Sleep Related Movement Disorders

Association with Menopause and Pregnancy

JAN WESSTRÖM
Abstract


It is known that sleep problems affect people’s wellbeing and has great consequences for public health.

Restless legs syndrome (RLS) gives uncomfortable sensations in the legs at rest, leading to an irresistible need for activity. It aggravates in evening and at night. Therefore, RLS provides poorer sleep and can affect quality of life through fatigue, family life and social activities, work, and comorbidity. It is demonstrated a dysfunction of the dopaminergic system in the brain with low levels of dopamine and / or less sensitive dopamine receptors. RLS is more common in women and the prevalence increases with age and during pregnancy.

Periodic limb movements are characterized by uncontrolled stretching movements of the legs, especially the toes, ankles, knees and hips during sleep. They last between 0.5 and 5 seconds, and can cause brief awakenings leading to daytime sleepiness. The clinical significance of PLM is rather controversial and PLM is sometimes seen in healthy people with no daytime symptoms.

RLS is a subjective diagnosis and translated with the help of questionnaires. PLM however, can objectively be evaluated by polysomnography.

Depression is common during and after pregnancy. It is not known whether women with RLS during pregnancy have a higher risk of prenatal or postpartum depression.

The aims of this thesis was to examine the prevalence, associated symptoms and comorbidities, in particular, vasomotor symptoms, menopause, and hormone replacement therapy (HRT) use, among women who suffer from RLS and PLMs. We also evaluated the impact of RLS and PLMs on health related quality of life (HRQoL), and if RLS before and during pregnancy increases the risk of antenatal or postpartum depressive symptoms.

Three different populations were used. Paper 1-3 were cross-sectional and included 5000 resp. 10000 randomly selected women from the general populations of Dalarna and Uppsala County. Questionnaires, polysomnographic recordings, blood tests etc. were used. Paper 4 was a longitudinal cohort study where 1428 pregnant women in Uppsala County were followed.

In summary, data included in this thesis points out that RLS and PLMs are more common in women with estrogen deficiency-related symptoms of menopause. RLS-positive women had an impaired mental HRQoL compared to RLS-negative women and more often suffered from comorbidities. Data also revealed that women with RLS before and during pregnancy are at increased risk for depression during and after pregnancy.

Keywords: Sleep, Restless Legs Syndrome, Women, Menopause, Pregnancy, Depression

Jan Wesström, Uppsala University, Department of Women's and Children's Health, Obstetrics and Gynaecology, Akademiska sjukhuset, SE-751 85 Uppsala, Sweden.

© Jan Wesström 2013

ISSN 1651-6206
ISBN 978-91-554-8703-4
urn:nbn:se:uu:diva-204149 (http://urn.kb.se/resolve?urn=nbn:se:uu:diva-204149)
List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


III  Wesström J, Ulfberg J, Sundström-Poromaa I, Lindberg E. Periodic limb movements are associated with vasomotor symptom. *Submitted manuscript.*

IV  Wesström J, Skalkidou A, Manconi M, Fulda S, Sundström-Poromaa I. Restless legs syndrome is associated with perinatal depression. *Submitted manuscript.*

Reprints were made with permission from the respective publishers.
Contents

Introduction...........................................................................................................9
Sleep......................................................................................................................9
    Polysomnography..........................................................................................10
    Sleep architecture.........................................................................................10
    REM sleep.....................................................................................................11
    Sleep duration .............................................................................................12
    Sleep loss, hormonal release, and metabolism........................................13
    Sleep and other comorbidities....................................................................13
Sleep and women .............................................................................................14
    Female sexual hormones in the brain.........................................................15
Menopause .........................................................................................................16
    Symptoms in menopause............................................................................18
Sleep and menopause .......................................................................................19
Sleep during and after pregnancy..................................................................20
Restless legs syndrome....................................................................................21
    RLS and menopause....................................................................................23
    RLS and pregnancy.....................................................................................23
    Treatment of RLS in pregnancy .................................................................24
Periodic limb movements................................................................................25
Sleep and depression ......................................................................................26
RLS and depression..........................................................................................27
Pregnancy and depression................................................................................27
Health-related quality of life and restless legs syndrome...............................28

Aims.................................................................................................................31

Materials and methods....................................................................................32
    Subjects .......................................................................................................32
        Studies I-II .............................................................................................32
        Study III ................................................................................................32
        Study IV ...............................................................................................33
    Methods........................................................................................................33
        RLS questionnaires ...............................................................................33
            Studies I-III.......................................................................................33
            Study IV ..........................................................................................33
        HRQoL questionnaire .............................................................................34
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>CH-RLSQ11</td>
<td>Cambridge-Hopkins RLS Short-Form 2</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
</tr>
<tr>
<td>EEG</td>
<td>Electroencephalography</td>
</tr>
<tr>
<td>EPDS</td>
<td>Edinburgh depression scale</td>
</tr>
<tr>
<td>FSH</td>
<td>Follicle-stimulating hormone</td>
</tr>
<tr>
<td>GABA</td>
<td>$\gamma$-aminobutyric acid</td>
</tr>
<tr>
<td>HRQoL</td>
<td>Health-related quality of life</td>
</tr>
<tr>
<td>HRT</td>
<td>Hormone replacement therapy</td>
</tr>
<tr>
<td>IRLSSG</td>
<td>International Restless Legs Syndrome Study Group</td>
</tr>
<tr>
<td>MDD</td>
<td>Major depressive disorder</td>
</tr>
<tr>
<td>NREM</td>
<td>Non-rapid eye movement</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>PLM</td>
<td>Periodic limb movement</td>
</tr>
<tr>
<td>PLMD</td>
<td>Periodic limb movement disorder</td>
</tr>
<tr>
<td>PM</td>
<td>Portable monitoring</td>
</tr>
<tr>
<td>PPD</td>
<td>Postpartum depression</td>
</tr>
<tr>
<td>PPV</td>
<td>Positive predictive value</td>
</tr>
<tr>
<td>PSG</td>
<td>Polysomnography</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
</tr>
<tr>
<td>REM</td>
<td>Rapid eye movement</td>
</tr>
<tr>
<td>RLS</td>
<td>Restless legs syndrome</td>
</tr>
<tr>
<td>SF-36</td>
<td>Short form health survey 36</td>
</tr>
<tr>
<td>SF-12</td>
<td>Short form health survey 12</td>
</tr>
<tr>
<td>SSRI</td>
<td>Selective serotonin reuptake inhibitor</td>
</tr>
<tr>
<td>STRAW</td>
<td>Stages of Reproductive Aging Workshop</td>
</tr>
<tr>
<td>SWS</td>
<td>Slow wave sleep</td>
</tr>
</tbody>
</table>
Introduction

Sleep
Knowledge regarding normal sleep and sleep disorders has increased in recent decades, but many unanswered questions remain. Sleep is a normal physiologic state in which an organism is apparently unconscious and not responsive to stimuli for a short period of time, although brain activity may still be periodically very high. The importance of sleep function is not fully understood, but it has been suggested to be a recovery period in which the body can rest and heal, while the brain processes impressions from the previous wakefulness period (1).

Although the metabolism of the body decreases during sleep, the brain has a higher metabolic rate during rapid eye movement (REM) sleep than it has in the awake state. Learning is facilitated by good sleep, as is the storing of long-term memories. Sleep is one of our most obvious circadian rhythms, controlled by a biological clock in the hypothalamus. Close to the hypothalamus is the melatonin-producing pineal gland. Secretion of this hormone is stimulated by darkness and reaches its peak at 02:00 AM. Melatonin secretion simplifies and accelerates sleep onset and induces the small reduction in body temperature that occurs during the night (2). It has been shown that the quality of sleep increases with a lower body temperature (3).

Numerous important physiological processes occur during sleep (4). For instance, the immune system is strengthened; collapse of the immune system is a cause of death in extreme and prolonged sleep withdrawal (5). Several hormones are secreted during sleep (4). Growth hormone secretion increases in men just after sleep onset, during slow wave sleep (SWS). The effect of sleep on growth hormone levels is especially evident in men, but can also be seen in women (6). Cortisol levels are also controlled by the circadian rhythm, with lowest levels in the evening and first part of the night, followed by an abrupt rise in the latter part of the night. Awakenings (final as well as during the rest period) induce a pulse in cortisol secretion. Even moderate changes in the sleep cycle affect cortisol levels (7).
Polysomnography

Polysomnography (PSG) is a multiparametric test that objectively records sleep. It is used as a diagnostic tool in sleep medicine, and the test result is called a polysomnogram. PSG is usually performed during the night, when most people are asleep, but shift workers and people with circadian rhythm disorders can take the test at other times of day. PSG monitors many body functions, including brain activity (electroencephalography, EEG), eye movements (electrooculography), muscle activity (electromyography), heart rhythm (electrocardiography), breathing (thermistor), and peripheral pulse-oximetry. PSG has been used to diagnose various sleep disorders, including narcolepsy, hypersomnia, periodic limb movement disorder (PLMD), REM behavior disorder, parasomnia, and sleep apnea. Furthermore, PSG is often included in the investigation of patients with daytime sleepiness (8).

Portable monitoring (PM) is another diagnostic test of sleep that can be used in the home environment. It is available as an alternative to nocturnal sleep registration in a hospital-based sleep laboratory. Benefits are greater convenience and lower cost; PM devices are less costly than the complete PSG system, and the presence of a technologist is not required. One drawback is that fewer physiological variables are measured during the PM than PSG (9). In this thesis, PSG is used for evaluation of periodic limb movements (PLMs).

Sleep architecture

Sleep stages occur in 90- to 120-min cycles, with four to five cycles occurring during a typical night of sleep (Figure 1). In the first cycle, the individual passes from wakefulness briefly into stage 1 sleep, and then into stages 2 and 3. Subsequent cycles consist of stage 2, stage 3, and REM sleep. In the second half of the night, stage 2 and REM sleep alternate. Wakefulness, stage 1, and stage 3 (i.e., deep sleep) are usually absent during the second half of the night, but may occasionally occur.

![Figure 1. Normal hypnogram. Red line = REM sleep](image)

Sleep and its reciprocal daily relationship with wakefulness are governed by two regulatory systems: (1) the circadian system, which times the rhythm of the sleep-wake cycle and consolidates sleep and wakefulness into biphasic states, and (2) the homeostatic drive for sleep (sleep homeostat), which dic-
tates the amount and intensity of sleep based on the duration of prior wakefulness (10).

Circadian rhythmicity is an endogenous oscillation with an ~24-hour period that is generated in the suprachiasmatic nuclei of the hypothalamus (11). The generation of oscillations in neurons of the suprachiasmatic nuclei involves a series of clock genes (12). Circadian timing is transmitted to other areas of the brain and the periphery via other parts of the hypothalamus, which also controls the activity of the sympathetic nervous system. Circadian signaling is also achieved through hormones, including melatonin. The mechanisms responsible for measuring the duration of prior wakefulness and for the homeostatic control of sleep have not been fully studied (13).

In mammals and birds, sleep is divided into two broad types: REM and non-rapid eye movement (NREM or non-REM) sleep. Each type has a distinct set of associated physiological and neurological features. NREM sleep accounts for 75-80% of sleep time and is further divided into three stages (Figure 2).

- Stage 1: This is a stage between sleep and wakefulness. The muscles are active, and the eyes roll slowly, opening and closing moderately. The EEG is characterized by low-voltage (low amplitude) mixed-frequency pattern (alpha activity).

- Stage 2: Theta activity. In this stage, it gradually becomes harder to awaken the sleeper. The alpha waves of the previous stage are interrupted by abrupt activity called sleep spindles (a 12–14 Hz waveform lasting at least 0.5 seconds and having a spindle-shaped appearance) and K-complexes (a waveform with two components: a negative wave followed by a positive wave, both lasting at least 0.5 seconds).

- Stage 3: Formerly divided into stages 3 and 4, this stage is called SWS. The sleeper is less responsive to the environment. Many environmental stimuli no longer produce any reactions. EEG includes moderate to high amounts of high-amplitude slow-wave activity.

**REM sleep**

When the sleeper enters REM sleep, most muscles become paralyzed. This level is also referred to as paradoxical sleep because the sleeper, although exhibiting EEG waves similar to a waking state, is harder to arouse than at any other sleep stage. Vital signs indicate that arousal and oxygen consumption are higher than when the sleeper is awake. An adult reaches REM approximately every 90 minutes, with the latter half of sleep being more domi-
nated by this stage. The function of REM sleep is uncertain, but a lack of it will impair the ability to learn complex tasks (14, 15).

