease.

Restless Legs Syndrome is a frequently undiagnosed sensorimotor disorder. The condition was first described by Thomas Willis in 1685. Karl Ekbom renewed interest in the syndrome and was the first to give a full description based on a large series of patients. In order to avoid negative or inaccurate descriptors as well as to honour pioneers in the field, the name “Willis-Ekbom Disease” has been proposed as an alternative name for the condition, however, this new name has not been universally adopted.

1.1 Epidemiology

RLS is one of the most common movement disorders, however, it is frequently underappreciated by primary care physicians. As would be expected, prevalence rates vary according to the definition of RLS used and the population studied. Generally speaking, studies investigating primary care populations have generally shown higher RLS prevalences compared to population-based studies.

1.1.1 Diagnostic criteria

Diagnostic criteria for RLS were first established by the International Restless Legs Study Group (IRLSSG) in 1995 and revised in 2003. Further revisions to the diagnostic criteria were made by the IRLSSG in 2011 but have yet to be formally published. Other diagnostic criteria have also been developed, however, these have been infrequently used. The discussion below primarily focuses on the 2003 revised criteria from the IRLSSG, as these have been the most frequently applied in the literature to date.
According to the 2003 revised criteria of the IRLSSG, in order to make a diagnosis, four essential diagnostic features must be present: 25

1. An urge to move the legs that is usually, but not always, accompanied or caused by uncomfortable and unpleasant leg sensations;

2. The symptoms begin or worsen during rest or inactivity;

3. The symptoms are partially or totally relieved by movements such as walking or stretching for at least as long as the activity continues;

4. The symptoms only occur or are worse in the evening or night than during the day.

In addition, special attention must be taken to ensure that the symptoms are not due to another condition that could result in a similar presentation. 12 RLS mimics include leg cramps, peripheral neuropathy, radiculopathy, positional discomfort and arthritic pains; patients whose symptoms can be explained primarily on the basis of another condition should not be diagnosed with having RLS. 29

Supportive clinical features are not essential in making the diagnosis, however, their presence can help resolve diagnostic uncertainties: 25

1. Periodic limb movements (discussed in further detail below): these occur in about 80% of patients with RLS, but are also commonly observed with increasing age and in other disorders, and are not specific for RLS.

2. Family history: the prevalence of RLS among first-degree relatives of people with RLS is 3 to 5 times greater than in people without RLS.

3. Response to low-dose dopaminergic treatment: essentially all patients with RLS demonstrate an initial response to dopaminergic therapy (e.g. L-dopa or dopamine receptor agonist) at doses considerably lower than those used for Parkinson’s disease.
In addition, it is important for physicians to appreciate that RLS symptoms can alternate legs and may be asymmetric.\textsuperscript{12} With progressive disease, involvement of the arms has been described in up to 48\% of patients.\textsuperscript{30} Rarely, patients can present with sensorimotor symptoms confined to the abdominal wall that, with the exception of leg involvement, satisfy the diagnostic criteria for RLS.\textsuperscript{31}

1.1.2 Prevalence according to Age, Gender & Race

RLS symptoms increase in prevalence with age.\textsuperscript{21, 23, 32, 33} Almost all studies demonstrate that RLS occurs more commonly in women,\textsuperscript{21-23, 33-42} particularly in those with greater parity;\textsuperscript{33} the association with parity suggests a link between RLS and sex hormones,\textsuperscript{33} but such an association has not been definitively established. The greater prevalence of RLS in women could also be explained by the strong association of RLS with iron deficiency (discussed below).\textsuperscript{43}

It has been suggested that RLS is more common in individuals of Northern European descent compared with Asians or Southern Europeans given the comparatively low prevalence of RLS initially reported in Turkey\textsuperscript{42} and Singapore,\textsuperscript{44} however, methodological issues may have significantly impacted these latter two studies\textsuperscript{21} and subsequent work from Korea has shown a prevalence more comparable to that observed in other countries.\textsuperscript{37} At this time, whether RLS prevalence varies significantly by race/ethnicity remains unclear; variations in reported prevalences may reflect differences in study methodologies, demographic factors, and unique population characteristics.\textsuperscript{23}

1.1.3 Prevalence in General and Primary Care Populations

Early studies that pre-dated the development of diagnostic criteria for RLS used personal interviews and demonstrated a prevalence of 7.0 to 15.0\% in the adult general population;\textsuperscript{45, 46} given the absence of diagnostic criteria available at the time of the studies, the accuracy of these prevalence estimates was uncertain. Subsequent population-based studies that utilized the 1995 diagnostic criteria and face-to-face interviews\textsuperscript{33, 36, 38, 39} or questionnaires\textsuperscript{40, 41} found somewhat lower prevalence rates between 5.8 and 11.4\%. More recently, large studies that used the 2003 RLS criteria have demonstrated prevalences in the range of 4.4 to 11.5\%; these
included population-based investigations that interviewed patients, as well as studies of primary care patients who were assessed using questionnaires.

A criticism of the previously-cited work was that many RLS cases were mild and of little medical significance, and that media attention to the disorder inflated disease prevalence and increased the use of medications where there was no medically significant disease to be treated. To address such criticism, investigators evaluated patients for “clinically-significant” or “medically-significant” RLS, or classified patients as “RLS sufferers”, if symptoms were associated with moderate-to-severe distress and occurred ≥2 times per week; studies that used these more stringent criteria demonstrated lower prevalences of 1.5 to 2.7% in the general population, and 2.7% in a primary care population. As would be expected, other studies investigating primary care populations have also generally shown higher RLS prevalences compared to population-based studies.

1.1.4 Prevalence in Selected Patient Populations

Almost 70% of patients with RLS have “primary” or “idiopathic” with no underlying etiology detected on physical examination, laboratory tests, or neuroimaging. Primary RLS should be strongly suspected in patients with early onset (before 45 years of age) and a positive family history.

In the remainder of patients, a clinical condition able to cause RLS is detected; these cases are referred to as “symptomatic RLS” and, not surprisingly, RLS occurs with a comparatively high frequency in patients with these conditions (discussed below). Disease-onset after the age of 45 years is more typical in the symptomatic form of RLS, which improves or disappears by addressing the underlying disorder; otherwise idiopathic and symptomatic cases are essentially clinically identical.

Iron deficiency, renal disease and pregnancy represent well-known risk factors for RLS. Other conditions, not necessarily causative of RLS (e.g. migraine), have also been observed to occur with greater frequency in RLS patients compared to non-RLS patients.
1.1.4.1 Iron Deficiency

The association of RLS with iron deficiency has been long appreciated, and many studies support this link. The appearance or worsening of RLS may be associated with low concentrations of ferritin, such as in the context of blood donations. Up to 31% of older patients with RLS have iron deficiency and iron supplementation has been demonstrated to reduce RLS symptoms. In many patients, iron deficiency is not detected because there is no anemia and low ferritin is the only pathological parameter.

1.1.4.2 Renal Disease

In patients with non-dialysis-dependent kidney disease, RLS is present in 26% and is associated with poor sleep quality and depression. In patients with end-stage / dialysis-dependent renal disease, up to 62% have RLS and its presence is associated with poorer quality of life and greater mortality.

1.1.4.3 Pregnancy

RLS incidence is elevated during pregnancy, with about 25% of women affected. The syndrome is strongly related to the 3rd trimester of pregnancy and tends to disappear around the time of delivery; affected women have lower values of hemoglobin and mean corpuscular volume compared with non-RLS subjects. Pregnancy itself may increase the risk for subsequent development of RLS.

1.1.4.4 Other Conditions and Medications

In one study of patients with type 2 diabetes, 45% met diagnostic criteria for RLS but only one-third of the patients were being treated for RLS. Other larger studies have also demonstrated an increased prevalence of RLS in patients with type 2 diabetes, however, several other studies have not demonstrated an increased prevalence. In diabetic patients, polyneuropathy represents the main risk factor for RLS; however, polyneuropathy only partially explains the increased prevalence of RLS in type 2 diabetics.

In addition, RLS has also been reported to occur with a greater prevalence in patients with migraine, myelopathy, radiculopathy, peripheral neuropathy, venous
insufficiency, fibromyalgia, osteoarthritis, respiratory disease, and even irritable bowel syndrome. Small-fibre neuropathy may be a contributing factor in patients with late-onset RLS. Furthermore, the use of certain medications, such as anti-histamines, anti-emetics, and certain anti-depressants, may trigger or exacerbate RLS symptoms; selective serotonin reuptake inhibitors (SSRIs) are particularly important in this regard.

1.2 Consequences of Restless Legs Syndrome

1.2.1 Vascular Consequences

As discussed in further detail later, emerging evidence suggests a link between RLS, cardiovascular events and cerebrovascular disease as well as an association of RLS with vascular risk factors such as hypertension, diabetes and obesity. Multiple mechanisms may mediate a link with all forms of vascular disease, and these include inflammation, oxidative stress, hypothalamic-pituitary-adrenal system activation, sleep disturbance and the well-recognized association of RLS with psychiatric conditions such as depression and anxiety disorders. Perhaps most important is the association with nocturnal PLMs, which occur in approximately 80% of patients with RLS. PLMs are known to induce transient episodes of sympathetic hyperactivity which are associated with heart rate and blood pressure elevations comparable to those observed during apneic episodes associated with OSA. These autonomic fluctuations could mediate vascular events by promoting inflammation and oxidative stress, which may increase the risk of atherosclerotic plaque formation and rupture. In addition, nocturnal autonomic dysfunction could deregulate daytime blood pressure and give rise to hypertension.

1.2.2 Non-vascular Consequences

RLS is associated with numerous negative effects and substantial economic and societal burden. Several studies have demonstrated that patients with RLS have poorer quality of life compared to those in the general population. Quality of life in RLS is as low as in other chronic neurological disorders such as Parkinson’s disease and stroke. These findings have been demonstrated in Western and non-Western countries.
The poor quality of life observed in RLS may be due to several comorbid psychiatric issues that are more common in people with RLS, such as depressive symptoms, major depressive disorder, panic disorder and generalized anxiety disorder; treatment with SSRIs may further exacerbate RLS symptoms. RLS may be a risk factor for major depressive disorder in patients greater than 65 years of age. Psychological dysfunction occurs in multiple domains in patients with both treated and untreated RLS, and RLS severity correlates with higher psychological impairment. Preliminary work suggests that RLS symptoms may give rise to depression and anxiety disorders, however, the relationship between psychiatric issues and RLS requires further investigation and may be bidirectional.

Sleep complaints may also play a prominent role in mediating the poor quality of life observed. Numerous epidemiological studies have reported that patients with RLS have difficulty initiating and maintaining sleep, and experience non-restorative sleep; these complaints are 2 to 3 times more likely in patients with RLS compared to those without the syndrome. Excessive daytime sleepiness has also been assessed in this patient population, usually with use of the Epworth Sleepiness Scale (ESS). Research studies that used the ESS demonstrated mixed results as to whether RLS and non-RLS individuals differ in daytime sleepiness. It may be the case that, despite experiencing chronically disrupted sleep, patients with RLS do not experience profound daytime sleepiness.

The chronic sleep loss observed in RLS may be expected to contribute towards cognitive deficits. In keeping with this, executive dysfunction has been demonstrated in patients with RLS, similar to what is observed in patients with acute sleep deprivation. However, more careful scrutiny has revealed that patients with RLS perform better than sleep-restricted controls on tasks that are sensitive to sleep loss; this suggests that RLS subjects may show a relative degree of increased psychomotor vigilance.

Finally, for reasons that are not entirely clear, males with RLS have been shown to have a higher overall mortality; this association is independent of known risk factors, such as hypertension, cardiovascular disease, chronic conditions, body mass index, lifestyle factors, sleep duration and other sleep-related disorders. The increased mortality in RLS has been demonstrated to be most frequently associated with respiratory disease, endocrine disease, nutritional/metabolic disease, and immunologic disorders.
1.3 Questionnaires to Diagnose RLS & Rate Its Severity

Given the relative ease of administration and cost-effectiveness, many prior investigations have used questionnaires to diagnose RLS and rate its severity. Many RLS diagnostic questionnaires exist, but all address the four essential 2003 criteria outlined above. If a diagnosis of RLS is based exclusively on the results of a questionnaire, 16% of patients who meet all four criteria will be found to have an alternative diagnosis when interviewed by a physician expert. This highlights the need to exclude similarly-presenting “RLS mimics”. The addition of questions that specifically exclude RLS mimics can increase the specificity of an RLS diagnostic questionnaire to 94% (e.g. the Cambridge-Hopkins Diagnostic Questionnaire for RLS). Since RLS is a subjective clinical diagnosis, assessment by a physician experienced in diagnosing RLS remains the gold standard.

Scales that assess the severity of RLS symptoms in patients with a confirmed diagnosis have also been developed. Such a scale has been rigorously validated for research and clinical purposes by the International Restless Legs Syndrome Study Group. It contains 10 items that assess the frequency and severity of RLS symptoms over the preceding week. Responses are graded from 0 to 4 (e.g. 0 = absence of symptoms, 4 = very severe symptoms), with a maximum total score of 40. Another RLS severity scale has also been developed by investigators at Johns Hopkins University; this scale has been validated against objective measures of RLS such as sleep efficiency and periodic limb movement index, and also correlates RLS severity to biological measures such as serum ferritin and brain iron in the substantia nigra. Neither of these two scales assesses the number of limbs involved or the rapidity with which symptoms develop when a patient first sits or lies down.

1.4 Management

1.4.1 Initial Evaluation

Initial management involves ruling out symptomatic and/or contributing disorders. Since RLS is frequently associated with iron deficiency, all patients should be tested for serum ferritin level and iron saturation, which are thought to be the most sensitive measures of iron deficiency. Testing iron stores is particularly important if a history of anemia, gastrointestinal hemorrhage, frequent blood donation, or menorrhagia is present. No other
laboratory tests are routinely indicated. If the ferritin level is <45 µg/L, then iron therapy should be considered, since these levels have been demonstrated to correspond with RLS severity. Many iron preparations, such as ferrous sulfate or ferrous gluconate, are available. Iron should be administered with a total daily amount of elemental iron of 150-200 mg. Vitamin C (200 mg) should be added to each dose to enhance absorption. Serum ferritin concentration should be rechecked every 6 months.

Assessing for renal disease and B12 deficiency, if clinically appropriate, may also be warranted. If the neurological examination suggests an associated peripheral neuropathy, radiculopathy or myelopathy, then electromyography, nerve conduction studies and/or imaging should be requested. Addressing other concomitant sleep disorders is also important, such as insufficient sleep time and obstructive sleep apnea, since these can exacerbate RLS symptoms.

In addition, other preventive non-pharmacologic approaches should be considered, including regular exercise, reducing caffeine, alcohol or nicotine intake, and reducing or discontinuing the use of exacerbating medications.

1.4.2 Medical Therapy

1.4.2.1 Dopamine agonists

Even after symptomatic causes have been addressed, many patients still require medical therapy. Dopaminergic agents are considered the first line of treatment in idiopathic RLS. The dopaminergic agonists pramipexole and ropinirole are usual first choices, and have had their effectiveness demonstrated in several randomized controlled trials. Doses utilized to manage RLS are considerably lower than those used in Parkinson’s disease. Generally speaking, treatment with pramipexole is initiated at a dose of 0.125 mg, while ropinirole is started with a dose of 0.25-0.5 mg; both are administered 1 to 2 hours before symptom onset (usually bedtime), and increased every few days until relief is obtained. An alternative option is rotigotine, which is supplied as a once daily transdermal patch with doses of 1-3 mg.
Nausea, nasal congestion and leg edema may occur with any dopamine agonist, and rotigotine may result in skin irritation under the patch. Three other more concerning side effects may limit long-term use of these agents: augmentation, impulse control disorders, and daytime sleepiness.\(^\text{12}\)

Augmentation is the development of worsening RLS symptoms progressively earlier in the day after administration of dopaminergic medication, and has been demonstrated to occur in at least 42% of patients treated with pramipexole for the duration of nearly a decade.\(^\text{115}\) It may take the form of earlier onset of symptoms, worsening of pre-existing symptoms or spread of symptoms to the arms.\(^\text{12}\) Increases in the dose of medication to cover the extended symptomatic period relieve the symptoms in the short-term, but ultimately, symptoms begin to appear even earlier, accompanied by a noticeable decrease in the duration of action and the effectiveness of the drug.\(^\text{111}\) Augmentation can be avoided by maintaining low doses of dopaminergic agents and ensuring iron sufficiency.\(^\text{116}\) Non-dopaminergics and opiates (discussed below) can be used when patients experience augmentation with more than one dopaminergic agent.\(^\text{117}\) In the past, levodopa was used more frequently in the initial management of RLS but has fallen out of favour given its high incidence of augmentation (up to 80%).\(^\text{118}\)

Impulse control disorders include pathological gambling, compulsive shopping and hypersexuality.\(^\text{12}\) In one case-control study, 17% of patients with RLS treated with dopamine agonists experienced impulse control disorders.\(^\text{119}\) All patients treated with these agents should be warned about impulse control disorders, and this warning should be repeated at every clinic visit.\(^\text{12}\) The mean time from starting a dopaminergic agonist to the onset of an impulse control disorder is 9 months; in almost every case, the impulse control disorder resolves after discontinuation of the drug.\(^\text{119}\)

Finally, while initially under-appreciated,\(^\text{111}\) excessive daytime sleepiness can occur in more than 50% of patients using dopaminergic agonists for RLS. Sleep attacks have also been reported in about 10%; the risk is greatest in those taking higher doses.\(^\text{115}\)
1.4.2.2 Calcium channel alpha-2-delta ligands

Gabapentin,\textsuperscript{120} pregabalin,\textsuperscript{121} and gabapentin enacarbil\textsuperscript{122} (a gabapentin prodrug) have all been demonstrated to be effective in RLS. These drugs can be administered 1 to 3 times a day, depending on the timing of RLS symptoms. Class side effects include hypersomnia, dizziness, unsteadiness, weight gain and depression. Augmentation has not been reported.\textsuperscript{12}

1.4.2.3 Opioids

Opioid medications are highly effective in RLS, however, these medications are associated with many unfavourable side effects. They can worsen concomitant obstructive sleep apnea and provoke central apneas. In addition, opioid medications can cause constipation, sleepiness, cognitive impairment and gait disturbance. Finally, issues surrounding dependence must also be appreciated prior to initiating therapy.\textsuperscript{12} For these reasons, opioids are typically reserved for severe or refractory cases. Of note, augmentation has not been reported with the use of opioid medications.\textsuperscript{111}

1.4.2.4 Benzodiazepines and Benzodiazepine Agonists

Clonazepam has been used historically, although it primarily reduces arousals from nocturnal events and/or acts as a sedative, and has little direct effect on the condition itself. For this reason, clonazepam may be helpful in patients with mild or intermittent RLS, particularly in patients who also suffer from insomnia.\textsuperscript{12} The newer shorter-acting benzodiazepine agonists, such as zolpidem, may induce nocturnal behaviors such as sleep-walking and sleep-eating.\textsuperscript{12} Similar to the calcium channel alpha-2-delta ligands and opioid medications, augmentation has not been reported with the use of these medications.\textsuperscript{111}

1.5 Gaps in the Literature Relevant to Current Study

- The prevalence of RLS after stroke has yet to be explored in detail. At this time, only a single study has studied post-stroke RLS.\textsuperscript{14} In that study, 7% had a diagnosis of RLS prior to their stroke and when those with a prior history of RLS were excluded, 12% were found to have newly-diagnosed RLS after their stroke. These results need confirmation in other cohorts of patients with cerebrovascular disease. Ideally, major risk factors for RLS (e.g. iron deficiency and renal disease) would also be noted.
With regards to post-stroke/TIA RLS, several other contributions to the literature would also be beneficial:

- Investigators have yet to study RLS severity after stroke; aside from overall prevalence, which proportion of cases are mild or “clinically-significant” is unknown.
  - In order to enhance diagnostic accuracy, future studies would ideally use physician diagnoses to avoid false positive cases from RLS “mimics”.

- The clinical characteristics (e.g. lesion location and presenting neurological symptoms) of patients who developed RLS after a stroke have not been compared to those who did not develop RLS. An understanding of such features could help identify patients at higher risk for developing RLS after a stroke.

- Despite a strong association in other patient populations, the association of RLS with quality of life and depression has yet to be explored after stroke.

- Finally, no studies to date have explored the prevalence and features of RLS after TIA; this remains an unexamined area of research that may have potentially important implications for patient care.

In summary, RLS is prevalent and associated with poor quality of life; it can be diagnosed using a questionnaire and readily managed. Its prevalence, clinical features and impact after TIA/stroke are uncertain; these are areas in need of active exploration.
2 Sleep-Related Movement Disorder #2: Periodic Limb Movements of Sleep

2.1 Definition

Periodic limb movements, originally called nocturnal myoclonus, are detected in approximately 80% of patients with RLS. These are repetitive movements that frequently occur as stereotypic triple flexion responses involving the great toe, ankle and hip; video analysis of PLMs reveals similarities to the Babinski response. The duration of PLMs is at least 0.5–10s, and they recur in sequences of four or more events at 5–90s intervals; they are associated with a minimum amplitude increase of 8µV above the resting electromyogram (EMG) voltage in the anterior tibialis surface electrode. Leg movements associated with arousals from respiratory events during sleep are excluded. PLMs occur more often in the first half of the night than the second, and usually do not persist into REM sleep. PLMs typically involve the lower limbs, but can also involve the arms in more advanced cases.

PLMs may occur not only during sleep but also in the waking state. These are called periodic limb movements in wake (PLMW) and appear similar to PLMs but have a longer duration. Both PLMW and PLMs are thought to represent motor manifestations of RLS.

PLMs occurring in patients with otherwise unexplained insomnia and/or hypersomnia is defined as periodic limb movement disorder (PLMD). This diagnosis requires polysomnography confirmation and is based on the exclusion of other causes of sleep disturbance.

Traditionally, a PLM index ≥ 5 per hour of sleep has been considered abnormal, however, this cut-off may require revision in light of research indicating that some healthy middle-aged individuals without any sleep disturbance may have PLM indices > 10 per hour of sleep. Nonetheless, higher PLM indices may carry clinical significance. For example, a PLM index cut-off of ≥30 PLMs per hour of sleep has been shown to be clinically relevant with regards to the development of incident cardiovascular disease; a cut-off of ≥45 PLMs per hour of sleep has been associated with the presence of serum inflammatory markers.
2.2 Clinical Significance

As discussed by Silber (2013), the non-specific nature of PLMs and their occurrence in a wide range of disorders raises the question as to whether they have any clinical significance of their own or are simply an epiphenomenon of other disorders. While the presence of PLMs is thought to be associated with the complaint of non-restorative sleep, no definite relationship has been detected between the presence of PLMs and symptoms of insomnia or hypersomnia. Likewise, no association has been found between PLMs and polysomnography measures such as total sleep time, arousal index and sleep efficiency.

Given the increased prevalence of PLMs with conditions associated with dopamine deficiency (e.g. RLS, RBD, Parkinson’s disease and antidepressant medication use), it has been postulated that PLMs could be a potential biological marker for dopaminergic mechanisms.

The association of PLMs with vascular disease is an emerging area of study, and one of the focuses of the current study. As discussed earlier, the nocturnal autonomic fluctuations observed in the context of PLMs may be pertinent in the pathogenesis of vascular disease; greater PLM indices may be more strongly associated with vascular outcomes. This concept is discussed in greater detail later in this chapter.

2.3 Methods of Detection

The “gold standard” tool to measure PLMs is polysomnography using standard criteria. However, the use of polysomnography is hampered by its high cost and long waiting lists. In addition, since PLMs can vary from night to night, recordings across multiple nights are often necessary to obtain an accurate assessment of PLM frequency. Such factors have led to the development of a variety of ambulatory sleep study systems, including actigraphy.