Figure 2. Polysomnographic record of sleep stages. a = stage 1, b = stage 2, c and d = stage 3, e = REM

**Sleep duration**

Clinical wisdom and supporting research suggest that most people require approximately 8 hours of sleep nightly. However, there appears to be considerable variation around the mean, with many people claiming to need only 4 to 6 hours of sleep (16). In 2008, the National Sleep Foundation conducted a survey of Americans' sleep durations (17). On average, American adults slept 6 hours 40 minutes on weekdays and 7 hours 25 minutes during the weekends. In 1960, the average sleep duration was 8.5 hours (18). Thus, sleep duration has decreased by an estimated 1.5 to 2 hours in less than 50 years. Usually people manage quite well to sleep a little less for shorter periods of time, and during these times, sleep is most likely more effective (13).
A return to normal sleep quotas after a period of sleep deprivation results in rebound sleep, in which deep sleep and REM sleep appear in quantities higher than expected for several nights after normal sleep duration has resumed. It is probably possible to compensate for lost sleep time on weekends or other times off, at least for a short period of time (19). On the other hand, more prolonged sleep deprivation can lead to sleepiness, sadness, irritability, concentration, memory difficulties, and pain (20). The proportion of adults in the population sleeping less than 7 hours per night has increased from 16% to 37% over the past 40 years (17), a lifestyle change that may have negative metabolic and/or psychological consequences.

**Sleep loss, hormonal release, and metabolism**
Recent research have shown that chronic sleep deprivation increases the risk of obesity by influencing appetite-regulating hormones (21). For example, the satiety hormone leptin is released by adipocytes and provides information about energy status to hypothalamic regulatory centers. Leptin has a nocturnal maximum, which likely inhibits hunger during the overnight fast (22). Another hunger hormone that is affected by sleep is ghrelin, which decreases rapidly after a meal and is released from the gastric mucosa. Despite the absence of food intake, ghrelin levels also decrease during the second part of the night, suggesting an inhibitory effect of sleep per se. Increased ghrelin levels stimulate appetite, particularly for calorie-dense foods with high carbohydrate content (23).

Another possible route for how sleep influences obesity is via glucose metabolism. Reduced sleep decreases insulin sensitivity without adequate compensation in beta-cell function, resulting in impaired glucose tolerance and increased diabetes risk (24). The brain is almost entirely dependent on glucose for energy and is the main site for glucose storage. Therefore, it is not surprising that the major changes in brain activity associated with the transition between sleep and wakefulness require adjustment of glucose tolerance. During night time, fasting glucose levels remain stable or fall only minimally. This situation is not the case while fasting during daytime. Certain mechanisms during sleep must play a role in preventing hypoglycemia (24).

**Sleep and other comorbidities**
The risk of other comorbidities has also been shown to increase with sleep deprivation. Shorter duration of sleep is associated with a greater likelihood of developing hypertension (25), other adverse cardiovascular outcomes, including myocardial infarction (26-28), and depression (29). Evidence suggests that sleep deprivation may be associated with an increased risk of mortality. For example, a recent observational study reported that subjects who slept less than 6 hours per night had a mortality risk that was four-fold that of normal sleepers (30).
Sleep and women

The above research demonstrates that sleep disorders can have a major impact on physical and mental health. As sleep disorders are more common in women, it is important to investigate if sleep disturbances are influenced by major reproductive events, such as menopause and/or pregnancy. However, the vast majority of sleep research has been conducted in men (31). Only during recent decades have research groups begun to highlight aspects of sleep and sleep disorders in women (32).

Subjective complaints of insufficient or non-restorative sleep affect between 10% and 35% of the general population (17). These complaints are more common from woman than men, especially after 40 years of age (33). Prevalence studies throughout the world have reported that women are 1.3 to 1.8 times more likely to develop sleep problems than men (34). Reasons for these sex-related differences are not clear, but many hypotheses have been put forward. Depression and insomnia are common in women, and these disorders are closely interrelated (35). Additionally, many women not only hold paid jobs in midlife, but they still take more responsibility for family life, including the care of children, spouse, aging parents, or other elderly relatives. Their “second shift” often involves night time on-call duty. For some women, sleep may be disrupted by a bed partner’s snoring or awakenings (32). Other important factors among aging women may be the use of medication and weight gain (36).

Although sleep problems and sleep disorders occur in all age groups, menopause (37) and pregnancy (38) are associated with an increased incidence of sleep problems. It is not clear if it is menopause per se, its vasomotor symptoms, or other age-related diseases that cause this association (34). Sex and reproductive hormones influence circadian timing and sleep homeostasis (39) and may, therefore, be responsible for sex differences in the sleep-wake cycle. In humans, sex differences in the sleep-wake cycle appear to increase in response to sleep loss, suggesting that the sleep homeostat is regulated differently in women and men (39). Generally, women exhibit slightly more SWS, more sleep spindles during SWS, and higher basal slow wave activity than men (40, 41), suggesting that women have a higher basal sleep pressure. Women also have a slower age-related reduction of slow wave activity (42).

One of the most common sleep syndromes, obstructive sleep apnea syndrome, is more common in men than in women (4% and 2%, respectively), but the prevalence rate in postmenopausal women is similar to that in men (43). On the other hand, restless legs syndrome (RLS) is twice as common in women compared to men (44). The prevalence in the general population of occasional insomnia has been reported at 27% and 9% in women and men,
respectively (45). Prevalence figures of sleep disturbances (e.g., sleep-related movement disorders) in menopausal and pregnant women in Sweden have been sparsely reported.

Female sexual hormones in the brain
In addition to their effects on reproductive organs, sexuality, and reproduction, estrogen and progesterone have various effects in the brain. Estrogen is generally thought to be neuroprotective, acting through genomic mechanisms to modulate the synthesis, release, and metabolism of many neuropeptides and neurotransmitters. Estrogen leads to neuronal repair and assists in neuronal survival (46, 47). By interacting with important neurotransmitters, estrogen has the ability to influence various brain functions, such as cognitive abilities, mood, coordination, pain, and even sleep.

Specifically, estrogen increases the formation of the neurotransmitter acetylcholine (48), found in the synapses between the nerve and muscle cells. Acetylcholine is also present in the cerebral cortex, where it maintains normal electrical activity and, thus, alertness. Estrogen influences serotonergic neurotransmission at several levels, including the synthesis and degradation of serotonin, and the gene expression of pre- and postsynaptic serotonin receptors (49). Among its other roles, serotonin is involved in sleep, alertness, aggressiveness, impulsivity, appetite, and sexual desire. Estrogen has stimulatory and inhibitory effects on the dopaminergic system (50). Dopamine is a key neurotransmitter in the central nervous system. Dopamine occurs in many important systems that regulate muscle movements, alertness, joy, enthusiasm, reward, and creativity. Estrogen upregulates noradrenalin (51), a hormone that increases the heart rate and raises the blood pressure.

The effect of progesterone in the nervous system is not as well studied as that of estrogen. Progesterone is metabolized to neuroactive metabolites, which activate the γ-aminobutyric acid (GABA) A receptor (52). Among the most-studied progesterone metabolites, allopregnanolone and pregnanolone have sedative properties in healthy subjects (53, 54). Very few studies have objectively characterized the effects of progesterone administration on sleep (55), although preclinical studies have shown that neuroactive progesterone metabolites, besides their sedative-like effects, increase the proportion of NREM sleep (56). Novel data suggest that endogenous progesterone given to normally cycling women had no effect on objective sleep (57). Thus, progesterone does not appear to act as a conventional hypnotic (i.e., it does not induce artificial sleepiness), but rather as a “physiologic” regulator. Progesterone (or specifically designed progesterone agonists) might provide novel therapeutic strategies for the treatment of sleep disturbances (58).
The typical effects of ovarian hormones on sleep may be studied across the menstrual cycle, when predictable changes in estradiol and progesterone levels occur. Among healthy women, the duration of self-reported nocturnal sleep time has been noted to be shortest around the time of ovulation and longest prior to menses when progesterone levels are highest (the luteal phase) (59). Studies have reported better sleep quality during the follicular phase than during the luteal phase (60). Subjective sleepiness has been observed to increase during the luteal phase (61). On the other hand, an increased self-reported latency to sleep onset during the luteal phase has also been described (60). However, when sleep quality is objectively evaluated in healthy fertile women by PSG recordings, it is surprisingly similar across different parts of the menstrual cycle (62).

Pronounced changes in female hormone levels are evident during pregnancy and childbirth (typically up to 100-fold increases in estradiol and 10-fold increases in progesterone serum concentrations) (63). The fact that sleep disorders occur early in pregnancy, before the major increase in body weight and volume, suggests an endocrine genesis. Further work is needed to clarify the relationship between female sex hormones and sleep.

**Menopause**

Menopause is defined as the point in life when permanent cessation of menstruation occurs (i.e., the last menstrual bleeding). During menopause, the ovaries cease producing estrogen, progesterone, and testosterone, causing the entire reproductive system to gradually shut down. The pituitary gland responds to this situation by irregularly increasing the secretion of follicle-stimulating hormone (FSH) (Figure 3).
The term “perimenopause” is used to describe the period that commences when the first features of approaching menopause begin (persistent difference in cycle length) until at least 1 year after the final menstrual bleeding. Perimenopause usually extends over a period of 1 to 2 years, but can last between 6 months and 5 years and, sometimes, several years.

To obtain a common view of the course of events during the reproductive aging of women, the Stages of Reproductive Aging Workshop (STRAW) + 10 classification was developed (64). This classification is widely considered to be the gold standard. It is aimed to facilitate the comparison of studies in the field and to aid clinicians in their decision-making. The STRAW classification divides a woman's reproductive stages into seven stages (-5 to +2), as explained in Figure 4.
Menopause usually occurs between 45 and 55 years of age. The mean age of menopause in the industrialized world is approximately 51 years. Because life expectancy has increased rapidly in recent centuries, women live about one-third of their lives after menopause.

**Symptoms in menopause**

An estimated 75% of postmenopausal women will experience noticeable discomfort, and about 50% will need some kind of medical treatment (65). In Sweden, approximately 10-15% percent of women in menopause are currently treated with hormone replacement therapy (HRT). Hot flashes are the most common symptom of menopause, affecting as many as 80% of women. Hot flashes are the result of a thermoregulatory heat-dissipation response, involving vasodilatation and increased heart rate. They typically are expressed as a sudden sensation of warmth, followed by mild to profuse sweating that lasts roughly 1 to 5 minutes. Hot flashes may occur a few to many times daily. Many women have mood swings and insomnia, vaginal dryness, and discomfort with urination. Other symptoms that may occur, but that are less strongly associated with menopause, include memory impairment, lower self-esteem, irritability, difficulty concentrating, joint pain, decreased libido, muscle aches, depression, lethargy, and dizziness (65).

---

**Figure 4. STRAW + 10 classification**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Terminology</th>
<th>Reproductive</th>
<th>Menopausal Transition</th>
<th>Postmenopause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td>Peak</td>
<td>Late</td>
<td>Early</td>
<td>Late</td>
</tr>
<tr>
<td>Duration</td>
<td>variable</td>
<td>variable</td>
<td>1-3 years</td>
<td>2 years (1+1)</td>
</tr>
</tbody>
</table>

**Principal Criteria**

<table>
<thead>
<tr>
<th>Menstrual Cycle</th>
<th>Variable to regular</th>
<th>Regular</th>
<th>Subtle changes in Flow/Length</th>
<th>Variable Length Persistent ≥7-day difference in length of consecutive cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interval of amenorrhea of &gt;60 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Supportive Criteria**

<table>
<thead>
<tr>
<th>Endocrine</th>
<th>FSH</th>
<th>AMH</th>
<th>Inhibin B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Low</td>
<td>Low Variable*</td>
<td>Low Variable*</td>
<td>&gt;25 IU/L**</td>
</tr>
<tr>
<td>Stabilizes Very Low</td>
<td>Very Low</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Antral Follicle Count 2-10 mm**

| Low | Low | Low | Low | Very Low | Very Low |

**Descriptive Characteristics**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Vasomotor symptoms</th>
<th>Vasomotor symptoms</th>
<th>Increasing symptoms of urogenital atrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevate</td>
<td>Likely</td>
<td>Most Likely</td>
<td></td>
</tr>
</tbody>
</table>

*Blood draw on cycle days 2-5 = elevated

**Approximate expected level based on assays using current pituitary standard**
Sleep and menopause

Although women report sleep complaints more often than men do at all ages, the period right after menopause seems to be a particularly difficult time. In the peri- and postmenopausal periods, the incidence of reported sleep disturbances rises to approximately 25-50% (48). Later, nearly half of women aged 55 to 64 years report sleeping poorly at least a few nights a week. Older women report more problems with maintaining sleep than with sleep onset (36).