The use of actigraphy can facilitate PLM recordings over multiple nights in a cost-effective manner. In PLM validation studies, actigraphy is usually used in a high resolution mode (short epochs; e.g. 5-second intervals) and compared to EMG data derived from a simultaneous actigraphy-polysomnography study. Patients are asked to keep a concomitant
sleep log, which assists with artifact rejection and the accurate determination of the time of lights on/off.\textsuperscript{127}

While early reports suggested that actigraphy may inaccurately detect PLMs,\textsuperscript{135, 136} subsequent studies have demonstrated that various actigraphy devices can be highly sensitive and specific\textsuperscript{137-139} compared to polysomnography for the measurement of PLMs. One of these devices, the Actigraph (developed by Cambridge Neuro-Technology Ltd, Cambridge, UK) requires patients to wear the unit at the dorsum of each foot at the base of the big toe using tape at night;\textsuperscript{137} for the Actigraph, placement at the base of the toes is more accurate than placement at the ankles.\textsuperscript{139} The PAM-RL device is placed at the ankles prior to sleep.\textsuperscript{138} Preliminary work also suggests that wrist actigraphy may predict those at higher risk for PLMD and sleep-disordered breathing, however at this time, wrist actigraphy cannot differentiate between different sleep disorders.\textsuperscript{140}

\section*{2.4 Prevalence}

\subsection*{2.4.1 General Population}

The precise prevalence of PLMs in the general population is not known because large epidemiological studies have not been performed using polysomnography or actigraphy. In a large questionnaire study of 18,980 subjects from the general population aged 15–100 years, 3.9\% of participants endorsed experiencing symptoms consistent with PLMs;\textsuperscript{141} however, since PLMs are most accurately diagnosed using electrophysiological testing (e.g. polysomnography or actigraphy), questionnaire data alone is unreliable in determining the precise prevalence in the general population. Smaller studies using polysomnography have demonstrated that PLMs are rare in childhood\textsuperscript{142} and increase in prevalence with age.\textsuperscript{127} In elderly, PLMs have been observed in individuals with\textsuperscript{143} and without sleep issues.\textsuperscript{130, 144}

\subsection*{2.4.2 Sleep Disorders}

As noted above, the majority of patients with RLS have \( \geq 5 \) PLMs per hour of sleep,\textsuperscript{89} however, most individuals with PLMs do not have RLS. In one study of patients with RLS, PLM frequency was associated with RLS severity,\textsuperscript{145} but this finding was not confirmed in another study.\textsuperscript{127} Elevated PLM indices can also be seen in other sleep disorders such as
narcolepsy, where PLMs have been observed to respond to L-dopa. PLMs are also commonly seen in patients with obstructive sleep apnea (OSA), either in association with apneas or independently from apneic events. Therapy with continuous positive airway pressure (CPAP) has been shown to either decrease or increase PLMs according to the baseline severity of the OSA. Finally, in REM sleep behavior disorder (RBD), 70% of patients have a PLM index > 10 / hour of sleep and PLMs are observed to occur during REM sleep.

2.4.3 Non-Sleep Disorders

In addition, several studies have reported elevated PLM indices in patients with non-sleep disorders. Unfortunately, many of these reports did not compare patient populations to age-matched controls, thus making meaningful interpretation difficult. In studies that did use age-matched controls, patients with congestive heart failure, alcohol dependence, Parkinson’s disease and Multiple System Atrophy have been shown to have elevated PLM indices. The increased prevalence in patients with untreated Parkinson’s disease has been interpreted to be due to a dopaminergic deficiency, the same neurotransmitter deficiency seen in RLS/PLMs.

2.4.4 Antidepressant Medications

PLM indexes at thresholds considered to be of potential clinical significance were reported to be more statistically prevalent in users of selective serotonin reuptake inhibitors (SSRIs) and venlafaxine compared with patients taking bupropion and a control group; venlafaxine and SSRI-induced PLMs may be the result of enhanced serotoninergic availability and secondarily decreased dopaminergic effects. Alternatively, serotoninergic innervation of interneurons may also activate motoneurons; this modulation turns off during sleep, an effect which SSRIs block. Thus, SSRIs may give rise to increased PLMs indices.

2.5 Treatment

The optimal treatment of PLMs and PLMD has yet to be established. Asymptomatic PLMs are typically ignored if they are found as a coincidental observation on polysomnography, though this may need to be reconsidered in light of emerging evidence of PLMs as a potential
vascular risk factor. Few reports have been published on the treatment of patients with PLMs and PLMD, and most of these were open studies.\textsuperscript{127} Recommendations for therapy usually originate from studies in patients with RLS, and dopaminergic agents are typically first-line therapy (discussed above).

It is important to ensure that limb movements are not a feature of untreated sleep apnea, or milder forms of upper airway resistance that terminate in a leg movement as part of an arousal. Use of a nasal pressure transducer for assessment of airway function may be particularly important in this regard.

2.6 Gaps in the Literature Relevant to Current Study

- The prevalence of PLMs after TIA or stroke has yet to be reported.
  
  - Ideally, the prevalence of PLMs in a post-TIA/stroke population would be compared to that observed in age-matched controls, and the effects of RLS/PLM-associated conditions (e.g. iron deficiency and renal impairment) as well as medications (e.g. SSRIs) would also be considered.

- The association of PLMs with quality of life, depressive symptoms and clinical symptoms post-TIA/stroke has also not been explored.

- The location of lesions associated with post-stroke PLMs have not been studied to date in any series of patients; only case reports (reviewed below) discuss the appearance of PLMs after stroke and the associated cerebrovascular lesions.
3 Association of Sleep-Related Movement Disorders with Stroke

In the first two sections of this chapter, an overview of the Sleep-Related Movement Disorders RLS and PLMs was provided. In the following section, what is already known about the association of RLS and PLMs with cerebrovascular disease is reviewed. Sleep-related movement disorders may be related to cerebrovascular disease in two non-mutually exclusive ways:

1. Cerebrovascular disease can give rise to sleep-related movement disorders by lesioning specific brain regions or pathways implicated in the pathogenesis of these sleep disorders.

2. Sleep-related movement disorders can contribute to the development of cerebrovascular disease via several mechanisms.

We begin the section by discussing the postulated pathogenesis of RLS and PLMs; this provides background information for the following discussion on the development of sleep-related movement disorders after stroke. Afterwards, several postulated mechanisms that could explain how RLS and PLMs could contribute to the development of cerebrovascular disease are reviewed. The section is concluded by reviewing the current epidemiological evidence that links RLS and PLMs with cerebrovascular and cardiovascular disease.

3.1 Postulated Pathogenesis for RLS and PLMs

3.1.1 Genetic factors

Molecular genetic studies have identified at least three major susceptibility loci in families from Canada and other countries around the world. RLS may be a condition that is not caused by single genetic defect, but could be a disorder with complex inheritance, such as is the case with many other neurological disorders such as Alzheimer’s disease or migraine. Only in early onset cases with a positive family history is there strong evidence that a major genetic susceptibility could explain the syndrome; otherwise, genetic and symptomatic forms of RLS do not clinically differ.
The first locus conferring susceptibility to RLS was found in a Canadian family on chromosome 12q and was associated with an autosomal recessive mode of inheritance.\textsuperscript{155} This locus has been confirmed in five more families, but the investigators have cautioned that genetic heterogeneity should be considered.\textsuperscript{156} Another locus was found on chromosome 14q in a three-generation Italian family, and later confirmed in a Canadian family.\textsuperscript{157, 158} Finally, using a model-based linkage analysis with the assumption of an autosomal dominant mode of inheritance, a 9p linkage for RLS in two large families from the United States was detected.\textsuperscript{159}

Nonetheless, more recent studies have pointed to other chromosomes as being significantly implicated in RLS. In a large genome-wide association study, highly significant associations were found between RLS and variants in three genes located on chromosomes 2p, 6p and 15q; two independent replications confirmed these associations.\textsuperscript{160} These results have been replicated in subsequent studies that examined populations from Europe\textsuperscript{161} and the United States.\textsuperscript{162} The genes most strongly implicated in RLS have been found to be MEIS1, BTBD9, MAP2K5, and SKOR1; each genetic variant of these alleles carries an increased risk for RLS of approximately 50%.\textsuperscript{160} Of interest is the fact that the MEIS1 gene is involved with a regulatory network important in motor neuron development, and SKOR1 is involved with regulation of the development of dorsal horn sensory pathways.\textsuperscript{163} While little is known at this time about the exact function of these genes, further developments in our understanding of these genes may reveal important insights into the pathogenesis of RLS.

A genetic risk factor for periodic limb movements in sleep has also been identified on the BTBD9 gene found on chromosome 6p; interestingly, this sequence variant was not a gene specifically for RLS since the investigators observed the highest odds ratio in subjects with periodic limb movements in sleep without RLS. As this group became increasingly diluted with subjects with RLS, the association with the single nucleotide polymorphism became less and less apparent.\textsuperscript{164} It has been proposed by Winkelman (2007)\textsuperscript{165} that PLMs may serve as an endophenotype for RLS. Endophenotypes are “relatively simple, stable biologic phenomena that can be measured objectively and are genetically determined.”\textsuperscript{165} Disorders with complex phenotype and heritability, such as RLS, are increasingly being dissected into
their component parts with the use of endophenotypes with the hope that the endophenotype will have a more straightforward genetic and pathophysiological basis.\textsuperscript{165}

### 3.1.2 Dopamine Deficiency

Links between iron deficiency and reductions in central dopaminergic tone\textsuperscript{166}, as well as the finding that central dopamine signaling exhibits a daily rhythm with the nadir in the evening\textsuperscript{167}, are clues that RLS ultimately reflects hypo-functioning of brain dopamine signaling.\textsuperscript{168} Perhaps the strongest support for a dopaminergic abnormality in RLS is the fact that dopamine receptor agonists are first-line treatment for the relief of both motor (i.e. PLMs) and sensory symptoms in RLS.\textsuperscript{169}

Nevertheless, a central dopamine hypothesis has endured despite the absence of any compelling biologic evidence of dopaminergic dysfunction in RLS patients.\textsuperscript{168} For example, genetic association studies do not point to RLS susceptibility residing in variants of proteins involved in dopamine synthesis or signaling.\textsuperscript{170} Also, CSF analyses of dopamine and its major metabolites are normal in patients with RLS.\textsuperscript{171} As noted by Trenkwalder et al. (2005),\textsuperscript{56} the essentially normal pre-synaptic dopaminergic binding studies using $^{18}$F-dopa PET\textsuperscript{172-174} or β-CIT-SPECT\textsuperscript{175-177} in patients with RLS lends support to the hypothesis that other dopaminergic pathways may be more involved in the pathophysiological mechanisms of the syndrome rather than the nigrostriatal system.\textsuperscript{178}

In addition, neurophysiological studies in patients with RLS also demonstrate evidence of altered function of the descending spinal tracts, peripheral nervous system influence, changes in the inter-neural circuitry at the spinal level itself, or combinations of these three possibilities.\textsuperscript{179} Furthermore, increased spinal cord excitability in patients with RLS/PLMs\textsuperscript{180} and the onset of PLMs after spinal cord injury\textsuperscript{181} have been reported. Finally, peripheral somatosensory input is not a necessary condition for the syndrome: a patient with RLS symptoms in the absent portions of his lower extremities, after bilateral above-the-knee amputations, responded well to dopamine agonist treatment.\textsuperscript{182} Collectively, such work has lent support for the involvement of brainstem-spinal mechanisms in the pathogenesis of RLS. While the study of animal models in RLS is still in its early stages, the dopaminergic A11
The diencephalospinal pathway (discussed below) has received particular interest as a possible pathophysiological correlate of RLS.\textsuperscript{183}

### 3.1.3 Hypofunction of the A11 Dopaminergic Diencephalospinal Pathway

Dopamine is traditionally thought to be synthesized in four major regions of the brain that, in turn, give rise to four distinct axonal pathways (nigrostriatal, mesolimbic, mesocortical, and tuberoinfundibular).\textsuperscript{168} However, there exists another small diencephalic dopaminergic cluster in the dorsal-posterior hypothalamus designated the A11 region.\textsuperscript{184, 185} Neurons in the A11 region exhibit local hypothalamic connections, project to the neocortex and the serotonergic dorsal raphe nucleus, and they descend as the sole source of spinal dopamine mainly through the dorsolateral funiculus.\textsuperscript{168} A11 spinal projections converge in the dorsal horn of the spinal cord and the intermediolateral nucleus, which is the origin of the sympathetic preganglionic pathways.\textsuperscript{168} Given their location and unique connections, it has been proposed that any loss of A11 dopamine modulation to the dorsal horn could result in disinhibition of sensory inputs, enhanced sympathetic output to the periphery (including somatic muscle fibres) and the occurrence of RLS sensory symptoms, such as motor restlessness.\textsuperscript{168} In addition, A11 neuronal dysfunction may induce alterations in autonomic output, which could be associated with surges in sympathetic drive consistent with the increases in heart rate and blood pressure seen in association with PLMs during sleep;\textsuperscript{168} as discussed below, these fluctuations in heart rate and blood pressure may increase the risk of developing future stroke and other vascular disease.\textsuperscript{161} Furthermore, since descending pathways from the A11 region also project to the serotonergic dorsal raphe nucleus, whose effects are excitatory, increased serotonin levels (as is seen with SSRI use) would increase spinal sympathetic activity and worsen RLS and PLMs;\textsuperscript{168} consistent with this, research has demonstrated that use of SSRIs is associated with worsening of PLMs (figure 1).\textsuperscript{186}

Dysfunction or atrophy of the A11 cells could explain the excellent response to treatment with dopaminergic drugs.\textsuperscript{56} In addition, although speculative, it has been proposed by Trenkwalder et al. (2005) that since A11 cells are in close proximity to the hypothalamic circadian pacemaker (i.e. the suprachiasmatic nucleus), the circadian rhythmicity seen in RLS may also be explained.\textsuperscript{56} Furthermore, because A11 diencephalospinal axons are long
and extensive, their integrity is susceptible to compromise by various ageing-related or pathological processes,\textsuperscript{168} which could account for the rising prevalence of RLS\textsuperscript{23} and PLMs\textsuperscript{127} with age. Compromised cell function would also be anticipated to manifest itself via progressive caudorostral degeneration,\textsuperscript{168} and give rise to lower extremity symptoms first and then upper extremity involvement, consistent with what is observed clinically.\textsuperscript{30}

While this model is promising, it is important to keep in mind that all key features associated with RLS cannot be explained by an animal model, particularly the sensory component (i.e. the urge to move the legs or the unpleasant sensations).\textsuperscript{187} In these investigations, animal models likely better address the motor manifestations (e.g. PLMs) of the syndrome, rather than the subjective sensory symptoms.

A major limitation of the A11 model is that lesions of the A11 system have yet to be demonstrated to influence motor activity in sleep. Another animal model that has been proposed is that which involves a lesion at the ventral mesopontine junction. Such a lesion has been demonstrated to increase periodic and isolated leg movements during sleep, similar to that seen in human RLS/PLMs.\textsuperscript{188}
Figure 1. Schematic representation of known A11 projections, their interaction with spinal circuits, and hypothetical consequences in RLS. (1) Dopamine inhibits preganglionic sympathetics in the intermediolateral cell column (IML) via the A11 diencephalospinal pathway. In contrast, serotonergic dorsal raphe descending neurons have strong excitatory actions in the IML; thus, in the absence of the actions of the dopaminergic A11 diencephalospinal pathway, basal sympathetic tone may increase. (2) Increased adrenaline via innervation of skeletal muscle may irritate muscle spindles. (3) The resulting enhanced input from pain-encoding muscle afferents in lamina I are insufficiently suppressed in the absence of dopamine. (4) Abnormal sensations, in turn, are perceived at the cortical level. These abnormal sensations are further enhanced by compromised A11 dopaminergic input at the cortical level.
3.1.4 Iron Deficiency

Aside from dopamine deficiency, iron depletion should be regarded as the most relevant additional factor for the clinical manifestation of RLS. All conditions that compromise iron availability increase the risk of RLS, leading to a higher-than-expected prevalence of RLS in these conditions.43

Iron depletion is assessed clinically by measuring serum ferritin; RLS severity correlates with the serum ferritin level, even when the ferritin level is in the normal range.64, 108 Treatment with iron reduces RLS symptoms.64 In patients with idiopathic RLS and normal serum ferritin levels, 65% have a reduction in CSF ferritin and an increase in CSF transferrin,189 suggesting that brain iron storage may be reduced in idiopathic RLS patients. Lending support to this idea is an MRI study which demonstrated decreased brain iron concentrations in the substantia nigra and putamen compared to controls; the level of abnormality correlated with the severity of RLS symptoms.109 A neuropathological study also demonstrated decreased staining for iron in the brains of patients with RLS.190

Iron may be implicated in the transport of dopamine in the brains of patients with RLS.191 In addition, iron is a necessary cofactor for tyrosine hydroxylase (the rate-limiting step in the production of dopamine), and it has been suggested that this may provide iron-dopaminergic link.68 Decreased activity of tyrosine hydroxylase would result in a reduction in dopamine formation and could reduce the amount of dopamine available to bind to postsynaptic receptors.53

Interestingly, for reasons that are unclear at this time, iron deficiency anemia has been reported to be associated with an increased risk of both arterial and venous stroke in early childhood.192, 193 This has not been reported in the adult literature.

3.1.5 Non-dopaminergic Mechanisms

Despite multiple factors suggesting a strong association of RLS with dopamine deficiency, many sleep features in RLS are not explained by a primary dopamine deficiency. For example, while dopaminergic treatments provide effective symptomatic relief and reduce PLMs, they fail to significantly decrease the sleep loss seen in the condition, do not reduce
sleep-related arousals, nor address the abnormal cycling alternating pattern of sleep associated with the syndrome. These factors have prompted investigators to search for other neurotransmitter systems that could be associated with RLS.

One study investigated the role of the excitatory neurotransmitter glutamate in 28 patients with RLS and 20 age- and gender-matched controls using magnetic resonance spectroscopy (MRS) of the right thalamus. The patients with RLS had higher levels of thalamic glutamate; in addition, levels of glutamate correlated with the wake time during sleep as well as with all other RLS-related polysomnographic sleep variables except for PLM index. Overall, these results were among the first to identify the involvement of a non-dopaminergic neural system in RLS, and the first to demonstrate a relationship between a neurotransmitter and the primary morbidity of RLS - sleep disruption. The involvement of the thalamus indicated that the mechanism underlying sleep disruption in RLS may be mediated by thalamocortical activation. Moreover, the findings also suggested that the core sensory features and sleep disturbance seen in RLS may have a separate pathophysiology from that of RLS-related PLMs.

A link between glutamate excess and iron deficiency has been proposed by multiple animal models. Gestational and lactational dietary iron deficiency have been shown to reduce brain iron and significantly increase striatal glutamate. In addition, mice with a genetic H-ferritin deficiency producing a condition similar to the H-ferritin deficiency seen in patients with RLS also show increased glutamate in several brain regions.

### 3.1.6 Dissociating Motor, Sensory and Sleep Manifestations in RLS

From a neurobiological point of view, it has been proposed that RLS may be divided into three discrete components: primary sensory-motor symptoms, PLMs and sleep disturbance. As eluded to above, dissociation of the subjective sensory symptoms of RLS (e.g. motor restlessness) from the objective motor symptoms (e.g. PLMs) may be supported on the basis of genetic studies as well as animal models supporting the A11 dopaminergic diencephalospinal pathway; the dissociation of the sleep disturbance observed in RLS from other manifestations of the syndrome have been postulated to be on the basis of a non-dopaminergic mechanism. Such a pathophysiological model, if confirmed in further studies,
would undoubtedly have clinical management and treatment implications for both RLS patients and their care-providers.

3.2 Sleep-Related Movement Disorders as a Consequence of Stroke

Several studies have reported the development of de-novo RLS after stroke, and these reports have shed light on the possible neural substrates underlying this movement disorder. The first report was on a 62-year-old male who sustained a lacunar stroke within the left thalamus; six years after his cerebrovascular event, he developed unpleasant sensory symptoms in the right leg that met criteria for RLS. His sensory symptoms responded to therapy with dopaminergic agents, and polysomnography demonstrated frequent PLMs in the right leg; PLMs were infrequent in the left leg. The unilateral PLMs and sensory symptoms, which were contralateral to a single well-defined subcortical lesion, constituted support for the diagnosis of unilateral post-stroke RLS, although the development of symptoms 6 years after the stroke begged the question as to whether other factors were also implicated. A subsequent case report described the development of bilateral RLS in a 48-year-old woman within 3 days of sustaining an infarction in the right lenticulostriate region; again, PLMs were observed on polysomnography. Although these were only case reports, one of which described the appearance of RLS six years post-stroke, these initial studies suggested that functional disturbance of a sensorimotor network loop after subcortical infarction could play a key role in the pathogenesis of RLS.

A larger series that prospectively recruited ischemic stroke patients provided stronger support for the involvement of subcortical structures in the pathogenesis of RLS. In this study, 7% had a diagnosis of RLS prior to their stroke; when those with a prior history of RLS were excluded, 12% were newly diagnosed with RLS after their cerebrovascular event. RLS symptoms appeared within one week after the stroke (mean 1.8 days; range 1-4 days). Most of the patients had bilateral symptoms and all (but two with very mild RLS symptoms) responded to treatment with a dopamine agonist. Stroke-related RLS was found most commonly in patients with lesions affecting the subcortical white matter and deep gray matter nuclei. Specifically, infarcts involved the basal ganglia/corona radiata (30.3%), pons (22.2%), thalamus (14.3%), internal capsule (12.5%) and only rarely affected the cortex.
The findings of this larger study confirmed the earlier reports that stroke-related RLS was most common after infarction of subcortical structures and further demonstrated that RLS was less likely after cortical involvement.

Support for brain regions involved in the pathogenesis of PLMs has come from several case reports that described the development of PLMs after stroke in patients who did not previously experience this nocturnal phenomenon; in these studies, the presence or absence of RLS was not reported. Post-stroke PLMs have been reported in association with lesions in the corona radiata, basal ganglia, and pons; a single report describes PLMs after cerebellar infarction.

Collectively, these results suggest that involvement of subcortical structures is most likely to result in RLS sensory symptoms. Given the unknown RLS status in the case reports which observed post-stroke PLMs, it is difficult to conclude as to which specific part of the central nervous system is most implicated in the generation of PLMs. Further work will be necessary to more definitively establish which brain regions are most important to generate RLS, PLMs and their combination.

3.3 Vascular Disease as a Consequence of Sleep-Related Movement Disorders

As per the previous discussion, it is fairly well-established that Restless Legs Syndrome and Periodic Limb Movements can result after stroke. However, whether these conditions can contribute to the development of cerebrovascular disease is still under considerable debate. Preliminary evidence suggests that this may be plausible and below we discuss seven mechanisms that could mediate this link.

3.3.1 Repeated Autonomic Arousals / Sympathetic Hyperactivity Caused by Periodic Limb Movements in Sleep

As discussed above in relation to the A11 dopaminergic diencephalospinal pathway, nocturnal sympathetic over-activity is associated with PLMs. A significant rise in heart rate has been noted following the onset of PLMs in patients with or without RLS, even in
the absence of arousals noted on electroencephalogram (EEG); these are significantly greater than the heart rate elevations seen after waking leg movements.204

Elevations in blood pressure (BP) have also been reported in association with PLMs. Early evidence came from a case report of a patient with narcolepsy and PLMs. In this individual, the occurrence of PLMs was associated with a mean increase in systolic BP of 23%, which is comparable to the BP elevations seen in patients with obstructive sleep apnea during obstructive events.205 In another study that used noninvasive beat-to-beat BP monitoring in ten patients with RLS, there were significant increases in BP with all forms of PLMs, with an average increase of systolic BP of 22 mmHg and diastolic BP of 11 mm Hg; BP changes were greatest in PLMs associated with microarousals compared to PLMs without microarousals.206 In a third study that examined 10 patients with 601 limb movements using continuous BP monitoring, it was again concluded that there was a statistically significant rise in systolic and diastolic BP after all forms of PLMs.207 Finally, PLMS have been demonstrated to be associated with sudden and significant increases of heart rate and BP in both healthy subjects and RLS patients, however, these autonomic changes are more pronounced in those with RLS.208

As mentioned by Walters and Rye,15 it is still unclear whether PLMs themselves or the arousals associated with PLMs are linked to the nocturnal heart rate and blood pressure elevations observed. Arousals from sleep occur in normal individuals and are associated with elevated heart rate and blood pressure.209 However, as mentioned above, while PLMs with arousals evoke the greatest blood pressure elevations,206, 207 PLMs not associated with arousals also evoked comparable BP rises, suggesting that the contribution of arousals alone was not as great as that of the PLMs; in addition, heart rate changes are seen even in the absence of EEG arousals.204, 210 One issue is that current measures and definitions for arousals are imprecise and non-specific; for example, a knock on a door can elicit an arousal in the form of a K-complex.211 A goal of future work should be to clarify the relative contributions of PLMs, a diagnosis of RLS and more precisely-defined arousals to transient nocturnal sympathetic hyperactivity.

Having RLS may further modulate the autonomic change associated with a PLM.208 PLMs could be linked with vascular disease because they are associated with nocturnal autonomic
hyperactivity, which may give rise to significance fluctuations in BP – a factor known to be associated with cerebrovascular disease (discussed below). In addition, nocturnal autonomic dysfunction could also deregulate daytime blood pressure, giving rise to daytime hypertension.\textsuperscript{15} Furthermore, experimental models have shown that pulsatile blood flow, which may come as a result of transient blood pressure elevations associated with PLMs, may promote inflammation and oxidative stress and increase the risk of atherosclerotic plaque formation and rupture.\textsuperscript{90, 91}

3.3.2 Inflammation

The observation by Weinstock et al. that 95\% of the 38 medical conditions known to be highly associated with RLS are inflammatory or immunological in nature led to the investigation of inflammatory markers in RLS.\textsuperscript{212} It has been proposed that inflammation could give rise to central nervous system iron deficiency that could induce RLS. Alternatively, an immune reaction to a gastrointestinal bacteria or other antigen may hypothetically cause RLS via direct immunological attack on the central or peripheral nervous system.\textsuperscript{212}

Two reports support the link of RLS/PLMs with inflammation. In a study of 137 patients with RLS, accelerometers were used on five consecutive nights to detect PLMs. Serum C-reactive protein (CRP) was measured as a marker of systemic inflammation. RLS patients with $\geq 45$ PLMs per hour had an odds ratio of 3.56 for having an elevated CRP compared to RLS patients with $\leq 45$ PLMs per hour.\textsuperscript{132} In another study of 70 patients who underwent polysomnography, elevated CRP levels were seen in patients with a PLM index $\geq 15$ compared to those with lower PLM indices. A weak positive correlation was found between PLM index and CRP ($r=0.24$, $p=0.05$), however, this relationship was only marginally statistically significant in the linear regression model ($p=0.07$).\textsuperscript{213}

Of note, several prior studies have demonstrated that the presence of RLS itself is not associated with elevated CRP levels.\textsuperscript{71, 214} Collectively, these findings suggest that the disruption of sleep or associated sympathetic arousals related to PLMs, rather than the sensory manifestations of RLS, are most strongly associated with systemic inflammation as
assessed by CRP.\textsuperscript{132} Of course, as mentioned by Weinstock,\textsuperscript{212} the possibility that RLS is triggered by inflammation cannot be ruled out on the basis of these studies.

### 3.3.3 Oxidative Stress

The earliest suggestion of an association of RLS with oxidative stress came from a dermatologist who was treating a young man for a skin problem with large doses of vitamin E; this treatment successfully relieved the patient’s dermatosis, however, the patient was particularly grateful because this therapy also alleviated his severe muscle cramps that followed heavy exercise. In light of this observation, the dermatologist extrapolated the use of vitamin E to treating patients with RLS. He reportedly successfully treated his office nurse, an RLS patient, and several other RLS patients using vitamin E in the form of d-α-tocopheryl acetate.\textsuperscript{215} He postulated that the mechanism involved in the effectiveness of vitamin E was via its role as an antioxidant.\textsuperscript{215}

Oxidative stress is defined as a process in which the dynamic balance between oxidants and antioxidants is intensely shifted toward oxidative potentials.\textsuperscript{216} Reactive oxygen species are highly reactive molecules that, when present in excess, overwhelm the protective systems and result in cell damage and protein and lipid peroxidation.\textsuperscript{217} Two case-control studies have demonstrated results which would support the role of oxidative stress in the pathogenesis of RLS.

In the first study, 50 patients with untreated RLS were compared with 50 gender- and age-matched healthy controls. Rather than measure separate oxidant or antioxidant molecules, total oxidant and antioxidant status, an oxidative stress index and indicators of lipid peroxidation were measured. Compared to controls, the patients with RLS were found to have biomarker activity consistent with oxidative stress; such activity was significantly greater than in the controls.\textsuperscript{218} In the second smaller study, 22 patients with primary RLS were compared to 20 age- and gender-matched healthy subjects. Total thiol level (an antioxidant and marker of oxidative protein damage), nitric oxide (an antioxidant and inhibitor of lipid peroxidation) and malondialdehyde (a marker of lipid peroxidation) were measured in the two groups. As would be expected, serum nitric oxide and thiol levels were lower in the RLS patient group than in controls ($p = 0.007$ and $p = 0.017$, respectively);
serum malondialdehyde levels was also found to be higher in patients with RLS than in controls (p = 0.008, respectively). Collectively, these results suggested that patients with RLS may be under oxidative stress.

Finally, the role of oxidative stress in RLS is supported by the results of a single randomized, double-blind, placebo-controlled trial. In this study, 60 stable hemodialysis patients with RLS were randomly allocated to four fifteen-patient parallel groups to receive vitamin C (200 mg) and vitamin E (400 mg), vitamin C (200 mg) and placebo, vitamin E (400 mg) and placebo, and double placebo daily for eight weeks. International Restless Legs Scale (IRLS) scores were measured for all patients at baseline and at the end of treatment phase, with the primary outcome being the absolute change in IRLS score from baseline to the end of the treatment phase. IRLS scores significantly decreased in each of the three treatment groups compared with the double placebo group (p<0.001), however, there were no differences observed between the treatment groups. It was concluded that vitamins C and E and their combination were safe and effective treatments for reducing the severity of RLS in hemodialysis patients over the short-term.

Further exploration of the role of oxidative stress in RLS remains an exciting area of study. It will be particularly interesting to delineate the role PLMs may have in modulating this association.

### 3.3.4 Hypothalamic-Pituitary-Adrenal (HPA) System Activation

HPA system activation has been shown to increase the risk of developing the metabolic syndrome and cardiovascular disease. In addition, HPA system activation, manifesting as enhanced nocturnal cortisol secretion, has been demonstrated in insomnia, and thus may be associated with the sleep disturbance seen in patients with RLS. The link between depression and RLS may also be mediated by HPA system activation, since depression itself is associated with HPA system activation.

Two small studies failed to demonstrate an association between HPA system activation and RLS, however, these investigations may have been hampered by important methodological issues. A third larger study assessed nocturnal urinary cortisol excretion in 73 patients with RLS and 34 healthy controls, controlling for age and gender. The investigators
found significantly increased nocturnal cortisol excretion in RLS. The results suggested that nocturnal HPA system overactivity occurs in RLS and that RLS-induced sleep disruption could be the mediator of the HPA system activation. Of note, cortisol levels were unrelated to the frequency of PLMs, suggesting that the presence of PLMs may not completely explain the heightened HPA activity in RLS.227

3.3.5 Sleep Disturbance

Sleep impairment is consistently reported in RLS and the reason most RLS patients seek medical help.49, 97 Those with RLS report significantly longer sleep onset latency,81, 228, 229 greater sleep disturbance,230-232 shorter sleep duration,48, 228, 233 poorer sleep quality,81, 229, 230 greater daytime sleepiness81, 230, 231 and a higher prevalence of insomnia;35, 234 up to 40% of those with insomnia may suffer from RLS.81, 234 In turn, sleep disturbance can promote a host of vascular risk factors, such as hypertension,235 diabetes,236 dyslipidemia237 and obesity.238 Chronic sleep deprivation has been shown to increase daytime IL-6 and tumor necrosis factor239 levels compared to night-time levels; while sleep deprivation does not change the overall amount of either cytokine secreted over a 24-hour period, there is a shift in the timing of the release of these cytokines from night to day in the context of sleep deprivation. One may speculate as to whether the brain is more susceptible to vascular damage when these inflammatory cytokines are secreted during the daytime as compared to night.

Sleep disturbance can also lead to other mechanisms postulated to be associated with vascular disease in the context of RLS/PLMs, such as oxidative stress,240 activation of the hypothalamic-pituitary-adrenal axis241 and depression.242 Impaired sleep has been linked with an increased risk for cardiovascular disease morbidity and mortality.243 An intriguing area of work is the observation that amyloid β dynamics may be modulated by acute and chronic sleep deprivation in mice.244 Amyloid β, a pathological hallmark of Alzheimer’s disease,245 is toxic to vascular endothelium and neurons; amyloid β-40 deposits in arterioles and capillaries in vulnerable brain regions causing occlusion, inflammation, hemorrhage and vessel obliteration.246 Such findings suggest that amyloid deposition may
play an important role in linking sleep disturbance with vascular disease, particularly small vessel disease of the brain.

### 3.3.6 Association with Depression and Anxiety Disorders

Many studies have demonstrated that RLS is strongly associated with depressive symptoms, anxiety and panic disorder. Similar to sleep disturbance, depression has been linked to an elevated risk for diabetes, metabolic syndrome, cardiovascular disease and stroke. Preliminary work also suggests that untreated PLMs may also be associated with depressive and anxiety symptoms.

### 3.3.7 Vascular Risk Factors

The association of RLS with hypertension, hyperlipidemia, diabetes, obesity and cardiovascular disease was systematically reviewed by Innes et al. in 2011. This review considered all reports published in the English language between 1995 and 2010; studies that did not specify diagnostic criteria for RLS or did not incorporate any of the four 2003 diagnostic criteria established by the IRLSSG were excluded.

In what follows, the results reported by Innes et al. are reviewed; using the same methodology utilized by Innes et al. (2011), further research that has been published since the time of that review is also highlighted. Evidence supporting an association of PLMs with each of hypertension, hyperlipidemia, diabetes and obesity is also discussed.

#### 3.3.7.1 Hypertension

Seventeen studies have investigated the association of hypertension with RLS; all were cross-sectional in nature with the exception of one Canadian case-control study. Of these, 10 supported a positive association of RLS with hypertension: four studies documented a non-statistically significantly increased risk for hypertension among those with and without RLS, and six studies reported a statistically significant positive association between RLS and hypertension. In the single case-control study, hypertension was significantly more prevalent in males with RLS compared to males without the condition (odds ratio [OR] of 2.1). In contrast, five studies yielded no evidence of an association, while two small population-based studies in European elderly patients reported significantly lower prevalence...
rates of hypertension in those with RLS compared to those without RLS. In some of the studies discussed above, patients were being treated for hypertension while in others whether elevated blood pressure was being managed was not reported. More recent research has suggested that women with RLS have a higher prevalence of hypertension, and that the prevalence of hypertension increases with more frequent RLS symptoms; for example, the adjusted ORs for women who reported RLS 5 to 14 times per month and ≥15 times per month were 1.06 (95% CI: 0.94-1.18) and 1.41 (95% CI: 1.24-1.61), respectively, compared with those without the symptoms (p trend: <0.0001).

Normally, blood pressure decreases by 10-20% during non-rapid eye movement sleep. Patients whose nocturnal blood pressures decrease by only <10% at night are classified as “non-dippers,” and this abnormal pattern of blood pressure variation has been demonstrated to be an independent predictor of cardiovascular risk. It has been shown that clinically diagnosed RLS is associated with this unfavourable non-dipping pattern.

None of the studies discussed above investigated the effect of PLMs on blood pressure.

Several reasons may explain the inconsistent results among the studies, including variations in study population characteristics and the methods used to diagnose hypertension and RLS. Furthermore, whether or not patients were being treated for their hypertension, as well as medication effects also need to be considered: common anti-hypertensive agents such as beta blockers have been shown to alleviate RLS symptoms, and dopamine agonists used to treat RLS can lower blood pressure; these findings may potentially influence observed relationships between hypertension and RLS.

The association of PLMs with daytime hypertension remains relatively unexplored, as only three studies have examined this link. In 91 patients with essential hypertension, more than 18% had PLMs, a prevalence noted by the authors to be considerably higher than that seen in normal controls. Unfortunately, no control group was reported, so a definitive conclusion could not be reached; also the definition for PLMs used differed from that used in later studies. In a larger study reported in abstract form, 861 patients with self-reported RLS underwent polysomnography. The likelihood of hypertension increased with PLM severity,
with a PLM index of greater than 30 doubling the risk of hypertension. Finally, a trend for higher daytime blood pressure (BP) was observed in children with PLMs compared to those without PLMs (p = 0.084 for systolic BP, p = 0.051 for diastolic BP).

Overall, the link between RLS, PLMs and hypertension remains incompletely characterized. Ongoing work will be needed to determine whether the nocturnal autonomic fluctuations and sympathetic hyperactivity seen in the context of PLMs contributes to the development of daytime hypertension, or whether these night-time variations in heart rate and blood pressure contribute to the possible development of vascular disease in the absence of daytime hypertension. In addition, whether RLS (independent of PLMs), or vice versa, contributes to the development of hypertension will also be important to ascertain; evaluating medication-free patients may be helpful in this regard.

### 3.3.7.2 Hyperlipidemia

At least five studies (four cross-sectional and one case-control) report on the possible link between RLS and hyperlipidemia. Two of these demonstrated significantly positive associations between RLS and hyperlipidemia. In a Canadian case control study (n=218), those with RLS were 3.3 times more likely to have a disorder of lipid metabolism compared to controls matched by age, gender and postal code. Likewise, in a large study of Israeli primary care patients (n=1,537), a 1.6-fold increased probability of hyperlipidemia was observed in adults with RLS compared to those without RLS after controlling for age and gender. In both of these studies, the effects of sleep apnea and PLMs were not evaluated in the possible link between RLS and dyslipidemia.

One more recent study reported a higher prevalence of hyperlipidemia in patients with RLS compared to those without RLS, however, the finding was explained by a higher frequency of hyperlipidemia in patients also affected by OSA; once the patients with OSA were excluded, the relationship between RLS and hyperlipidemia could not be demonstrated. The authors concluded that the absence of an association of RLS with other medical conditions studied (e.g. diabetes, renal and liver disease) reinforced the suspicion that PLMs may have a fundamental role in linking RLS/PLMs with vascular disease. In contrast to
earlier reports, a single study involving 667 French elders reported a lower prevalence of hyperlipidemia in those with RLS compared to those without RLS.\textsuperscript{229}

Hyperlipidemia may also be a risk factor for RLS: One study of 30,262 women demonstrated an OR of 1.17 for the presence of RLS in patients with hypercholesterolemia compared to those without this condition; this association was significant despite controlling for age, aspirin assignment, postmenopausal status, and hormone and oral contraception use.\textsuperscript{265}

Overall the evidence remains limited and a possible link between RLS and hyperlipidemia has yet to be firmly established; future work should consider the effects of PLMs and OSA when studying this association. The association of PLMs with dyslipidemia has yet to be explored.

3.3.7.3 Diabetes

In the review by Innes et al. (2011), 24 studies were found which evaluated the association of diabetes with RLS: Twelve studies documented statistically significant positive associations, seven reported positive but non-statistically significant associations, four indicated no association, and one reported mixed findings.\textsuperscript{88} A more recent cross-sectional study (n=22,786 participants of the US Physicians’ Health Studies) also demonstrated that men with RLS were more likely to have diabetes and vice versa.\textsuperscript{266} Similarly, in the Women’s Health Study (n=30,262 female health professionals) there was an OR of 1.19 (95% CI 1.04-1.35, p for trend <0.01) for the presence of RLS in women with diabetes compared to those without diabetes.\textsuperscript{265}

Overall, most (although not all) studies to date suggest a positive bidirectional relationship between RLS and diabetes even after controlling for age, gender, body-mass index (BMI), smoking and other potentially confounding factors.\textsuperscript{88}

With respect to PLMs, one study demonstrated that 31% of 41 patients with diabetes had a PLM index >5; as with many prior studies, a control group was not reported.\textsuperscript{267} Otherwise, the association of PLMs with diabetes has yet to be directly evaluated.
3.3.7.4 Obesity

There is a modest association between BMI and RLS.\textsuperscript{88} Eighteen studies (one case-control, 17 cross-sectional) have assessed this association: 10 large population-based studies demonstrated significant associations between RLS and obesity, while eight studies suggested no evidence of such a link.\textsuperscript{88} In the studies that did demonstrate a positive association, adults with RLS were approximately 20-50\% more likely to be obese than those without RLS,\textsuperscript{88} two studies suggested a significant dose response relationship between current BMI and RLS risk.\textsuperscript{32, 268} In addition, research has demonstrated that obesity and weight gain in early adulthood (age 18-21 years) increases the risk for the subsequent development of RLS.\textsuperscript{268} Similarly, another study demonstrated an OR of 1.35 (95\% CI 1.17-1.56, p for trend <0.01) for the presence of RLS in obese patients compared to non-obese patients.\textsuperscript{265} As with dyslipidemia and diabetes, the association of PLMs with obesity requires further study.

3.3.8 Summary Concerning Proposed Mechanisms Linking RLS and PLMs with Vascular Disease

Overall, the pathways linking RLS and PLMs with nocturnal hyperactivity, inflammation, oxidative stress, HPA system activation, co-morbid conditions (e.g. sleep and mood disturbances) and vascular risk factors are complex and often bidirectional. Multiple underlying mechanisms are likely and may operate in a synergistic, mutually exacerbating manner.\textsuperscript{88} Vascular risk factors have been demonstrated to be risk factors for RLS,\textsuperscript{269} and emerging evidence suggests that the opposite is also true, particularly with respect to diabetes and obesity. Teasing out the relative contributions of RLS and/or PLMs to each of the postulated mechanisms discussed will be an important future step.

3.4 Epidemiological Evidence of an Association of Vascular Disease with Restless Legs Syndrome / Periodic Limb Movements

3.4.1 Cardiovascular disease

There is a robust association of RLS with cardiovascular disease.\textsuperscript{88} Of the one case-control and 14 cross-sectional studies identified by Innes et al. (2011),\textsuperscript{88} only one cross-sectional
study of Icelandic and Swedish adults indicated no relationship between RLS and cardiovascular disease; this study did not examine RLS frequency, severity or duration. The remainder reported a positive association, although in one the relationship was non-statistically significant and in another was only marginally significant; the remaining 11 studies noted statistically significant positive associations, with odds ratios ranging from 1.4 (95% CI 1.06-1.88) to 2.9 (95% CI 1.18-7.23). Two studies demonstrated a dose-response relationship between RLS and cardiovascular disease; both of these were large population-based studies in US adults. In the Wisconsin Sleep Cohort, patients with daily RLS symptoms had a statistically significantly increased prevalence of cardiovascular disease compared to those with no RLS symptoms (OR=2.58, 95% CI 1.38-4.84). Similarly, in the Sleep Heart Health Study, in patients with RLS symptoms 16-23 times per month there was an odds ratio of 3.18 (95% CI 1.48-6.85) for the prevalence of coronary artery disease compared to those without RLS; this relationship persisted despite controlling for age, gender, race, vascular risk factors and apnea-hypopnea index.

Aside from cross-sectional studies, one prospective study also supports the relationship between RLS and cardiovascular disease: It has been reported that women with physician-diagnosed RLS for a duration of at least 3 years have an elevated risk of incident coronary heart disease (adjusted hazard ratio [HR]=1.80 [95% CI 1.07-3.01], for non-fatal myocardial infarction, HR=1.49 [95% CI 0.55-4.04], and for fatal coronary heart disease; all comparisons relative to women without RLS); such results suggest that RLS or RLS-associated conditions may contribute to the development of cardiovascular disease. Another prospective study did not demonstrate an increased risk of incident cardiovascular disease in patients with RLS, however, this study had several methodological limitations: RLS was self-reported rather than physician-diagnosed, and no information on RLS frequency, severity or duration of symptoms was available.

Overall, the literature strongly suggests an association of RLS with cardiovascular disease. Several methodological issues are apparent, however, in this area of research. Associations with cardiovascular disease are strongest with greater RLS severity, frequency and duration; failure to capture these features may result in the inability to report a positive association. As
discussed earlier, physician-diagnosed RLS is also important in order to minimize false positive diagnoses from RLS mimics.

The studies above did not consider the effects of PLMs on the association of RLS with cardiovascular disease, however, two prospective studies have demonstrate that elevated PLM indices may also be significantly implicated. For example, in a study of 2911 men who underwent in-home polysomnography, patients with a PLM index $\geq 30$ at baseline had a higher risk of incident cardiovascular events during the four-year follow-up period (relative hazard 1.31; 95% CI 1.01-1.70; adjusted for age, BMI and clinic site; results did not remain statistically significant after adjusting for vascular risk factors). Another study demonstrated increased heart failure and mortality over a median 33-month follow-up period in patients who had a PLM index $\geq 35$/hour at baseline (OR=1.62, 95% CI 1.14-2.30, p=0.007 for heart failure; OR=1.77, 95% CI 1.12-2.79, p=0.014 for mortality). The possible association between RLS/PLMs and cardiovascular disease may be because PLMs are associated with left ventricular hypertrophy (LVH) or other LV structural abnormalities.

The association of RLS and PLMs with cardiovascular disease is an exciting area of work with potentially practice-changing implications. The relative contributions of RLS sensory symptoms and PLMs should be explored in future work. Such work may lead to treatment trials which evaluate whether treatment of RLS or PLMs reduces incident cardiovascular disease.

### 3.4.2 Cerebrovascular disease

Despite a fairly strong association of RLS and PLMs with cardiovascular disease, only limited evidence supports an association of stroke with either RLS or PLMs.

With regards to the association of RLS with stroke, one case-control, two cross-sectional and one prospective study were identified, and all provide statistically significant support for a positive association. The case-control study of 218 RLS patients (and 872 control subjects from the general population matched on age, gender and postal code) from a Canadian sleep disorders clinic reported odds ratios of 3.2 in males and 8.0 in females for the prevalence of cerebrovascular disease in patients with RLS compared to those without RLS (confidence intervals were not reported). In the Sleep Heart Health Study, the composite outcome of
“cardiovascular disease” was defined as physician-diagnosed stroke, coronary artery disease or heart failure; in patients with RLS symptoms 16-23 times per month there was an odds ratio of 3.92 (95% CI 1.92-8.03) for the prevalence of cardiovascular disease compared to those without RLS; this relationship persisted despite controlling for age, gender, race, vascular risk factors and apnea-hypopnea index; since this was a composite endpoint, associations between RLS and the specific components of the composite endpoint were either non-significant or not commented upon.\(^{272}\) A single cross-sectional study also supports the idea that stroke may be a risk factor for RLS (OR=1.4, 95% CI 1.05-1.86).\(^{266}\) This is not surprising given the fact that many case reports have reported the onset of RLS after stroke (see section 3.2: Restless Legs Syndrome / Periodic Limb Movements as a Consequence of Stroke). Finally, in the single prospective cohort study that followed 1986 men over 10 years, there was a relative odds of 1.67 (adjusted for age, social class, smoking, alcohol consumption and neck circumference; 95% CI 1.07-2.60, p=0.024) for developing stroke during the follow-up period in patients with RLS compared to non-RLS participants.\(^{277}\)

With regards to PLMs, one retrospective and one prospective study were identified, and these provide mixed results. In the retrospective study there was a significantly higher prevalence of PLMs on polysomnography in 40 patients with self-reported stroke compared with 40 patients without stroke but matched for age, gender, and confounds such as diabetes, hypertension, polyneuropathy, anemia, antidepressants, fatigue, RLS, sleep apnea and snoring (1.9±0.7 vs. 11.7±3.4; p=0.006); while these findings are not unexpected since PLMs can manifest after stroke, should PLMs be demonstrated to be significantly associated with vascular disease these results may have implications for secondary stroke prevention.\(^{278}\) A prospective study that followed 2911 men over a 4-year period did not find significantly increased cerebrovascular events in participants with elevated PLM indices at baseline, although a greater frequency of incident cardiovascular events was identified.\(^{131}\)

Overall, the association of RLS with stroke, and the relative importance of PLMs, is in need of further study.
3.5 Gaps in the Literature Relevant to Current Study

- The association between RLS, PLMs and cerebrovascular disease remains incompletely characterized.