Paradoxically, there is a disagreement between subjective reports of poor sleep in menopausal women and findings from objective studies in the sleep laboratory. Peri- and postmenopausal women are twice as likely as premenopausal women to report dissatisfaction with their sleep. They also describe more trouble initiating and maintaining sleep. Sleep laboratory studies, however, found that postmenopausal women had better overall sleep than premenopausal women. They displayed more SWS (16% vs. 13% of stages 3-4) and slept longer (388 vs. 374 min), findings at odds with the assumption that menopause invariably impairs sleep quality (66).

Vasomotor symptoms in perimenopause and menopause correlate strongly with sleep complaints. Women with hot flashes report more arousals and awakenings from sleep than do pre- or postmenopausal women without hot flashes (67). Vasomotor symptoms have been strongly associated with chronic insomnia (67). The likelihood that hot flashes will disrupt sleep may vary over the course of the night. A sleep laboratory study found that in the first half of the night, most hot flashes directly preceded arousals and awakenings; in the second half of the night, the reverse was true (68). REM sleep, more prominent in the second half of the night, may suppress hot flashes and associated arousals and awakenings (68).

Sleep disturbance in menopause has been attributed to low estrogen levels. A clear subjective improvement of sleep quality is experienced by most women after the initiation of HRT (34, 69, 70). However, no clear objective improvement in sleep quality (by PSG) after initiation of HRT has been reported (66). Because many peri- and postmenopausal women still report improved sleep after initiation of HRT, it is often recommended as a first-line treatment of sleep disorders in this time period (in the absence of contraindications). If the woman does not experience improved sleep after about 3 to 6 months of HRT, then causes of sleep problems other than hormone deficiency should be considered (48, 71).

The incongruence between subjective and objective findings in previous studies calls into question the use of the traditional PSG technique as a “gold
standard,” and points to the need for additional ways for objectively measuring sleep quality (72). A recent study in pre- and postmenopausal women used spectral analysis of EEG, which provided additional information about sleep (73). Beta EEG power reflects arousal levels during sleep and has been shown to be more prevalent in patients with insomnia who reported less satisfactory sleep (73). Interestingly, the study found elevated beta power in late peri- and postmenopausal women. This technology could provide an objective measure of disturbed sleep quality in these women (73).

Another possible reason for the increased frequency of awakenings in peri- and postmenopausal women could be an increased prevalence of RLS and PLM in these age groups. Symptoms of menopause, such as sleep disturbances, may interact with the symptoms of RLS and PLM in various ways. Increased awake time due to either condition can be a linking factor, frustrating prevalence estimation. More knowledge in this field should be obtained.

Sleep during and after pregnancy

Most women (78%) report their sleep quality to be worse during the childbearing period than in any other time of their lives (74), with nulliparas being at higher risk of insufficient sleep than multiparas (75). Early symptoms of pregnancy include fatigue and sleep disturbances. As early as the 10th week of pregnancy, 10-15% of women report disturbed sleep caused by nausea and/or urinary frequency (75, 76). Sleep in the second trimester is often less fragmented, but fetal movements and heartburn may be disruptive. In the last trimester, 65-80% of women report multiple sleep-impairing symptoms, such as nocturia, backaches, shortness of breath, leg cramps, irregular contractions, breast tenderness, carpal tunnel / joint pain, pruritus, snoring, sleep apnea, forced bed body position, anxiety for the delivery, and vivid dreams or nightmares (76-78).

Most women report two or three awakenings during the night and about 7½ hours of sleep, but some report as little as 3 or 4 hours of sleep at the end of pregnancy (79). Falling asleep is less problematic than maintaining sleep. Sleep loss during pregnancy is accumulated from frequent awakenings during the night. When sleep is objectively measured, pregnant women sleep about 7 hours, 30 minutes less than they self-report. Brief awakenings over the course of the night can total up to 45 to 60 minutes (80). Insufficient sleep during the third trimester can increase the risk of complications in labor. Compared to those who slept more than 7 hours per night, nulliparas who have an average sleep time of less than 6 hours per night a few weeks before delivery labored about 12 hours longer and were 4.4 times more likely to have a caesarean section (81).
Sleep continues to be disrupted in the postpartum period, from the day of delivery through the first 3 months postpartum. Primiparas and women experiencing a caesarean section were often more affected by sleep disruption (74% and 73%, respectively) than multiparas and women with vaginal births (82). After delivery and until the infant is sleeping through the night, a new mother’s sleep is disrupted by infant care needs (82). Sleep efficiency, defined as the ratio of time spent asleep (total sleep time) to the amount of time spent in bed, averages about 90% during a healthy pregnancy. Sleep efficiency falls to about 77% during the first month in novice mothers, but only to about 84% in experienced mothers. Sleep efficiency remains lower for primiparas compared to multiparas even at 3 months postpartum (75). There is sparse research on differences in sleep between women who breastfeed and formula feed during the postpartum period. However, it has been reported that lactating women have more SWS, less light sleep (stages 1 and 2), and fewer arousals compared to non-lactating women, but no difference in the total sleep time or amount of REM sleep (83).

New parents have different preferences when it comes to nighttime sleeping habits. Some, especially in the Western world, find it more desirable to have the infant sleep alone in a separate bed in or outside the parents’ bedroom. On the other hand, co-sleeping practices exist throughout the world (84). Advantages of bed-sharing include facilitated breastfeeding and parental-infant bonding (85). Mothers at 2 to 4 months postpartum may have more arousals when bed-sharing with their infant, but sleep efficiency does not appear to be affected when sleeping-alone nights are compared to bed-sharing nights (86).

Sleep disturbances in the postpartum period may have severe repercussions for some women. Women with bipolar disorder are at increased risk for postpartum psychosis, and it is generally thought that disturbed diurnal rhythms and/or sleep deprivation are important contributing factors for onset of the disorder (87). In addition, chronic sleep loss in the postpartum period can also be due to or be the cause of postpartum depression (PPD) (88).

Restless legs syndrome

This thesis focuses on sleep-related movement disorders in relation to reproductive states in women. The two specific sleep-related movement disorders that are investigated are RLS and PLM.

RLS is a common neurological movement disorder with a female preponderance and increased prevalence with age. Affected persons experience a strong urge to move the extremities, most often the legs, while at rest. Symp-
toms, which worsen in the evening and during the night, are usually accompanied by an unpleasant experience of a creeping, crawling, tingling, sometimes painful sensation in the affected limb. Symptoms are alleviated by movement and commonly affect sleep, which, in turn, can interfere with daily functioning and work performance (89). In some cases, the symptoms can be very disturbing, making evening relaxation and falling asleep almost impossible. Comorbidity with respiratory symptoms, decreased lung function (90), fibromyalgia (91), migraine (92), depression (93), diabetes (94), hypertension, and cardiovascular diseases (95) among RLS patients has been reported. There is still unawareness in the health care system about RLS (96).

The symptoms associated with RLS fit well with what could be expected with decreased production or release of dopamine, or with decreased sensitivity of the dopamine receptors. Positron emission tomography studies have demonstrated differences in the dopaminergic system in the basal ganglia, brain stem, thalamus, and cerebellum in RLS patients (97-99). Furthermore, drugs with dopamine agonistic and antagonistic effects have good palliative effects on RLS symptoms (100).

RLS is common in patients with iron deficiency, with or without anemia (101, 102). Tyrosine hydroxylase, an important enzyme in dopamine synthesis, requires iron as a cofactor (103). Therefore, iron deficiency may affect dopamine production indirectly. Serum ferritin levels are reduced in RLS patients compared with controls (102). Most patients with severe RLS have ferritin levels < 50 g/L (104). Iron supplementation can improve RLS in some patients (105). Iron is the most abundant transition metal in the human brain, and ferritin is the primary iron storage protein in the brain. Serum and cerebrospinal fluid (CSF) levels of iron, ferritin, and transferrin have been measured in patients with idiopathic RLS. One report showed a 65% decrease in CSF ferritin and 300% increase in CSF transferrin in RLS patients compared to age-matched healthy controls, despite normal serum levels of ferritin and transferrin (101). Magnetic resonance imaging has revealed lower levels of stored iron in brain areas of importance for RLS (106). Finally, data suggest that the capacity for iron transport to the central nervous system is abnormal in idiopathic RLS (107, 108).

Given the female preponderance for RLS and the sleep disturbances experienced by women during the menopausal transition and pregnancy, it is possible that female sex steroids influence development of RLS. In fact, an increased prevalence of RLS has been found in periods of higher estrogen levels, such as pregnancy (109). Additionally, RLS is more common in pregnant women with higher estrogen levels than in pregnant women with lower levels (110). One might expect a decrease in the prevalence of RLS in
the end and after the fertile period when estrogen levels gradually decrease; however, this finding has not been observed in several studies, which instead have revealed an increase in RLS prevalence after menopause (44).

**RLS and menopause**

RLS is common among women, particularly with advancing age (111). However, not much is known about the association between menopause and RLS. Available epidemiological data have been unable to clarify whether menopausal symptoms and/or associated decreased levels of ovarian hormones contribute to the increased prevalence of RLS in aging women (44). Men also report more frequent and more pronounced symptoms of RLS with increasing age (112). It may be that increased morbidity linked to aging leads to an incorrect estimation of the RLS prevalence, or that pre-existing RLS becomes more evident in women who also have poor sleep in peri-menopause. Another possible cause for the increasing RLS prevalence during and after menopause may be depletion of iron stores through the frequently profuse and protracted menstrual bleeds at the end of a woman’s fertile period (102).

It has been suggested that peri- or postmenopausal treatment with HRT for menopausal symptoms may affect the clinical picture of RLS in middle-aged or elderly women. Unfortunately, no randomized controlled trial (RCT) has investigated this issue. A report describing a small retrospective observational study found that RLS-positive individuals (RLS-positives) were prescribed estrogen more often than RLS negatives; however, the number of women taking estrogen was too small to assume any statistical significance (113). Another report described a small study investigating the impact of female hormones on RLS symptom severity, and proposed that no relationship was plausible. However, the response rate was low, the study design was retrospective, the sample was not from the general population, and there was no information as to whether HRT use was current or past (114). Thus, available data are insufficient for any strong conclusions to be drawn about how menopause or its symptoms affect the risk for RLS or its known consequences (e.g., comorbidity and other aspects of well-being).

**RLS and pregnancy**

Before the four diagnostic criteria from the International RLS Study Group (IRLSSG) were established, the prevalence of RLS during pregnancy was found to be between 12% and 27%. In recent prevalence studies using the criteria, the prevalence range is narrower, between 26% and 30% (44). One recent Swedish observational longitudinal prevalence study reported an RLS prevalence of 29.6% in the third trimester. However, the diagnosis threshold for frequency of symptoms was only one episode per month (115).
If RLS existed before pregnancy, with no other condition that increases the risk for disease, then RLS is classified as primary or idiopathic RLS. When RLS arises de novo during pregnancy, it is regarded as secondary or symptomatic (116). In primary RLS, the symptom intensity often increases during pregnancy, especially in the last trimester, with severity peaking during the last weeks before parturition (117, 118). Secondary RLS during pregnancy usually disappears quickly after childbirth (118, 119). Transient RLS in previous pregnancies has been associated with a four-fold increased risk for future development of chronic idiopathic RLS and an elevated risk of new transient symptoms in future pregnancies (120). RLS during pregnancy has the same symptomatology as RLS outside the childbearing period. However, because pregnancy itself often results in sleep problems, it can be difficult to determine how much effect RLS per se has in this context. Women who have given birth to one or several children have a higher risk of developing RLS, whereas nulliparas have a risk equal to that of men (121).

Because RLS occurs more often and is more symptomatic in late pregnancy, with consequent poor sleep, the risk for pregnancy and childbirth complications with RLS as the main cause should be elevated. However, these complications (e.g., longer labor and increased risk for caesarean section) have been shown to be more common in women with poor sleep quality in late pregnancy, regardless of the reason (122). Overall, knowledge concerning RLS during pregnancy and its consequences is scarce. Because poor sleep is bidirectionally linked to depression in and outside of the pregnancy period, further studies on the association between RLS during pregnancy and perinatal depression are warranted.