- The emerging literature suggests that different manifestations of RLS (e.g. sensory [i.e. motor restlessness], motor [i.e. PLMs] and arousals in sleep) may be dissociated on a genetic, neurotransmitter and possibly even a neuroanatomical level; such a possibility is particularly important to keep in mind with regards to the present study, since acute stroke and TIA generally cause focal impairment of a single region of the brain and may thus preferentially impact varying components of the Restless Legs Syndrome depending on the site of involvement.

- On the basis of several case reports and one case series, RLS sensory symptoms seem to be most strongly associated with lesions in the deep subcortical structures (e.g. basal ganglia, thalamus and internal capsule); this possibility needs to be evaluated in further research.

- The animal models that suggested involvement of the A11 diencephalospinal pathway in the pathogenesis of RLS/PLMs mostly focused on the motor component of RLS (i.e. PLMs) since motor (as opposed to sensory) manifestations are best evaluated via use of animal models; such thinking would lead one to believe that brainstem-spinal pathways would be most important in the pathogenesis of PLMs. This idea is purely speculative and needs to be evaluated in future research.

- The post-stroke literature most strongly implicates the following brain regions in association with RLS/PLMs, and these regions should be considered “regions of interest” for future studies exploring the neural correlates of RLS/PLMs:
  
a) Brainstem  
b) Thalamus  
c) Internal capsule  
d) Basal ganglia (e.g. caudate nucleus and putamen)

- In addition, on the basis of the proposed A11 diencephalospinal pathway (figure 1), cortical involvement is also postulated and both (e) frontal and (f) parietal regions would
be plausible neural correlates given their relevance to motor and sensory functions, respectively.

- Several mechanisms have been postulated to link RLS/PLMs with vascular disease; with regards to the current study, sleep efficiency (a marker of sleep disturbance) should be considered in analyses that attempt to associate RLS/PLMs with vascular disease.

### 3.6 Areas of Future Exploration Suggested by Current Literature

- The Sleep-Related Movements Disorders RLS and PLMs are prevalent and can occur as a result of stroke. However, their prevalence, and association with quality of life and WMHs (discussed in the next section) after TIA/stroke remain uncertain.

- Patients with TIA and minor stroke are at high risk for a number of unfavourable but modifiable co-morbidities such as sleep disorders, and thus serve as an appropriate population to examine the relationship of RLS and PLMs with cerebrovascular disease.
4 White Matter Hyperintensities of Presumed Vascular Origin

“Small vessel disease” (SVD) refers to all pathological processes that affect the small arteries and veins of the brain, and typically manifest in subcortical regions and the brainstem. White matter hyperintensities (WMHs) of presumed vascular origin are a form of cerebral SVD.279 Aside from WMHs, SVD also includes other pathologies such as small subcortical infarcts (e.g. lacunar strokes), lacunes, perivascular spaces, cerebral microbleeds and brain atrophy.279, 280 In addition, microinfarcts are another form of SVD of the brain, but their size is below the lower limit of spatial resolution of MRI at conventional field strengths (1.5 or 3.0 Tesla) used in clinical practice, and higher resolution MRI is necessary to detect these lesions.281

Given their clinical importance and the relative simplicity with which they can be assessed, WMHs serve as an excellent biomarker for vascular disease282 and will be the focus of the following discussion. Despite common pathophysiological mechanisms linking WMHs and SRMDs, this association remains under-investigated.

4.1 Definition

White matter hyperintensities are rounded areas of increased signal intensity on T2-weighted and fluid-attenuated inversion recovery (FLAIR) MRI, and often have decreased signal intensity on T1-weighted MRI; on CT, they appear hypodense. They are typically located in the periventricular and deep white matter of the cerebral hemispheres, in the basal ganglia, in the pons, and occasionally in other parts of the brainstem and cerebellum. WMHs are typically distributed in a symmetrical manner, but occasionally manifest asymmetrically. As they accumulate, WMHs coalesce and form large confluent lesions. Whether periventricular or deeply distributed lesions are caused by distinct mechanisms or represent different stages of the same pathological process is unclear.283
These lesions are often considered “silent” because they are not accompanied by classically defined stroke syndromes, however, as discussed below, they may not be entirely asymptomatic as patients with these lesions often have evidence of cognitive and other functional impairment.284

4.2 Prevalence and Risk Factors

WMHs increase in prevalence with age. In the general population, prevalence ranges from 11-21% in adults aged around 64, to a prevalence of 94% at age 82.282 In addition, females have a higher prevalence of WMHs compared to males,285, 286 possibly reflecting a survival bias; female gender has also been shown to be associated with progression of WMHs.287, 288

Aside from age and gender, hypertension is the other key risk factor for WMHs.283 Despite a well-recognized association, the relationship between blood pressure and WMHs is complex. It is unclear as to whether prior or present hypertension is most important in the development of WMHs.283 Both prior and current hypertension have been shown to predict the progression of WMHs in some289, 290 but not all291 studies. Observational studies have demonstrated that effective treatment with anti-hypertensive agents slows the progression of WMHs.283 However, randomized controlled trials have shown little292 or no293 role for blood pressure therapy in slowing the progression of WMHs.

In terms of other risk factors for SVD, smoking has been linked with WMHs.287 Hyperlipidemia has not been shown to be independently associated with WMHs and treatment with a statin agent has not been shown to slow the progression of WMHs.294 Likewise, a link with diabetes could be hypothesized on the basis of diabetic susceptibility to SVD, however, such a link has not been confirmed.283

In keeping with their association with SVD, WMHs are more common in patients with acute lacunar stroke than in patients with other stroke subtypes,295 and are also associated with other forms of SVD such as lacunes,296 perivascular spaces,297 microbleeds298 and brain atrophy.299
### 4.3 Pathophysiology

Table 1. Selected Proposed Mechanisms for White Matter Hyperintensities (rows), and their Overlap with Mechanisms Postulated to be involved in the Pathogenesis of Sleep-Related Movement Disorders (columns)

<table>
<thead>
<tr>
<th>Table 1. Proposed Mechanisms for White Matter Hyperintensities</th>
<th>Mechanisms Described in RLS and/or PLMs (discussed in detail in section 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Blood pressure dysregulation</td>
</tr>
<tr>
<td>Small vessel disease (atherosclerosis, lipohyalinosis, arterial tortuosity)</td>
<td>+ (see text)</td>
</tr>
<tr>
<td>Dysregulation of cerebral blood pressure</td>
<td>PLMs associated with nocturnal variability in heart rate and blood pressure</td>
</tr>
<tr>
<td>Damage to endothelial cells</td>
<td>+PLMs associated with ↑CRP[12, 213]</td>
</tr>
<tr>
<td>Inflammation</td>
<td>↑ C-reactive protein (CRP)</td>
</tr>
<tr>
<td>Oxidative stress</td>
<td>↑ Biomarker activity</td>
</tr>
<tr>
<td>Amyloid deposition</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CRP=C-reactive protein; IL-6=Interleukin-6; PLMs=periodic limb movement of sleep; RCT=randomized controlled trial; TNF=tumour necrosis factor
4.3.1 Small Vessel Disease

White matter hyperintensities most commonly occur in the deep white matter, which is supplied by small blood vessels that irrigate mostly vascular border zones with little collateral supply. For this reason, these regions of cerebral white matter are particularly prone to ischemia.301

Several lines of evidence support the concept that alterations in small, terminal cerebral arteries are associated with white matter changes. WMHs are associated with age and hypertension, which are factors known to promote arteriosclerosis, fibrinoid necrosis and lipohyalinosis in the small arteries of the brain;279 these processes can result in arterial blood vessel collapse.302 In addition, arterial tortuosity, accelerated by ageing and atherosclerosis, increases vascular resistance and necessitates higher perfusion pressure to irrigate the deep white matter.246

One consequence of these pathological changes is complete occlusion of a lumen with resulting acute, focal ischemia in the corresponding area of tissue; clinically, a covert or overt small infarction of the white matter could result.303 Another possibility is stenosis of a small blood vessel that could lead to chronic ischemia and subsequently a cerebral infarction.304

4.3.2 Dysregulation of Cerebral Blood Pressure

Given the vulnerability of the subcortical white matter to ischemia, abnormal diurnal and postprandial blood pressure (BP) decreases can lead to white matter lesions.305 Normally, the nocturnal BP decreases by 10-20% during non-rapid eye movement sleep as compared with daytime levels.306 It has been demonstrated that elderly patients with extreme “dipping” of their nocturnal systolic blood pressure (≥20% decrease compared to wake systolic blood pressure) have more severe WMHs than those with more moderate drops in their nocturnal blood pressures.307 In addition, elderly hypertensive patients with marked postprandial hypotension have also been shown to have advanced silent cerebrovascular damage,308 and in the Cardiovascular Health Study there was also a suggestion of a relationship between orthostatic hypotension and WMHs.285
While blood pressure drops may be pertinent in the pathogenesis of white matter disease, it may actually be the blood pressure oscillations that warrant special attention. Blood pressure variability is postulated to cause mechanical stress on the vascular system, leading to vascular remodeling; in addition, variability of blood flow caused by BP oscillations is thought to induce sheer stress, platelet activation, leading to atherosclerosis and a potentially hypercoaguable state. Variability in blood pressure has been demonstrated to be associated with silent cerebral damage in multiple studies. In addition, in the Honolulu-Asia Aging study, systolic blood pressure variability (three clinic readings over six years) was associated with white matter lesions on brain imaging 25 years later. The prominent nocturnal fluctuations in blood pressure associated with PLMs may thus be essential in mediating the link between RLS/PLMs and vascular disease such as WMHs.

4.3.3 Damage to Endothelial Cells

4.3.3.1 Inflammation

Given the association of inflammatory markers with WMHs, it has been suggested that inflammation may play a significant role in white matter disease. In terms of laboratory markers, elevated plasma C-reactive protein (CRP) and interleukin-6 (IL-6) have been implicated; both are inflammatory markers and involved in the pathogenesis of atherosclerosis via the activation of endothelial and arterial smooth muscle cells. Both CRP and IL-6 were associated with the presence of WMHs and brain infarcts in the Cardiovascular Health Study (n=3437), in the Three City-Dijon Cohort (n=1841), and in 194 neurologically asymptomatic Japanese patients. In the Rotterdam Scan Study (n=1033), higher CRP levels were associated with presence and progression of white matter lesions. A small study (n=44 subjects with silent brain infarction and 53 normal controls) showed that combined measurements of CRP, IL-6 and protein-conjugated acrolein predicted silent brain infarction with 89% sensitivity and 91% specificity. Another marker of inflammatory endothelial cell activation, soluble intercellular adhesion molecule-1 (sICAM-1), has also been shown to be associated with the extent of WMHs in asymptomatic elderly subjects. Similarly, vascular cell adhesion molecule-1 (VCAM-1) has been demonstrated to be associated with the presence of severe periventricular white matter lesions, however, the association of sICAM-1 with subcortical WMHs was not seen; such findings suggest
that inflammatory processes may be particularly relevant in the pathogenesis of periventricular white matter lesions.

Not all studies have shown an association of CRP with WMHs. For example, in a community-based sample of 689 elderly Japanese subjects, higher CRP levels were seen in those with greater small vessel disease-related lesions, but this association did not survive adjustments for cardiovascular risk factors and carotid atherosclerosis. In the Austrian Stroke Prevention Study (n=700), serum CRP was a marker for active carotid atherosclerosis but not for small vessel disease. Furthermore, elevated CRP levels have been showed to be associated with executive dysfunction and abnormalities on diffusion tensor imaging, but not with measures of WMHs or brain atrophy.

4.3.3.2 Oxidative Stress

While the role of oxidative stress is well established in atherosclerosis, only indirect evidence links oxidative stress with WMHs. RNA expression in the blood of patients with WMHs has been demonstrated to be consistent with roles of systemic oxidative stress and inflammation. Two markers of oxidative stress (serum nitric oxide metabolites and urinary 8-iso-PG F2alpha) have been shown to correlate with the severity of periventricular white matter hyperintensities. In addition, diffusion tensor imaging-defined white matter lesions in older individuals are characterized by free radical injury to myelin and other neuroaxonal elements. In addition, current smoking (a contributor to oxidative stress) has been found to be at increased risk of WMHs, and smokers derive some benefit against WMHs with increasing levels of plasma anti-oxidants.

4.3.3.3 Amyloid Deposition

Amyloid β (Aβ) is toxic to vascular endothelium and neurons; Aβ40 deposits in arterioles and most capillaries in vulnerable brain regions causing occlusion, inflammation, hemorrhage and vessel obliteration. In addition, in patients with the apolipoprotein E (APOE) epsilon4 allele, higher amyloid beta peptide levels are associated with more lacunar infarcts and white matter lesions in elderly subjects.
4.3.3.4 Other Mechanisms

Finally, intrinsic blood vessel alterations could also disrupt the blood-brain barrier, leading to endothelial failure and chronic leakage of plasma and macromolecules in the white matter, inflammation can also affect the integrity of the blood-brain barrier. In the elderly, blood-brain dysfunction is associated with white matter hyperintensities and postmortem studies combining brain MRI and histopathology have also supported blood-brain barrier disruption in the pathogenesis of white matter lesions.

With regards to periventricular hyperintensities, evolving evidence supports the process of venous collagenosis, a non-inflammatory mural disease of the periventricular veins. Periventricular venous collagenosis is thought to induce ischemia by increasing vascular resistance, leaking fluid (vasogenic edema), compromising interstitial fluid circulation and impairing clearance of amyloid deposits.

In addition, numerous other mechanisms including apoptosis and genetic factors, and laboratory markers (such as homocysteine and microalbuminuria) are also significantly implicated in the pathogenesis of WMHs, but have been much less studied in the context of sleep disorders.

4.4 Clinical Implications of WMHs

In cross-sectional analyses, gait and balance disorders have been shown to be associated with more severe age-related white matter changes. In patients with Alzheimer’s disease, slower gait velocity secondary to shorter stride length has been shown to be associated with WMHs. As reviewed by Santos et al., late-life depression may also be linked with WMHs.

Furthermore, the presence of WMHs predicts an increased risk of incident clinical cerebrovascular infarction; this is supported by the results of multiple population-based studies and studies in high risk populations. In addition, in a single study of patients who presented with symptomatic lacunar strokes, headache or dizziness, progression of WMHs predicted incident stroke.
Aside from risk of overt stroke, it is generally accepted that patients with WMHs have poorer cognitive function. For example, community-based studies reporting on cognitive abnormalities in elderly persons with WMHs have demonstrated associations with poorer performance IQ, executive function, psychomotor speed and memory.

Not only are WMHs concerning for overt stroke, cognitive dysfunction, and gait impairment, evolving evidence suggests that they may be a preclinical marker for age-related cognitive decline and dementia. It has been demonstrated that acceleration of the WMH burden is a change that emerges early in the pre-symptomatic phase leading to mild cognitive impairment (MCI). In addition, microstructural white matter changes, as demonstrated by diffusion tensor imaging, are present in cognitively normal individuals in the pre-MCI stage and may serve as a potential imaging marker of early AD-related brain changes. Following longitudinal changes in white matter disease may thus be useful in determining those at risk for progressive cognitive deterioration. A meta-analysis of population-based studies and reports of high risk populations demonstrated an increased risk of dementia with WMHs (HR 1.9, 95% CI 1.3 to 2.8, p=0.002). In addition, progression of WMHs has also been demonstrated to predict incident dementia in two studies.

Finally, WMHs have also been demonstrated to be associated with risk of death in a meta-analysis of several population-based and studies of high risk populations (hazards ratio 2.0, confidence interval [CI] 1.6 to 2.7, p<0.001).

### 4.5 Association of WMHs with Sleep Disorders

#### 4.5.1 Sleep-Related Movement Disorders

Only a few small studies have explored the association of RLS or PLMs with WMHs or silent stroke; most of these were published as abstracts. One study published in abstract form found that RLS and stroke risk factors interacted to create a greater risk for silent stroke, as measured by microvascular ischemic disease in 19 patients, more than one would have anticipated from the stroke risk factors alone. Another study, also published as an abstract, found that cerebral microvascular ischemic lesions were more common in patients with RLS for ≥ 10 years compared to patients with RLS for < 10 years (p<0.007), suggesting that years of transient heart rate and blood pressure elevations associated with PLMs in the context of
RLS were needed to develop silent stroke. Alternatively, given the close association of RLS to diabetes and obesity, years of having these co-morbidities could have also mediated the link with cerebral microvascular ischemic insults. The only published peer-reviewed article examining the association between RLS and stroke did not find a positive association between RLS and silent stroke. In this study, MRI scans from 26 patients with RLS and 241 controls from an earlier population-based study were assessed for silent infarction. There were no significant differences in rates of MRI-detected silent stroke among patients with or without RLS (p=0.18).

With regards to PLMs, a preliminary study published as an abstract retrospectively examined 45 behavioral neurology clinic patients who underwent polysomnography and neuroimaging with MRI. After correcting for daytime hypertension, the presence of white matter hyperintensities was strongly positively correlated with total limb movements per hour of sleep (r=0.70, p<0.01). These results suggested that periodic (and possibly even non-periodic) limb movements could contribute to repeated episodes of nocturnal hypertension that could lead to the development of white matter hyperintensities.

Clearly, further studies will be needed to more conclusively investigate the association of RLS/PLMs with WMHs.

4.5.2 Obstructive Sleep Apnea

Neuroimaging studies have provided mixed results with regards to the association of OSA with WHMs. Nine studies that examine this association have been published in English; five studies support this link, while four do not.

Early data in favour of an association of WMHs with OSA came from a study of 78 previously independent patients who had presented with acute stroke; using multiple regression analysis, severity of WMD on CT imaging independently correlated with AHI on polysomnography even after controlling for age and stroke severity (R²=0.07, p<0.05). Four subsequent MRI studies were congruent with this finding. In first of these studies, 146 high-risk, community-dwelling Japanese individuals were evaluated; nocturnal hypoxia, as assessed by overnight pulse oximetry, was associated with increased silent cerebral disease on MRI (OR=2.2, p=0.026). In the second study, silent brain infarction (SBI) detected by
MRI was more common in 24 patients with polysomnography-diagnosed moderate to severe OSA compared to 15 obese controls free of co-morbidities (25.0% vs. 6.7%; p<0.05). In addition, the presence of SBI was associated with increased serum levels of markers of platelet activation in patients with moderate-severe OSA vs. the controls (p<0.05); CPAP therapy reduced levels of these biomarkers, thus providing a possible biological mechanism for the link between SBI and OSA.\(^{361}\) The third report was a cross-sectional study of 192 patients who underwent brain MRI and polysomnography; the prevalence of silent lacunar infarction among subjects with moderate and severe OSA (AHI \(\geq 15/h\); n=148) was higher than among the control subjects (AHI<5; n=19) and the patients with mild OSA (AHI=5-15/h; n=25) (p < 0.0001).\(^{362}\) The fourth and largest investigation to-date was a Korean population-based, cross-sectional study in which 503 individuals previously free of diagnosed cardiac or neurologic disease underwent MRI and portable one-night polysomnography; logistic regression analyses adjusted for covariates (age, gender, BMI, hypertension, diabetes, hyperlipidemia, heavy alcohol use and current smoking) revealed that moderate to severe OSA was significantly associated with the presence of WMC (OR=2.03, 95% CI 1.02-4.05; p<0.05) compared with no OSA. In this study, AHI and WMC were positively correlated (r=0.17, p<0.0001).\(^{363}\) In all five of the previously mentioned studies, the effect of RLS or PLMs on WMHs was not investigated.

Four studies suggest that silent stroke is not associated with sleep-disordered breathing.\(^{364-367}\) Davies et al. performed a case-control study of 45 sleep clinic patients with moderate to severe OSA and 45 control subjects without excessive sleepiness or polysomnographic evidence of OSA; participants were matched for age, BMI, alcohol and cigarette consumption, treated hypertension, and ischemic heart disease. Despite significant increases in daytime and night-time blood pressures in the OSA patients during 24-hour ambulatory blood pressure recordings, there was no excess of MRI-evident subclinical cerebrovascular disease in the OSA patients compared to the carefully matched controls.\(^{364}\) In another study of 62 hypertensive patients who had both a polysomnogram and brain MRI, no association was found between white matter disease on MRI and severity of OSA (p=0.9).\(^{365}\) In a study of 789 individuals aged 68 years or older from the Sleep Heart Health Study, the arousal index (number of arousals per hour of sleep during home polysomnography), rather than the AHI, was inversely correlated with brainstem white matter disease (OR=0.75 for a SD
increase in the arousal index, 95% CI 0.62-0.92); the authors suggested that the arousal response may be a protective mechanism against WMD in the brainstem.366 Finally, a report also using patients from the Sleep Heart Health Study (n=843) demonstrated that individuals who showed progression in WMD were significantly more likely to have an increased number of central apneas, rather than obstructive apneas, compared to those who did not have progression of WMD.368 Again, all these studies did not evaluate the effect of RLS or PLMs on WMHs.

Collectively, these studies provide mixed results concerning the association of WMHs and silent stroke with OSA. The conflicting results likely reflect the different methods used to assess white matter disease and OSA, as well as the varying populations studied. Even in a large study where a positive association was detected, the correlation coefficient was quite small (r=0.17),363 suggesting that the impact of AHI on WMD is relatively minor. As already mentioned, despite plausible biological mechanisms linking RLS and/or PLMs with WMHs, these conditions were not evaluated in any of the previously mentioned studies. Future studies should evaluate RLS and PLMs, as well as other sleep variables previously suggested to be important in the pathogenesis of WHMs, such as AHI,363 lowest oxygen saturation (as a marker of nocturnal hypoxia360), and arousal index.366

4.6 Gaps in the Literature Relevant to Current Study

WHMs serve as an excellent biomarker for incident vascular events and are easily assessed by neuroimaging. Despite overlapping mechanisms, the association of SRMDs (particularly RLS/PLMs) with WMHs remains relatively unexplored. As reviewed above, a few considerations will be important for future research:

- Future studies should control for the effect of known risk factors for WMHs, particularly age, gender and hypertension.

- Sleep variables postulated to be important in the pathogenesis of WMHs should also be considered; aside from PLMs, these include apnea-hypopnea index, lowest oxygen saturation (as a marker of hypoxia) and arousal index.
5 Transient Ischemic Attack and Minor Stroke

5.1 Rationale to Investigate this Patient Population

In the present study, we chose to investigate patients presenting with transient ischemic attack (TIA) and minor stroke because this population is at increased risk for a number of unfavourable co-morbidities. First of all, there is a high prevalence of sleep disorders such as OSA and nocturnal hypoxia; the atypical clinical manifestations in this patient population may lead to under-recognition and treatment of sleep disorders. In addition, despite sustaining non-disabling vascular events, this population is at increased risk for reduced quality of life and depressive symptoms. The elevated risk for sleep disorders, depressive symptoms and poor quality of life may partly mediate the elevated risk of vascular events seen in this patient population: if left untreated, 25% of patients with a TIA will have a cardiovascular or cerebrovascular event or die during the 90 days following the TIA.

Despite being at high risk for several significant non-vascular and vascular outcomes, patients with TIA and minor stroke can have markedly improved outcomes if their underlying co-morbidities are promptly addressed. For example, carefully tailored stroke care programs significantly improve patient satisfaction. Furthermore, addressing known vascular risk factors early after a TIA or minor stroke leads to a 30-80% relative reduction in the 90-day risk of future stroke.

Because of their high risk for various unfavourable co-morbidities, particularly sleep issues, this patient population was deemed to be suitable to investigate the possible association of SRMDs with cerebrovascular disease. Early assessment of RLS and PLMs in this patient population may help uncover treatable sleep conditions associated with adverse consequences; such work could pave the way for future studies which reveal that treatment of SRMDs early after a TIA or minor stroke enhances future outcomes. In addition, use of this population may facilitate detection of WMHs, since patients with TIA and minor stroke are known to have a higher prevalence of WMHs compared to non-stroke/TIA cohorts.
5.2 Defining TIA and Minor Stroke

In the past, TIAs were operationally-defined as any focal cerebral ischemic event with symptoms lasting <24 hours. However, many studies have demonstrated that this old definition was unsuitable because 30-50% of TIAs diagnosed using this classic definition showed brain injury on diffusion-weighted magnetic resonance imaging (MRI). The current definition, and that used in the present study, emphasizes a tissue-based approach: TIA is defined as “a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction.” Thus, patients can have a transient neurological event of any duration, but imaging must be negative for acute infarction; if imaging does demonstrate acute infarction, the patient is classified as having had a stroke or CNS infarction, in keeping with a recent statement from the American Heart Association/American Stroke Association. These definitions permit a more objective and precise method for determining whether a patient is diagnosed with a stroke or TIA.