Treatment of RLS in pregnancy

In general, RLS during pregnancy is treated pharmacologically only if the symptoms are of such difficulty that therapy is inevitable. With milder symptoms, it may be sufficient to inform the patient that symptoms usually regress after delivery. If a pregnant RLS patient shows an iron deficiency or low serum ferritin level, then intravenous iron preparations may be advantageous (123-125). Intravenous iron does not cross the placenta (126), and it is approved for use even during the first trimester of pregnancy. Two double-blind RCTs of oral iron supplementation in RLS showed conflicting results. One reported an improvement of RLS symptoms (127). In contrast, in men and non-pregnant women with low serum ferritin, oral iron was not very effective (128). Folic acid deficiency must also be corrected (129). Smoking cessation, reduced caffeine intake, and avoidance of physical activities near bedtime might also be advised. Very premature data are available concerning the possibility of using dopaminergic drugs during pregnancy; however, it is still too early to conclude whether these drugs are safe for use in pregnancy (130).
Periodic limb movements

PLM, previously known as nocturnal myoclonus (131), is a sleep disorder characterized by uncontrollable movement of the lower extremities, specifically the toes, ankles, knees, and hips, typically lasting between 0.5 and 5 seconds. The patient is often unaware of these movements. PLMs may cause microarousals, leaving the affected patient fatigued the following day. PLM is often an incidental finding during PSG. It is measured by surface electromyography from the tibialis anterior muscle (15). International Classification of Sleep Disorders-2 criteria for PLM disorder (PLMD) are as follows: (1) PSG should demonstrate repetitive movements that are 0.5 to 5 seconds in duration, typically separated by an interval of 20 to 40 seconds (range, 5–90 seconds); (2) PLM index should exceed 15 movements per hour of sleep (in adults); (3) clinical evidence of disturbed sleep or daytime fatigue must exist; (4) the PLMs should not be better explained by another disorder, medication use, or substance use disorder.

PLM is common, but the exact prevalence in the general population is not known. It has been reported that PLM is found in 30% of individuals aged 50–65 years and in 45% of individuals over 65 years (132). In a large telephone interview survey from the general population, the prevalence of PLMD was estimated at 3.9% and was more common in women. In this survey, the questions used were: According to you, or your bed partner, do you move your limbs a lot during sleep? If so, it was also asked how many nights per week or month this movement occurred. Finally, to diagnose PLMD, questions about daytime sleepiness were posed (133).

The pathophysiologic mechanisms of PLM are unclear, but abnormal hyperexcitability (or diminished inhibition) in the lumbosacral and cervical segments of the spinal cord has been hypothesized as a possible cause (134). PLM has also been reported to be associated with increased activity of the sympathetic nervous system (135), which can lead to elevated blood pressure and heart rate (136). The clinical relevance of PLM alone is still under discussion. Several observational studies have reported a significant independent association between PLM and cardiovascular disease (137-140). One recent prospective cohort study from Canada reported that patients with heart failure and a PLM index >5 events/h had an independent significant risk for death (138). Patients with a history of stroke have been shown to have a greater prevalence and severity of PLMs than control patients (139).

The relationship between menopause or menopausal symptoms and PLM has not been investigated. There are some conflicting data from small studies concerning the effect of transdermal estrogen on PLM. In a study from Finland, no difference in incidence or intensity of nocturnal PLMs was re-
ported (47); however, a significant decrease in PLMs was observed in a study among Brazilian women (141). Most patients with RLS also have increased presence of PLMs (142). Investigation of the PLM index by PSG could increase knowledge in the field of sleep-related movement disorders and menopause. If PLM, with its increased incidence of arousals, is more common in menopausal women, then it may also contribute to the deteriorated sleep quality that many of these women experience.

Sleep and depression

Diagnosis of major depressive disorder (MDD) requires that a patient exhibit at least four of the following symptoms for a period of at least 2 weeks: 1) marked diminished interest or pleasure in all, or almost all, activities, 2) significant weight loss or gain, or decrease or increase in appetite, 3) insomnia or hypersomnia, 4) psychomotor agitation or retardation, 5) fatigue or loss of energy, 6) feelings of worthlessness or excessive or inappropriate guilt, 7) diminished ability to think or concentrate, or indecisiveness, 8) recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide. All but the last symptom must be present nearly every day (143). The gold standard for a depression diagnosis is a standardized psychiatric interview.

The point prevalence of MDD is 5-9% in women and 2-3% in men, with a lifetime risk of 10-25% and 5-12%, respectively (144). MDD is associated with serious chronic health problems, such as heart disease, diabetes, cerebrovascular disease, and osteoporosis (145). Although all types of people are at risk of developing depression, MDD has a greater incidence in women and the elderly (146, 147). In women, changes in hormone levels throughout life likely play a role in the increased incidence. Typical susceptibility periods include the luteal phase of the menstrual cycle, pregnancy, the postpartum period, and perimenopause.

Most individuals with depression experience sleep disturbances. Alterations in the ratio of REM sleep to NREM sleep, decreased SWS, and impaired sleep continuity are among the most robust markers for MDD (148). Individuals with sleep disturbances have a 10-fold risk of developing depression compared to those who sleep well (149), and it has been estimated that 90% of patients with depression complain of poor sleep quality. A recent large population-based Norwegian study further established the bidirectional association between depression and insomnia. Both insomnia and depression significantly predicted the onset of the other disorder. Participants who had insomnia had an odds ratio (OR) of 6.2 of developing depression, and individuals with depression had an OR of 6.7 of developing insomnia (150).
If sleep problems are present during the depression episode, the risk of more severe and longer disease duration is elevated (151). In addition, sleep disturbances are associated with a higher risk for relapse. Recent studies have shown that both pharmacological and non-pharmacological interventions for insomnia can prevent depression or mitigate its symptoms (151). Sleep is, therefore, an important factor to consider when diagnosing and treating depression (151). Pharmacological treatment of coexisting depression and sleep disturbance may be tainted with clinical concerns. Selective serotonin reuptake inhibitors (SSRIs) effectively improve mood in many patients, but they may also cause or worsen insomnia (152).

RLS and depression

Many studies have shown an association between RLS and depressive episodes (93, 95, 153, 154). A recent large prospective study suggested an increased risk of developing clinically relevant depression symptoms in subjects suffering from RLS (155). However, the association between the two conditions is complex. Several symptoms, such as fatigue, disturbed sleep, diminished concentration, and psychomotor agitation, could both be interpreted as symptoms of either condition (156, 157). A recent study reported that clinically relevant depressive symptoms at baseline were associated with new-onset RLS, and that RLS predicted incident depressive symptoms (158). However, pain and social isolation are also predictors for depression (159, 160), and these symptoms are frequently observed in people with RLS (95, 161). It is possible that a third factor is associated with both RLS and depression, falsely suggesting a causal association between the two. One such factor could be an abnormality in dopaminergic transmission, which is found in both RLS (162) and depression (163).

Pregnancy and depression

Approximately 14% of pregnant women report symptoms of depression, and 3.3% of pregnant women suffer from MDD (164). Independent of other risk factors, depression during pregnancy has been associated with growth retardation in the fetus, premature birth, low birth weight, and sleeping disturbances in the infant (165, 166). Depression that occurs during pregnancy or up to 12 months after pregnancy, so-called postpartum depression (PPD), is one of the most common complications of pregnancy. PPD affects approximately 7-10% of women during the first year after childbirth (167, 168). Besides depression, other symptoms could be thoughts about harming the baby, fear of not being good enough in the new role as a parent, and concerns for the child’s health (169). Children of women with depression during
pregnancy or in the postpartum period are at increased risk for emotional or psychological disturbances, even after the neonatal period (170, 171). Depression is associated with an increased risk of suicide, which is the cause of up to 20% of all deaths in the postpartum period (172).

Antenatal and postpartum depression are difficult to prevent; early follow-up, frequent healthcare contacts, and therapy sessions have not been shown to reduce their incidence (173). The most important predictor of PPD is a past history of depression in life or during pregnancy (174). Other risk factors are sleep disturbances, stress, socioeconomic problems, and domestic violence (175, 176). Endocrine factors are also relevant (177). Improved understanding of risk factors for PPD would be of great importance for early identification and help for women at risk. Modern antidepressant medication with SSRIs is effective during pregnancy, but unfortunately has been associated with obstetric complications (e.g. spontaneous abortion, stillbirth, prematurity) and specific effects on the fetus (e.g. respiratory distress, endocrine and metabolic distress, and cardiac malformations) (178, 179). Psychotherapy could be effective in ante- and postnatal depression (180), but there is often a shortage of therapists trained in the area. The intervention is time-consuming, which can lead to logistical problems and, thus, low compliance. Identifying an effective and safe form of treatment, with less side effects, for depression during and after pregnancy is of great importance.

One factor that has received attention in terms of importance for antenatal and postpartum depression is poor sleep (181, 182). The relationship between disturbed sleep and depression is well-known (149), and adequate advice to improve sleep in pregnant and postpartum depressed mothers should be first-line therapy in mild or moderate depression. However, the relationship between sleep-related movement disorders and depression, during or after pregnancy, has not been assessed.

Health-related quality of life and restless legs syndrome

One way of defining the concept of health-related quality of life (HRQoL) is: “The extent to which one’s usual or expected physical, emotional, and social well-being are affected by a medical condition or its treatment” (183). Individual patients with the same objective health status can report dissimilar HRQoLs, due to unique differences in expectations and coping abilities. Thus, the HRQoL must be measured from the individual’s viewpoint.

There are several reasons for the growing interest in HRQoL. Interventions are increasingly being aimed at improving the patient’s quality of life (QoL) rather than preventing their premature death (e.g., hip replacement, hypnot-
ics). As people live longer, they become more susceptible to disorders and conditions that decrease their QoL. With the greater amount of shared decision-making in health care, patients are requesting treatments that can improve their HRQoL (184). Previous studies focusing on gender differences in HRQoL reported consistently worse results in women. The reason for this finding, attributed variously to sociocultural, socioeconomic, and biomedical factors, has been a subject of controversy (185). It has been proposed that women have a greater “inclusiveness” of information sources when making self-assessed health judgments, and that these judgments are based on a wider range of health- and non-health-related factors compared to men (186).

Daytime dysfunction and QoL impairment are important and salient consequences of living with chronically disturbed sleep on a daily basis. There has been less interest in the daytime aspects of poor sleep compared with nighttime symptoms and sleep parameters. Thus far, very few articles have been specifically designed to assess the impact of insomnia on QoL (151). Most articles have been devoted to the impact of sleep disorders on the QoL of patients suffering from other morbidities (e.g., cancer, diabetes, and depression). Recent recommendations from leading researchers in the field encourage further investigations into the waking consequences, HRQoL, and correlates of sleep disorders (187-190).

Impaired QoL is most likely a consequence of RLS, and there is a growing knowledge in the area. In literature databases, eight prevalence studies were found concerning RLS and HRQoL (see paper 2). However, as in most research fields, there were some methodological differences between these studies. Studies used different questionnaires to measure HRQoL among RLS patients. Whereas some studies examined QoL in clinical samples, others examined the general population. There were also differences in how control groups were chosen; some used general population norms, others RLS negatives in the studied group. Some studies have suggested that RLS affects the physical more than the mental aspects of QoL (191-194), but there are studies in favor of the opposite (113, 121). In several studies, RLS-positives were shown to score their own health below population norms, analogous with patients suffering from other chronic medical conditions.

As previously described, sleep-related movement disorders are associated with several other comorbidities. However, to the best of our knowledge, only one previous study has addressed the question of whether it is the sleep-related movement disorder or the comorbidity that results in poor HRQoL (193). Thus, there is likely a lack of knowledge in this specific area.
Aims

The overall purpose of this thesis was to increase knowledge about sleep-related movement disorders and their consequences among Swedish women.

The specific aims were:

- to estimate the prevalence of RLS in a population-based sample of Swedish women;
- to examine associated symptoms and comorbidities, in particular, vasomotor symptoms, menopause, and HRT use, among women who suffer from RLS;
- to evaluate the unique impact of RLS on HRQoL in a population-based sample of Swedish women;
- to evaluate if PLMs are more common in postmenopausal women and/or among women with vasomotor symptoms;
- to analyze the influence of PLMs on self-reported HRQoL; and
- to evaluate if RLS during pregnancy increases the risk of antenatal or postpartum depressive symptoms.
Materials and methods

Subjects

Studies I-II
A random sample of 5000 women between the ages of 18 and 64 years was selected from the general population of Dalarna County, Sweden. Names and addresses of those selected were obtained from SPAR (the official Swedish database covering the total population of Sweden). Subjects were sent a questionnaire by ordinary post. Within 3–5 months after the initial mailing, non-responders were sent a reminder. A total of 3475 women (69.5%) responded. Thereafter, a new random sample among the remaining non-responders was selected (n = 401). These women were contacted by telephone by a trained telephone interviewer, and 41 subjects accepted the interview. Hence, the total response rate for the study was 70.3%. The study was approved by the Independent Research Ethics Committee in Uppsala.

Study III
A total of 10,000 women (age ≥ 20 years) were randomly selected from the general population of the municipality of Uppsala, Sweden. Potential participants were sent postal questionnaires that included questions about demographics, sleep disturbances, and hormonal status, with a total response rate of 71.6%.

In the second phase of the study, 400 women (age range, 20–70 years) were randomly selected from the responders of the first phase, with the goal of oversampling women who reported snoring (195). Women with severe somatic or psychiatric disease, who were likely to be unable to manage the ambulatory recording equipment, were excluded. The women underwent a full-night PSG recording in their own homes (with the exception of six recordings, which were performed at the clinic). Complete PSG recordings were obtained from all subjects. However, due to technical difficulties, PLMs could not be scored in seven women. In addition, 49 women did not complete the questionnaire concerning hormonal status and were excluded. Finally, data from 344 women were available for analysis. Informed consent was obtained from all participants, and the study was approved by the Independent Research Ethics Committee in Uppsala.
**Study IV**

In study IV, we used data from the Biology, Affect, Sleep, Imaging, Cognition, and PPD (BASIC) study, a longitudinal study investigating biological correlates to mood and anxiety disorders during pregnancy and in the post-partum period. The present sub-study was conducted between January 2010 and September 2012. During this time interval, 1686 women were included in the BASIC cohort. Women were enrolled in gestational weeks 16 to 17. They completed password-protected web-based surveys in gestational week 17, gestational week 32, and at 6 weeks post-delivery. For the purpose of the present study, questions on RLS from gestational week 32 were included in the survey.

**Methods**

**RLS questionnaires**

*Studies I-III*

A questionnaire containing diagnostic questions on RLS, together with questions regarding general health, sleep problems, reproductive health, and menopausal state, was used in studies I-III. RLS was diagnosed according to the IRLSSG standardized criteria (196), which were later modified (157) and validated (197). Essential criteria for RLS are: (1) An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs; (2) The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity, such as lying or sitting; (3) The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues; (4) The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night. All four criteria had to be met for the diagnosis of RLS in studies I-III. No time frame for the symptoms was required for RLS diagnosis, and no cut-off for frequency of symptoms was used.

*Study IV*

In study IV, the Cambridge-Hopkins RLS Short-Form 2 diagnostic questionnaire (CH-RLSQ11)(198), developed by Allen et al., was used. Although the IRLSSG criteria adequately define RLS, these four criteria have a relatively poor positive predictive value (PPV) of <50% in population studies (199). As leg cramps and positional discomfort are common in pregnant women, it was reasonable to use a questionnaire with a better ability to exclude common confounding conditions. The CH-RLSQ11 has a PPV of 85.5% in population-based surveys (200).
A Swedish translation of the CH-RLSQ11 was developed and approved by the public Swedish Administrative Services Agency. The questionnaire includes 11 questions: 7 diagnostic and 4 for further characterization of the condition. The content of the 7 questions used for scoring RLS are: 1) Do you have, or have you had, recurrent uncomfortable feelings or sensations in your legs while you are sitting or lying down? (yes/no); 2) Do you, or have you, had a recurrent need or urge to move your legs while you were sitting or lying down? (yes/no); 3) Are you more likely to have these feelings when you are resting (either sitting or lying down) or when you are physically active? (resting/active); 4) If you get up or move around when you have these feelings, do these feelings get any better while you actually keep moving? (yes/no/don’t know); 5) Which times of day are these feelings in your legs most likely to occur? (morning/mid-day/afternoon/evening/night/about equal at all times); 6) Will simply changing leg position by itself usually relieve these feelings? (usually relieves/does not usually relieve/don’t know); 7a) Are these feelings ever due to muscle cramps? (yes/no/don’t know); 7b) If so, are they always due to muscle cramps? (yes/no/don’t know)

<table>
<thead>
<tr>
<th>Scoring responses used to define RLS were as follows:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 = yes, 2 = yes, 3 = resting, 4 = yes, 5 = not equal or morning, 6 = does not usually relieve, 7a = no, 7b = no</td>
</tr>
</tbody>
</table>

The four additional characterization questions from the CH-RLSQ11 questionnaire are: 8) Do these feelings occur only when sitting or only when lying down? (neither/only when sitting/only when lying down/both when sitting and when lying down); 9) When you actually experience the feelings in your legs, how severe are they? (not at all/a little bit/moderately/extremely severe); 10) In the past 12 months, how often did you experience these feelings in your legs? (every day/4–5 days per week/2–3 days per week/1 day per week/2 days per month/1 day per month or less/never).

For all cases, the minimum frequency of RLS symptoms had to be at least 2 days per week. The use of two different definitions of RLS (probable and definite RLS) allowed for comparison with previous studies in pregnant populations that have mostly used the IRLSSG criteria. Finally, in addition to the CH-RLSQ11 questionnaire, we also asked for age at RLS onset to distinguish between de novo onset cases and pre-pregnancy RLS.

**HRQoL questionnaire**

To evaluate patient-reported health in study II, the Short-Form Health Survey (SF-12) was used. This instrument has been used to assess and compare HRQoL across a range of patient populations with different medical conditions. SF-12 scores range from 1 to 100 for each attribute. A higher score on
the physical or mental component summary indicates better physical or mental health, respectively (201). The shorter 12-item SF-12 was considered to be a more practical alternative for the purpose of large population-based comparisons.

In study III, the SF-36 was used to evaluate patient-reported health. This instrument assesses an individual’s HRQoL across a range of patient populations with different medical conditions. SF-36 scores range from 1 to 100 for each attribute. A higher score on the physical or mental component summary indicates better physical or mental QoL, respectively (202). There is a high degree of correspondence between SF-12 and SF-36 in terms of summarized physical and mental health factors (203).

**Self-reported depression**

The Edinburgh Perinatal Depression Scale (EPDS) is an internationally used, 10-item, self-reporting questionnaire designed as a screening tool to identify depressive symptoms in the perinatal period (204). Murray et al. showed that an EPDS score of $\geq 12$ points correctly identifies 77% of mothers experiencing a minor or major depressive episode. Test specificity for this cut-off value was estimated to be 93% (205). Therefore, for study IV, a threshold of 13 points was used to define cases of antenatal depression (206), and 12 points was used as threshold to define cases with PPD (207). The different cut-off values are due to the separate validation studies.

**Additional questionnaires and clinical variables**

Data on demographics, sleep habits, self-reported overt diseases, and menopausal status were collected in studies I-IV (for details, see each paper). Different questions were used to establish the menopausal status in studies I and III (for details, see each paper). In study III, analyses of FSH, analyzed by routine methods at the Department of Clinical Chemistry, Uppsala University Hospital, were available. However, during the study period, the laboratory methods for FSH determination changed; therefore, the FSH levels in this study were used merely to confirm menopausal status, using the reference intervals determined for each laboratory method. Blood pressure, weight, and height were collected on the day after PSG recordings in study III.

**Polysomnography**

*Study III*

The ambulatory EMBLA system (Flaga Inc., Reykjavik, Iceland) was used for PSG recordings, which were performed between November 2001 and February 2004, as described in detail previously (195). The recording montage included continuous bipolar EEG (C3-A2, C4-A1, left and right hori-
Leg activity was recorded from both anterior tibialis muscles. Data were downloaded to analysis software (Somnologica, Flaga, Inc. Reykjavik, Iceland). For a useful recording, a minimum sleep time of 4 hours was required, and no parameter was allowed to be lost for more than 20 minutes during the recording. To obtain the maximum quality and objective assessment of the PSG measures, each recording was evaluated according to PLM scoring rules from the American Academy of Sleep Medicine (2007 Manual) (208), by an external registered PSG technologist who was blinded to the hormonal status of the individuals.

For study III, the diagnosis of PLM was made in women who had a PLM index >15 events/h (n = 93). To examine the consequences of PLM arousals further, women with PLM indexes > 15 events/h and PLM arousal indexes > 5 events/h were determined to be suffering from PLM arousals (n = 49). The control group included 243 women with PLM indexes < 15 events/h and PLM arousal indexes < 5 events/h.

**Statistical methods**

**Study I**

Multivariate analyses were used to estimate the risk, approximated by the OR, of suffering from RLS-associated symptoms. ORs and 95% confidence intervals (CIs) were calculated by multiple logistic regressions to determine the influence of potential confounding factors (e.g., age, smoking, alcohol and coffee consumption, and intake of sleeping pills). Women without confirmed RLS (e.g., those who did not meet all four criteria in the validated RLS questions) served as a control group.

**Study II**

SF-12 summary scores for RLS-positive women were compared to those for RLS-negative women using ANCOVA, with adjustment for age, obesity, self-reported diabetes, heart problems, depression, and muscle and joint pain. Women without confirmed RLS (i.e., those who did not meet all four RLS criteria) served as a control group. The unique burden of RLS was analyzed by excluding RLS-positive women from the four self-reported diagnostic groups: diabetes, heart problems, depression, and muscle and joint pain, and by excluding subjects with these diagnoses from the group of RLS-positive women, “pure estimates of RLS-positive women”. In this way, we tried to ensure that we were comparing the RLS-component with different comorbidities / disease states, and that we were analyzing the unique burden that RLS places on an individual’s HRQoL.
Study III
Multiple logistic regression analyses were performed to estimate the risk, approximated by the adjusted OR, of suffering from PLMs associated with vasomotor symptoms. ORs and 95% CIs were calculated by multiple logistic regressions to determine the influence of potential confounding factors. The inclusion of confounding variables was based on significant findings in the bivariate analyses, with the exception of smoking and apnea-hypopnea index, which were forced into the model. The latter variable was included because of the oversampling of women with obstructive sleep disorder, who were categorized as having an apnea-hypopnea index > 15. Measures of self-rated physical health, according to the physical component summary of the SF36, were categorized in quartiles, with subjects having scores in the highest quartile denoted as controls.

Study IV
Differences between RLS cases and controls were analyzed with chi-squared tests or Student’s t-tests, as appropriate. Differences between probable RLS, definite RLS, and controls were analyzed by analysis of variance (ANOVA). Joint analyses of statistical predictors for depression were analyzed using multiple logistic regression analysis. In all studies, a P-value < 0.05 was considered to be statistically significant. All statistical analyses were performed with SPSS Statistics, version 20 (IBM, Armonk, NY).
Summary of results

Study I

The response rate to the population-based questionnaire was 70.3%. Among the responding subjects, 15.7% \((n = 551/3516)\) were diagnosed with RLS. When the sample was separated into four 10-year cohorts (25–34, 35–44, 45–54 and 55–64 years of age), we observed an increasing prevalence with increasing age (Figure 5).

![Figure 5. Prevalence of RLS among Swedish women](image)

Women suffering from RLS more often suffered from depression, heart disease, and muscle and joint pain, whereas no such associations were noted for diabetes or hypertension. There was a strong association between vasomotor symptom and RLS; 90% of women with vasomotor symptoms (night sweats) at any frequency reported themselves to be in the climacteric state. No statistical relationship between HRT use, postmenopausal state, and RLS was found. Subjects with an RLS diagnosis were more affected by symptoms of insomnia, problems maintaining sleep, and excessive daytime sleepiness than control subjects. Likewise, waking up not feeling refreshed was reported by RLS sufferers more frequently. Subjects who rated their overall sleep quality as not satisfactory were more common among subjects with RLS diagnosis than among women without RLS symptoms. RLS subjects were more likely to suffer from morning headache (Table 1).
### Table 1.

Statistics for women with \((n = 551)\) or without RLS \((n = 2950)\)

<table>
<thead>
<tr>
<th>Variable</th>
<th>RLS</th>
<th>No RLS</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n)</td>
<td>%</td>
<td>(n)</td>
<td>%</td>
</tr>
<tr>
<td>Impaired sleep quality</td>
<td>164</td>
<td>29.8</td>
<td>391</td>
<td>13.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trouble initiating sleep</td>
<td>154</td>
<td>27.9</td>
<td>348</td>
<td>11.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trouble maintaining sleep</td>
<td>278</td>
<td>50.5</td>
<td>903</td>
<td>30.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Awakening with breathing problems</td>
<td>11</td>
<td>2.0</td>
<td>34</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mouth dryness on awakening</td>
<td>154</td>
<td>27.9</td>
<td>420</td>
<td>14.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morning headache</td>
<td>69</td>
<td>12.5</td>
<td>182</td>
<td>6.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Snoring</td>
<td>125</td>
<td>26.5</td>
<td>468</td>
<td>18.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not refreshed on awakening</td>
<td>217</td>
<td>39.4</td>
<td>683</td>
<td>23.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>243</td>
<td>44.1</td>
<td>208</td>
<td>24.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daytime sleepiness</td>
<td>232</td>
<td>42.1</td>
<td>630</td>
<td>21.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Involuntarily falling asleep</td>
<td>28</td>
<td>5.1</td>
<td>83</td>
<td>2.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleeping pill use (^b)</td>
<td>57</td>
<td>10.3</td>
<td>89</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>63</td>
<td>11.4</td>
<td>247</td>
<td>8.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>16</td>
<td>2.9</td>
<td>63</td>
<td>2.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart problems</td>
<td>18</td>
<td>3.3</td>
<td>36</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impaired physical fitness</td>
<td>93</td>
<td>16.9</td>
<td>408</td>
<td>13.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle and joint pain</td>
<td>217</td>
<td>39.4</td>
<td>678</td>
<td>23.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>73</td>
<td>13.2</td>
<td>169</td>
<td>5.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tension</td>
<td>171</td>
<td>31.0</td>
<td>658</td>
<td>22.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other psychological symptoms</td>
<td>27</td>
<td>4.9</td>
<td>88</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasomotor symptoms (^a)</td>
<td>168</td>
<td>30.5</td>
<td>468</td>
<td>15.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postmenopausal state (^c)</td>
<td>288</td>
<td>52.3</td>
<td>1103</td>
<td>37.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of HRT</td>
<td>64</td>
<td>11.6</td>
<td>200</td>
<td>6.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ORs were adjusted for age, smoking, alcohol and coffee consumption, and use of sleeping pills. Missing values were present in some of the factors in \((n = 1-4)\).