5.3 What Makes a TIA “High Risk”?

Although most patients with a TIA will have a benign short-term course, some will have a greater risk of stroke during the period that follows the TIA. Several prognostic scores for short-term risk of stroke after TIA have been proposed, the most popular of which is the ABCD2 score (discussed in detail in the Methods chapter). This score dictates that patients presenting with motor or speech disturbance have a greater risk of stroke than other clinical presentations. Other “high risk” clinical manifestations include presentation with a greater than 50% carotid artery stenosis as well as atrial fibrillation that is not anticoagulated. By selecting “high risk” (as opposed to “low risk”) TIA patients, we obtained study patients that were as similar as possible to the minor stroke patients, and ultimately attempted to recruit an overall homogenous study population. Combining TIA and minor stroke patients is frequently performed in the stroke literature.

5.4 Gaps in the Literature Related to the Current Study

The prevalence and impact of SRMDs after TIA and minor stroke have yet to be explored in the present literature. Future work should also determine whether OSA is associated with the SRMDs in this patient population. In addition, upcoming investigations should keep in mind
that patients with TIA and minor stroke may manifest atypically with SRMDs, as is the case with sleep-disordered breathing. Should the SRMDs be found to be prevalent and associated with negative outcomes in the study population, future work should explore whether early treatment modifies outcomes.

In addition, as discussed above, in order to maximize objectivity, definitions for TIA and stroke should be tissue- rather than time-based.
6 Research Aims & Hypothesis

6.1 **Primary Aim:** Association of Sleep-Related Movement Disorders with White Matter Hyperintensities

As reviewed above, the work to date suggests a possible association of WMHs with RLS and/or PLMs. Cerebrovascular disease is known to give rise to SRMDs. Emerging evidence suggests that the opposite may also be true: SRMDs may contribute to the development of cerebrovascular disease via their associations with nocturnal heart rate and blood pressure variability, inflammation, oxidative stress, hypothalamic-pituitary-adrenal system activation, sleep disruption, depression and vascular risk factors; WMHs themselves also share many of these same pathophysiological mechanisms (table 1). Despite this possible connection, the association between RLS, PLMs and WMHs has yet to be sufficiently explored. The primary purpose of the present research was to investigate this association in a cross-sectional observational study.

6.1.1 Hypothesis Concerning RLS/PLMs and WMHs

We hypothesized that in patients with recent stroke or TIA a diagnosis of RLS and/or elevated PLM indices would be associated with greater quantities of WMHs on brain imaging.

6.2 **Secondary Aim:** Characterization of Sleep-Related Movement Disorders after TIA and Stroke

As noted above, only a single study\(^ {14} \) has explored the prevalence of post-stroke RLS. Despite the closely-knit relationship of minor stroke with TIA,\(^ {376} \) no studies have explored the prevalence of RLS after TIA; in addition, no work to-date has looked at PLM prevalence after either stroke or TIA. Furthermore, the association of RLS and/or PLMs with quality of life after stroke or TIA has yet to be explored. Finally, the clinical and neuroimaging features of post-stroke/TIA RLS and/or PLMs have yet to be described in detail.

Given these gaps in the current literature, secondary goals of the present work were to investigate, in an exploratory, non-hypothesis-drive manner, the following:
• RLS prevalence after TIA and stroke using the current 2003 IRLSSG criteria for RLS, as well as using a more stringent definition of “clinically-significant” RLS.

• PLM prevalence after TIA and stroke.

• The association of RLS and/or PLMs with quality of life and depressive symptoms in the TIA and stroke population.

• The clinical characteristics (e.g. presenting neurological symptoms) and neuro-imaging lesion locations of patients with RLS and/or PLMs compared to patients who do not have (or do not develop) these conditions.

The goals of these two research aims are not mutually exclusive. Delineating the clinical and neuro-anatomical basis for RLS and/or PLMs after TIA and stroke (aim #2) may provide valuable insights into understanding an association between vascular disease (e.g. WMHs), RLS and PLMs (aim #1). In addition, a mechanistic explanation for the role of RLS/PLMs in the possible generation of vascular disease may be developed via exploration of these two aims.

Overall, these two research aims will explore the prevalence and comorbidity associated with RLS and PLMs in a high-risk population (i.e. high-risk TIA and minor stroke) of patients with cerebrovascular disease.
Chapter 3

7 Methods

7.1 Ethics

Institutional ethics was obtained prior to the initiation of the study. Written, informed consent was provided by all study participants.

7.2 Study Population

This was an observational, single-centre cross-sectional study. Patients were approached to participate in the study if they had presented to the Sunnybrook Emergency Department, Secondary Stroke Prevention Clinic, or inpatient ward with a transient ischemic attack (TIA) or minor stroke which fulfilled the inclusion/exclusion criteria. Recruitment took place over the course of approximately 14 months.

7.2.1 Inclusion criteria

We consecutively recruited patients presenting within 14 days of symptoms of either a (a) high risk TIA or (b) minor stroke. A high risk TIA was defined as: (i) transient, acute motor or speech disturbance lasting at least 5 minutes, or (ii) any TIA associated with >50% ipsilateral carotid stenosis (presumed to be symptomatic) or atrial fibrillation not currently anti-coagulated. A mild stroke was defined as focal neurological deficits with CT/MRI changes and a National Institutes of Health Stroke Scale\textsuperscript{380} (NIHSS) score $\leq 5$.

7.2.2 Exclusion criteria

Patients with the following were excluded: (i) language barrier or cognitive impairment restricting the ability to answer questionnaires or participate with overnight polysomnography; (ii) life expectancy less than 12 months, as determined by the investigator using clinical information available at the time of recruitment; (iii) somatoform disorder diagnosed by treating physician to account for the patient’s acute symptoms.
7.2.3 Control Group for PLM Prevalence

Since the precise prevalence of PLMs in the general population is not known, we compared the PLM indices of our study population to those of age-, gender and apnea-hypopnea index (AHI)-matched controls who had attended a prior diagnostic polysomnogram at the Sunnybrook Hospital Sleep Laboratory. CPAP titrations (in-lab sleep studies used to calibrate CPAP therapy) were excluded since CPAP is known to modulate PLM indices. AHIs were matched within a value of +/- 3.5 or 20% of study patient AHIs. If no matching control with an appropriate AHI was found for a given study patient’s age and gender, patients one year older were reviewed, followed by patients one year younger, if necessary; if a suitable matching control was still not found after this step, patients two years older were reviewed, followed by patients two years younger, if necessary.

7.3 Procedure

7.3.1 Clinical Information

The following clinical data were obtained during the encounter with the participant:

(a) Age, gender; (b) clinical symptoms associated with the incident TIA or stroke; these were coded with as many of the following clinical descriptors as required: limb weakness, dysarthria, aphasia, any sensory loss/change, coordination impairment (excluding gait disturbance), gait impairment, cognitive impairment (excluding aphasia), any visual disturbance, and/or vertigo; (c) current medications, particularly anti-hypertensive agents and SSRIs; (d) past medical history, including prior history of myocardial infarction, diabetes, prior or current smoking, atrial fibrillation, and migraine. Since hypertension and hyperlipidemia are inaccurately self-reported, we defined hypertension as self-reported hypertension or use of an anti-hypertensive medication; hypertension was not defined according to measured blood pressure because blood pressure is typically elevated during the hours/days following a TIA or stroke. Hyperlipidemia was defined as a low-density lipoprotein (LDL) of greater than 2.0mmol/L, the cut-off recommended by the Canadian Best Practice Stroke Prevention Guidelines. Renal failure was defined as an elevated creatinine greater than 106umol/L. Low ferritin was defined as a ferritin level of less than 45µg/L.
7.3.2 Clinical Assessment Scales

The following scales were also administered during the encounter:

(a) National Institutes of Health Stroke Scale (NIHSS): The NIHSS is a 15-item impairment scale, which provides a quantitative measure of key components of a standard neurological examination. Scores range from 0-42 (lower scores indicate less neurological impairment). The scale has established reliability and validity in clinical research and has been used in many major trials. Administration by non-neurologists has been shown to be reliable, as has a certification DVD, even across multiple venues. For the present work, all study personnel administering the scale completed online NIHSS certification.

(b) Barthel Index: This is a 10-item scale that addresses various activities of daily living and mobility. Items are rated based on the amount of assistance required to complete each activity, and scores range from 0 to 100 (higher scores indicate greater functional independence with activities of daily living). The Barthel Index has excellent inter-rater reliability, internal consistency, and validity in the acute stroke setting.

(c) Stroke Specific Quality of Life Scale (SSQoL): This tool consists of 49 items which are individually graded on a 5-point Likert scale. Twelve domains are covered which include social roles, energy, work and productivity, mobility, upper extremity function, mood and personality. Scores range from 0 to 245, with higher scores indicating greater quality of life. This scale has been shown to have excellent internal consistency, construct validity and content/face validity.

(d) Centre for Epidemiological Studies Depression Scale (CESD): This scale ranges from a score of 0 to 60, with higher scores indicating the presence of more depressive symptomatology. This measure has been found to be both reliable and valid as a screening tool for assessing depressive symptoms in stroke patients, and is also sensitive and specific.

(e) Montreal Cognitive Assessment (MoCA): Scores range from 0 to 30, with higher scores indicating better cognition. This instrument has been found to be a feasible cognitive
screening tool in stroke trials\textsuperscript{395} and to have excellent sensitivity and specificity compared to the Mini-Mental Status Examination in the post-stroke or TIA setting.\textsuperscript{396, 397}

(f) ABCD2 Recurrence Risk score\textsuperscript{378} (obtained in TIA patients only): This score is used to predict the risk of stroke after a TIA, and is scored as follows: Age $\geq$ 60 years = 1; systolic BP $\geq$140 and/or diastolic BP $\geq$90 = 1; clinical features of: unilateral weakness (with or without speech disturbance) = 2, speech disturbance alone = 1, other symptoms = 0; duration of symptoms: 60 minutes = 2, 10–59 min = 1, < 10 min = 0; prior diagnosis of diabetes = 1 point. Higher scores indicate a greater risk of stroke at 2, 7 and 90 days.\textsuperscript{378}

7.3.3 Sleep-Related Questionnaires

In addition, the following two sleep-related questionnaires scales were also completed by patients:

(a) Night Questionnaire: This tool includes the Epworth Sleepiness Scale, which assesses patients for excessive daytime sleepiness; higher scores indicate greater daytime sleepiness.\textsuperscript{398} In addition, this questionnaire elicits usual sleeping habits (e.g. bed and wake times, perceived sleep onset latency, etc.), as well as habitual snoring, motor restlessness, narcolepsy symptoms, dream enactment and various other sleep-related concerns. Patients were also questioned about a prior history of RLS.

(b) Restless Legs Syndrome Diagnostic Questionnaire: A diagnosis of RLS was identified from responses to a series of questions asked on the “RLS Diagnostic Questionnaire.” Patients who endorsed diagnostic criteria for RLS on this questionnaire were further evaluated in-person by a sleep neurologist; if the patient declined attending an in-person evaluation, the participant was interviewed in detail via telephone. Evaluation by a sleep physician ensured false positive diagnoses by similarly-presenting RLS mimics (e.g. leg cramps, peripheral neuropathy, radiculopathy, positional discomfort and arthritic pain) were avoided.

Questions on the “RLS Diagnostic Questionnaire” were developed using diagnostic criteria established by the IRLSSG in 2003,\textsuperscript{25} and a similar questionnaire has been used in several large studies.\textsuperscript{272, 399} The algorithm utilized to make a diagnosis of RLS is illustrated below
(Figure 2). In brief, positive responses to the first three “yes/no” questions were required to diagnose RLS. For the fourth question, subjects were given multiple choices of activity level during symptom appearance; to be diagnosed with RLS, they had to endorse “resting” or “sitting or lying down”. The fifth question asked about the timing of symptoms; to be diagnosed with RLS, patients had to endorse the occurrence of symptoms at night, or worsening of symptoms at night compared to earlier in the day.

Figure 2. Restless Legs Syndrome Diagnostic Questionnaire algorithm used to determine RLS status.

Additional questions regarding how troublesome (i.e. hardly at all/a little/moderately/a lot/extremely) and frequency (i.e. less than once a month/about once a month/2-4 days a month/5-15 days a month/most days [16-23 days a month]/daily [6 days a week or more]) of
RLS symptoms were also addressed. In keeping with prior research, “clinically-significant RLS” was defined as symptoms occurring at least 5 to 15 days per month with at least moderate distress; \(^{272}\) “mild RLS” was diagnosed in patients with RLS that did not meet criteria for “clinically-significant RLS”.

### 7.3.4 Neuroimaging

Magnetic resonance imaging (MRI) and computed tomography (CT) were acquired at Sunnybrook Health Sciences Centre; if CT and MRI were performed in the same patient, only MRI data was used in the analyses. 1.5 T MRI (General Electric Medical Systems) included the following acquisitions in axial planes: (i) T2 Fluid Attenuated Inversion Recovery (FLAIR) sequence with inversion time=2150ms, repetition time=8600ms, echo time=115ms, flip angle=90°, matrix size=512x512, field of view=24cm, slice thickness=5.0 mm; (ii) a Diffusion Weighted Image (DWI) sequence with inversion time=0; repetition time=7000ms, echo time=70ms, flip angle=90°; matrix size=256x256, field of view=27cm, slice thickness=5.0mm.

For CT, a General Electric Medical Systems Light Speed VCT was used. CT-head axial images were acquired with a slice thickness of 5mm. Other technical parameters were as follows: matrix size=512x512, FOV= 25cm, exposure time=1000ms, X-ray tube current=280mA.

### 7.3.4.1 Quantification of White Matter Hyperintensities

Severity of WMHs were visually quantified using a validated rating scale for global WMHs. Global WMHs appearing hyper-intense on FLAIR and hypo-dense on CT were assessed with the Age Related White Matter Change (ARWMC) Scale,\(^{400}\) which assesses on a Likert scale from 0-3 the degree of WMHs in bilateral frontal, occipital-parietal, basal ganglia, temporal and infratentorial brain regions. With the exception of the basal ganglia sub-score, a score of 3 is given for the presence of fully confluent WMH lesions; a score of 1 is given for those WMHs that appear focal; and a score of 2 is given to those WMHs that are beginning to appear confluent. For the basal ganglia sub-score, a single observed focal lesion (\(\geq 5\) mm) is given a score of 1, two or more focal lesions are scored 2, and confluent lesions are scored 3.\(^{400}\)
7.3.4.2 Determination of Acute and Chronic Stroke & Stroke Volumes

We classified presentation with stroke on the basis of either an acute stroke lesion on CT or a DWI positive lesion on MRI. Acute stroke lesions on CT were defined as areas of significant hypodensity (compared with contralateral tissue) that were associated with the reported acute stroke symptom presentation. Similarly, stroke lesions on DWI were defined as areas of hyperintensity compared to contralateral tissue. A diagnosis of “prior stroke” was made on the basis of: (i) radiologist reports and (ii) the presence of a chronic appearing infarction on FLAIR imaging or CT. TIA was classified in the absence of a neuroimaging-proven acute infarction. This methodology permitted an objective, neuroimaging-based diagnosis of TIA vs. stroke as well as acute stroke vs. chronic stroke.

In order to compute stroke volumes, infarcted tissues were visually identified and planimetrically traced by a trained operator based on intensity changes compared to contralateral tissue. All stroke localizations were confirmed by a formal neuroradiologist report. Acutely infarcted tissues appearing hyper-intense on diffusion weighted imaging were traced using ANALYZE 8.0 (Biomedical Imaging Resource, Mayo Foundation, Rochester, MN, USA). Chronic infarction volumes were calculated by tracing both the hypo-dense stroke core and the surrounding hyper-intense stroke penumbra on FLAIR MRI or hypodensities on CT using ANALYZE 8.0 software.

Acute and chronic stroke lesions were classified in the following categories based on their association with RLS and/or PLMs based on our literature review: (a) brainstem, (b) thalamus, (c) internal capsule, (d) basal ganglia (e.g. caudate nucleus and putamen), (e) frontal cortex, and (f) parietal cortex.

7.3.5 Polysomnography

Patients were given the option of undergoing overnight polysomnography. All polysomnograms were recorded on digital equipment (Compumedics Neuroscan, Australia) using standard recording and scoring methods. During each study, monitoring of the following took place: EEG (electrodes C3, C4, O1, O2), A1, A2 (reference leads at the mastoids), electro-oculogram, surface EMG (mentalis/submentalis, anterior tibialis), respiratory measures (abdominal and thoracic effort [measured with respiratory inductive
plethysmography belts], nasal/oral pressure [measured with a nasal/oral pressure transducer], nasal/oral flow [measured with a thermistor]), oxygen saturation, and a 2-lead ECG. All studies were videotaped and audiovisual recordings were time-synchronized to the remainder of the data.

Sleep was manually staged according to criteria from the American Academy of Sleep Medicine. All studies were interpreted by a diplomate of the American Board of Sleep Medicine and scored by a registered polysomnographic technologist. All patients who completed a sleep study attended an in-person consultation with a sleep neurologist and all detected sleep-related disorders were managed promptly.

In our analyses, we used a PLM index cut-off of 30 PLMs per hour of sleep to stratify PLM indices; as discussed above, this cut-off has been shown to be clinically relevant with respect to vascular events in prior research.

7.4 Statistical Analyses

Descriptive characteristics of the subjects are reported comparing those with and without a PLM index ≥ 30 per hour of sleep, those with and without RLS, as well as those with clinically significant RLS or “mild” cases (i.e. RLS patients whose symptoms did not meet criteria for clinically significant RLS). Continuous measures were summarized using means and standard deviations, and compared using independent samples t-tests. Categorical measures were summarized using percentages and compared using chi-square tests. Bonferroni corrections for multiple comparisons were made according to the number of computations being performed. Spearman or Pearson’s correlations of total ARWMC scores with the study variables were also computed.

Forced enter linear regression models were used to test the hypothesis that a diagnosis of RLS and/or elevated nocturnal PLM indices would be associated with the severity of WMHs assessed on the ARWMC scale. Covariates were selected on the basis of their relevance to WMHs based on our literature review. We tested three models:

**Model 1:** PLMs and/or RLS as a predictor of ARWMC, adjusted for age, gender and hypertension
**Model 2:** PLMs and/or RLS as a predictor of ARWMC, adjusted for sleep efficiency, apnea-hypopnea index (AHI), arousal index, and lowest oxygenation saturation

**Model 3:** PLMs and/or RLS as a predictor of ARWMC, adjusted for age, gender and hypertension, sleep efficiency, apnea-hypopnea index (AHI), arousal index, and lowest oxygenation saturation (i.e. models 1 + 2)

For all analyses, variables were log, square or square root transformed where possible to achieve or approximate a normal distribution; the Shapiro-Wilk test was used to assess for normality, and a significant result (p<0.05) indicated a non-normally distributed variable. No violations of assumptions for multiple linear regression (independence, normality of error distribution, and homoscedasticity of residuals) as well as no significant multicollinearity (variance inflation factor = 1.1 – 3.5) were found. The number of variables tested by each linear regression model was dictated by our sample size.

Finally, inter-rater reliabilities for the stroke tracings and ARWMC ratings were examined using Intra-Class Correlation Coefficients (ICC) for absolute agreement with 10 gold standards produced by a research radiologist. ICCs were computed for the trained rater who completed the stroke tracings and the ARWMC scale. Statistical analyses were conducted using P.A.S.W. Statistics 18.0 (SPSS Inc., IL, USA).
Chapter 4

8 Results

8.1 Recruitment

During the 14-month recruitment period, 288 patients met inclusion criteria. One hundred and ninety-one patients were excluded. Of these, 136 declined to participate and another 45 patients met one of the exclusion criteria. An additional six patients were originally enrolled with a suspected TIA, but were later found to have an alternative diagnosis to account for their symptoms (i.e. central retinal artery/vein occlusion [2 patients], marijuana intoxication [1], somatoform disorder [1], epilepsy [1] and complicated migraine [1]). Finally, 4 patients had incomplete data collected and were also excluded (Figure 3).

Figure 3. Flowchart of patient recruitment

During the 14-month recruitment period, 288 patients met inclusion criteria. One hundred and ninety-one patients were excluded. Of these, 136 declined to participate and another 45 patients met one of the exclusion criteria. An additional six patients were originally enrolled with a suspected TIA, but were later found to have an alternative diagnosis to account for their symptoms (i.e. central retinal artery/vein occlusion [2 patients], marijuana intoxication [1], somatoform disorder [1], epilepsy [1] and complicated migraine [1]). Finally, 4 patients had incomplete data collected and were also excluded (Figure 3).
Ninety-seven patients were ultimately enrolled, all of whom had full data collected. Compared to the 191 excluded patients, study participants were significantly more likely to be younger and recruited as an outpatient (table 2).

**Table 2. Basic Characteristics of Study Participants vs. Excluded Patients**

SD = standard deviation

*p<0.017 (significant after Bonferroni correction for 3 comparisons)

<table>
<thead>
<tr>
<th>Study Participants ((n=97))</th>
<th>Excluded Patients ((n=191))</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (± SD)</td>
<td>67.4 ± 15.2</td>
<td>74.2 ± 14.3</td>
</tr>
<tr>
<td>Male gender – %</td>
<td>49%</td>
<td>50%</td>
</tr>
<tr>
<td>Outpatients – %</td>
<td>45% ((n=94))</td>
<td>28% ((n=190))</td>
</tr>
</tbody>
</table>

The general characteristics of the 97 study participants are displayed in table 3 (column 2). Forty-four of these patients completed an overnight sleep study and were included in the analyses which examined PLM index and other polysomnography variables (table 3, column 3). There were no statistically significant differences among those who did and did not complete a sleep study but there was a trend for those who completed a sleep study to be younger, male, have higher scores on the Barthel index and endorse greater depressive symptoms (table 3, columns 3-5).
Table 3. General Characteristics of Study Participants

<table>
<thead>
<tr>
<th></th>
<th>Study Population (n=97)</th>
<th>Patients who Completed Sleep Study (n = 44)†</th>
<th>Patients who Did Not Complete Sleep Study (n = 53)†</th>
<th>p-value (column 3 vs. 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (± SD)</td>
<td>67.4 ± 15.2</td>
<td>65.5 ± 13.3</td>
<td>69.0 ± 16.7</td>
<td>0.15</td>
</tr>
<tr>
<td>Male gender – %</td>
<td>49%</td>
<td>59%</td>
<td>42%</td>
<td>0.09</td>
</tr>
<tr>
<td>Stroke as Presenting Event (as opposed to TIA) – %</td>
<td>51%</td>
<td>48%</td>
<td>53%</td>
<td>0.62</td>
</tr>
<tr>
<td>New Stroke Volume (mm³) (± SD)</td>
<td>6117.7 ± 23785.5</td>
<td>3364.0 ± 9312.2</td>
<td>8299.9 ± 30714.0</td>
<td>0.81</td>
</tr>
<tr>
<td>Old Stroke Volume (mm³) (± SD)</td>
<td>2003.28 ± 6781.2</td>
<td>1963.9 ± 5828.9</td>
<td>2034.5 ± 7505.7</td>
<td>0.30</td>
</tr>
<tr>
<td>Age Related White Matter Changes Scale score (mean ± SD)</td>
<td>7.9 ± 6.1</td>
<td>6.9 ± 5.1</td>
<td>8.6 ± 6.8</td>
<td>0.17</td>
</tr>
<tr>
<td>National Institutes of Health Stroke Scale (± SD)</td>
<td>0.72 ± 1.0</td>
<td>0.73 ± 0.95</td>
<td>0.71 ± 1.1</td>
<td>0.91</td>
</tr>
<tr>
<td>Barthel Index (± SD)</td>
<td>95.6 ± 9.1</td>
<td>97.1 ± 7.6</td>
<td>94.4 ± 10.1</td>
<td>0.15</td>
</tr>
<tr>
<td>Stroke Specific Quality of Life (± SD)</td>
<td>208.7 ± 31.4</td>
<td>209.8 ± 35.9</td>
<td>207.8 ± 27.2</td>
<td>0.76</td>
</tr>
<tr>
<td>Center for Epidemiologic Studies Depression Scale (± SD)</td>
<td>10.7 ± 9.6</td>
<td>12.3 ± 10.5</td>
<td>9.4 ± 8.5</td>
<td>0.13</td>
</tr>
<tr>
<td>Montréal Cognitive Assessment (± SD)</td>
<td>24.3 ± 4.0</td>
<td>24.2 ± 4.0</td>
<td>24.4 ± 4.2</td>
<td>0.77</td>
</tr>
<tr>
<td>Epworth Sleepiness Scale score (± SD)</td>
<td>6.6 ± 4.0</td>
<td>6.6 ± 4.3</td>
<td>6.6 ± 3.7</td>
<td>0.56</td>
</tr>
</tbody>
</table>

SD = standard deviation.
† Patients in columns 3 and 4 are a subset of those reported in column 2.
Categorical variables were compared using chi-square tests; continuous variables compared using independent samples t-tests; p-values are based on comparisons made using transformed variables.
8.2 Timing of Study Assessments

All patients were recruited and had baseline assessments (i.e. collection of clinical information, assessment scales, and sleep-related questionnaires) completed within two weeks of the onset of their stroke or TIA. Neuroimaging was generally completed within 4 weeks of the presenting cerebrovascular event. Sleep studies were performed on average 2 months after the TIA or stroke (mean 66.1 days). All patients who endorsed symptoms consistent with RLS on the RLS diagnostic questionnaire were reviewed in-person (n=20) or via telephone (n=5) by a sleep physician to ensure symptoms were not due to an RLS mimic (table 4); one patient could not contacted for assessment because she had left the province. As discussed further below, in patients who did not have a prior history of RLS, the RLS diagnostic questionnaire provided two false positive results.