\(^a\) Result was significant after excluding women taking HRT \((OR 1.99, CI 1.58-2.49)\).

### Study II

Complete responses with answers in every domain in the SF-12 were obtained from 3420 (68.4\%) subjects. Compared with mental SF-12 scores for the RLS-negatives in our population, mental HRQoL of the RLS sample in our study was lower in every age group, 25–34 \((P < 0.001)\), 45–54 \((P < 0.01)\), and 55–64 \((P < 0.001)\) years, but significance was not obtained in the
35–44 years age group (Figure 6). Physical SF-12 scores for RLS-positive women were also below scores for RLS-negatives in every age group, but the difference was only significant among women aged 45–54 years ($P < 0.05$, Figure 6).

After we had removed comorbidities as confounding factors, the RLS-component still influenced HRQoL, indicating that RLS has a unique burden on HRQoL. Women with depression (age groups 35–64 years) and women with diabetes (age groups 35–44 and 55–64 years) estimated their mental health to be worse than that of RLS-positive women. Women with heart problems and muscle and joint pain did not assess their mental health any differently from RLS-positive women. The oldest women with self-reported diabetes, depression, and muscle and joint pain (age group 55–64 years) estimated their physical health to be significantly worse than that of RLS-positive women. Younger women with self-reported diabetes, heart problems, or depression did not assess their physical health any differently from RLS-positive women (Figure 7).
Study III

In study III, 344 women were available for analysis. Of these, 243 women had a PLM index ≤ 15 events/h and a PLM arousal index < 5 and were denoted as controls. A total of 93 women had a PLM index > 15 events/h (women with PLM) and, of these, 49 also had a PLM arousal index > 5 (women with PLM arousals). As shown in Table 2, women with PLMs more often suffered from peri- and postmenopausal vasomotor symptoms, whereas postmenopausal status per se, after adjustment for age, did not remain a significant explanatory variable. PLMs did not seem to affect HRQoL.

Figure 7. Mental and physical HRQoL in RLS and other morbidities
Table 2.

Statistics for the explanatory variables of PLMs index > 15

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasomotor symptoms</td>
<td>1.86</td>
<td>1.03–3.37</td>
</tr>
<tr>
<td>FSH in postmenopausal range</td>
<td>1.22</td>
<td>0.57–2.61</td>
</tr>
<tr>
<td>Age</td>
<td>1.03</td>
<td>0.99–1.07</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.44</td>
<td>0.74–2.81</td>
</tr>
<tr>
<td>RLS</td>
<td>4.37</td>
<td>2.53–7.55</td>
</tr>
<tr>
<td>Apnea-hypopnea index &gt; 15</td>
<td>1.00</td>
<td>0.55–1.81</td>
</tr>
<tr>
<td>Self-rated physical health</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highest quartile</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Intermediate quartiles</td>
<td>1.38</td>
<td>0.67–2.82</td>
</tr>
<tr>
<td>Lowest quartile</td>
<td>2.03</td>
<td>0.89–4.61</td>
</tr>
</tbody>
</table>

ORs were adjusted for all variables in the table.

Study IV

Of the 1686 women who participated in the BASIC study while our RLS sub-study was open, 1428 (84.7%) filled out the RLS questions in gestational week 32. The control group included 792 women who did not report any uncomfortable or unpleasant sensations in their legs or any urge to move their legs. A total of 192 women who reported either one of these items were excluded. Among the remaining 444 women, 18.5% fulfilled the IRLSSG criteria (probable RLS) and 9.4% fulfilled the CH-RLSQ11 criteria (definite RLS). Of those with frequency of symptoms at least 2–3 days/week, the prevalence of RLS was 12.3% and 6.6% for probable and definite RLS, respectively (Figure 8).
Figure 8. Study population in study IV

EPDS scores were available from 925 women (95.6%) in gestational week 17, from 968 women (100%) in gestational week 32, and from 745 women (77.0%) in postpartum week 6. Depression scores in prenatal weeks 17 and 32, and postpartum week 6 were higher among women with definite RLS (Table 3), and were especially pronounced in those with moderate or severe early-onset RLS (Table 4)
Table 3.

Risk for depression by pregnancy week and RLS / psychiatric history

<table>
<thead>
<tr>
<th>Week</th>
<th>RLS / Psychiatric history</th>
<th>Adj. OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational week 17</td>
<td>Probable RLS (IRLSSG)</td>
<td>1.86 (0.82–4.23)</td>
</tr>
<tr>
<td></td>
<td>Definite RLS (CH-RLSQ11)</td>
<td>2.56 (1.27–5.18)</td>
</tr>
<tr>
<td></td>
<td>Prior psychiatric history</td>
<td>3.12 (1.75–5.57)</td>
</tr>
<tr>
<td>Gestational week 32</td>
<td>Probable RLS (IRLSSG)</td>
<td>0.81 (0.33–1.97)</td>
</tr>
<tr>
<td></td>
<td>Definite RLS (CH-RLSQ11)</td>
<td>2.00 (1.08–3.71)</td>
</tr>
<tr>
<td></td>
<td>Prior psychiatric history</td>
<td>2.29 (1.36–3.84)</td>
</tr>
<tr>
<td>Postpartum week 6</td>
<td>Probable RLS (IRLSSG)</td>
<td>0.94 (0.42–2.11)</td>
</tr>
<tr>
<td></td>
<td>Definite RLS (CH-RLSQ11)</td>
<td>1.96 (1.04–3.70)</td>
</tr>
<tr>
<td></td>
<td>Prior psychiatric history</td>
<td>2.19 (1.31–3.67)</td>
</tr>
</tbody>
</table>

Multiple logistic regression, adjusted for parity and pre-pregnancy smoking.

Table 4.

Risk for depression by pregnancy week, RLS onset, and symptom severity

<table>
<thead>
<tr>
<th>Week</th>
<th>RLS onset / severity</th>
<th>Adj. OR for depression (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational week 17</td>
<td>Pre-pregnancy RLS with severe symptoms</td>
<td>4.29 (2.11–8.72)</td>
</tr>
<tr>
<td></td>
<td>De novo RLS with severe symptoms</td>
<td>1.57 (0.61–4.03)</td>
</tr>
<tr>
<td>Gestational week 32</td>
<td>Pre-pregnancy RLS with severe symptoms</td>
<td>2.96 (1.56–5.62)</td>
</tr>
<tr>
<td></td>
<td>De novo RLS with severe symptoms</td>
<td>1.01 (0.41–2.51)</td>
</tr>
<tr>
<td>Postpartum week 6</td>
<td>Pre-pregnancy RLS with severe symptoms</td>
<td>2.41 (1.23–4.71)</td>
</tr>
<tr>
<td></td>
<td>De novo RLS with severe symptoms</td>
<td>1.26 (0.52–3.03)</td>
</tr>
</tbody>
</table>

Multiple logistic regression, adjusted for parity, pre-pregnancy smoking, and psychiatric history.
Discussion

General conclusions

RLS has been called “the most common disorder you've never heard of”. Public and health-care practitioner awareness of RLS has slowly increased, presumably due to access to efficient treatment (100). Results from studies in this thesis suggest that RLS is common in the Swedish female population, associated with severe comorbidities and reduced QoL. RLS and PLM appeared to be associated with vasomotor symptoms in middle-aged women, although no association with postmenopausal status was found. During pregnancy, RLS was associated with antenatal and postpartum depression, mainly among women who had RLS prior to the onset of pregnancy. These findings demonstrate the importance of taking these common sleep disorders seriously. Future research resources should be invested to clarify the hormonal link between RLS and PLM, and research priority should be given to the treatment of pregnancy-related RLS, especially given the relationship with antenatal and postpartum depression.

Methodological considerations

In this thesis, we used two different questionnaires to diagnose RLS. The PPV depends on the prevalence of a condition in a population, with a high prevalence leading to high PPV. The PPV is defined as the proportion of individuals who test positive for a disease who really are positive, according to some gold standard measure for the disorder. In recent years, the PPV of RLS screening questionnaires has been found to be relatively low. When we planned this thesis, an indisputable RLS diagnosis was considered to be obtained by four affirmative answers to the four questions on the IRLSSG survey. Currently, this instrument is expected to have up to a 50% false-positive identification of RLS. Many individuals who are RLS-positive by the screening form can have symptoms of other conditions of the extremities similar to those that characterize RLS (“mimics”) and, thus, falsely meet the four diagnostic criteria (196). The CH-RLSQ11 questionnaire, developed by Richard Allen's group in Boston, MA, USA, is thought to be more specific (i.e., have a higher PPV), thereby resulting in improved accuracy of the RLS diagnosis. The error rate is lower and the false-positive population is estimated to be about 7-10% (195).
Discussions concerning the previously mostly used self-administered screening forms and their often low PPVs gained momentum during work on this thesis. Therefore, knowledge on this subject was only considered within the framework of study IV, the final study in this thesis. However, published studies on RLS still usually use the four diagnostic questions developed by IRLSSG. Various research groups continue their efforts to design even better diagnostic tools. In retrospect, more accurate estimates of RLS prevalence would probably have been obtained in studies I and II if the CH-RLSQ11, which was not available at that time, had been used.

If leg cramps, positional discomfort, and RLS simultaneously affect a pregnant woman, then a self-administered questionnaire-based discrimination between the conditions can be difficult. To secure differentiation between these states, a diagnostic interview by an expert in the area is preferable and recommended (and is currently the gold standard for RLS diagnosis). However, interviews are time- and resource-intensive. For that reason, they are infrequently used in large studies with many subjects, as was the circumstance in the studies included in this thesis.

Studies III and IV used study populations who had different original aims; study III was sampled for the evaluation of sleep-disordered breathing and study IV for the investigation of biological correlates of antenatal and postpartum depression. Therefore, the data in these studies may not be used to estimate population-based prevalence rates of PLMs or RLS in middle-aged or pregnant women, respectively. However, for the associative analyses between vasomotor symptoms, menopause, and PLMs, or between RLS and depression in pregnant women, the study designs were considered reasonable. Needless to say, additional questions on anemia, including access to ferritin analyses in pregnant women, would have contributed to the overall understanding of RLS during pregnancy.

Study IV
The study utilized data of women in the BASIC database. The survey was planned to have a population-based approach, but it included a few women who were born outside Sweden. The participants were frequently nulliparas and university educated (Sundström-Poromaa, unpublished observations). These circumstances could possibly affect the generalizability of the results. A second limitation is the lack of a detailed, pre-pregnancy psychiatric status. Although we controlled for prior psychiatric disorders, we cannot fully distinguish whether increased depression rates during pregnancy in women with pre-existing RLS represented new-onset depressive symptoms during pregnancy or were simply a continuation or exacerbation of pre-existing depressive symptoms.
Reflections on the results

Prevalence of RLS
The findings of study suggested a relatively high prevalence of RLS among Swedish women (15.7%) compared to several other investigations in Europe (5.7-14.2%) (209-211). Several methodological issues may account for the observed differences in RLS prevalence, such as differences in population characteristics (i.e. clinical vs. general populations) and assessment methods (i.e. questionnaires vs. clinical interviews). The development of RLS diagnostic criteria has led to improved homogeneity between studies, allowing more accurate comparisons to be made with previously published population-based surveys. Consistent with other studies, the results of study I showed an increased prevalence of RLS with increasing age (209-211).