Table 4. Timing of Study Assessments

<table>
<thead>
<tr>
<th>Time from presenting event (TIA or stroke) till:</th>
<th>Mean ± SD (days)</th>
<th>Minimum, Maximum (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study recruitment (n=97)</td>
<td>3.9 ± 3.5</td>
<td>0, 13</td>
</tr>
<tr>
<td>Neuroimaging (n=97)</td>
<td>4.7 ± 7.1</td>
<td>0, 55</td>
</tr>
<tr>
<td>Sleep study (n=44)</td>
<td>66.1 ± 61.4</td>
<td>8, 227</td>
</tr>
<tr>
<td>Sleep physician assessment (n=25)</td>
<td>119.3 ± 87.5</td>
<td>1, 316</td>
</tr>
</tbody>
</table>

SD = standard deviation; TIA = transient ischemic attack

8.3 Reliability Analysis for Stroke Tracings and ARWMC Scoring

Reliability analysis for absolute agreement revealed high inter-rater reliability for the imaging analyst conducting the ischemic infarction tracings and ARWMC ratings compared with gold standards produced by a neuroradiologist. The intra-class correlation coefficient
(ICC) for the stroke tracings was \( r^2=0.97 \) (\( p=0.0001 \)) and the ICC for the ARWMC scoring was \( r^2=0.96 \) (\( p=0.0001 \)).

### 8.4 Association of Restless Legs Syndrome and/or Periodic Limb Movements with White Matter Hyperintensities

There were no statistically significant differences in ARWMC scores between the patients with and without RLS (\( p=0.19 \); table 5). The same held true for those with clinically significant RLS vs. the non-RLS patients (6.1 vs. 8.3; \( p=0.29 \)), and the mild RLS cases vs. the non-RLS participants (6.7 vs. 8.3; \( p=0.39 \)).

In contrast, patients with PLM indices \( \geq 30 \) had higher ARWMC scores compared to those with lower PLM indices (table 5). This relationship held true even if a lower PLM index cut-off of 15 was used (5.8 vs. 9.1; \( p<0.05 \)).

#### Table 5. Age Related White Matter Changes Scale Score According to RLS Status and PLM Index

<table>
<thead>
<tr>
<th>Age Related White Matter Changes Scale score (mean ± SD)</th>
<th>RLS diagnosis (n = 24)</th>
<th>No RLS diagnosis (n=73)</th>
<th>p-value</th>
<th>PLM index &lt;30 (n=35)</th>
<th>PLM index ≥30 (n=9)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Related White Matter Changes Scale score (mean ± SD)</td>
<td>6.4 ± 4.1</td>
<td>8.3 ± 6.6</td>
<td>0.19</td>
<td>5.9 ± 4.9</td>
<td>10.8 ± 3.6</td>
<td>0.009*</td>
</tr>
</tbody>
</table>

*SD=standard deviation.
Continuous variable (ARWMC score) was compared using independent samples t-tests.

Only 12 patients with RLS underwent a sleep study; as can be seen in table 6, the effect of PLMs on WMHs was not strengthened by the presence of RLS, however, small numbers limit the ability to make any definitive conclusion.
Table 6. Age Related White Matter Changes Scale Score According to PLM Index Stratified by Presence or Absence of RLS Diagnosis

<table>
<thead>
<tr>
<th>RLS diagnosis</th>
<th>PLM index &lt;30 (n=10)</th>
<th>PLM index &gt;30 (n=2)</th>
<th>p-value</th>
<th>No RLS diagnosis</th>
<th>PLM index &lt;30 (n=25)</th>
<th>PLM index &gt;30 (n=7)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Related White Matter Changes Scale score (mean ± SD)</td>
<td>7.5 ± 0.7</td>
<td>6.3 ± 4.4</td>
<td>0.43</td>
<td>5.8 ± 5.2</td>
<td>11.7 ± 3.5</td>
<td>0.009*</td>
<td></td>
</tr>
</tbody>
</table>

SD=standard deviation. 
Continuous variable (ARWMC score) was compared using independent samples t-tests. *p<0.05

ARWMC scores were significantly correlated with age. Correlations of ARWMC score with hypertension and PLM index approached significance (table 7). A scatterplot of ARWMC versus PLM portrays this correlation (figure 4). RLS status was not significantly correlated with ARWMC scores, age gender or hypertension (table 7); stratifying by mild or clinically-significant RLS also did not produce statistically significant correlations (data not shown).

PLM index was also not statistically significantly correlated with age, gender or hypertension, suggesting that the association of PLMs with WMHs was independent of these vascular risk factors (table 7).

Table 7. Correlations between ARWMC score, RLS diagnosis, PLM index, Age, Gender and Hypertension (n=97, except for PLM index [n=44])

<table>
<thead>
<tr>
<th>ARWMC</th>
<th>RLS diagnosis</th>
<th>PLM index§</th>
<th>Age</th>
<th>Gender</th>
<th>Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>0.408* (0.020)</td>
<td>0.295** (0.003)</td>
<td>0.095</td>
<td>0.212* (0.037)</td>
</tr>
<tr>
<td>RLS diagnosis</td>
<td>1</td>
<td>0.160</td>
<td>0.023</td>
<td>-0.090</td>
<td>-0.017</td>
</tr>
<tr>
<td>PLM index§</td>
<td>1</td>
<td>0.226</td>
<td>0.021</td>
<td>0.280</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1</td>
<td>-0.168</td>
<td>0.209* (0.040)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.0035, significant after Bonferroni correction for 14 comparisons 
p-values less than 0.05 are reported in brackets below the correlations. 
§ PLM data is based on only the 44 patients who underwent polysomnography. 
Pearson or Spearman correlation coefficients were calculated for continuous or categorical variables, respectively; p-values are based on correlations made using transformed variables, where necessary.
Figure 4. Scatterplot of Age-Related White Matter Changes score vs. Periodic Limb Movement index (n=44; patients who completed polysomnography)
ARWMC scores were not statistically significantly correlated with sleep efficiency, AHI, lowest oxygen saturation in sleep or arousal index (table 8).

Table 8. Correlations between ARWMC score, PLM index, Sleep Efficiency and Respiratory-Related Sleep Variables (n=44)

<table>
<thead>
<tr>
<th></th>
<th>PLM index</th>
<th>Sleep Efficiency</th>
<th>Apnea-Hypopnea Index (AHI)</th>
<th>Lowest Oxygen Saturation</th>
<th>Arousal Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARWMC</td>
<td>0.408*</td>
<td>0.013</td>
<td>0.066</td>
<td>-0.082</td>
<td>0.186</td>
</tr>
<tr>
<td>(0.020)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLM index</td>
<td>1</td>
<td>-0.088</td>
<td>-0.065</td>
<td>-0.176</td>
<td>0.005</td>
</tr>
</tbody>
</table>

*p<0.05
**p<0.006 (significant after Bonferroni correction for 9 comparisons)

p-values less than 0.05 are reported in brackets below the correlations.

Pearson correlation coefficients were calculated for these continuous variables; p-values are based on correlations made using transformed variables, where necessary.

Furthermore, ARWMC scores were not statistically significantly correlated with sleep architecture variables such as percentage of N1, N2, N3 or REM sleep or REM sleep latency (table 9).

Table 9. Correlations between ARWMC score, PLM index and Sleep Architecture Variables (n=44, unless otherwise stated)

<table>
<thead>
<tr>
<th></th>
<th>Percent N1</th>
<th>Percent N3</th>
<th>Percent REM Sleep</th>
<th>REM Latency (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARWMC</td>
<td>0.331*</td>
<td>-0.227</td>
<td>-0.143</td>
<td>-0.096</td>
</tr>
<tr>
<td>(0.028)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLM index</td>
<td>0.106</td>
<td>-0.320</td>
<td>-0.020</td>
<td>-0.177</td>
</tr>
</tbody>
</table>

*p<0.05
**p<0.006 (significant after Bonferroni correction for 8 comparisons)

p-values less than 0.05 are reported in brackets below the correlations.

Pearson correlation coefficients were calculated for these continuous variables; p-values are based on correlations made using transformed variables, where necessary.
We tested three linear regression models to examine the association of ARWMC score with PLM index. Model 1 assessed the effects of known vascular risk factors for WMHs (age, gender and hypertension); model 2 examined the effects of potentially significant polysomnography variables (sleep efficiency, apnea-hypopnea index, arousal index, and lowest oxygen saturation); the third model tested all the variables examined in models 1 and 2. As can be seen in table 10, all three models demonstrated that PLMs were a significant predictor of ARWMC scores; adding RLS status to the models did not significantly change this association.

Table 10. Linear regression models examining association of ARWMC score with PLMs, RLS diagnosis, known vascular risk factors and polysomnography variables (n=44; patients who underwent polysomnography)

<table>
<thead>
<tr>
<th></th>
<th>Model 1 (Adjusted for age, gender, hypertension)</th>
<th>Model 2 (Adjusted for sleep efficiency, apnea-hypopnea index, arousal index, lowest oxygen saturation)</th>
<th>Model 3 (Models 1 + 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Periodic Limb Movement Index</strong></td>
<td>Effect on ARWMC ($\beta$) 3.677</td>
<td>SE 1.725</td>
<td>p-value 0.04*</td>
</tr>
<tr>
<td><strong>RLS status</strong></td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
</tbody>
</table>

*p<0.05
**p<0.01
ARWMC = age-related white matter changes score
SE = standard error
ns=not significant
Transformed variables were used in the analyses, where necessary.
8.5 Characterization of Restless Legs Syndrome after TIA and Minor Stroke

8.5.1 RLS Prevalence

Twenty-five percent (24/97) of the study population endorsed the 2003 IRLSSG criteria for RLS. In the patients diagnosed with RLS, symptoms were confirmed by a physician to be secondary to RLS, rather than an RLS mimic, in all but one of the patients who could not be reached because she had moved out of the province.

Eleven of the patients with RLS (11.3% [11/97] of the study population) noted that their RLS symptoms occurred at least 5 to 15 days per month with at least moderate distress, and were diagnosed with “clinically-significant RLS”; the remaining thirteen patients with RLS (13.4% [13/97]) were diagnosed with “mild RLS”. As would be expected, more patients with clinically-significant RLS were being treated with dopaminergic therapy than those with mild RLS, but this finding was not statistically significantly different (50% vs. 23%; p=0.21).

Fourteen patients (14.4% [14/97] of the study population) endorsed a history of RLS prior to their TIA or stroke. Two of these patients did not endorse RLS symptoms after their cerebrovascular event. Of the 12 patients who did endorse RLS symptoms after their cerebrovascular event, five cases were mild and seven were clinically-significant.

8.5.2 General Characteristics of RLS Patients

There were no statistically significant differences in age, gender, stroke volumes, neurological/functional status or daytime sleepiness among those with or without RLS. Patients diagnosed with RLS were just as likely to have presented with either a TIA or stroke (table 11).
Table 11. General Characteristics of Study Patients Stratified by RLS Status

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>RLS diagnosis (n = 24)</th>
<th>No RLS diagnosis (n=73)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (± SD)</td>
<td>68.8 ± 13.0</td>
<td>67.0 ± 16.0</td>
<td>0.72</td>
</tr>
<tr>
<td>Male gender – %</td>
<td>42%</td>
<td>52%</td>
<td>0.38</td>
</tr>
<tr>
<td>Neuroimaging-confirmed Stroke as Presenting Event (as opposed to TIA) – %</td>
<td>42%</td>
<td>53%</td>
<td>0.32</td>
</tr>
<tr>
<td>New Stroke Volume (mm$^3$) (± SD)</td>
<td>4233.6 ± 11698.0</td>
<td>6754.6 ± 26704.5</td>
<td>0.29</td>
</tr>
<tr>
<td>Old Stroke Volume (mm$^3$) (± SD)</td>
<td>1707.5 ± 6615.3</td>
<td>2103.3 ± 6879.8</td>
<td>0.79</td>
</tr>
<tr>
<td>National Institutes of Health Stroke Scale (± SD)</td>
<td>0.55 ± 0.91</td>
<td>0.77 ± 1.07</td>
<td>0.37</td>
</tr>
<tr>
<td>Barthel Index (± SD)</td>
<td>97.0 ± 5.3</td>
<td>95.2 ± 10.1</td>
<td>0.42</td>
</tr>
<tr>
<td>Epworth Sleepiness Scale score (± SD)</td>
<td>6.3 ± 4.2</td>
<td>6.7 ± 3.9</td>
<td>0.65</td>
</tr>
</tbody>
</table>

SD = standard deviation.
Categorical variables were compared using chi-square tests; continuous variables compared using independent samples t-tests; p-values are based on comparisons made using transformed variables, where necessary.

8.5.3 Accuracy of RLS Questionnaire

In the patients who did not have a prior history of RLS, the RLS diagnostic questionnaire provided two false positive results. In these patients, after the physician assessment it was determined that the RLS-like symptoms were due to muscle cramps or positional discomfort rather than RLS. The RLS questionnaire also provided one false negative result in a patient who initially did not endorse an urge to move his legs, but did so when reviewed by the physician.

8.5.4 Association of RLS Diagnosis with Quality of Life, Depressive Symptoms and Cognition

When analyzed altogether, the patients with RLS endorsed poorer quality of life on the Stroke-Specific Quality of Life scale compared to those without RLS. When stratified by severity, those with clinically-significant RLS also showed poorer quality of life, but quality of life in patients with mild RLS was not significantly different than in those without RLS.
The patients with clinically-significant RLS also endorsed more depressive symptoms than those without RLS, and there was a trend for the same in all the patients with RLS (table 12).

Table 12. Quality of Life and Depressive Symptoms according to RLS status (n=97)

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>All RLS patients (n = 24)</th>
<th>Clinically-significant (CS) RLS (n=11)†</th>
<th>Mild RLS (n=13)†</th>
<th>No RLS diagnosis (n=73)</th>
<th>p-values: All vs. no RLS CS vs. no RLS Mild vs. no RLS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke Specific Quality of Life (± SD)</td>
<td>192.2 ± 32.8</td>
<td>184.7 ± 34.3</td>
<td>199.0 ± 31.1</td>
<td>214.0 ± 29.2</td>
<td>0.003** 0.003** 0.106</td>
</tr>
<tr>
<td>Center for Epidemiologic Studies Depression Scale (± SD)</td>
<td>14.4 ± 11.5</td>
<td>17.6 ± 12.4</td>
<td>11.4 ± 10.4</td>
<td>9.6 ± 8.6</td>
<td>0.033* 0.008** 0.500</td>
</tr>
</tbody>
</table>

CS = clinically-significant; SD = standard deviation
† Patients in columns 3 and 4 are a subset of those reported in column 2.
Continuous variables were compared using independent samples t-tests.
*p<0.05
**p≤0.008, significant after Bonferroni correction for 6 comparisons

Clinically-significant RLS was significantly correlated with poorer quality of life and there was a trend for a correlation with greater depressive symptoms; such correlations were not seen in those with mild RLS. As would be expected, quality of life and depressive symptoms were strongly negatively correlated (table 13).
Table 13. Correlations between Quality of Life, Depressive Symptoms and RLS status (n=97)

<table>
<thead>
<tr>
<th>RLS diagnosis</th>
<th>Clinically-Significant RLS</th>
<th>Mild RLS</th>
<th>Stroke Specific Quality of Life</th>
<th>Center for Epidemiologic Studies Depression Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>RLS diagnosis</td>
<td>1</td>
<td>n/a</td>
<td>n/a</td>
<td>0.314** (0.002)</td>
</tr>
<tr>
<td>Clinically-Significant RLS</td>
<td>1</td>
<td>n/a</td>
<td>-0.307** (0.005)</td>
<td>0.259* (0.017)</td>
</tr>
<tr>
<td>Mild RLS</td>
<td>1</td>
<td></td>
<td>-0.201</td>
<td>0.063</td>
</tr>
<tr>
<td>Stroke Specific Quality of Life</td>
<td></td>
<td>1</td>
<td>-0.554** (&lt;0.0001)</td>
<td></td>
</tr>
</tbody>
</table>

*p<0.05
**p<0.007, significant after Bonferroni correction for 7 comparisons
p-values less than 0.05 are reported in brackets below the correlations.
Pearson or Spearman correlation coefficients were calculated for continuous or categorical variables, respectively.

8.5.5 Association of RLS Diagnosis with Medical Co-Morbidities and Medication Use

The patients with RLS were more likely to have a prior history of migraine compared to those without RLS (p=0.004; significant after Bonferroni correction). This was also seen in the mild and clinically-significant RLS subgroups (p<0.01 and 0.05, respectively; data not shown). There were no differences in prior vascular events, vascular risk factors, renal failure, low ferritin or SSRI medication use in the patients with RLS compared to the non-RLS patients (table 14).
Table 14. Medical Co-Morbidities and Medication Use according to RLS status (n=97, unless otherwise stated)

<table>
<thead>
<tr>
<th></th>
<th>RLS diagnosis (n = 24)</th>
<th>No RLS diagnosis (n=73)</th>
<th>p-values: All vs. no RLS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior stroke (%)</td>
<td>13</td>
<td>29</td>
<td>0.11</td>
</tr>
<tr>
<td>(as noted on imaging)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior Myocardial Infarction (%)</td>
<td>0</td>
<td>11</td>
<td>0.09</td>
</tr>
<tr>
<td>Hypertension or use of anti-hypertensive medication (%)</td>
<td>67</td>
<td>68</td>
<td>0.87</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>53</td>
<td>57</td>
<td>0.74</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>25</td>
<td>25</td>
<td>0.97</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>29</td>
<td>15</td>
<td>0.12</td>
</tr>
<tr>
<td>Migraine (%)</td>
<td>29</td>
<td>7</td>
<td>0.004*</td>
</tr>
<tr>
<td>Renal failure (%)</td>
<td>4</td>
<td>12</td>
<td>0.25</td>
</tr>
<tr>
<td>(creatinine &gt; 106µmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low ferritin (%)</td>
<td>14</td>
<td>22</td>
<td>0.66</td>
</tr>
<tr>
<td>(&lt; 45µg/L) (n=25)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSRI medication use (%)</td>
<td>14</td>
<td>6</td>
<td>0.21</td>
</tr>
<tr>
<td>(n=94)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p<0.005, significant after Bonferroni correction for 10 comparisons
Categorical variables were compared using chi-square tests.

8.5.6 Association of RLS Diagnosis with Presenting Stroke/TIA Clinical Symptoms & Stroke Lesion Location

The most common stroke or TIA-related presenting symptoms in those with RLS were limb weakness (63%), aphasia (42%) and sensory loss (33%), however, these symptoms were not statistically significantly different than in those without RLS (p>0.05; data not shown).

There was no single consistent lesion location implicated across all RLS groups (table 15). Involvement of the internal capsule approached statistical significance in the patients with mild RLS (p=0.004; not significant after Bonferroni correction) and when all the RLS
patients were analyzed together (p=0.06); however, none of the patients with clinically-significant RLS had a lesion in the internal capsule.

**Table 15. Lesion Locations according to RLS status (n=97)**

<table>
<thead>
<tr>
<th>Lesion Location</th>
<th>RLS diagnosis (n = 24)</th>
<th>Clinically-significant RLS (n=11)†</th>
<th>Mild RLS (n=13)†</th>
<th>No RLS diagnosis (n=73)</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>All vs. no RLS</td>
</tr>
<tr>
<td>Brainstem (%)</td>
<td>4</td>
<td>0</td>
<td>8</td>
<td>7</td>
<td>0.64</td>
</tr>
<tr>
<td>Thalamus (%)</td>
<td>13</td>
<td>27</td>
<td>0</td>
<td>18</td>
<td>0.54</td>
</tr>
<tr>
<td>Internal capsule (%)</td>
<td>13</td>
<td>0</td>
<td>23</td>
<td>3</td>
<td>0.06</td>
</tr>
<tr>
<td>Basal Ganglia (%)</td>
<td>8</td>
<td>0</td>
<td>15</td>
<td>15</td>
<td>0.40</td>
</tr>
<tr>
<td>Frontal (%)</td>
<td>17</td>
<td>9</td>
<td>23</td>
<td>21</td>
<td>0.68</td>
</tr>
<tr>
<td>Parietal (%)</td>
<td>13</td>
<td>18</td>
<td>8</td>
<td>19</td>
<td>0.46</td>
</tr>
</tbody>
</table>

CS = clinically significant
† Patients in columns 3 and 4 are a subset of those reported in column 2.

*p<0.05

**p<0.003, significant after Bonferroni correction for 18 comparisons (no statistically significant results in this table)

Categorical variables were compared using chi-square tests.

### 8.5.7 Association of RLS Diagnosis with Polysomnography Variables

There were no differences in several potentially important polysomnography variables (i.e. sleep efficiency, apnea-hypopnea index, respiratory disturbance index, lowest oxygen saturation, arousal index, PLM index and sleep architecture variables) among the RLS and non-RLS patients (p>0.05 for all comparisons; data not shown).
8.6 Characterization of Periodic Limb Movements after TIA and Minor Stroke

Patients with a PLM index ≥30 were more likely to have presented with a stroke in contrast to a TIA, but otherwise there were no statistically significant differences in age, gender, stroke volumes, neurological/functional status, or daytime sleepiness among those with a PLM index greater or less than 30 (table 16).

Table 16. General Characteristics of Study Patients Stratified by PLM index (n=44; patients who underwent overnight polysomnography)

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>PLM index &lt;30/hr (n=35)</th>
<th>PLM index ≥30/hr (n=9)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (± SD)</td>
<td>64.4 ± 14.2</td>
<td>69.4 ± 7.7</td>
<td>0.41</td>
</tr>
<tr>
<td>Male gender – %</td>
<td>54%</td>
<td>78%</td>
<td>0.20</td>
</tr>
<tr>
<td>Neuroimaging-confirmed Stroke as Presenting Event – %</td>
<td>34%</td>
<td>100%</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>New Stroke Volume (mm³) (± SD)</td>
<td>2459.6 ± 8358.0</td>
<td>7207.6 ± 12559.4</td>
<td>0.84</td>
</tr>
<tr>
<td>Old Stroke Volume (mm³) (± SD)</td>
<td>2162.4 ± 6409.0</td>
<td>1120.3 ± 2087.5</td>
<td>0.33</td>
</tr>
<tr>
<td>National Institutes of Health Stroke Scale (± SD)</td>
<td>0.69 ± 1.00</td>
<td>0.89 ± 0.78</td>
<td>0.58</td>
</tr>
<tr>
<td>Barthel Index (± SD)</td>
<td>97.0 ± 8.3</td>
<td>97.8 ± 4.4</td>
<td>0.78</td>
</tr>
<tr>
<td>Epworth Sleepiness Scale score (± SD)</td>
<td>6.3 ± 4.6</td>
<td>7.3 ± 3.2</td>
<td>0.33</td>
</tr>
</tbody>
</table>

SD = standard deviation.
Categorical variables were compared using chi-square tests; continuous variables compared using independent samples t-tests; p-values are based on comparisons made using transformed variables, if necessary.

8.6.1 PLM Prevalence in Study Population Compared to Age, Gender and AHI-matched Controls

Compared to 44 age-, gender- and AHI-matched controls who had attended a prior diagnostic polysomnogram at the Sunnybrook Health Sciences Centre Sleep Laboratory, PLM indices in our study population of TIA and minor stroke patients were statistically significantly higher ($\chi^2 = 7.98, p=0.019$; figure 5).
Figure 5. Periodic Limb Movement Indices in Age, Gender and AHI-matched Controls vs. Study Population of TIA and Minor Stroke Patients

Note: Frequencies are in brackets below the percentages. Percentages do not add to 100% because of rounding.

18% (8/44) of the age-, gender- and AHI-matched controls endorsed a history of RLS on a self-reported questionnaire; this was not statistically significantly different from the percentage of patients in our study who completed a sleep study and were diagnosed with RLS using the RLS diagnostic questionnaire (27.2% [12/44]; $\chi^2 = 1.035, p=0.31$). In addition, identical numbers of patients in both the control group (5/44) and study population (5/44) reported use of an SSRI.
8.6.2 Association of PLM index with Quality of Life, Depressive Symptoms, Medical Co-Morbidities and Medication Use

In contrast to what was observed with RLS status, there was no association of PLM index with quality of life or depressive symptoms (data not shown).

There was a trend for patients with a PLM index ≥30 to have been more likely to have had a prior myocardial infarction (p=0.02; not significant after Bonferroni correction). Otherwise, there were no significant differences in prior vascular events, vascular risk factors, renal failure, low ferritin or SSRI medication use in the patients with PLM indices greater or less than 30 (table 17).

**Table 17. Medical Co-Morbidities and Medication Use according to PLM Index (n=44, unless otherwise stated)**

<table>
<thead>
<tr>
<th></th>
<th>PLM index &lt;30 (n=35)</th>
<th>PLM index ≥30 (n=9)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior stroke (%)</td>
<td>23</td>
<td>22</td>
<td>0.97</td>
</tr>
<tr>
<td>(as noted on imaging)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior Myocardial Infarction (%)</td>
<td>6</td>
<td>33</td>
<td>0.02*</td>
</tr>
<tr>
<td>Hypertension or use of anti-hypertensive medication (%)</td>
<td>57</td>
<td>78</td>
<td>0.26</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>45</td>
<td>67</td>
<td>0.26</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>20</td>
<td>44</td>
<td>0.13</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>17</td>
<td>22</td>
<td>0.73</td>
</tr>
<tr>
<td>Migraine (%)</td>
<td>11</td>
<td>0</td>
<td>0.29</td>
</tr>
<tr>
<td>Renal failure (%) (creatinine &gt; 106µmol/L)</td>
<td>11</td>
<td>22</td>
<td>0.40</td>
</tr>
<tr>
<td>Low ferritin (%) (≤ 45µg/L) (n=16)</td>
<td>15</td>
<td>33</td>
<td>0.47</td>
</tr>
<tr>
<td>SSRI medication use (%) (n=43)</td>
<td>15</td>
<td>0</td>
<td>0.22</td>
</tr>
</tbody>
</table>

*p<0.05
**p<0.005, significant after Bonferroni correction for 10 comparisons
Categorical variables were compared using chi-square tests.

### 8.6.3 Association of PLM Index with Presenting Stroke/TIA Clinical Symptoms & Stroke Lesion Location

In the patients with PLM indices $\geq 30$, the most common presenting symptoms were limb weakness (66%), dysarthria (43%), aphasia (37%) and sensory loss (29%), but these findings were not statistically significantly different than in those with lower PLM indices ($p>0.05$; data not shown).

Lesions involving the brainstem, specifically the midbrain, were more common in the patients with PLM indices $\geq 30$ compared to those with lower PLM indices ($p=0.004$; significant after Bonferroni correction; table 18). Lesions in other brain regions were not more likely to be found in those with elevated PLM indices compared to those with lower PLM indices.

#### Table 18. Lesion Locations according to PLM Index (n=44)

<table>
<thead>
<tr>
<th>Location</th>
<th>PLM index &lt;30 (n=35)</th>
<th>PLM index $\geq$30 (n=9)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brainstem (%)</td>
<td>0</td>
<td>22</td>
<td>0.004**</td>
</tr>
<tr>
<td>Thalamus (%)</td>
<td>14</td>
<td>11</td>
<td>0.81</td>
</tr>
<tr>
<td>Internal capsule (%)</td>
<td>3</td>
<td>0</td>
<td>0.61</td>
</tr>
<tr>
<td>Basal ganglia (%)</td>
<td>11</td>
<td>33</td>
<td>0.11</td>
</tr>
<tr>
<td>Frontal (%)</td>
<td>20</td>
<td>33</td>
<td>0.40</td>
</tr>
<tr>
<td>Parietal (%)</td>
<td>17</td>
<td>22</td>
<td>0.73</td>
</tr>
</tbody>
</table>

**p<0.008, significant after Bonferroni correction for 6 comparisons
Categorical variables were compared using chi-square tests.

### 8.6.4 Association of PLM Index with Polysomnography Variables

There were no differences in several potentially important polysomnography variables (i.e. sleep efficiency, apnea-hypopnea index, respiratory disturbance index, lowest oxygen saturation, and arousal index) among the patients with PLM indices greater or less than 30 ($p>0.05$ for all comparisons; data not shown).
8.7 Overlap of RLS Diagnosis with PLM Index

Twelve patients with RLS (7 clinically-significant, 5 mild) underwent polysomnography. The mean PLM index was not different in those with or without RLS; this was also true in the patients with mild or clinically-significant RLS compared to those without RLS (table 19). In addition, PLM indices were similar between the two RLS subgroups (16.6 vs. 17.0; $p=0.98$).

Table 19. PLM Index According to RLS Status

<table>
<thead>
<tr>
<th></th>
<th>RLS diagnosis (n = 12)</th>
<th>Clinically-significant RLS (n=7)†</th>
<th>Mild RLS (n=5)†</th>
<th>No RLS diagnosis (n=32)</th>
<th>$p$-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLM index (±SD)</td>
<td>16.8 ± 21.6</td>
<td>17.0 ± 26.3</td>
<td>16.6 ± 15.9</td>
<td>18.3 ± 25.0</td>
<td>0.35</td>
</tr>
</tbody>
</table>

SD = standard deviation
† Patients in columns 3 and 4 are a subset of those reported in column 2.
Continuous variables compared using independent samples t-tests.

Figure 6 illustrates the overlap of RLS with PLM indices in the 44 study participants who underwent polysomnography. Fifteen of these patients had neither RLS nor PLMs. In contrast, 17 patients had PLMs only, in the absence of RLS symptoms; 7 of these patients had a PLM index greater than 30 and all of these patients had presented with a stroke.

Of the 12 patients with RLS who underwent polysomnography, eight (66% [8/12]) had a PLM index greater than 5. PLM index was not correlated with RLS severity or frequency, even when the 4 patients with RLS only (but no PLMs) were excluded ($p>0.05$; data not shown). There was no critical PLM index threshold that was associated with a diagnosis of RLS; indeed, PLM indices appeared greater in many of the patients without RLS (figure 7).
Figure 6. Venn Diagram of Overlap of RLS Diagnosis with PLM Index (n=44, all patients who underwent polysomnography)
*PLMs = PLM index > 5 per hour of sleep
Figure 7. Scatterplot of PLM Index According to RLS Status
Chapter 5

9 Discussion

9.1 Summary and Interpretation of Results

Five main findings emerge from this study:

1) Elevated PLM indices, rather than a diagnosis of RLS, were associated with white matter hyperintensities, a form of small vessel disease of the brain.

2) RLS was present in 25% of the study population; 11% met criteria for clinically-significant RLS. The presence of RLS was associated with poorer quality of life. In the patients with clinically-significant RLS, in addition to endorsing poorer quality of life, they also noted more depressive symptoms. Furthermore, patients with RLS were more likely to have a prior history of migraine.

3) The prevalence of PLMs in our study population of TIA and minor stroke patients was greater than that of age-, gender- and AHI-matched controls who had previously undergone polysomnography for various sleep-related concerns at our sleep laboratory. Severe PLMs were detected more commonly after presentation with a stroke than a TIA.

4) In terms of determining neural correlates associated with RLS and PLMs, our technique was limited and our sample size was too small to make conclusive results. RLS and PLMs had no single predominant neuroanatomical localization in our study.

5) Sixty-six percent of the 12 patients with RLS who underwent a sleep study had a PLM index $\geq 5$. Severity of RLS was not associated with PLM index, and there was no critical PLM index threshold that was associated with a diagnosis of RLS.

9.1.1 Association of White Matter Hyperintensities with Periodic Limb Movements of Sleep

Contrary to our hypothesis, a diagnosis of RLS (even that which was clinically-significant) was not associated with the presence of WMHs. Instead the objective motor manifestation of
RLS (i.e. PLMs) was significantly associated with the severity of WMHs. This relationship was further supported by a linear regression analysis: after controlling for vascular risk factors known to be pertinent in the pathogenesis of WMHs (i.e. age, gender and hypertension) and sleep variables postulated to be important in vascular disease (sleep efficiency, apnea-hypopnea index, lowest oxygenation, and arousal index), PLM index was still significantly associated with ARWMC score ($\beta=5.003$, SE=1.889, $p=0.016$); RLS status did not affect this relationship.

There are at least three explanations as to why WMHs, a form of pre-TIA/stroke cerebrovascular disease, could have been found in association with PLMs:

1. PLMs may be implicated in the pathogenesis of WMHs.

2. WMHs may cause or exacerbate PLMs.

3. Explanations 1 and 2 co-occur and are not mutually exclusive.

9.1.1.1 Explanation #1: PLMs Cause WMHs

As discussed above, six mechanisms have been proposed to link SRMDs with vascular disease. Two of these mechanisms (autonomic fluctuations and inflammatory changes) are primarily driven by the effect of PLMs, rather than a diagnosis of RLS. Aside from its association with RLS, depression may also serve as an additional link between PLMs and vascular disease.

PLM index was not correlated with age, gender or hypertension, the vascular risk factors most commonly implicated in the pathogenesis of white matter hyperintensities of the brain (table 7). Prior work has suggested that PLMs may be associated with daytime hypertension in adults, however, we were not able to replicate this result. Our findings suggested that the association of PLMs with white matter disease was not significantly modulated by these traditional vascular risk factors.

It is fairly well-established that PLMs are associated with surges of nocturnal sympathetic hyperactivity which manifest as transient elevations in night-time heart rate and blood pressure. Recurrent surges in blood pressure every night for many years or decades may
cause repeated mechanical stress on the vasculature, leading to vascular remodeling; in addition, variability of blood flow caused by BP oscillations is thought to induce shear stress, platelet activation, leading to atherosclerosis and a potentially hypercoaguable state. At this time, whether the inflections in heart rate and blood pressure caused by PLMs are sufficient to cause cerebrovascular disease is unknown. Elevated PLM indices have been demonstrated to be associated with incident cardiovascular events and structural changes of the left ventricle of the heart, however, whether PLMs are similarly linked with silent or overt cerebrovascular disease is uncertain. Our study is among the first to demonstrate an association of PLMs with cerebrovascular disease.

An obvious limitation of our study was that we did not actually measure the elevations of heart rate and blood pressure that have been suggested to be important in the pathogenesis of small vessel disease of the brain. Future research should attempt to objectively quantify these markers of autonomic hyperactivity and their association with white matter hyperintensities and clinical cerebrovascular events.

ARWMC scores were not significantly correlated with any of the other sleep variables examined (i.e. AHI, lowest oxygen saturation in sleep, arousal index, sleep efficiency or sleep architecture; tables 8 and 9). This suggested that white matter hyperintensities and PLM index were linked via factors that are not captured by these measures.

Nocturnal hypoxia and sleep-disordered breathing, examined in our study via the AHI and lowest oxygen saturation in sleep, are strongly implicated in the pathogenesis of vascular disease via OSA. However, as reviewed above, the link between OSA and cerebral WMHs is less well-established; of note, all prior studies that explored the relationship between AHI and WMHs did not report on PLMs, and many only used portable polysomnography units that could not measure limb movements in sleep. In our study, neither the AHI nor lowest oxygen saturation in sleep were predictive of ARWMC score, even if the PLM index was removed from the linear regression analysis (data not shown).

The interaction of respiratory events and PLMs may be a particularly important area of future exploration. Since hypopneas and apneas cause recurrent nocturnal hypoxia and PLMs initiate transient fluctuations in heart rate and blood pressure, their combination may be
particularly potent in the development of vascular disease; in keeping with this idea, preliminary work published in abstract form at a recent international sleep conference suggested that respiratory-related limb movements in sleep may be significantly associated with incident cardiovascular events. Using current scoring rules, leg movements associated with respiratory events during sleep are typically ignored, however, this practice may need to be re-evaluated in light of the possibility that respiratory-related limb movements may in fact be important predictors of vascular disease.

The autonomic hyperactivity that occurs in the context of PLMs may or may not occur in association with nocturnal arousals. As a result, these surges of sympathetic activity may occur in the absence of elevation of the arousal index. In our study, arousal index was not significantly associated with WMHs, but further research should re-evaluate this association and particularly whether PLMs associated with arousals are more strongly associated with vascular disease than PLMs without arousals. As mentioned earlier, current measures of arousal are imprecise and as such may be a limitation in future studies.

While sleep disruption is a known feature of RLS, PLMs have been shown to have essentially no relationship with the sleep fragmentation seen in RLS, not surprisingly, sleep efficiency, an objective measure of sleep disruption, was neither significantly associated with PLM index nor ARWMC score in our study (table 8).

Another mechanism that may link PLMs with WMHs is inflammation. As discussed above, in a single study of patients with RLS, those with elevated PLM indices (≥45 PLMs per hour of sleep) had an odds ratio of 3.56 for having an elevated CRP, a marker of systemic inflammation, compared to RLS patients with lower PLM indices. In that study the presence of RLS by itself was not reported to be associated with increased levels of serum CRP, suggesting that PLMs were the main modulator of the elevated CRP levels. Indeed, prior work has suggested that RLS itself is not associated with elevated levels of inflammatory markers. These findings underscore the importance of PLMs, rather than a diagnosis of RLS, in mediating inflammation as a possible linking mechanism.

Finally, depression has also been linked with elevated PLM indices. Depression can lead to HPA system activation and is associated with traditional vascular risk factors, and thus
can also mediate the possible relationship between PLMs and vascular disease. The current study was likely underpowered to demonstrate an association of PLMs with depressive symptoms.

9.1.1.2 Explanation #2: WMHs Cause or Exacerbate PLMs

As WMHs develop over the course of many years, they may disrupt cortical-subcortical-brainstem pathways that are particularly important in the pathogenesis of PLMs. As discussed above, the pathways implicated in PLMs are still being determined via animal and human research. Deep subcortical and brainstem white matter may be involved, and responsible pathways could be potentially negatively impacted by the presence of slowly accumulating white matter pathology. Whether the small vessel disease pathology that gives rise to the WMHs could actually be sufficient to cause PLMs is unknown.

Alternatively, the presence of WMHs may make pathways important in the pathogenesis of PLMs particularly vulnerable to ischemic insult and thus exacerbate the PLM index in the acute TIA or stroke setting. In our study, all 9 patients who had an elevated PLM index of ≥30 had presented with acute stroke; it is plausible that pre-existing white matter changes plus the new acute stroke lesion may have significantly altered the pathways implicated in the pathogenesis of PLMs more than the effect of the acute stroke alone. In this view, the presence of PLMs after stroke or TIA would serve as a marker of prior vascular disease burden. Again, whether the small vessel disease pathology that gives rise to the WMHs could actually exacerbate PLMs in the setting of stroke is entirely speculative.

9.1.1.3 Summary: Association of WMHs with PLMs

Overall, while the association of PLMs with vascular disease is intriguing, future work in the form of prospective studies will be needed to determine the direction of the relationship of PLMs with WMHs. It will also be important to determine whether PLMs not associated with RLS (e.g. secondary to stroke or spinal cord injury but in patients who do not endorse diagnostic criteria for RLS) are also significantly implicated in vascular disease; our study suggested that RLS status was not implicated in the association with WMHs, however, given the close association of RLS with PLMs, this needs to be confirmed in future larger studies.
If PLMs are actually demonstrated to be a risk factor for vascular disease, randomized controlled trials will be necessary to determine whether treating PLMs reduces incident vascular disease. Even if PLMs were not significantly involved in the pathogenesis of an initial cerebrovascular event, whether their presence after a stroke or TIA confers additional risk of future vascular events or carries implications for recovery needs to be established. This area of work has the potential to be an exciting and clinically-relevant area of study.

9.1.2 RLS is Prevalent and Associated with Poor Quality of Life after High Risk TIA and Minor Stroke

9.1.2.1 RLS prevalence

In our study, 25% (95% confidence interval: 16 – 34%) of the study population endorsed the 2003 IRLSSG criteria\textsuperscript{25} for RLS. This was considerably higher than the 4 to 11.5% that has been found in population-based and primary care studies that used the same 2003 RLS diagnostic criteria (reviewed above). This high prevalence of RLS was not explained by differences in renal failure, low ferritin or SSRI medication use between the patients with and without RLS (table 14).

In the only other study that examined post-stroke RLS, 7% had a diagnosis of RLS prior to their stroke and, after excluding those with a prior diagnosis of RLS, 12% were found to have newly-diagnosed RLS after their stroke, thus yielding an approximate prevalence of 19% for post-stroke RLS (confidence intervals were not reported).\textsuperscript{14} When our confidence intervals are considered, our prevalence estimate falls in line with that of the earlier study. Nonetheless, several differences in methodology between our study and the prior report\textsuperscript{14} may explain the slight differences in RLS prevalences reported. In the earlier study, strokes of all severity were included while in our study we only included those with minor stroke or high-risk TIA. One interpretation could be that patients with more severe stroke may not be able to appreciate the sensory symptoms associated with RLS due to sensory loss as a result of their stroke, or may not have the mobility or capability of moving their limb(s) to reduce RLS symptoms; these factors could have reduced the prevalence of RLS observed in the prior study. We found that 58% of our study patients diagnosed with RLS had presented with TIA, while 42% had presented with minor stroke (table 11); while this difference was not statistically significantly different, this finding suggested that patients with less clinically
severe cerebrovascular events (e.g. TIA) could also be at risk for RLS after their event. Another explanation for the high prevalence of RLS in patients with TIA is that RLS may predispose patients to developing a TIA; alternatively, patients with TIA may already have prior neurological damage that may lead to RLS. In addition, while we assessed our patients within two weeks of their event, the earlier study assessed for RLS 1 month post-stroke. We may have picked up early manifestations, some of which may have resolved by the time one month had elapsed; participant follow-up has been arranged in order to assess for this possibility.

Eleven percent of our study population was diagnosed with clinically significant RLS. Again, this is greater than the 1.5 to 2.7% that has been previously reported in general and primary care populations.34, 37, 48, 51

Our high RLS prevalence rates underscore the fact that RLS is likely underdiagnosed in the post-TIA/stroke setting, regardless of definition used. Given the association of RLS with poor health outcomes (discussed below), more attention surrounding screening, diagnosing and managing RLS may be warranted in the post-TIA/stroke setting.

9.1.2.2 Association of RLS with Poorer Quality of Life

Patients with RLS are known to have poorer quality of life compared to those in the general population.94 Impaired quality of life has also been demonstrated in patients with RLS who have chronic renal404 or liver disease,405 however, the association of poor quality of life in RLS after TIA or stroke has not been previously reported.

In our study, the presence of RLS was associated with poorer quality of life in the patients with RLS compared to those who did not have RLS. RLS was associated with poorer quality of life even when the effect of depressive symptoms was accounted for, and vice versa (data not shown). When stratified by disease severity, those with clinically-significant RLS also endorsed poorer quality of life, however, quality of life in patients with mild RLS was not significantly different than in those without RLS. In addition, the patients with clinically-significant RLS also endorsed more depressive symptoms than those without RLS, and there was a trend for the same in all the patients with RLS; again, those with mild RLS did not endorse significantly more depressive symptoms than those without RLS (table 12).
These findings suggest that there is a mild phenotype of RLS that may arise after TIA or stroke that meets formal diagnostic criteria, however, has little consequence to patients, at least in terms of quality of life and depressive symptoms. On the other hand, our results also demonstrate that clinically-significant RLS may carry significant associations with poor quality of life and depressive symptoms in the post-TIA/stroke setting. Given the relatively high prevalence of RLS detected in our study, routine screening for RLS after TIA or stroke may be warranted to help improve quality of life and reduce depressive symptoms. Future trials should assess whether treating RLS after stroke or TIA improves quality of life.

Whether the poor quality of life observed is driven by the depressive symptoms, or vice versa, is unclear at this time. Further analyses will be needed to determine the direction of this relationship; advanced statistical tools such as path analysis\cite{406} may be helpful in this regard. In addition, the possibility that RLS symptoms exacerbate depressive symptomatology after TIA or stroke should also be explored. Furthermore, it is plausible that patients with depressive symptoms have a negative outlook, and are more likely to report non-specific sensory symptoms (e.g. the motor restlessness seen in RLS) as well as reduced quality of life.

### 9.1.2.3 Association of RLS with Migraine

Patients with RLS were significantly more likely to have endorsed a prior history of migraine compared to those without RLS. This has been demonstrated in prior studies;\cite{57-59} one study also demonstrated a co-association with depression.\cite{57} Interestingly, lesioning the A11 region facilitates the trigeminovascular nociception that occurs in the context of migraine; therefore, shared dopaminergic dysfunction in the A11 nucleus may be the neuroanatomical substrate linking migraine and RLS.\cite{59}

### 9.1.3 High Prevalence of PLMs after TIA & Minor Stroke

The prevalence of PLMs in our study population of TIA and minor stroke patients was greater than that of age, gender and AHI-matched controls that had previously undergone polysomnography for various sleep-related concerns ($\chi^2 = 7.98, p=0.019$; figure 5). Such a
result is not surprising given the fact that several case reports have demonstrated the occurrence of PLMs after stroke.

PLMs also occurred after TIA: a PLM index $\geq 5$ per hour of sleep was found in 57% of those presenting with TIA and in 57% of those presenting with stroke. However, all patients who were found to have a severely elevated PLM index ($\geq 30$ per hour of sleep) had presented with stroke. New and old stroke volumes were comparable between those with and without elevated PLM indices (table 16), suggesting that key brain regions needed to be involved in the development or exacerbation of PLMs after stroke.

A history of prior myocardial infarction was observed more frequently in the patients with elevated PLM indices compared to those with lower PLM indices; although this difference only approached statistical significance ($p=0.02$; table 17), such a result deserves comment particularly since our study was likely underpowered to detect a significant difference in prior cardiovascular events. This observation is in keeping with prior prospective studies that have demonstrated increased cardiovascular events in patients with elevated PLM indices at baseline. Furthermore, the association of elevated PLM indices with both prior cardiovascular events and WMHs (i.e. pre-stroke/TIA cerebrovascular disease) may be interpreted to lend support to arguments in favor of the presence of PLMs being a risk factor for vascular disease.

There were no significant differences in renal failure, low ferritin or SSRI medication use between the patients with and without elevated PLMs (table 17), suggesting that these factors did not play an important role in contributing to elevated PLM indices as a group.

### 9.1.4 Neural Correlates Associated with RLS and PLMs

The emerging literature suggests that different components of the Restless Legs Syndrome (e.g. sensory [i.e. motor restlessness], motor [i.e. PLMs] and arousals in sleep) may be dissociated on a neurotransmitter and therefore even possibly on a neuroanatomical level. Such a possibility is especially important to keep in mind with regards to the present study, since acute stroke and TIA generally cause focal impairment of a single portion of the central nervous system and thus may preferentially impact different components of the Restless Legs Syndrome depending on the site of involvement. If such a view is considered, it is then not
surprising that patients with a diagnosis of RLS vs. those with elevated PLM indices presented with different lesion localizations in our preliminary analyses.

Because our sample size was small (particularly in those who underwent a sleep study and were assessed for PLMs) and our methodology rudimentary, these results should be taken as a preliminary hypothesis-generating first step prior to future studies that utilize more precise lesion mapping analyses. Our limited sample size did not permit performing lesion localization analyses on only the patients presenting with first-ever stroke (i.e. patients who presented with neuroimaging confirmed-stroke and did not have evidence of a chronic infarction on imaging). In addition, we opted to include patients with TIA because >20% of these patients had chronic infarction(s) on their imaging which was/were thought to be potentially important in preliminary analyses assessing the neural correlates of RLS and PLMs. Despite the simplicity of our technique, some potentially hypothesis-generating results emerged.

Our findings suggested that brainstem involvement (particularly lesions involving the midbrain) may be associated with elevated PLM indices (p=0.004; table 18). Based on these preliminary results, it could be hypothesized that a midbrain locomotor region may be significantly implicated in the pathogenesis of PLMs. In addition, involvement of midbrain nuclei such as the substantia nigra (nigrostriatal pathway) and dorsal raphe nuclei are implicated in the pathogenesis of REM sleep behavior disorder, in which PLMs are frequent.

Additional analyses revealed that the PLM index was most strongly correlated with WMHs in the right (r=0.411, p=0.020) and left (r=0.435, p=0.013) frontal regions. Collectively, an entirely speculative proposal is that cortical-brainstem pathways may be implicated in the pathogenesis of PLMs; this is similar to what has been postulated in the context of the A11 diencephalospinal pathway (figure 1) which, as discussed earlier, serves as a possible model for the motor component of RLS (i.e. PLMs). Obviously, such a proposition is simply speculative at this time and will need to be further developed using more sophisticated imaging techniques and a larger sample size.
Our results in the patients with RLS did not reach statistical significance, but there was a trend for the internal capsule to be implicated in the patients with mild RLS (p=0.004; table 15). In a prior series of patients with post-stroke RLS, lesions were most commonly found in the basal ganglia/corona radiata (30.3%), pons (22.2%), thalamus (14.3%), and internal capsule (12.5%); such findings underscored the importance of subcortical structures in the development of post-stroke RLS (in that study, patients with a history of prior RLS were excluded). Our methodology was not precise enough to differentiate precisely which subcortical structure was most important in association with a diagnosis of RLS, but future planned analyses will be invaluable in this regard.

Overall, our preliminary results suggested that the subjective symptoms caused by RLS may be more localizable to subcortical structures, while the more objective PLMs may be best attributed to cortical-brainstem disruption. One could hypothesize that cortical-brainstem pathways may need to pass through subcortical structures, such as the internal capsule, thalamus or basal ganglia, and this may serve as the neuroanatomical basis for why RLS sensory symptoms and PLMs are so closely related.

9.1.5 Overlap of RLS with PLMs

Prior research has demonstrated that approximately 80% of patients with RLS have a PLM index $\geq 5$ per hour of sleep. In our study, only 66% of the 12 patients with RLS who underwent a sleep study had a PLM index $\geq 5$ per hour of sleep. Our small sample size may explain why a lower than expected percentage of RLS patients was found to have PLMs; this overlap should be re-assessed in a larger study sample. Alternatively, SRMDs may manifest atypically after cerebrovascular disease, as is seen in post-TIA/stroke OSA where patients do not exhibit excessive daytime sleepiness despite still having elevated AHIs; this apparent disconnect between subjective and objective features may be characteristic of post-TIA/stroke sleep disorders. In our study, of those who underwent a sleep study, one-third of patients did not manifest with PLMs despite endorsing subjective RLS symptoms.

Consistent with prior research, our results support the notion that PLM frequency is not correlated with RLS severity. In the 12 patients (7 clinically-significant, 5 mild) with RLS who underwent polysomnography, the mean PLM indices were not statistically different in
those with or without RLS, nor in the patients with mild or clinically-significant RLS compared to those without RLS, or even between the mild and clinically-significant RLS subgroups (table 19). In addition, there were no differences in sleep efficiency, AHI, lowest oxygen saturation in sleep and arousal index in the patients with or without RLS, as well as in the patients with mild or clinically-significant RLS compared to those without RLS; this suggested that the sleep disruption commonly observed in RLS was independent of these sleep variables.

Finally, there was no critical PLM index threshold that was associated with a diagnosis of RLS; indeed, PLM indices appeared greater in many of the patients without RLS (figure 7). In the 9 patients with a PLM index \( \geq 30 \) per hour of sleep, only two endorsed symptoms consistent with RLS; all 9 of these patients had presented with a stroke.

The number of participants with RLS who underwent polysomnography in our study was small and our results need to be interpreted with caution. In addition, as is seen in OSA, sleep disorders may manifest atypically after cerebrovascular disease such as TIA and minor stroke. The selective impairment of focal brain regions after TIA or stroke may give rise to clinical manifestations of sleep disorders that are unlike those seen in non-stroke/TIA populations. This may explain the lack of a clear overlap of RLS with PLMs. Overall, our results should be taken as an initial investigation of RLS and PLMs in early stage minor stroke and high-risk TIA; future larger studies will likely provide more definitive conclusions.

9.2 Study Strengths

9.2.1 Novel findings

Our study adds at least three new findings to the current literature:

(1) Our work is the first to report a positive association of PLMs with WMHs after accounting for the effects of age, vascular risk factors and other sleep variables, and among the first to report a positive association of PLMs with cerebrovascular disease.

(2) Our research is the first to report the prevalence of clinically-significant RLS and its association with poor quality of life and depressive symptoms after high-risk TIA and minor
stroke. Whether the poor quality of life observed is driven by the depressive symptoms, or vice versa, is unclear at this time. In addition, the possibility that RLS symptoms exacerbate depressive symptomatology after TIA or stroke is also unknown.

(3) Finally, our study is the first to report an increased prevalence of PLMs in prospectively recruited TIA and stroke patients compared to matched controls.

9.2.2 Sleep Laboratory Polysomnography Used

All patients who completed a sleep study in the present research trial underwent polysomnography in the same academic centre sleep laboratory. This provided the gold standard measurement for all sleep study variables examined. In addition, in order to reduce bias, nearly all the sleep records were scored by the same sleep technologist.

9.2.3 Physician-Confirmed RLS

In order to ensure that RLS diagnoses were not due to RLS mimics, all patients endorsing RLS criteria on the RLS diagnostic questionnaire were further evaluated by a sleep physician. This ensured that false positive results arising from use of the RLS diagnostic questionnaire were minimized.

9.3 Study Limitations

9.3.1 Small Sample Size

Our small sample size restricted the ability to draw conclusions in several of our analyses, including those that looked at lesion localization for a diagnosis of RLS or an elevated PLM index; in addition, the small number of patients who completed a sleep study limited our ability to definitively comment on the overlap between RLS and PLMs in our study population. Future studies should enroll a larger sample size, possibly by removing restrictions on the inclusion criteria utilized, and also by enrolling patients at different time points after a stroke.
9.3.2 Inability to Imply Causation

The cross-sectional nature of our study rendered us unable to imply causation when certain associations were found (e.g. association of PLMs with WMHs). As discussed below, future prospective studies will be necessary to determine the direction of the association of PLMs with WMHs.

9.3.3 Inability to Generalize to Non-Stroke/TIA Populations

Furthermore, since our study was conducted on high risk TIA and minor stroke patients, whether our results generalize to other study populations (e.g. a population-based sample) is unknown. As discussed below, future research should investigate large population-based cohorts and evaluate a broad range of co-morbidities, such as cardiovascular disease, renal or other systemic disease.

9.3.4 Lack of Willingness/Interest to Undergo Overnight Sleep Study

We were struck by the lack of willingness/interest among consenting study participants to complete a single overnight sleep study. Despite receiving clear information about the possible benefits of a sleep study in terms of vascular risk factor modification and overall health benefits, only about half of the recruited population opted for a sleep study; by the time data analysis took place, only 45% (44/97) of the study population had actually completed a sleep study. Despite the lack of interest among study participants, there were no statistically significant differences between those who did and did not complete a sleep study (table 3).

There is strikingly little data in the literature that comments on the factors or deterrents associated with patient recruitment for in-hospital polysomnography. In the Sleep Heart Health Study, which used home polysomnography, patients who were ultimately recruited into the study were slightly younger, had more years of education, were more likely to snore, had higher Epworth sleepiness scale scores and blood pressures, and also had slightly higher body mass indices.\textsuperscript{408}
Patients’ perception of overnight sleep studies, as well as motivating or deterring factors will be an important area of study for the future. Such work will greatly affect the study design and financial considerations of trials which opt to use in-hospital polysomnography.

9.3.5 Methodology Used to Diagnose RLS

In the patients who did not have a prior history of RLS, the RLS diagnostic questionnaire provided two false positive results and one false negative result. All patients endorsing RLS symptoms on the RLS questionnaire were assessed by a physician in order to rule out false positive diagnoses that may have been secondary to RLS mimics (e.g. leg cramps, peripheral neuropathy, radiculopathy, positional discomfort and arthritic pain); patients who underwent a sleep study were also assessed by a physician. While this methodology adequately excluded false positive diagnoses, it could not address false negative diagnoses that may have arisen from the RLS questionnaire we used. For example, if a patient with RLS symptoms misunderstood the questionnaire questions and mistakenly responded in a manner that indicated he/she did not have RLS, our study design would not have permitted us to catch this false negative questionnaire respondent.

In addition, because some patients (n=5) were not interested in being assessed in-person regarding their RLS symptoms, they were interviewed in detail over the telephone. This could have created an ascertainment bias regarding the assessment of RLS mimics. Finally, in some cases, there was a several month delay before a physician assessment took place to confirm the diagnosis of RLS. As discussed below, future studies should utilize questionnaires that have relatively high sensitivities and specificities in the absence of a physician assessment.

9.3.6 Control Population Used to Compare PLM Prevalence in Our Study Population

The prevalence of PLMs in our study population was compared to that seen in age-, gender and AHI-matched controls who had attended a prior diagnostic polysomnogram at the Sunnybrook Hospital Sleep Laboratory. This control group would be representative of a patients presenting to a sleep laboratory, but not of the general population. The prevalence of PLMs in the general population has not been thoroughly investigated but this gap in the
literature may be addressed by future large population-based studies that use actigraphy or polysomnography. Follow-up data on our control population is not available at this time, but could be an important direction for future work.

9.4 Alternative Approaches for Present Study

9.4.1 Alternative Questionnaires

9.4.1.1 RLS Diagnostic and Severity Questionnaires

An alternative questionnaire that could have been used was the Cambridge-Hopkins Diagnostic Questionnaire for RLS; this questionnaire has a sensitivity of 87.2% and a specificity of 94.4% against a physician expert for the diagnosis of RLS. This questionnaire consists of only seven questions and is feasible to use of the research setting, particularly since a physician assessment is not required.

While the RLS diagnostic questionnaire used in our study was previously utilized by the highly-cited Sleep Heart Health Study, its sensitivity and specificity have yet to be reported. As discussed earlier, when using this questionnaire, care must be taken to ensure that symptoms are not due to another medical condition that could result in a similar presentation to RLS (e.g. cramps, peripheral neuropathy, radiculopathy). In our study, the sensitivity and specificity of the RLS diagnostic questionnaire could not be determined because not all patients underwent the “gold standard” physician assessment.

In addition, standardized RLS severity scales (e.g. International RLS Study Group Rating Scale) could have been utilized rather than simply asking about the frequency and severity of symptoms.

9.4.1.2 Quality of Life Questionnaire

An alternative questionnaire that could have been used instead of the Stroke-Specific Quality of Life scale was the Neuro-QOL, which is a brief, reliable and standardized quality-of-life assessment tool validated across different neurological conditions. Use of such a questionnaire would permit comparing quality of life in post-TIA/stroke RLS with those who have other neurological disorders.
9.4.2 Other Study Variables to Consider

With an increased sample size, more variables could have been tested in the linear regression analyses that tested for an association between ARWMC scores and PLM indices. In our study, we assessed the effects of three vascular risk factors (age, gender and hypertension) that are known to be most strongly associated with WMHs. However, other vascular risk factors such as body mass index, hyperlipidemia, diabetes and smoking could also have been tested if the sample size was larger. In addition, the timing of the overnight sleep study in relation to the date of the cerebrovascular event could also be included in future analyses; of note, whether PLM frequency actually changes over time after a TIA or stroke is unknown at present, but might be an important area of future study.

With regards to our RLS analyses, the duration of RLS symptoms (rather than disease frequency and severity) could be an additional variable that may have implications for vascular disease, quality of life and depressive symptoms. RLS disease duration will obviously be most important in patients with a prior history of RLS (rather than de novo RLS) in the acute TIA/stroke setting, however, if future studies examine RLS in chronic stroke patients, this may be a more relevant variable.

Finally, the location of white matter hyperintensities should be assessed in future analyses with regards to association with PLM index, other sleep variables and various study outcome measures.
Chapter 6

10 Future Directions

10.1 Prospective Population-Based Studies to Examine the Association of SRMDs with Vascular Disease

In the present study, the cross-sectional nature of the work made causation impossible to imply. Future work should prospectively follow large population-based cohorts, such as that of the Ontario Health Study. Participants can undergo at baseline several nights of polysomnographic or, more practically/economically, actigraphy recordings for PLMs. Since PLMs are known to vary night-to-night, they need to be measured across multiple nights to ensure an accurate measurement of their frequency. In addition, questionnaires could assess for a diagnosis of RLS. Outcomes assessed over time should include incident cerebrovascular and cardiovascular events.

In addition to simply tracking vascular events over time, these studies should also attempt to identify mechanisms mediating the possible link between PLMs and vascular disease. Variables that could be investigated include the pathophysiological mechanisms we have described earlier, such as nocturnal sympathetic activity (i.e. heart rate and blood pressure), polysomnographic markers of disrupted sleep (e.g. sleep efficiency, wake minutes during sleep period, sleep latency), markers of systemic inflammation (e.g. CRP), markers of oxidative stress (e.g. nitric oxide), and markers of HPA system activation (e.g. cortisol excretion). In addition, vascular risk factors and prior vascular events should be elucidated as should comorbid conditions that could give rise to vascular disease (e.g. depression, mood disorders, etc.).

Overall, large population-based studies will be critical in understanding the direction of the relationship of SRMDs with vascular disease. Since most these patients will be free of cerebrovascular disease at baseline, TIA or stroke will not be present to confound assessments. A large sample size will be important to permit controlling for the effects of diverse contributing or confounding variables.
10.2 Prospective Studies to Examine Effect of PLMs on Stroke Recovery

In addition, baseline PLM frequency after stroke should be correlated with the degree of stroke recovery achieved after fixed time points. Given emerging evidence that PLMs are implicated in the pathogenesis of vascular disease, it is plausible that the presence of PLMs may also hamper recovery from stroke via similar pathophysiological mechanisms that have been proposed to link PLMs with vascular events. Not only may PLMs prove to be a biomarker for stroke recovery, they may also add to our understanding of stroke recovery mechanisms. Furthermore, if PLMs are demonstrated to be associated with incident vascular events and/or poor recovery from stroke in well-designed prospective trials, the role of treating PLMs using standard therapy (e.g. low-dose dopamine agonists) could be explored via randomized controlled trials.

10.3 Treatment of RLS after Stroke or TIA

Another important finding in our study was that the presence of clinically-significant RLS was associated with poor quality of life and depressive symptoms. It is not known whether the association of RLS with poor quality of life and depressive symptoms generalizes to patients with more severe cerebrovascular events. In addition, whether treatment of RLS after TIA or stroke improves quality of life or depressive symptoms has yet to be explored. Since quality of life and depressive symptoms are closely correlated, future work in this area should explore the nature of the interactions among RLS, quality of life and depressive symptoms; one possibility is that the poor quality of life seen in patients with RLS is actually secondary to depressive symptoms, rather than the RLS symptoms themselves. Carefully designed trials and advanced statistical tools could assist in exploring these questions. One challenge will be that SSRIs can actually exacerbate RLS and PLMs, so other antidepressants drug classes may be preferable in this clinical scenario. Furthermore, dopamine agonists can precipitate psychotic symptoms (e.g. hallucinations) in those with a prior psychiatric history complicated by co-morbid psychosis; in such a scenario, the calcium channel alpha-2-delta ligands (e.g. Gabapentin) may serve as a suitable therapeutic alternative.
10.4 Screening for RLS after Stroke or TIA

If the treatment of RLS after TIA or stroke is found to improve outcomes, it would be reasonable to routinely screen patients with cerebrovascular events for RLS, especially since a considerably high proportion of our study population (25% using 2003 criteria, 11% using a definition for “clinically-significant” RLS) was found to have RLS. Short questionnaires could be used to screen large numbers of patients as part of the routine clinical evaluation and without disrupting the flow of care (e.g. patient could fill out a screening questionnaire while seated in the waiting room). Such questionnaires could be completed by patients themselves, without the assistance of any medical professional. Should a preliminary screen prove positive, the physician could verify with the patient their clinical symptoms, order polysomnography (if clinically indicated) and eventually initiate treatment, if deemed necessary.

10.5 Volumetric / Lesion Localization Studies to Investigate Neural Correlates for PLMs & RLS

Our preliminary lesion localization results are intriguing, however, more precise methodology should be used to determine the neural correlates for the subjective sensory manifestations of RLS and the more objective PLMs. Brain lesions of patients with RLS and/or PLMs could be overlapped and compared or subtracted from overlays of patients without RLS and/or PLMs. While such a technique may be helpful for binary outcomes (e.g. the presence or absence of RLS), a cut-off must be applied for continuous variables and information reflecting varying degrees of disease severity may be lost (e.g. PLM index). Another method that could be particularly helpful in this regard is voxel-based lesion-symptom mapping (VBLSM). Rather than require patients to be grouped according to a binary outcome, this technique permits use of continuous values (e.g. PLM index) and lesion information. By analyzing continuous data on a voxel-by-voxel basis, lesion maps are produced which identify the region(s) of the brain most strongly associated with the variable of interest. VBLSM could be used not only for PLM index, but for other continuous polysomnography variables, such as sleep efficiency, apnea-hypopnea index and arousal index; it could also be used in the context of RLS severity rating scales.
10.6 Exploration of Factors Dissuading Patients from Undergoing Overnight Polysomnography

A striking finding in our study was the high rate of patients unwilling or uninterested in undergoing overnight polysomnography. Despite being safe, relatively non-invasive and having the potential to uncover treatable medical disorders associated with important medical outcomes, it was difficult to convince patients to undergo a sleep study, despite the fact that these patients had already consented to being part of a research study. Future research should explore the reasons patients are uninterested in undergoing overnight polysomnography; this work could be initially qualitative in nature. As significant variables are uncovered, more quantitative tools (e.g. questionnaires with Likert scales) could be utilized.

10.7 Development and Application of Robust Home Sleep Monitoring Tools

Finally, while in-hospital polysomnography clearly has advantages over home monitoring, patient preference, long waiting lists and high costs make routine home monitoring a more feasible option to routinely screen for sleep disorders after cerebrovascular events. Patients with abnormal or equivocal results on a home monitoring test can be further evaluated during in-hospital overnight polysomnography.

Actigraphs are being used to detect PLMs in several commercially available home sleep monitoring units. In order to refine the PLM detection algorithms presently being used, actigraphs should be simultaneously placed on patients undergoing polysomnography, and EMG and actigraphic recordings be compared. Such an approach will assist in determining the precise actigraphic signals which represent a PLM.

Finally, clinicians managing patients with cerebrovascular disease should work closely with their sleep physician colleagues in order to facilitate the use of home monitoring devices on a routine basis. In the ideal clinical scenario, a sleep assessment would become part of the routine post-stroke/TIA care pathway and formal neurophysiological testing would occur early after a cerebrovascular event much in the same way that ruling out important risk factors (e.g. hypertension, hyperlipidemia and diabetes) occurs in an expedited manner.
Chapter 7

11 Conclusions

11.1 Association of PLMs with Vascular Disease

PLM index, not RLS status, was independently associated with the extent of WMHs, even after controlling for vascular risk factors and other sleep variables. Whether PLMs are implicated in the pathogenesis of WMHs and other forms of vascular disease, or whether WMHs cause or exacerbate PLMs in the post-TIA/stroke setting is uncertain. Future large population-based prospective studies should examine the direction of this relationship, and whether PLMs may actually be a vascular risk factor. In addition, the mechanisms that may link PLMs with vascular disease also need to be more definitively delineated.

11.2 Post-TIA/Stroke RLS

RLS was prevalent after TIA and minor stroke, with 25% of patients endorsing standard RLS criteria and 11% endorsing criteria for clinically-significant RLS. Clinically-significant RLS was associated with significantly poorer quality of life and more depressive symptoms compared to that seen in patients without RLS. Whether the poor quality of life observed is driven by the depressive symptoms, or vice versa, is unclear at this time; further analyses will be needed to determine the direction of this relationship. In addition, the possibility that RLS symptoms exacerbate depressive symptomatology after TIA or stroke should also be explored. Given its relatively high prevalence and association with poor quality of life and depressive symptoms, future studies should examine whether regular screening for RLS is warranted in the post-TIA/stroke setting.

11.3 Post-TIA/Stroke PLMs

The prevalence of PLMs in our study population of TIA and minor stroke patients was greater than that of age-, gender- and AHI-matched controls who had previously undergone polysomnography for various sleep-related concerns. PLMs ≥5 per hour of sleep were detected after both TIA and stroke, however, severe PLM indices (≥30 per hour of sleep) were detected only after stroke.
11.4 Sleep-Related Movement Disorders in the Context of Obstructive Sleep Apnea in the Post-TIA/Stroke Setting

In our study, 25% of the study participants were diagnosed with OSA (AHI ≥ 15) and 12.5% were diagnosed with severe OSA (AHI ≥ 30). Similarly, 25% of participants were diagnosed with RLS and 11% with clinically-significant RLS. While other studies have generally demonstrated higher prevalences of OSA after cerebrovascular events, the prevalence of RLS or PLMs has been rarely assessed, so its precise prevalence must still be established in larger studies. Similar to OSA, SRMDs appear to be significantly associated with unfavourable outcomes, and may be intimately associated with vascular disease. Nonetheless, as discussed above (section 4.5.2), studies investigating the association of OSA with WMHs have revealed conflicting results. Given these findings, a particularly important area of future investigation will be to assess whether OSA and the SRMDs significantly interact to contribute to stronger associations with vascular disease, and other adverse outcomes, than either condition alone.

11.5 Clinical Implications

In conclusion, our study demonstrated that in patients presenting early after a high-risk TIA or minor stroke, the sleep-related movement disorders RLS and PLMs were prevalent and associated with significant comorbidity. In the case of PLMs, an association with vascular disease in the form of white matter hyperintensities was detected, while the patients with clinically-significant RLS were noted to have lower quality of life and more depressive symptoms.

Consistent with the emerging literature, our study adds further support for a significant association between PLMs, RLS and cerebrovascular disease. While OSA has traditionally been the focus of the majority of studies examining sleep disorders in the context of cerebrovascular disease, more recent work (including that of the present study) strongly suggests an important role for PLMs and RLS. On-going research should carefully characterize the nature of the relationship between the PLMs, RLS and vascular disease. Undoubtedly, increased recognition of RLS and PLMs is warranted among clinicians.
managing acute cerebrovascular disease, as is on-going enthusiasm for this novel and potentially clinically-relevant area of investigation.
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