Two weaknesses of this study are that no timeframe of RLS symptoms was required and no assessment of RLS severity was made. In the large REST study, the prevalence of RLS symptoms at any frequency was 7.2%, whereas RLS symptoms during the last week were prevalent in 5.0% of subjects (males and females) (192). In the INSTANT study, half of the identified subjects reported symptoms occurring at least once a week (210). Similarly, a recent Swedish study reported that 64% of RLS sufferers had severe or very severe RLS symptoms during the previous week (93). Considering these observations, the results in our study fit well with previous findings.

Vasomotor symptoms, menopause, HRT, and RLS
The findings in this thesis suggested that RLS is associated with vasomotor symptoms in middle-aged women, although no association with postmenopausal status could be found. There was no relationship between RLS, PLM, and HRT use. The relationship between vasomotor symptoms during the menopausal transition and RLS could be due to declining estrogen secretion from the ovaries, which may lead to changes in brain neurotransmitters and instability in the hypothalamic thermoregulatory center. Women suffering from hot flushes have been shown to have a narrow thermoneutral zone, within which sweating, peripheral vasodilatation, and shivering do not occur (212). Beta-endorphin, noradrenalin, and serotonin neurotransmitter systems are involved in the pathophysiology underlying hot flushes (213, 214).
Noradrenalin and serotonin reuptake inhibitors are currently being evaluated as alternative treatments to HRT for hot flashes (215).

In study I, use of HRT to treat the vasomotor symptoms was not associated with increased risk of RLS. One reason why HRT use was not associated with RLS symptoms could be the low frequency of HRT users among postmenopausal women in the present study (indicating a type II error). However, it could also indicate that HRT is, in fact, beneficial for RLS. The role of HRT in the exacerbation and pathophysiology of RLS is unclear. A few prior studies have discussed the possibility that postmenopausal intake of estrogen (HRT) may play a role in the clinical manifestation of RLS. Thus far, the results from cross-sectional studies have been conflicting. In one US study, a positive association with RLS was found with prescribed estrogen with or without progesterone (74% taking HRT vs. 38% not on HRT, \( P < 0.0001 \)) (216). Reports from European studies, however, have failed to suggest any association between HRT and RLS (113, 114). The report of a recent general population-based prospective study on RLS incidence found that HRT users had higher incidence of RLS over 4 years than those who did not use HRT (11.6% vs. 5.3%, OR 2.446, CI 1.172–5.104, \( P = 0.017 \)) (217). Participants whose responses suggested possible alternate diagnoses (e.g., discomfort from leg cramps / pain while exercising [claudication]) were excluded to decrease the number of false positives.

Cross-sectional and observational studies are confounded by the indication for use of a specific treatment. For this reason, an RCT would be the only way to establish if HRT is of value for RLS. To date, only one such RCT has been performed, reporting that women on a combined therapy (estrogen and progesterone) complained of less symptoms of RLS than those who only took one of the two hormones (218). The strong association between vasomotor symptoms and RLS in the present study further emphasizes the need to evaluate HRT as a possible treatment for RLS in postmenopausal women suffering from vasomotor symptoms.

**Comorbidities and RLS**

Women suffering from RLS more often reported comorbid depression and heart disease, whereas no such associations were noted for diabetes and hypertension. In our study population, depression was twice as common in the RLS-positive sample as in the control group. Results of some recent studies have indicated an association between depressed mood, depression, and RLS. However, it is unclear whether RLS-induced sleep impairment increases the risk of psychiatric disorders or vice versa (95, 153, 161, 219). The association might also be explained by the proposed involvement of the dopaminergic system in both depression (220) and RLS (221). The role of antidepressant drugs in RLS development is also unclear. One European
survey found that the use of SSRIs was a risk factor for RLS (133), but three later studies did not support this finding (93, 216, 222).

Little is known about the association between RLS and heart disease. In a Swedish study from 2001, male RLS subjects more often suffered from heart problems, and an association was found between RLS and hypertension (95). Reports of a study performed in five European countries noted a significantly higher risk for heart disease and hypertension among RLS patients (133). No significant association was seen between RLS and treatment for hypertension or heart disease in the general adult population in Norway or Denmark (209). In our female population, there was a significant comorbidity between heart problems and RLS but not with hypertension.

**RLS and HRQoL**

The main finding in study II was that RLS was associated with impaired self-reported mental health across most age groups, even after adjustment for disease comorbidities. In contrast, physical health was only impaired among RLS-positive women aged 45–64 years. Our results indicate that RLS among women affects the mental more than the physical aspects of QoL. A clinically meaningful difference in HRQoL between groups has been suggested to be equivalent to a half-standard deviation, which in our study would be 3–4 points in the SF scales (223). Based on this assumption, the differences between RLS-positive and RLS-negative women concerning mental aspects of QoL in our study would not only be statistically significant, but also clinically meaningful. Our findings are consistent with the results of a US study which, after controlling for the impact of age, gender, and comorbidities, showed that RLS-positive women reported a unique burden of both physical and mental aspects of HRQoL compared with general US population norms (193). We also found impaired HRQoL values among women with chronic conditions, such as diabetes, heart problems, depression, and muscle and joint pain. Hence, our results further suggest that RLS per se is associated with a unique impairment in HRQoL.

In most studies on RLS and HRQoL, adjustments for comorbidities have not been made. In addition, only severely affected RLS subjects have been included in the evaluation of the SF-36 outcomes. Although we included all RLS-positive women in our analyses, without using a timeframe or severity scale and with the limitation of the RLS criteria in mind, there was still a clear meaningful difference between RLS-negative and RLS-positive women concerning their mental health. This result indicates that HRQoL may be affected even among women with only mild RLS symptoms.

A limitation of the study was that the diagnosis of depression was not ensured by validated questionnaires for estimation of depressive symptoms (or
clinical diagnostic interviews). Thus, the SF-12 mental health scores reported by depressive patients in our study may not be comparable to those of clinically depressed patients. In conclusion, the impaired well-being among women with RLS reveals the importance of identifying women with this condition and evaluating their need for medication or other measures to improve their QoL.

PLM, menopause, and vasomotor symptoms
The main finding of study III was that women with PLMs more often suffered from peri- and postmenopausal vasomotor symptoms. However, postmenopausal status per se, after adjustment for age, did not remain a significant explanatory variable. These findings are in accordance with the results from study I, in which vasomotor symptoms during the menopausal transition, but not postmenopausal status, were associated with increased occurrence of RLS (224).

The mechanisms by which the consequences of decreased ovarian function (vasomotor symptoms) are associated with PLMs, but not with menopause per se (increased FSH levels), are not clear. The most straightforward explanation could be that women with PLMs have disturbed sleep and/or arousals. Thus, these women might spend more time awake and are more inclined to note vasomotor symptoms, such as night sweats. Vasomotor symptoms are considered to be indicative of estrogen deficiency, although no clear-cut relationship between serum concentrations of estrogen (or FSH) have been reported (225). It is possible that the loss of estrogen, which has multiple effects on neuronal function and neurotransmitter systems, might influence the propensity to develop PLMs.

Estrogen receptors are expressed in brain areas responsible for sleep regulation (226). Estrogen signaling increases acetylcholine synthesis and regulates serotonin turnover, transport, and binding in the brain (49). Estrogen has both agonistic and antagonistic effects on the dopaminergic system (227). Long-term exposure to estrogen increases dopamine uptake and decreases dopamine concentrations in dopaminergic areas in the brain (228). It has been hypothesized that decreased estrogen levels could worsen sleep movement disorders by decreasing the abundance of dopamine receptors or impacting the activity of catechol-O-methyltransferase, the enzyme that degrades dopamine (48).

Emerging evidence also suggests that symptoms associated with sleep-related movement disorders may be associated with a low oxygenation of peripheral tissues. Remodeling of the capillary geometry and a lower maximal oxygen uptake have been found in the tibialis anterior muscles of RLS patients (229). Estrogen has been shown to improve vascularization (230)
and to increase nitric oxide production and vasodilation (231), ultimately leading to an increased oxygen supply. Nitric oxide, which has been reported to influence dopaminergic processes (232, 233), may provide a link between the peripheral and central hypotheses of the origin of RLS or PLM (233). In addition, higher metabolism in the periphery during night sweats could lead to a build-up of lactic acid in the muscles, leading to an increased excitability of nerve-muscle plates and more frequent PLMs (234).

Although we found that PLMs were significantly associated with vasomotor symptoms, no such association was found in women with PLM arousals. Study III was likely underpowered for analyses on PLM arousals, indicating a type II error. On the other hand, arousals are common in women with PLMs, and spectral EEG may provide objective sleep measures indicating higher arousal levels in women with vasomotor symptoms (73). Our findings of an association between vasomotor symptoms and PLMs adds further complexity to the picture, and points to the fact that the mechanisms involved in arousals, whether associated with PLMs or vasomotor symptoms, remain insufficiently clarified. Future studies should address the possibility of using HRT in postmenopausal women with PLMD.

In study III, PSG recordings were available for only a single night, which is an important limitation for the interpretation of our findings. Because of the observed night-to-night variability of PLMs, particularly in RLS patients (235), it has been suggested that two consecutive full nights of PLM recordings may be necessary to make a valid estimate of the PLM index. However, this conclusion comes mostly from studies involving patients with sleep disorders such as RLS and PLMD (236).

**PLM and HRQoL**

In study III, we found that the physical but not the mental aspect of the HRQoL was affected in women with PLMs. Previous studies have shown associations of PLMs with other diseases and conditions that affect HRQoL, including RLS. However, there are little previous data concerning the relationship of PLM alone with HRQoL. A search of the PubMed electronic database revealed only one such study, which showed no association between PLM alone and self-rated health (237). The clinical significance of PLMs is discussed in previous papers. More studies are needed to clarify this field.

**RLS, antenatal and postpartum depression**

In study IV, we observed a relationship between RLS and antenatal and postpartum depression. Specifically, we found that women with RLS onset before pregnancy (idiopathic RLS) who also reported moderate or severe symptoms during pregnancy had an increased risk for both antenatal and
postpartum depression, whereas this was not the case in women with de novo onset of RLS during pregnancy.

One possible mechanism by which RLS could lead to depression during pregnancy is the disturbed sleep associated with RLS symptoms. Disturbed sleep is a well-established and independent risk factor for the development of depression (238, 239). A growing body of evidence suggests that disturbed sleep is not just a symptom of depression, but may actually precede and predict the onset of the depression (240). Among pregnant women with pre-existing RLS, pre-pregnancy sleep disturbances may worsen during pregnancy, thus increasing their vulnerability to depression. Alternatively, the relationship between RLS and perinatal depression could be due to increasing RLS symptomatology—it is known that symptom severity of RLS increases during pregnancy (44).

Besides influencing sleep, the overall burden of RLS may render a women more susceptible to depression, particularly during pregnancy when efficient pharmacological treatment for RLS is generally not advised. Thus far, only one small German study has evaluated the safety of dopaminergic drugs for RLS during pregnancy. Although that study found no increased risk above baseline for major malformations or other adverse outcomes, comparisons were only performed to a reference sample of normal pregnancies, without matching for age, comedication, or other risk factors (130). Substantially greater exposure frequencies are needed before scientific results can be translated into clinical recommendations. Moreover, dopamine agonists may theoretically interfere with lactation. Preliminary findings suggest that infusion of ferric carboxymaltose is effective and safe for improving RLS symptoms in pregnant women with iron deficiency or anemia (125). It is yet unknown if this treatment also improves depressive symptoms during and after pregnancy.

A third possible mechanism by which RLS could influence perinatal depression resides in the interaction between pregnancy hormones (predominantly estradiol and progesterone) and their influence on dopaminergic neurotransmission (110, 241). During pregnancy, estradiol and progesterone serum concentrations are increased 100- and 10-fold, respectively (63). In non-pregnant women, estradiol is generally thought to increase dopaminergic neurotransmission in the ventral striatum (242). However, recent evidence has suggested that estradiol influence on dopamine may be dose-dependent and non-linear (50, 243). Although no studies have assessed the effect of extremely high estradiol levels, such as those encountered during pregnancy, the increased prevalence of RLS and depression during pregnancy could be an epiphenomenon of the final pathway for the ovarian steroid-dopaminergic interaction.
Regardless of symptom severity, women with de novo RLS during pregnancy were not at increased risk for developing antenatal or postpartum depression. However, in contrast to women with pre-pregnancy RLS, de novo pregnancy RLS symptoms may appear as typical somatic pregnancy symptoms and eventually disappear after delivery (118). For the clinician, it is important to establish if RLS symptoms during pregnancy are a pre-existing disorder or newly developed, particularly as pre-pregnancy RLS has a greater influence on the psychiatric well-being of women. The RLS history is also important due to recent findings suggesting that women with idiopathic RLS have a shorter sleep duration during pregnancy and decreased birth weight of neonates compared to pregnant women with de novo RLS (244).

In our data, the prevalence of RLS during pregnancy according to the IRLSSG standard criteria was 18.5%. In total, 12.3% of the women had symptoms more than 2–3 day/week. These numbers fit well with previous findings in pregnant populations, but are in the lower range (44). The most likely reason for the lower prevalence is the high cut-off of symptom frequency that we used to diagnose RLS. The even lower prevalence that was attributed to the CH-RLSQ11 questionnaire was primarily due to the exclusion of leg cramps and positional discomfort, which are RLS mimetics and common pregnancy complaints (200). In a review of nearly 50 community-based studies, RLS prevalence rates declined by half when a threshold for frequency and/or severity of symptoms was added to the standard IRLSSG criteria. When differential diagnoses are considered, the prevalence estimates become even lower (245).

In summary, women with RLS onset before pregnancy with moderate to severe symptoms during pregnancy had increased risks of antenatal and postpartum depression. This knowledge might be useful as an early predictor of perinatal depression and would indicate the need for more careful psychological assessment and management in these women. Currently, few treatment options are available in pregnant women for both RLS and depression. It remains to be established if RLS treatment can alleviate depressive symptoms. Given the impact of RLS on the psychological well-being of pregnant women, further intervention studies in pregnant populations should not only address RLS symptoms, but also target depressive symptomatology.
Restless legs syndrome (RLS) och periodic limb movements (PLM) är sömnstörningar i gruppen sleep related movement disorders. RLS är en vanlig neurologisk sjukdom där fler kvinnor än män är drabbade (~3:1). RLS ökar i förekomst med stigande ålder. Fyra positiva svar på frågor om diagnostiska kriterier ger diagnos: 1) Har du starkt behov av att röra på benen pga obehagliga känselförnimmelser? 2) Upptäcker de symtomen i vila och lindras av aktivitet? 3) Medför symtomen i benen ett obetvingligt behov av aktivitet? 4) Förvärras symtomen kvälls- och nattetid? 

RLS ger sämre sömn och kan därför via trötthet påverka livskvalité, familjeliv och sociala aktiviteter, arbetsprestation, komorbiditet med högre förekomst av bl.a. depression, diabetes och hypertoni. Det har hos RLS-patienter påvisats en störning i det dopaminerga hormonsystemet i hjärnan med låga dopaminlivnivåer och/eller få eller mindre känsliga dopaminreceptorer. Läkemedel med dopaminerga effekter har god lindrande effekt på RLS-symtom. RLS är vanligt under graviditet med förekomst upp mot 25 % enligt det mest använda diagnosinstrumentet. Vi vet att RLS som uppkommer under graviditet ofta går över efter förlossning men ökad risk finns för återinsjuknande vid nästkommande graviditet o/e längre fram i livet. RLS som fanns före graviditeten förvärras ofta under densamma och finns också kvar efter förlossningen.

PLM kännetecknas av okontrollerade sträckrörelser i ben, speciellt tårna, ankhar, knä och höfter under sömn. De varar mellan 0,5 och 5 sekunder och kan orsaka korta uppvaknanden ledande till dagtrötthet. Den kliniska betydelsen av PLM är dock omdiskuterad och PLM ses ibland hos friska personer utan dagsymtom. En övervägande del av RLS-drabbade har också PLM.

RLS är en subjektiv diagnos och sätts med hjälp av enkät, helst använd i intervju situation för att minska risken för falskt positivt utfall. PLM däremot kan objektivt diagnostiseras med polysomnografi.

Depression är vanligare under och efter graviditet. Det är inte känt om kvinnor med RLS under graviditet har större risk för depression.
Avhandlingens huvudsyften har varit att ta reda på hur vanligt RLS och PLM är bland svenska kvinnor, dess samband med menopaus och graviditet och sjukdomarnas konsekvenser.

**Delarbete 1**
Frågeställning: Hur vanligt är RLS bland svenska kvinnor och hur stor är risken för komorbiditet?
Metod: tvärsnittsstudie där enkäter skickades till 5000 slumpmässigt utvalda kvinnor i åldrarna 25-64 år från den allmänna befolkningen i Dalarnas län. Formulären inkluderande frågor om demografi, hälsa, sömn, RLS och hormonella parametrar.
Huvudfynd: RLS är vanligt bland svenska kvinnor och RLS är associerat med vasomotor syft mot, hjärtsjukdom, depression och smärta.

**Delarbete 2**
Frågeställning: Hur påverkar RLS kvinnors livskvalité?
Metod: till samma kohort som i arbete ett skickades också enkät om självskattad hälsa (SF-12). RLS patienter jämfördes med andra patientgrupper.
Huvudfynd: Kvinnor med RLS skattar sin mentala hälsa lägre än kvinnor utan RLS, i samma nivå som, eller sämre än, andra patientgrupper. Fysisk skattad hälsa påverkas inte lika mycket.

**Delarbete 3**
Frågeställning: År objektivt funna PLM vanligare bland kvinnor med vasomotorsymtom och påverkar det så fall dessa kvinnors hälsa?
Metod: tvärsnittstudie där enkät skickades till 10 000 kvinnor i Uppsala län. Formuläret innehöll frågor rörande demografi, hälsa, sömnstörningar, hormonell status samt självskattad hälsa. Bland dessa genomgick 400 kvinnor sömnregistrering. Trehundra fyrtioåtta polysomnografier analyserades med avseende på PLM. Blodprov togs för analys av föllikel stimulerande hormon (S-FSH),
Huvudfynd: Kvinnor med kliniskt signifikant PLM hade oftare vasomotor symtom, även efter justering för störfaktorer, exempelvis ålder.

**Delarbete 4**
Frågeställningar: Har RLS-positiva kvinnor ökad risk för depression under och efter graviditeten (PND)? Är det skillnad i prevalens PND om RLS fanns före graviditeten eller om symptom uppkommit de novo? Skiljer sig prevalensen åt beroende på vilket diagnosinstrument som används?
Metod: longitudinal kohortstudie där alla gravida kvinnor i Uppsala län tillfrågas på screeningultraljudet de vill delta. Om så följdes de under graviditeten och i puerperiet med web-baserade enkäter, inklusive RLS-dito och blodprover. Via MVC-journal hämtades uppgifter bl.a. om ev. graviditetets- o/e förlossningskomplikationer.

Huvudfynd: Kvinnor med RLS har större risk för depression under och efter graviditet. Det gäller särskilt om de har moderata eller svåra symtom av RLS redan före graviditeten. Prevalensen av RLS under graviditet skiljer sig mycket åt beroende på vilket diagnostiskt formulär som används och är betydligt lägre när andra bensymtom uteslutits.
Acknowledgments

This thesis was carried out at the Center for Clinical Research, Dalarna (CKF), and the Department of Women’s and Children’s Health, Uppsala University (KBH). I have met many people during this journey, and I am grateful for their input and support. I would especially like to thank:

All participating women in the studies for their time and contributions.

Inger Sundström-Poromaa, my main supervisor and a fantastic woman. I would like having your talents for just one day. It would be interesting to know how it feels! Thanks for dragging me through this, Inger!!

Staffan Nilsson, my first supervisor and the first person who thought it was possible for me to do this. Without you, there would have been nothing.

Jan Ulfberg, superior expert in sleep medicine and co-supervisor. With your friendly, confident personality, you have led me on the way and have learned me an awful lot, not least that patience is a great virtue.

Eva Lindberg, for excellent co-authorship, sharp gotlandic thoughts and for letting me use your large body of scientific data regarding Uppsala women's sleep.

Mauro Manconi, at Sleep and Epilepsy Centre of the Neurocenter of Southern Switzerland, Lugano, Switzerland for friendship, co-authorship, wisdom and, of course, the great hospitality offered by you and your beautiful wife, Barbara, when we were working together in your spectacular hometown of Lugano.

Stephany Fulda, at Sleep and Epilepsy Centre of the Neurocenter of Southern Switzerland, Lugano, Switzerland for excellent help with statistics and co-authoring. My good time in Lugano will always be remembered.

Richard Allen, at the John Hopkins Center for RLS, Baltimore, MD, USA, for advice, feedback, and providing me with the CH-RLSQ11 questionnaire.

Gunilla Lindberg, former head at the Department of Obstetrics and Gynecology in Falun, for giving me time and support.
Tomas Riman, current head at the Department of Obstetrics and Gynecology in Falun, for allowing our clinic to be the most active research unit in Falun Hospital. Thank you also for the fantastic sailing trips in the Stockholm archipelago.

Ann-Christin Cachrimanidou, who took a heavy workload in our obstetric ultrasound department when I was away for research. Despite that, you have always been supportive, and even interested, in my narrow field of research.

All of my other fantastic colleagues at the Department of Obstetrics and Gynecology in Falun who every day made it even more fun to go to our incredibly stimulating job. It has been a pleasure to work with you.

Alkistis Skalkidou, for our fantastic seminar trips to Greece and for your inspiration, knowledge, and practical help.

Charlotte Hellgren and Sara Sylvén, for your excellent work with BASIC, which is sure to generate a huge amount of research data. I am also grateful for having the opportunity to travel with you.

Lennart Myrsell, for instantly making me feel welcome at the sleep laboratory in Avesta hospital, for a second check up of PSG data, and the excellent management and planning of our fine sleep congress.

Hans Wickbom and all of the staff at the sleep laboratory at Avesta hospital, for a very rewarding time with you.

Romana Stehlik, for common hours in front of the polysomnography screens and for being a traveling companion at various congresses.

Paul Murphy, who helped me when I discovered that it takes a loooong time to interpret 400 PSGs.

Marianne Omne-Ponten, for excellent leadership and many wise words at CKF.

Erica Schytt, for support and good advice at CKF.

Maria Pilawa-Podgurski, a day at CKF without you is a boring day. One thing of all – to design posters with you is a delight.

Jan Ifver, for great help with statistics and use of the SPSS program.

My fellow PhD-students at CKF for their wise words and fun discussions during morning coffee breaks and at all of our seminars.
Fellow PhD students at the department for Women’s and Children’s Health, for interesting seminars and good company during our trips to Greece.

Senior colleagues at the antenatal department Uppsala University Hospital, especially Peter Lindgren, Karin Eurenius, Ajlana Lutvica, Eva Bergman, and Ove Axelsson, who, in the best way, shared their expert knowledge with me.

Mats Olofsson and Ove Axelsson, current and former heads of the Department of Women’s and Children’s Health, Uppsala University, for providing excellent working conditions at the institution

Lena Moby, for being such a good friend during our seminar trips on the Mediterranean.

The library att Uppsala University - Campus Gotland, for providing excellent conditions to work with this thesis even when I was supposed to have vacation

Hadley Hooper, Denver, CO, USA, for letting me use your beautiful painting for the cover of this book

Elisabeth Nordström, for your good cooperation in our clinical trials

All of the talented midwives at the antenatal clinic, who had to pick me up at CKF when I was absorbed by science and occasionally forgot an appointment time.

Mum and dad. I still love to make you proud.

My sister Lena. You know how important you were to me. Words are unnecessary.

My niece Annika, for all of your support to me and my family. We love you, you know that.

My brother-in-law Johan, for being around the family and for help with organizing the party.

My mother-in-law Elisabeth, for regularly cutting our unnecessarily large lawn at our summer house at the island of Gotland. When you replaced the drive belt on the lawnmower, it felt like an act of love to me.
**My wife Eva** because there is no one like you. Never a complaining word when I was away on research trips and worked late at CKF. “Life is actually a little simpler when there is just me and the kids at home,” you once told me, and the words spread like balm over my bad conscience. When you say that you long for me, your middle-aged man who over time has become slightly chubby and bald, I admire you even more, my beautiful woman!

**To my children Anders, Maria, and Hanna**, my absolutely unreserved love.
References

53. Sundstrom I, Andersson A, Nyberg S, Ashbrook D, Purdy RH, Backstrom T. Patients with premenstrual syndrome have a different sensitivity to a neuroactive steroid during the menstrual cycle compared to control subjects. Neuroendocrinology 1998 Feb;67(2):126-38.


122. Okun ML, Roberts JM, Marsland AL, Hall M. How disturbed sleep may be a risk factor for adverse pregnancy outcomes. Obstet Gynecol Surv 2009 Apr;64(4):273-80.


188. Kyle SD, Espie CA, Morgan K. "...Not just a minor thing, it is something major, which stops you from functioning daily": quality of life and daytime functioning in insomnia. Behav Sleep Med 2010;8(3):123-40.


226. Kruijver FP, Swaab DF. Sex hormone receptors are present in the human suprachiasmatic nucleus. Neuroendocrinology 2002 May;75(5):296-305.


A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine.