



Turun yliopisto
University of Turku

SLEEP IN CLIMACTERIC

Associative and Predictive Factors

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To my family

ABSTRACT

Laura Lampio – Sleep in Climacteric: Associative and Predictive Factors

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Sleep disturbances are common among climacteric women. However, results from polysomnography studies assessing sleep architecture are contradictory, and there is a lack of prospective polysomnography studies in menopausal women. Causal relationships between menopausal hormonal changes, vasomotor symptoms, aging, and other midlife factors remain to be answered.

This study aimed to characterize subjective sleep disturbances with cross-sectional design between premenopausal and postmenopausal women, and prospectively. Sleep architecture was measured prospectively in menopausal transition. The aim was to understand associations of sleep with menopausal hormonal changes, aging, other menopausal symptoms, and work. Furthermore, possible premenopausal health-related predictors for sleep disturbances during menopausal transition were examined. The study was conducted in 177 Finnish midlife women, recruited via newspaper announcements.

Sleep disturbances after menopause were characterized primarily by insomnia symptoms, but also by symptoms suggesting sleep-disordered breathing. Regarding sleep architecture, aging was associated with more fragmented sleep, lower sleep efficiency, and shorter sleep duration. Increasing follicle stimulating hormone concentration, indicating transition through menopause, was associated with more slow wave sleep. Workdays and vasomotor symptoms were associated with perceived sleep disturbances in postmenopausal women. Predictors for sleep disturbances in menopausal transition were identified in premenopause, such as depressive symptoms, personal crises, and poor perceived health.

Despite poorer subjective sleep quality after menopause, aging seems to be responsible for deteriorated sleep architecture. However, sleep in menopausal women may be more vulnerable to external factors. These data emphasize that not all menopausal sleep disturbances result from vasomotor symptoms, and premenopausal predictors for sleep disturbances are identifiable. Evaluation of sleep and risk factors, and timely interventions, should be provided for midlife women.

Keywords: woman, menopause, climacteric, subjective sleep quality, sleep architecture, polysomnography, vasomotor symptoms, depressive symptoms, work, prospective follow-up cohort, slow wave sleep

TIIVISTELMÄ

Laura Lampio – Uni vaihdevuosien aikana: siihen liittyvät ja sitä ennustavat tekijät

Turun yliopisto, Lääketieteellinen tiedekunta, Naistentaudit ja synnytykset, Keuhko-sairaudet ja kliininen allergologia, Turun kliininen tohtoriohjelma, Unitutkimusyksikkö

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Unihäiriöt ovat yleisiä vaihdevuosi-ikäisillä naisilla. Vaihdevuosien unipolygrafia-tutkimuksia on julkaistu vain vähän, eivätkä ne ole pystyneet osoittamaan selvää unen rakenteen huonontumista. Lisäksi pitkittäistutkimukset, joissa unen rakennetta on tutkittu unipolygrafiaalla, puuttuvat. On siis epäselvää, johtuvatko koetut unihäiriöt vaihdevuosien hormonaalisista muutoksista, muista vaihdevuosisoireista, ikääntymisestä vai yleisesti keski-ikään liittyvistä kuormittavista tekijöistä.

Tässä tutkimuksessa tutkittiin sekä poikkileikkaus- että pitkittäistutkimuksena millaista on koettu unenlaatu vaihdevuosissa. Lisäksi pitkittäistutkimuksella selvitettiin unen rakenteen muutoksia vaihdevuosien siirtymävaiheessa. Tavoitteena oli ymmärtää vaihdevuosissa tapahtuvan hormonitasapainon muuttumisen, ikääntymisen, muiden vaihdevuosisoireiden ja työn vaikutusta uneen. Lisäksi tavoitteena oli tutkia mahdollisia, jo ennen vaihdevuosiä havaittavia, vaihdevuosiajan unihäiriöitä ennustavia terveyteen liittyviä tekijöitä. Tutkimukseen osallistui 177 suomalaista keski-ikäistä naista, jotka rekrytoitiin tutkimukseen lehti-ilmoituksilla.

Koettu huonontunut unenlaatu vaihdevuosien jälkeen selittyi etenkin unettomuusoireilla, mutta osittain myös unenaikaisiin hengityshäiriöihin viittaavilla oireilla. Seuranta-tutkimuksessa ikääntyminen oli yhteydessä rikkonaisempaan ja lyhentyneeseen uneen, sekä alentuneeseen unitehokkuuteen. Nouseva follikkeliä stimuloivan hormonin pitoisuus, viitaten vaihdevuosiin siirtymiseen, puolestaan oli yllättäen yhteydessä lisääntyneeseen syvän unen määrään. Postmenopausaalisilla naisilla etenkin vasomotoriset oireet olivat yhteydessä huonontuneeseen unenlaatuun, ja lisäksi työpäivinä unenlaatu oli huonompi verrattuna premenopausaaliin naisiin. Tutkimuksessa havaittiin useita premenopausaalisia tekijöitä, jotka ennustivat vaihdevuosiajan unihäiriöitä. Näitä olivat muun muassa vaihdevuosiä edeltävät masennusoireet, henkilökohtaiset kriisit ja koettu huono yleinen terveydentila.

Vaihdevuosien jälkeen huonontuneeksi koetusta unenlaadusta huolimatta, epäedulliset unen rakenteen muutokset olivat yhteydessä ikääntymiseen, mutta eivät hormonaalisiin muutoksiin. Vaihdevuosi-ikäisten naisten uni vaikuttaa kuitenkin olevan herkempi erilaisille ulkoisille häiriötekijöille. Tämä tutkimus osoittaa, että kaikki vaihdevuosien aikaiset unihäiriöt eivät liity vasomotorisiin oireisiin, ja että riskitekijöitä vaihdevuosien aikaisille unihäiriöille voidaan osoittaa jo ennen vaihdevuosiä. Terveydenhuollossa tulisikin aktiivisesti kysyä keski-ikäisiltä naisilta myös unihäiriöistä ja niiden riskitekijöistä, ja tarvittaessa tarjota oikea-aikaista tukea ja hoitoa.

Avainsanat: nainen, vaihdevuodet, menopausi, koettu unenlaatu, unen rakenne, unipolygrafia, vasomotoriset oireet, masennusoireet, työ, etenevä seurantatutkimus, syvä uni

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ABBREVIATIONS

AASM	American Academy of Sleep Medicine
AHI	apnea-hypopnea-index
ANOVA	analysis of variance
ARI	arousal index
ASDA	American Sleep Disorders Association
BDI	Beck Depression Inventory
BMI	body mass index
BNSQ	Basic Nordic Sleep Questionnaire
CI	confidential interval
CNS	central nervous system
E ₁	estrone
E ₂	estradiol
EEG	electroencephalogram
EMG	electromyogram
EOG	electro-oculogram
FSH	follicle stimulating hormone
GABA	gamma-aminobutyric acid
HPO	hypothalamic-pituitary-ovarian axis
HT	hormone therapy
IU/L	international units per liter
LH	luteinizing hormone
N	number of participants
NREM	non-rapid eye movement sleep
NS	non-significant
ODI ₄	oxyhemoglobin desaturation of 4% units or more per hour
OR	odds ratio
PLMD	periodic limb movements disorder
PSG	polysomnography

REM	rapid eye movement
RLS	restless legs syndrome
S1/2/3/4	stage 1/2/3/4 NREM sleep
SaO ₂	arterial oxyhemoglobin saturation
SD	standard deviation
SDB	sleep-disordered breathing
SE	sleep efficiency
SHBG	sex hormone binding globulin
SL	sleep latency
SLD	sublaterodorsal tegmental nucleus
ST	sleep time
SWA	slow wave activity
SWAN	Study of Women's Health Across the Nation
SWS	slow wave sleep
TST	total sleep time
WASO	wake after sleep onset

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications, which are referred to in the text by Roman numbers I–IV. The original publications have been reproduced with the permission of the copyright holders.

- I **Lampio L**, Saaresranta T, Polo O, Polo-Kantola P. Subjective sleep in premenopausal and postmenopausal women on workdays and leisure days: a sleep diary study. *Menopause*. 2013 Jun;20(6):655-60.
- II **Lampio L**, Polo-Kantola P, Polo O, Kauko T, Aittokallio J, Saaresranta T. Sleep in midlife women: effects of menopause, vasomotor symptoms, and depressive symptoms. *Menopause*. 2014 Nov;21(11):1217-24.
- III **Lampio L**, Saaresranta T, Polo O, Engblom J, Polo-Kantola P. Predictors of sleep disturbance in menopausal transition. *Maturitas*. 2016 Dec;94:137-142.
- IV **Lampio L**, Polo-Kantola P, Himanen S-L, Kurki S, Huupponen E, Engblom J, Heinonen O, Polo O, Saaresranta T. Sleep during menopausal transition: A six-year follow-up. *Sleep*. 2017 Jul 1;40(7).

1 INTRODUCTION

Menopausal transition has become a target of intense research. The average age of menopause has largely remained unchanged, whereas life expectancy in industrial countries is constantly increasing, and thus women live now more than one third of their lifetime after menopause. Therefore, rising numbers of women undergo menopausal transition during the active phase of their work careers. Menopausal symptoms are associated with decreased quality of life (Avis et al., 2009) and impaired work ability (Jack et al., 2016). Thus, prevention and treatment of menopause-related symptoms and health problems are of the essence.

Good quality and sufficient quantity of sleep are necessary to an individual's health and normal function. Consequently, there is strong evidence that poor or insufficient sleep is associated with decreased quality of life, higher mental and somatic morbidity, and higher mortality (Cappuccio et al., 2010; Stranges et al., 2012). Chronic sleep disturbances are associated with notable economic burden as a result of increased work absenteeism, impaired work ability, and increased health care costs (Daley et al., 2009; Leger et al., 2010).

In menopausal transition, the change in hormonal milieu results in menopausal symptoms, of which vasomotor and depressive symptoms, as well as sleep disturbances, are the most typical. A total of 40–60% of menopausal women report sleep disturbances (Nelson, 2008). The deteriorated subjective sleep quality during menopausal transition and beyond has been verified in both cross-sectional and longitudinal studies (Polo-Kantola, 2011; Shaver et al., 2015). However, a discrepancy between subjective sleep quality and sleep architecture measured with polysomnography (PSG) exists in this group of women. The results of the few existing PSG studies have been contradictory, and most of these studies have not found any deterioration in sleep architecture (Polo-Kantola, 2011; Shaver et al., 2015).

It is not entirely clear whether menopausal sleep problems are directly caused by changes in concentrations of female sex hormones, by aging, or indirectly due to other menopausal symptoms. The prevalence of sleep-disordered breathing (SDB) also increases after menopause (Mirer et al., 2017; Young et al., 2003), and might contribute to sleep disturbances. Moreover, menopausal transition takes place in midlife, which is characterized by multiple stressful life events such as changing family roles, health concerns, or increased demands at work (Darling et al., 2012; Saaresranta, et al., 2013). The impact of these stressors cannot be overlooked in menopausal women with sleep disturbances.

This study was performed in collaboration with the Sleep Research Centre, the Department of Obstetrics and Gynaecology, and the Department of Pulmonary Diseases and Clinical

Allergology at the University of Turku. The aim of this study was to evaluate subjective sleep quality and sleep architecture in midlife Finnish women. Sleep was studied with cross-sectional design in premenopausal and postmenopausal women, as well as with longitudinal design in menopausal transition. The associations of work, as well as vasomotor and depressive symptoms, with sleep were also investigated. An additional aim was to identify possible risk factors already present in premenopause, for sleep disturbances in menopausal transition.

2 REVIEW OF LITERATURE

2.1 Menopause

2.1.1 Definition and physiology

Menopausal transition is a natural process that occurs as a part of normal aging in women. Menopause, defined as the final menstrual period, physiologically results from depletion of ovarian follicles. Perimenopause covers the time from the beginning of the first signs of declining ovarian function (irregular menstruation or vasomotor symptoms) until 12 months from the final menstruation. Postmenopause begins when menopause is diagnosed. The term “climacteric” is used to describe perimenopause and the part of the postmenopausal period in which climacteric symptoms occur. The previous classification of Stages of Reproductive Aging Workshop (STRAW +10) divides women’s late reproductive life into ten stages, according to menstrual cycle length and regularity (Harlow et al., 2012) (Figure 1).

Stage	-5	-4	-3b	-3a	-2	-1	+1 a	+1b	+1c	+2
Terminology	REPRODUCTIVE				MENOPAUSAL TRANSITION		POSTMENOPAUSE			
	Early	Peak	Late		Early	Late	Early		Late	
Duration	variable				variable	1-3 years	2 years (1+1)	3-6 years	Remaining lifespan	
PRINCIPAL CRITERIA										
Menstrual Cycle	Variable to regular	Regular	Regular	Subtle changes in Flow/ Length	Variable Length Persistent ≥7- day difference in length of consecutive cycles	Interval of amenorrhea of ≥=60 days				
SUPPORTIVE CRITERIA										
Endocrine FSH AMH Inhibin B			Low Low	Variable* Low Low	↑ Variable* Low Low	↑ >25 IU/L** Low Low	↑ Variable Low Low	Stabilizes Very Low Very Low		
Antral Follicle Count			Low	Low	Low	Low	Very Low	Very Low		
DESCRIPTIVE CHARACTERISTICS										
Symptoms						Vasomotor symptoms <i>Likely</i>	Vasomotor symptoms <i>Most Likely</i>		Increasing symptoms of urogenital atrophy	

* Blood draw on cycle days 2-5 ↑ = elevated

**Approximate expected level based on assays using current international pituitary standard⁶⁷⁻⁶⁹

Figure 1. The Stages of Reproductive Aging Workshop +10 staging system for reproductive aging in women. (Reprinted from Harlow et al. 2012, with permission from Elsevier).

The ovarian function begins to deteriorate, and the function of the hypothalamic-pituitary-ovarian (HPO) axis to change, already years before menopause, and thus endocrinological changes typically occur gradually. The first signs of approaching menopause are the decline in the number of oocytes and ovulatory cycles, leading to irregular menstrual cycles. The depletion of functional follicles in the ovaries causes a decrease of estradiol (E_2) and inhibin secretion from the ovaries. This leads to suppression of the negative feedback to control the production of gonadotrophins, resulting in increased follicle stimulating hormone (FSH) and luteinizing hormone (LH) production from the pituitary gland (Figure 2). After menopause, FSH concentrations are 10–15 times higher than in young women during the follicular phase (Burger, 1996). After the decline in ovarian estrogen production, the main estrogen is estrone (E_1), derived mainly from peripheral aromatization of androstenedione in muscle and adipose tissue. Since aromatization mostly takes place in adipose tissue, E_1 concentrations are higher in overweight postmenopausal women compared to their normal-weight counterparts (Burger, 1996). In addition, ovarian progesterone production decreases. The production of testosterone from ovaries remains quite unchanged, but adrenal production of dehydroepiandrosterone and dehydroepiandrosterone sulfate decreases, following a decrease in overall circulating androgen concentrations. Only a small percentage of testosterone is in biologically active, circulating form; testosterone is mostly bound to sex hormone binding globulin (SHBG). The concentration of SHBG rises progressively from late adolescence, accelerating after the age of 70 (Handelsman et al., 2016).

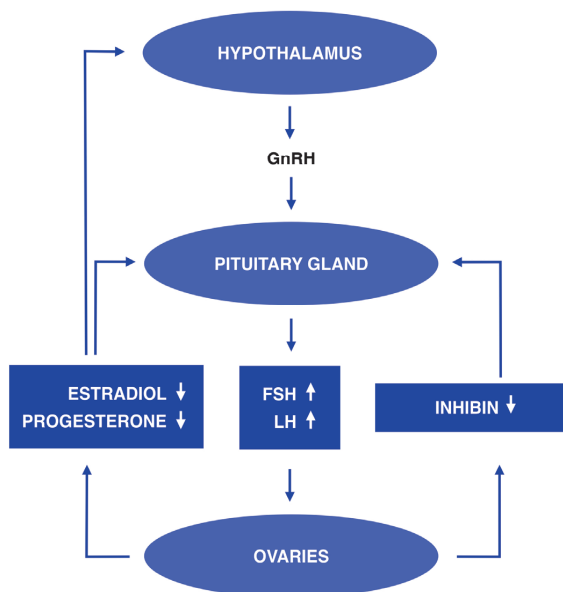


Figure 2. Changes in hypothalamic-pituitary-ovarian (HPO) axis during menopause. FSH, follicle stimulating hormone; LH, luteinizing hormone. (Modified from Mikkola, Vaihdeveduet in Naistentaudit ja synnytykset. 2011, with permission from Duodecim.)

The average age for natural menopause in Finland is 51 years (Luoto et al., 1994), and menopausal transition usually starts at about 47 years and lasts approximately five to eight years (Roberts et al., 2016). The current life expectancy for women in Finland is over 84 years (Statistics Finland, 2017).

2.1.2 Menopausal symptoms

As a consequence of fluctuations and decline in estrogen concentration, climacteric symptoms usually occur, especially during the menopausal transition. The occurrence and severity of symptoms vary widely; some women do not recognize any symptoms whereas, in some women, symptoms are extremely severe, leading to sick leave. Also, the duration of the symptoms varies, typically lasting one to five years. However, in some women, symptoms may persist more than 10 years (Avis et al., 2015; Freeman et al., 2011). In a longitudinal study, Avis and colleagues evaluated the duration of menopausal vasomotor symptoms over the menopausal transition among 3302 women, and found that frequent (≥ 6 days in the previous two weeks) vasomotor symptoms persisted for 4.5 years after menopause and lasted more than seven years for half of the women (Avis et al., 2015). Besides vasomotor symptoms, the most important climacteric symptoms are sleep disturbances, as well as depressive and anxiety symptoms. Other common symptoms include palpitations, headache, myalgia, memory impairment, vaginal dryness, and sexual dysfunction (Table 1).

Table 1. Typical menopausal symptoms and their occurrences.

Symptom	Occurrence (%)
Hot flashes and/or night sweats	36 – 87
Sleep problems	40 – 60
Mood symptoms	15 – 78
Weight gain	60 – 70
Muscle and/or joint pain	48 – 72
Palpitation	44 – 50
Headache	32 – 71
Memory impairment	41 – 44
Genitourinary symptoms	25 – 30
Sexual dysfunction	20 – 30

Brincaat et al. 1988, Kronenberg et al. 1990, Erkkola et al. 1991, Gold et al. 2000, Nelson 2008, Joffe et al. 2010, Archer et al. 2011, Santoro 2016.

2.1.2.1 Vasomotor symptoms

Vasomotor symptoms, referred to as hot flashes and night sweats, are the most typical menopausal symptoms, affecting up to 80% of women (Archer et al., 2011; Kronenberg, 1990). The precise mechanisms of vasomotor symptoms are poorly understood, but they are assumed to result from disturbance of the temperature-regulating system in the hypothalamus, triggered by a decline in estrogen concentration (Archer et al., 2011). Vasomotor symptoms may occur at any time of the day, and usually begin with sensations of heat or warmth in the upper body, caused by peripheral vasodilation, elevated skin blood flow, and temperature. These symptoms then spread to the head and lower body, producing sweating, reddening of the skin, and sometimes palpitations (Freedman, 2014). According to a theory proposed by Freedman and colleagues, who have done extensive research on vasomotor symptoms, hot flashes are triggered by small elevations in core body temperature acting within a narrowed thermoneutral zone. Core body temperature is regulated between an upper threshold for sweating and a lower threshold for shivering. Freedman and colleagues hypothesized that the heat dissipation response (peripheral vasodilation, sweating) of a hot flash would be provoked if core body temperature exceeds the upper threshold (Freedman, 2014). The duration of a flash usually ranges from one to five minutes, but some flashes may last up to 60 minutes (Archer et al., 2011; Freedman, 2014). Night sweats occur during sleep, possibly causing an awakening; women wake up covered with perspiration (Oldenhave et al., 1993). Factors related to the longer occurrence of vasomotor symptoms include pre- or early perimenopausal state, younger age, lower educational level, greater perceived stress, and symptom sensitivity, as well as higher depressive and anxiety symptoms at the first occurrence of vasomotor symptoms (Avis et al., 2015). In addition, higher body mass index (BMI) and African-American race have been linked to longer duration of vasomotor symptoms (Avis et al., 2015; Freeman et al., 2011).

2.1.2.2 Depressive symptoms

The risk for experiencing depressive symptoms increases during menopausal transition, presumably independently of other factors (Bromberger et al., 2007; Bromberger et al., 2011; Cohen et al., 2006; Freeman et al., 2006; Steinberg et al., 2008). A total of 15–50% of women report depressive symptoms during menopausal transition (Toffol et al., 2015). According to the longitudinal data of the Study of Women's Health Across the Nation (SWAN), women were two to four times more likely to develop a major depressive disorder in menopausal transition and in early postmenopause compared to premenopausal women, when adjusted for possible confounding factors (Bromberger et al., 2011). Fluctuations and an eventual drop in estrogen concentrations have been hypothesized to be responsible for impaired mood (Borrow et al., 2014; Soares, 2014). As a matter of fact, estrogen appears to be closely related to maintaining mood in women since, in conditions where E₂ concentrations sharply decrease, the risk for depressive symptoms increases

(Borrow et al., 2014; Douma et al., 2005). Furthermore, women who have experienced mood symptoms during the premenstrual phase of the menstrual cycle, during postpartum, or when taking hormonal contraceptives seem to be at risk for depressive symptoms in menopausal transition (Studd, 2011). It has been suggested that the effects of estrogen on serotonin and noradrenalin neurotransmission play an important role in the development of depressive symptoms in women. According to the literature, estrogen seems to act through numerous pathways resulting in increased serotonin and noradrenalin neurotransmission, both of which are considered significant contributors to the regulation of mood (Borrow et al., 2014; Soares, 2014). There is some evidence that menopausal hormone therapy (HT) alleviates depressive symptoms in menopausal transition, especially if combined with antidepressants (Borrow et al., 2014; Soares, 2014; Toffol et al., 2015; Westlund et al., 2003).

2.1.2.3 Cognitive symptoms

Memory problems and other cognitive complaints are common in menopausal women. In the cross-sectional SWAN study of 16,065 women aged 40–55 years, forgetfulness was reported in 44.0% of early perimenopausal women, 44.8% of late perimenopausal women, and 41% of postmenopausal women, while 31.2% of premenopausal women reported forgetfulness (Gold et al., 2000). Menopausal hormonal changes account for these changes, at least to some extent; according to longitudinal studies, the deterioration of memory performance across menopausal transition was evident after adjusting for age and other possible confounding factors (Epperson et al., 2013; Greendale et al., 2009). Studies that evaluated cognitive performance with objective measures have verified the complaints of menopausal women as well (Schaafsma et al., 2010; Weber et al., 2012). However, HT does not seem to improve cognitive performance after menopause (Henderson, 2014; Polo-Kantola et al., 1998).

2.2 Sleep

2.2.1 Sleep regulation

The sleep-wake cycle is regulated by two biological processes, which interact and balance each other. This “two-process model” is composed of circadian process C and homeostatic process S (Borbely, 1982). Circadian rhythm (*circa dia*) is an approximately 24-hour regulation cycle of the body’s internal processes and alertness levels, and is also found in plants and animals. This biological clock regulates the timing of sleep and in humans is located in the suprachiasmatic nucleus of the hypothalamus. Environmental light is the most important pacemaker of the circadian process, but daily fluctuations in core body temperature and plasma melatonin concentration, as well as other environmental, genetic, and age-related factors, influence the circadian process (Dogas et al., 2014). Sleep-wake

homeostasis, or process S, is an internal mechanism that produces a pressure to sleep and regulates sleep intensity; i.e. the longer we are awake, the stronger the need to sleep, and vice versa. Pressure to sleep is strongest in the initial part of the sleep period and decreases progressively. Slow wave activity (SWA) in an electroencephalogram (EEG) is considered to be a marker of the homeostatic process, and its occurrence is the highest in the beginning of sleep. As part of the homeostatic process, adenosine and nitric oxide accumulate in the basal forebrain during wakefulness and act as inhibitory neuromodulators (Porkka-Heiskanen, 2013). Regulation of sleep homeostasis probably occurs in the forebrain (Porkka-Heiskanen, 2013).

Several brain areas are involved in regulation of sleep, the most important of which are the medulla oblongata, pons, formation reticularis, midbrain, thalamus, hypothalamus, preoptic area, basal forebrain, hippocampus, and cerebral cortex. Sympathetic activity is predominant during wakefulness, which is induced by several neurochemical systems. The hypocretin neurons in the tuberal hypothalamus activate all other waking systems, including histaminergic neurons in the tuberomamillary nucleus, serotonergic neurons in the dorsal raphe nucleus, noradrenergic neurons in the locus coeruleus, and cholinergic neurons in the basal forebrain. These systems, in turn, activate the thalamus and cortex, leading to cortical activation and inhibition of inhibitory gamma-aminobutyric acid (GABA) neurons in the ventrolateral preoptic nucleus and median preoptic nucleus (Luppi et al., 2014).

During sleep, parasympathetic activity prevails and wake-promoting systems are inhibited. Neurons responsible for sleep onset and maintenance are primarily located in the preoptic area. GABA is the main inhibitory neurotransmitter in the brain. At sleep onset, GABAergic neurons in the ventrolateral preoptic nucleus and median preoptic nucleus are activated in response to the circadian clock (circadian process) and the accumulation of adenosine during wake (homeostatic process). These neurons inhibit all wake-promoting systems producing sleep, particularly slow wave sleep (SWS). Rapid eye movement (REM) sleep is thought to be produced by glutamatergic and GABAergic REM-on neurons located in the brainstem: more precisely, in the sublaterodorsal tegmental nucleus (SLD) and the posterior lateral hypothalamic area. These neurons also activate the REM-off monoaminergic neurons during REM. The disinhibited ascending SLD REM-on neurons induce cortical activation via their multiple projections. In turn, descending SLD REM-on neurons are thought to induce muscle atonia via the projections to glycinergic pre-motoneurons in gigantocellular reticular nuclei. The exit from REM is supposedly caused by the activation of wake and arousal systems (Luppi et al., 2014).

Various hormones are also involved in sleep regulation, such as growth hormone, cortisol, melatonin, prolactin, and ovarian hormones, usually via complex pathways not fully understood. Concentrations of growth hormone, prolactin, and melatonin are decreased in

older adults (Kalleinen et al., 2008; Toffol et al., 2014). Melatonin is secreted mainly from the pineal gland and is associated with the regulation of circadian rhythm. Light inhibits melatonin synthesis (Arendt, 2005). Melatonin secretion follows a circadian rhythm; it increases approximately two hours before sleep onset, reaches its highest level during the night, and decreases in the early morning. Administration of exogenous melatonin decreases sleep latency (Aeschbach et al., 2009). Growth hormone-releasing hormone stimulates growth hormone release, which in turn is related to the occurrence of SWS (Gronfier et al., 1998). Growth hormone is secreted in a pulsatile manner from the anterior pituitary gland, mostly at night and shortly after sleep onset, mainly during SWS (Holl et al., 1991; Van Cauter et al., 2000). However, the temporal relationship between growth hormone and SWS is weaker after menopause when compared to premenopause (Kalleinen et al., 2012). The secretion of prolactin is sleep-wake dependent; the concentration increases gradually after sleep onset and reaches its maximum during the end of sleep. A temporal relationship between prolactin release and SWA has been found, as well as an association between prolactin release and SWS (Steiger, 2003). Both growth hormone and prolactin concentrations have been shown to decrease after menopause, but the effects are reversible with HT (Kalleinen et al., 2008). Cortisol secretion follows a diurnal pattern; concentrations are lowest in the first half of the night and increase during the second half of the night, reaching the highest level in the early morning (Gronfier et al., 1998). Administration of exogenous cortisol increases SWS but decreases REM, probably because of negative feedback inhibition of corticotrophin-releasing hormone (corticotrophic axis) (Steiger, 2003). However, sleep disturbances have been associated with both daytime and nighttime elevated endogenous cortisol concentrations (Morgan et al., 2017; Spath-Schwalbe et al., 1991; Vgontzas et al., 2003). Progesterone has sedative properties (Lancel et al., 1996), and is a respiratory stimulant (Saareanta et al., 2002). Estrogen has several effects in the brain; its impact on sleep in humans has mostly been evaluated indirectly in HT studies (see Chapter 2.3.4).

2.2.2 Subjective sleep quality

The term “subjective sleep disturbances” usually refers to insomnia symptoms, but may include symptoms of other sleep disorders, e.g. SDB or restless legs syndrome (RLS). According to the American Academy of Sleep Medicine (AASM), the diagnosis of insomnia as a sleep disorder is defined by at least one nighttime symptom (e.g. difficulty initiating or maintaining sleep, or early morning awakening) together with at least one daytime symptom as a consequence of nighttime sleep difficulty (e.g. fatigue, tiredness, reduced attention, cognition or memory impairment, mood disturbance, or irritability), and where the sleep disturbances cannot be explained by inadequate opportunity to sleep or clear association with another disorder. In addition, the symptoms should occur at least three times per week, and the minimum duration of the condition should be at least three months (American Academy of Sleep Medicine, 2014). Insomnia symptoms, however, are

much more common than insomnia that is formally diagnosed (Riemann et al., 2014). Transient insomnia symptoms affect approximately 30–48% of the general population (Ellis, 2014), but chronic insomnia is diagnosed in approximately 10% (Baglioni et al., 2014). In the Finnish population, transient insomnia symptoms are reported in 30–45% and chronic insomnia in approximately 9–12% (Kronholm et al., 2016; Ohayon et al., 2002). Generally, older age, female sex, and lower socioeconomic status, as well as previously diagnosed insomnia, positive family history of insomnia, and poor perceived mental and general health are risk factors for insomnia (Ellis, 2014; Jarrin et al., 2017; LeBlanc et al., 2009; Morin et al., 2006).

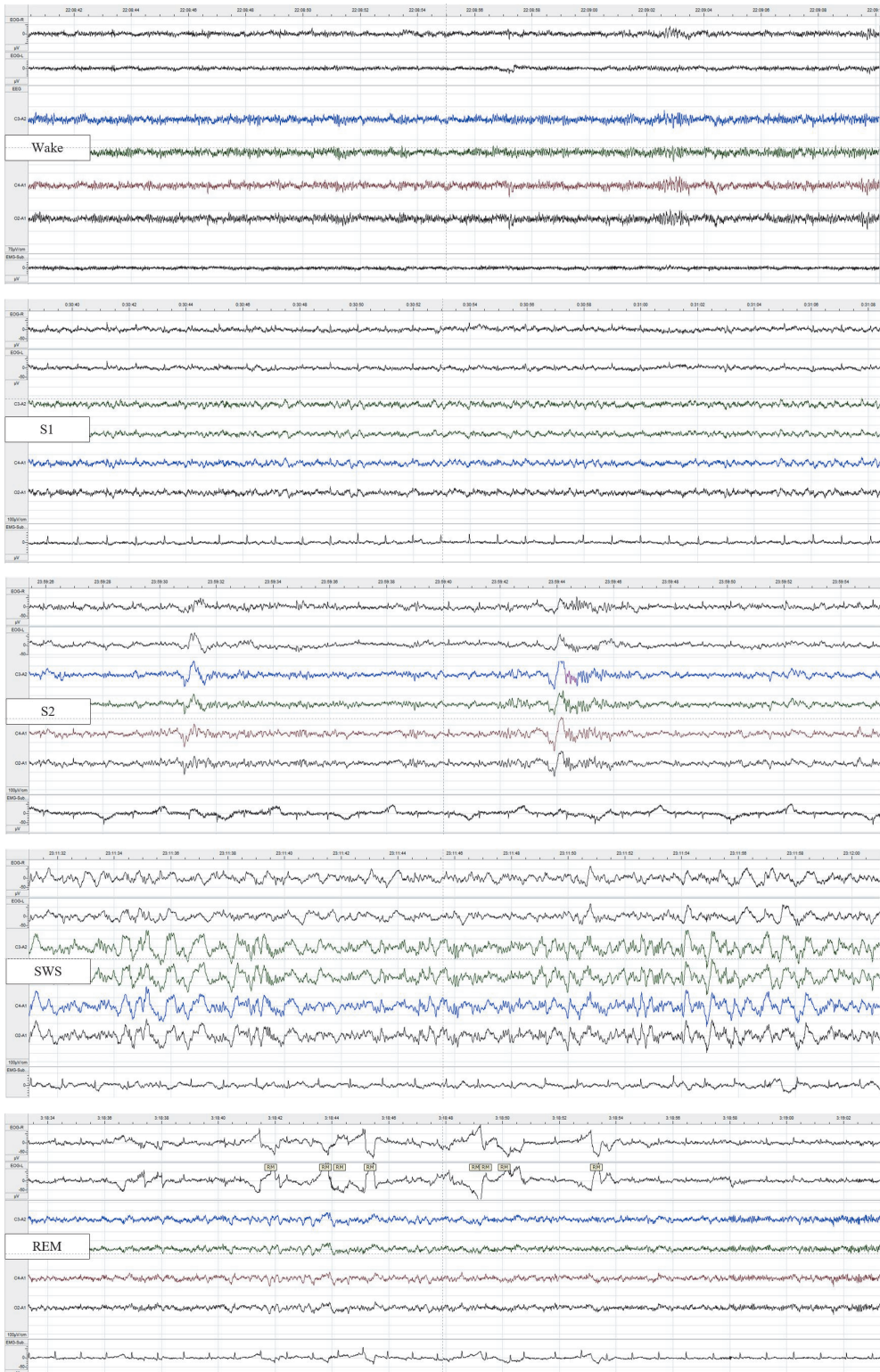
Perceived sleep disturbances and their consequences are clinically evaluated with structured questionnaires. Several validated questionnaires have been created. For example, the Insomnia Severity Index defines the severity of insomnia (Morin et al., 2011), while the Pittsburgh Sleep Quality Index (Buysse et al., 1989) and Basic Nordic Sleep Questionnaire (BNSQ) (Partinen et al., 1995) are general questionnaires that assess other sleep disorders in addition to insomnia. Furthermore, the Epworth Sleepiness Scale (Johns, 1991) and the Glasgow Sleep Effort Scale (Broomfield et al., 2005) evaluate daytime symptoms. Sleep diaries, usually covering a period of 14 days, are considered to be the “gold standard” in evaluating subjective sleep quality in clinical practice, and are also useful instruments in scientific research (Carney et al., 2012). In addition, it is necessary to examine the patient’s other physical and psychiatric morbidity, as well as to ask about the medication in use.

2.2.3 Sleep architecture

Sleep can be objectively measured with PSG, which consists of an EEG, electro-oculogram (EOG), and electromyogram (EMG). According to the conventional criteria of Rechtschaffen & Kales (Rechtschaffen et al., 1968), sleep is divided into wake, non-rapid eye movement (NREM) sleep, and REM sleep. NREM is further divided into stages S1–S4. S1 is regarded as a transition phase between wakefulness and sleep, seen primarily as synchronous mixed theta activity in an EEG. S2 is characterized as the appearance of sleep spindles and K complexes. S3 and S4 are usually grouped together as SWS. SWS represents the deepest sleep state, and is described as high-amplitude, low-frequency delta waves in an EEG. S3 is identified when high-voltage SWA accounts for 20–50% of the EEG activity in a 30-second analysis window (epoch), and S4 when SWA consists of more than 50%. The arousal threshold is lowest in S1 and highest in S4 sleep. REM sleep is characterized by rapid desynchronized low-amplitude EEG activity, loss of EMG activity, and presence of rapid eye movements. In the newer AASM criteria (Berry et al., 2017; Iber et al., 2007), stage 1 NREM sleep (N1) refers roughly to S1, stage 2 NREM sleep (N2) to S2, and stage 3 NREM (N3) to SWS in the conventional classification (Rechtschaffen et al., 1968). (Figures 3 and 4.)

NREM and REM sleep occur alternately throughout the night in periods of approximately 90 to 110 minutes, referred to as sleep cycles. Normally, sleep comprises 2–5 % of S1, 45–55% of S2, 13–23% of SWS, and 20–25% of REM in young adults (Dogas et al., 2014). SWS episodes are longest at the beginning of sleep and, as sleep progresses, NREM becomes shorter and lighter, comprising mostly S2 while REM episodes become longer. Sleep is interrupted by physiological short awakenings and arousals. (Figure 5). In addition to the percentages of sleep stages and total sleep time (TST), sleep latency (SL), sleep efficiency (SE), and the number of arousals and awakenings are typically determined from PSG-measured sleep. SE equals TST divided by time in bed, and is expressed as a percentage (%). The average sleep duration in the general population ranges from 7 to 8.5 hours. Short sleepers are usually defined as those with a sleep duration of ≤ 6 hours per night, while long sleepers have sleep durations of ≥ 9 hours per night. The first study to find a U-shaped association between sleep duration and mortality was completed in the 1960s (Hammond, 1964), and that finding has been confirmed in a number of later studies (Cai et al., 2015; Cappuccio et al., 2010b; Gallicchio et al., 2009). In addition, the U-shaped association between sleep duration and morbidity is well established (Capers et al., 2015; Cappuccio et al., 2010a; Guo et al., 2013; Kronholm et al., 2011; Meisinger et al., 2007).

Several methods are used to measure sleep and nocturnal breathing. In addition to PSG, sleep-wake rhythm can be studied with a wrist-actigraphy device. Breathing patterns, body movements, and heartbeat can be studied with ballistocardiographic sensors (Ekholm et al., 1992; Polo, 1992; Tenhunen et al., 2013). Nocturnal breathing can also be measured and characterized by using abdominal and thoracic belts, nasal prongs, finger pulse oximeters, transcutaneous carbon dioxide monitoring (Aittokallio et al., 2009; Rimpilä et al., 2014), and pulse transit time (Pitson et al., 1995). Nocturnal movement disorders are detected with movement sensors. Several novel solutions using health technology are available, but the validation and feasibility data for different applications are still scarce. These objective sleep measures are frequently used in scientific research, as well as for clinical purposes. However, the correspondence between subjectively and objectively measured sleep is not unambiguous (McCrae et al., 2005; Rosa et al., 2000; Westerlund et al., 2016; Åkerstedt et al., 1994). One study of 150 healthy men and women (mean age 67.5 years) observed a correspondence between subjective and objective sleep quality, measured with PSG, in men but not in women (Vitiello et al., 2004). In a study of 251 women, Åkerstedt et al. found that poor subjective sleep quality was related to short TST, long wake within TST, low SE, and a high number of awakenings (Åkerstedt et al., 2016). They also observed that older women were satisfied with poorer sleep architecture than younger women (Åkerstedt et al., 2016). However, it must be kept in mind that the individual's perceptions of sleep disturbance and daytime consequences are more likely to direct diagnosis and treatment.



◀ **Figure 3.** Wake and sleep stages (S1, S2, SWS, and REM). The two upper channels are EOG channels, the lower four are EEG channels (C3/A2, C4/A1, O1/A2, O2/A1), and the lowest is an EMG channel. In some sleep stages, ECG is shown in EMG. S1, stage 1 NREM sleep; NREM, non-rapid eye movement sleep; S2, stage 2 NREM sleep; SWS, slow wave sleep; REM, rapid eye movement sleep; EOG, electro-oculogram; EEG, electroencephalogram; EMG, electromyogram; ECG, electrocardiogram.

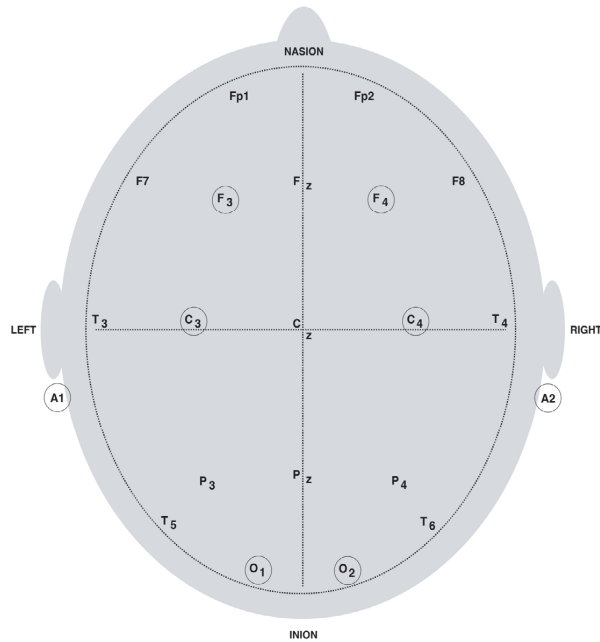


Figure 4. EEG channels normally used in polysomnography. In Study IV, channels C3/A2, C4/A1, O1/A2, and O2/A1 were used. Channels A1 and A2 are reference channels.

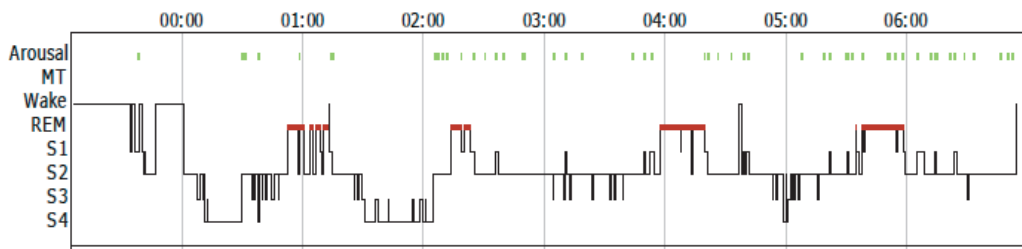


Figure 5. A sleep hypnogram. MT, movement time; REM, rapid eye movement sleep; S1, stage 1 NREM sleep; NREM, non-rapid eye movement; S2, stage 2 NREM sleep; S3, stage 3 NREM sleep; S4, stage 4 NREM sleep.

2.2.4 Importance of sleep

Good and sufficient sleep is necessary for overall well-being and function. Poor or inadequate sleep affects several dimensions of an individual's life. There is good evidence from general populations that chronic sleep disturbances, especially insomnia symptoms, are associated with both mental and physical negative health outcomes. Individuals with disturbed sleep are at higher risk for cardiovascular diseases (Fernandez-Mendoza et al., 2012; He et al., 2017; Laugsand et al., 2011; Laugsand et al., 2014), diabetes (Lai et al., 2013; Vgontzas et al., 2009), and depression (Baglioni et al., 2011), as well as for suicide attempts (Ribeiro et al., 2012). In addition, subsequent cognitive impairment has been reported, which is not directly associated with reduced alertness (Fortier-Brochu et al., 2012; Shekleton et al., 2014). Besides ill health, a decrease in quality of life is strongly associated with sleep disturbances (Ishak et al., 2012; Kyle et al., 2010).

The prevalence of insomnia symptoms among the Finnish working-age population is increasing (Kronholm et al., 2008; Kronholm et al., 2016), and this trend is also seen globally (Calem et al., 2012; Pallesen et al., 2014). Therefore, this common public health problem has major economic consequences as well (Daley et al., 2009; Leger et al., 2010). Sleep disturbances are related to increased work absenteeism (Lallukka et al., 2014; Rahkonen et al., 2012; Salo et al., 2010; Sivertsen et al., 2009), poor work performance (Bolge et al., 2009; Daley et al., 2009), accidents, and increased health care costs (Daley et al., 2009; Shahly et al., 2012). A recent population-based cohort study of 3760 working-aged Finnish men and women found that insomnia symptoms were associated with absence due to illness, but excessive daytime sleepiness, probable sleep apnea, and seasonal variations of sleep duration were not (Lallukka et al., 2014). In addition, a U-shaped association with sleep duration and absence due to illness was found (Lallukka et al., 2014). Furthermore, sleep disturbances have been shown to increase the risk for disability retirement (Lallukka et al., 2011). Hence, the economic burden of sleep disturbances, especially insomnia symptoms, is significant. For example, in the United States, the estimated yearly costs of insomnia symptoms due to poor work performance and work absenteeism are over \$60 billion (Kessler et al., 2011).

2.2.5 Sleep in women

Women report more disturbed or insufficient sleep in all ages across their lifespan (Mong et al., 2016; Zhang et al., 2006), and have higher risk for insomnia than men (Jaussent et al., 2011; Singareddy et al., 2012). Despite the fact that women are more dissatisfied with their sleep, a paradox exists. PSG studies have shown better sleep architecture in women compared to men, as men have more S1 sleep whereas women have more SWS (Porkka-Heiskanen et al., 2014). A study of 1324 women and men without sleep disturbances, aged 20–88 years, showed that women had longer TST, less S1, more SWS, and longer REM

latency than men (Bixler et al., 2009). After sleep deprivation, women also have more recovery sleep (Porkka-Heiskanen et al., 2014). In addition, RLS and periodic limb movement disorder (PLMD) are more prevalent in women (Berger et al., 2004; Porkka-Heiskanen et al., 2014). SDB is more common in men (Peppard et al., 2013); however, after menopause the prevalence in women approaches that of men (Mirer et al., 2017).

Estrogen and progesterone receptors are found in several brain areas responsible for sleep regulation (McEwen et al., 1994) and, in addition to reproductive functions, female sex hormones have a role in the regulation of sleep and circadian rhythms (Mong et al., 2016). However, the exact mechanisms are still largely unknown (Mong et al., 2016). Indeed, women are particularly prone to sleep disturbances in certain female life conditions where significant fluctuations of female sex hormones, especially estrogen, are present. These conditions include pregnancy, postpartum, and menopausal transition (Nowakowski et al., 2013; Polo-Kantola et al., 2017; Porkka-Heiskanen et al., 2014; Shaver et al., 2015). Moreover, small sleep architecture changes following the menstrual cycle have also been observed (Porkka-Heiskanen et al., 2014; Zheng et al., 2015), and women suffering from premenstrual syndrome and premenstrual dysphoric disorder typically perceive insomnia symptoms (Nowakowski et al., 2013).

2.3 Menopause and sleep

2.3.1 Subjective sleep quality

Among menopausal symptoms, sleep disturbances are perhaps the most bothersome, and are reported in 40–60% of menopausal women (Nelson, 2008). There is convincing evidence that the prevalence of perceived sleep disturbances increases in menopausal transition. This has been shown in several cross-sectional studies (Cheng et al., 2008; Hung et al., 2014; Kravitz et al., 2003; Shin et al., 2005; Sun et al., 2014; Timur et al., 2009; Young et al., 2003), as well as in several large longitudinal studies from the United States of America (Kravitz et al., 2008; Woods et al., 2010), the United Kingdom (Tom et al., 2010), and from Australia (Berecki-Gisolf et al., 2009). In the cross-sectional SWAN study with 12,603 women, sleep was evaluated with a single question about difficulty sleeping during the past 2 weeks (Kravitz et al., 2003). The prevalences for difficulty sleeping increased from premenopause (31.4%) to late perimenopause (45.4%), and plateaued through postmenopause (43.2%) after adjusting for age (Kravitz et al., 2003).

When subjective sleep quality has been evaluated more in detail, decreased sleep quality seems to be related mostly to nighttime awakenings, as well as to difficulty falling asleep (Cheng et al., 2008; Kravitz et al., 2008; Shin et al., 2005; Woods et al., 2010). According to the longitudinal SWAN study's seven-year follow-up with 3045 women, odds ratios (OR) for difficulty falling asleep and staying asleep increased through

menopausal transition, but decreased for early morning awakening from late perimenopause to postmenopause after adjusting for demographics, health-related factors, and health behavioral factors (Kravitz et al., 2008). In an Australian longitudinal study of over 8000 women, OR for difficulty sleeping was increased in all menopausal transition stages compared to premenopause, and was the highest in early postmenopause (Berecki-Gisolf et al., 2009). Another longitudinal study of 286 women found that, after adjustment of age and other confounding factors, only awakenings increased during the menopausal transition, whereas difficulty falling asleep decreased during early postmenopause (Woods et al., 2010). However, the Penn Ovarian Aging Study surprisingly did not find a relationship between poor sleep quality and menopausal stages (Freeman et al., 2015).

Some of the longitudinal studies were random population studies (Berecki-Gisolf et al., 2009; Freeman et al., 2015; Tom et al., 2010), but not all. Menopausal grouping was based on menstrual patterns in all studies. All longitudinal studies have used only 1–3 general questions of sleep quality or insomnia (Berecki-Gisolf et al., 2009; Freeman et al., 2015; Kravitz et al., 2008; Tom et al., 2010; Woods et al., 2010). (See Appendix 1.) Symptoms of SBD or excessive daytime sleepiness have been assessed in only a few cross-sectional studies (Chedraui et al., 2010; Cheng et al., 2008; Young et al., 2003). The association between FSH concentration and self-reported sleep has also been studied. Deteriorated subjective sleep quality has been associated with increasing FSH concentration in longitudinal studies (Kravitz et al., 2008; Woods et al., 2010), in line with the studies assessing sleep in different menopausal stages. In a study by Kravitz and colleagues, increasing FSH was associated with higher odds of waking up several times, whereas decreasing E_2 was associated with higher odds of difficulty falling and staying asleep (Kravitz et al., 2008).

2.3.2 Sleep architecture

Even though the evidence for decreasing subjective sleep quality during menopausal transition is strong, the PSG studies have not been able to find an association between physiological changes in sleep and subjective complaints. Furthermore, studies evaluating sleep duration, continuity and changes in sleep architecture in healthy women during menopausal transition, not focusing on vasomotor or depressive symptoms, are sparse. Generally, those studies have been cross-sectional and small-sample studies with only a few exceptions (Hachul et al., 2015; Young et al., 2003). Furthermore, comparing the studies is difficult because of varying menopausal grouping and age range and, in addition, some study protocols have included an adaptation night and some have not. Hence, the results have been contradictory, as some studies have found no differences in sleep architecture between pre- and postmenopausal women (Campbell et al., 2011; Freedman et al., 2004; Kalleinen et al., 2008; Shaver et al., 1988), while a few studies have reported

paradoxically better sleep patterns in postmenopausal women (Hachul et al., 2015; Sharkey et al., 2003; Young et al., 2003).

A cross-sectional study of 589 women showed that postmenopausal women had higher SE, more SWS, and less S2 than premenopausal women (Young et al., 2003). A recent study by Hachul et al. gained similar results in their cross-sectional study of 535 reproductive (mean age 34.6 years, SD 8.4), early postmenopausal (the first five years after menopause), and late postmenopausal (more than five years from menopause) women with a wide age range (20–80 years): Postmenopausal women had a higher amount of SWS compared to premenopausal women after adjustment for age, BMI, blood pressure, neck, waist, and hip circumference (Hachul et al., 2015). However, in that study, postmenopausal women also had a higher apnea-hypopnea index (AHI) and lower arterial oxyhemoglobin saturation (SaO₂) compared to premenopausal women (Hachul et al., 2015). Sleep parameters did not differ between early and late postmenopausal women in the adjusted analyses (Hachul et al., 2015), nor did parameters differ in their previous study of 30 early and late postmenopausal women aged 50–60 years (Hachul et al., 2009). Another large study (n = 931) by Hachul and colleagues with reproductive (mean age 38.8 years, SD 10.4) and postmenopausal (mean age 55.9 years, SD 7.9) women found that postmenopausal women had more SWS, less S2, and less REM sleep compared to reproductive women. However, the findings lost their significance after adjustment for age and BMI (Hachul et al., 2010). One Canadian study found that sleep architecture was worse in peri- and postmenopausal women compared to premenopausal women, as peri- and postmenopausal women had more wake after sleep onset (WASO) and lower SE compared to premenopausal women, but the participants were insomnia patients (Xu et al., 2011). Baker and colleagues found similar results in their cross-sectional study, where two groups of women in menopausal transition were compared. One group developed insomnia disorder during the transition and the other did not. The study found that menopausal women who had developed insomnia had shorter sleep duration, more WASO, and poorer SE compared to menopausal women who did not develop insomnia. However, the effect of menopause was not assessed (Baker et al., 2015). (Appendix 2.)

An association between FSH concentration and sleep architecture has been evaluated in a few studies, and in general, higher FSH concentration has been associated with negative findings in sleep architecture (Antonijevic et al., 2003; de Zambotti et al., 2015). A sub-study of the SWAN, however, concluded that a more rapid rate of FSH change was associated with higher SWS percentages and longer TST in the cross-sectional study of 365 pre-, peri- and postmenopausal women. They measured FSH annually over seven years prior to one sleep recording (Sowers et al., 2008). Another cross-sectional study on perimenopausal (aged 43–52 years) women with and without insomnia found that higher FSH concentrations were associated with increased WASO, awakenings, and arousals in perimenopausal women without insomnia after adjusting for age, BMI, and hot flashes. However, in perimenopausal women with insomnia, FSH did not correlate with PSG-

measured sleep. TST was associated with anxiety and depression (de Zambotti et al., 2015). (Appendix 2.) According to a small study that evaluated associations of sleep and HPO axis hormones in a group of pre- and postmenopausal women with diagnoses of depression, FSH level was positively associated with WASO and negatively associated with SWS (Antonijevic et al., 2003).

Spectral analysis of EEG has been proposed to provide additional information about sleep in menopausal women, considering the conflicting results from PSG studies, but the number of studies is small. In cross-sectional studies, SWA has not been found to be associated with menopausal status (Campbell et al., 2011; Kalleinen et al., 2008). However, Campbell and co-workers found that beta EEG power, indicative of arousal, was elevated in late perimenopausal and postmenopausal women compared to pre- and early perimenopausal women (Campbell et al., 2011).

2.3.3 Contributors to sleep impairment in menopausal transition

2.3.3.1 Vasomotor symptoms

Multiple factors may contribute to sleep disturbances in menopausal transition (Figure 6). Vasomotor symptoms, typically occurring at night, involve up to 80% of menopausal women (Archer et al., 2011; Joffe et al., 2010). Women with these symptoms may experience perspiration or palpitations during sleep and wake up to find themselves covered with sweat. The association of vasomotor symptoms and perceived sleep disturbances has been documented in several studies (Burlison et al., 2010; de Zambotti et al., 2014; Freeman et al., 2015; Ohayon, 2006; Xu et al., 2012). Earlier studies, however, did not find a correlation between reported vasomotor symptoms and objectively measured sleep (Freedman et al., 2004; Young et al., 2003), but more recent studies have found an association (de Zambotti et al., 2014; Joffe et al., 2013; Thurston et al., 2012). For example, Thurston and colleagues found that more vasomotor symptoms reported upon waking were associated with lower SE, higher WASO, and longer SL (Thurston et al., 2012). In addition, Campbell and colleagues found that beta EEG power, indicative of arousal, was elevated in late perimenopausal and postmenopausal women, which was at least partially explained by the association of beta power and reported hot flashes (Campbell et al., 2011). Vasomotor symptoms can be measured objectively using sternal skin conductance (Maki et al., 2008). Objectively detected vasomotor symptoms have been linked to sleep architecture deterioration in a number of studies (de Zambotti et al., 2014; Joffe et al., 2010; Joffe et al., 2013; Savard et al., 2013), but not in all (Freedman et al., 2004; Freedman et al., 2007; Thurston et al., 2012). In a study by Joffe and co-workers, women with vasomotor symptoms had more WASO, longer SL, and lower SE when measured with actigraphy (Joffe et al., 2013). Freedman et al. found that objectively measured hot flashes preceded PSG-measured arousals and awakenings in the first half of

the night, but not in the second half of the night. They speculated that REM sleep in the second half of the night suppresses hot flashes and associated arousals and awakenings (Freedman et al., 2006). A recent experimental study by Bianchi et al. induced hot flashes with a gonadotrophin-releasing hormone agonist to 28 premenopausal women, and concluded that hot flashes occur most commonly during light sleep (N1) and wake, typically preceding or occurring simultaneously with wake episodes (Bianchi et al., 2016). In that study, perceived hot flashes, but not objectively measured hot flashes, were linked to more transitions to wake or N1 measured with PSG (Bianchi et al., 2016).

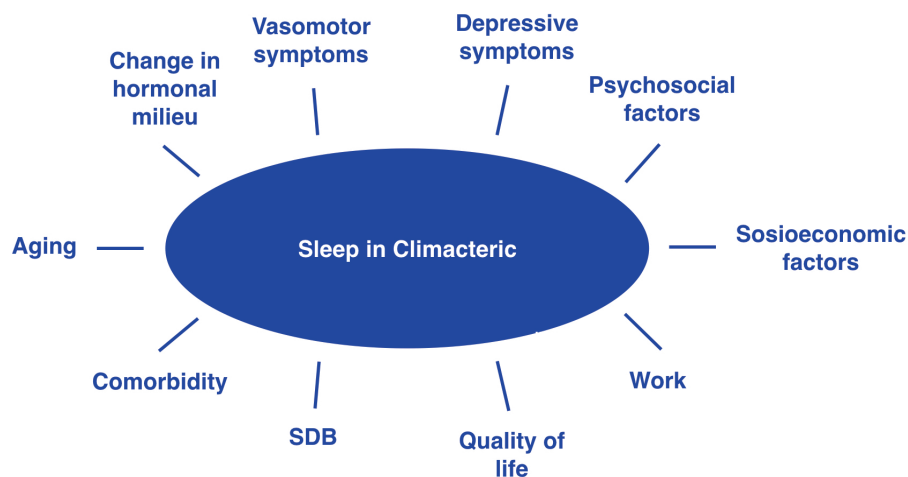


Figure 6. Associative factors with climacteric sleep disturbances.

2.3.3.2 *Depressive symptoms*

Depressed mood and clinical depression are important issues to consider in understanding menopausal sleep disturbances. It is well documented that depressive symptoms are frequently accompanied by sleep complaints, as sleep disturbances are probably one of the core symptoms of depression (Mendlewicz, 2009; Ohayon et al., 2003; Taylor et al., 2005). Further, the causality is presumably complex and bidirectional (Kahn et al., 2013; Sivertsen et al., 2012). The relationship between depressive symptoms and subjective sleep disturbances has been documented in women in menopausal transition as well (Brown et al., 2002; Burlison et al., 2010; Pien et al., 2008; Toffol et al., 2014). Changes in sleep architecture with occurrence of depressive symptoms have also been reported; in a study of 50 peri- and postmenopausal women, higher scores on the Beck Depression Inventory (BDI) were associated with decreased SE and shorter TST in perimenopausal women, and with a higher percentage of REM sleep in postmenopausal women (Toffol et al., 2014). However, not all studies have endorsed this finding (Cheng et al., 2008; Freedman et al., 2007). A sub-study of the SWAN found that mood symptoms were not

independently related to sleep architecture. In that study, anxiety symptoms were related to longer SL and lower SE; however, this was found only in women who also reported vasomotor symptoms (Kravitz et al., 2011). The previous “domino theory,” which assumes that sleep is first disrupted by vasomotor symptoms causing insomnia, and insomnia is then followed by depression (Eichling et al., 2005), currently has only partial support (Shaver et al., 2015). For example, an intervention study with perimenopausal women with depressive symptoms found that, in adjusted models, improvement in depression was predicted by improved sleep and increased E₂ levels, but not by reduction of vasomotor symptoms (Joffe et al., 2011). Therefore, the causality between these factors in relation to the decline in ovarian function still remains unanswered.

2.3.3.3 Sleep and aging

Normal aging might contribute to sleep disturbances in menopausal transition. The prevalence of sleep disturbances increases with age (Miner et al., 2017). Indeed, a reduction in both sleep quality and sleep quantity are expected in normal aging. In addition to structural changes in sleep architecture, alterations in circadian processes have been observed. In older adults, sleep becomes more superficial as the amount of S1 and S2 increase, whereas SWS decreases (Miner et al., 2017). In fact, the reduction of SWA begins soon after the age of 30 (Olini et al., 2014). However, the percentage of REM decreases only slightly, or remains mostly stable (Miner et al., 2017; Olini et al., 2014). Sleep also becomes more fragmented, as sleep hypnograms reveal frequent short awakenings and more frequent shifts from one sleep stage to another (Harmell et al., 2011). TST usually shortens, SL increases, and SE decreases; it is 90–95% in adolescents or young adults and only 80% in a 70-year old (Ohayon et al., 2004). Furthermore, the prevalence of primary sleep disorders increases with advancing age (Harmell et al., 2011; Olini et al., 2014).

Older adults have a phase advance in circadian rhythm compared to young adults. In addition, aging seems to deteriorate circadian regulation, since melatonin secretion, circadian modulation of REM sleep, and spindle frequency are reduced. The fact that SWA declines in older adults supports the theory that there are also changes in homeostatic regulation, although this has not yet been confirmed. (Olini et al., 2014)

2.3.3.4 Primary sleep disorders and other morbidity

Primary sleep disorders, such as SDB, RLS, and PLMD might contribute to menopausal sleep disturbances (Guidozzi, 2013; Polo-Kantola, 2011). SDB is characterized by snoring, airway obstruction, airway limitation, and excessive daytime sleepiness (Shneerson, 2000). AHI of five or more per hour of sleep is usually considered abnormal and indicates SDB (Shneerson, 2000). Before the menopausal transition, the prevalence of SDB is higher in men than in women (Peppard et al., 2013), but the prevalence increases

in women following menopausal transition (Anttalainen et al., 2006; Bixler et al., 2001; Mirer et al., 2017; Polesel et al., 2015; Young et al., 2003). The Wisconsin Sleep Cohort Study showed that, after adjusting for confounding factors (age, BMI, and smoking), postmenopausal women were 2.6 times more likely than premenopausal women to have AHI ≥ 5 per hour, and 3.5 times more likely to have AHI ≥ 15 per hour (Young et al., 2003). The increasing prevalence of SDB during menopausal transition might be due to the loss of the protective effect of female steroid hormones against SDB, especially progesterone (Bixler et al., 2001; Young et al., 2003), as well as changes in fat distribution after menopause (Polesel et al., 2015). However, in the recent longitudinal analyses by the Wisconsin Sleep Cohort Study, AHI increased from premenopause to peri- and postmenopause independently despite aging and changes in body habitus (Mirer et al., 2017). The clinical picture of SDB in women usually differs from that of men. Women are more symptomatic with lower AHI compared to men, have more prolonged partial upper airway obstruction, and report insomnia as a symptom of SDB more frequently (Anttalainen et al., 2016; Saaresranta et al., 2016). Perhaps because of the above-mentioned reasons, studies have shown that females have been underdiagnosed for SDB, as well as undertreated, when compared to men (Lindberg et al., 2017).

RLS is characterized by an irresistible urge to move one's legs in order to relieve uncomfortable sensations experienced during rest (Harmell et al., 2011). Symptoms usually occur in the evening and at night. In PLMD, a patient involuntarily moves limbs repeatedly during sleep, which may cause disruption of sleep (Harmell et al., 2011). The prevalence of both conditions increases with age, and RLS is shown to be more common in women (Harmell et al., 2011). Freedman et al. found periodic limb movements and apneas to be the best predictors for reduced SE in peri- and postmenopausal women reporting sleep disturbances in PSG measures (Freedman et al., 2007). In addition to primary sleep disorders, various other medical disorders, as well as associated medications, become more common with advancing age and may affect sleep (Plotkin, 2010). In one of the few prospective studies assessing predictors for menopausal sleep disturbances, medical diseases and use of prescribed medication predicted future sleep disturbances (Tom et al., 2009).

2.3.3.5 Work and menopause

Midlife women comprise a large proportion of the workforce in industrial countries and, during menopausal transition, women are usually at the most productive phase of their careers. However, there are a limited number of studies that address the impact of menopause on work, and work has usually not been the focus of interest in these studies. According to the literature, menopausal symptoms may negatively affect work ability (Geukes et al., 2012; Hammam et al., 2012; Jack et al., 2016; Simon et al., 2009). However, not all studies have found an association (Hickey et al., 2017). When evaluated more specifically, especially for sleep disturbances (Hammam et al., 2012; Simon et al.,

2009) and also for vasomotor symptoms (Griffiths et al., 2013; Simon et al., 2009; Whiteley et al., 2013), cognitive impairment (Griffiths et al., 2013; Mitchell et al., 2011), and mood symptoms (Griffiths et al., 2013), these studies show an association with difficulties at work or with lower work ability. In a study of 131 Egyptian teachers in menopausal transition (aged 46–59 years), the most important menopausal symptoms that affected their working capacity and performance were tiredness (83%) and sleep disturbances (64%) (Hammam et al., 2012). A larger study by Simon and colleagues of 961 women around menopause found that insomnia symptoms were the most problematic menopausal symptom to affect daily life and working performance (Simon et al., 2009). Recent studies have demonstrated that the presence of menopausal symptoms increases the likelihood of increased health care utilization and costs, as well as increased sick leave days and costs (Bolge et al., 2010; Kleinman et al., 2013; Whiteley et al., 2013a; Whiteley et al., 2013b). At least one study has assessed the burden of menopausal sleep disturbances on societal costs. Bolge and colleagues concluded that menopausal chronic insomnia, characterized by nighttime awakenings, was linked with increased health care utilization and associated costs, decreased work productivity, and decreased health-related quality of life after adjustment for demographics and comorbidity (Bolge et al., 2010).

Whereas menopause is linked to impaired work ability, psychosocial aspects of the working environment, including work stress or problems with colleagues, have been negatively associated with experience of menopausal symptoms (Hammam et al., 2012; Mishra et al., 2006). An Australian study of 476 peri- and postmenopausal women working in the higher education sector found that high supervisor support, being employed on a full-time basis, and having control over workplace temperature were independently associated with lower menopausal symptom reporting (Bariola et al., 2017). However, these studies have not specifically assessed sleep disturbances, but only menopausal symptoms in general. However, there is good evidence that job strain and high work demands are associated with increased prevalence of sleep disturbances in general populations (Chazelle et al., 2016; Halonen et al., 2017; Magnusson et al., 2014; Åkerstedt et al., 2015). In addition, a recent Finnish prospective study with over 24,000 participants (82% women, mean age 44 years) showed that the disappearance of job strain was associated with lower odds of insomnia symptoms (Halonen et al., 2017).

2.3.3.6 Psychosocial, socioeconomic and cultural factors

Besides menopausal hormonal changes, women face multiple challenges and personal life stressors in midlife. These might include changing roles in the family, loss of significant others, health concerns and worries about getting old, or changes and increasing demands at work or retirement (Darling et al., 2012). Women in perimenopause have higher levels of psychological distress compared to premenopausal women (Bromberger et al., 2001). A sub-study of the Seattle Midlife Women's Health Study found that employment, depressed mood, and poor perceived health were the most significant factors causing stress

in midlife women (Woods et al., 2009). Life stressors and experiencing stress in general might also contribute to sleep disturbances (Cuadros et al., 2012; Darling et al., 2012; Saaresranta et al., 2013). Woods and colleagues found in their multivariate model that perceived stress and poor perceived health were associated with difficulty initiating and maintaining sleep, as well as with early morning awakening (Woods et al., 2010). Indeed, perceived health, as well as quality of life, have been shown to contribute to sleep disturbances in menopausal women (Kravitz et al., 2011; Polo-Kantola et al., 2014; Woods et al., 2010). In menopausal transition, socioeconomic factors, like higher educational level (Blümel et al., 2012), lower financial strain (Hall et al., 2009), and satisfactory marriage (Troxel et al., 2009; Troxel et al., 2010) are associated with fewer sleep disturbances. Further, the prevalence of menopausal sleep disturbances depends on race and ethnicity: Caucasian women have higher rates of sleep disturbances in menopausal transition, while Hispanic women have lower rates (Kravitz et al., 2008).

2.3.4 Hormone therapy and sleep

HT, comprising estrogen combined with progestin, or estrogen alone for women with a history of hysterectomy, is the most effective treatment for climacteric symptoms (MacLennan et al., 2004). It has been shown to prevent bone loss and osteoporosis-related fractures (Cauley et al., 2003; de Villiers et al., 2016). When initiated before the age of 60 or within 10 years of menopause, HT—and more evidently, estrogen-alone therapy—may reduce the risk of myocardial infarction and all-cause mortality (Boardman et al., 2015; de Villiers et al., 2016; Harman et al., 2011; Savolainen-Peltonen et al., 2016). In addition, HT may reduce the risk for vascular dementia or Alzheimer's disease later in life, if initiated in early menopause (de Villiers et al., 2016; Mikkola et al., 2017). Oral, but not transdermal, administration of HT increases the risk for venous thromboembolism (Canonica et al., 2007; de Villiers et al., 2016). In addition, there is a slightly elevated risk for breast cancer that seems to be primarily, but not exclusively, related to the used progestin in combined therapy (Chlebowski et al., 2014; de Villiers et al., 2016; Manson et al., 2013). According to current opinion, the indication and possible contraindications (e.g. a history of breast cancer, gynecological cancer, venous thromboembolism, or severe cardiovascular diseases) should be evaluated before initiation of HT. HT should be used with the lowest effective dosage using transdermal administration when appropriate, and the duration should be considered individually in regard to the duration of climacteric symptoms, age, and possible risk factors (de Villiers et al., 2016).

Since both estrogen and progesterone have shown to impact sleep through several mechanisms (Porkka-Heiskanen et al., 2014), the effect of HT on sleep has been evaluated as well. However, the available studies are difficult to compare. The heterogeneity in study populations, tools to evaluate sleep, and various HT preparations (formulation, dose and type of administration) makes it difficult to draw conclusions. According to a recent meta-

analysis, HT modestly improves subjectively evaluated sleep, especially with co-occurring vasomotor symptoms (Cintron et al., 2017). However, the evidence of improved sleep without concomitant vasomotor symptoms is uncertain (Cintron et al., 2017; Shaver et al., 2015). In most of the studies, improvement of subjective sleep quality has co-occurred with improvement of vasomotor symptoms (Cintron et al., 2017; Hays et al., 2003; Savolainen-Peltonen et al., 2014; Welton et al., 2008). However, there are also some data of enhanced sleep quality with HT without the report of vasomotor symptoms (Polo-Kantola et al., 1999). PSG studies examining the effect of HT on sleep architecture in menopausal women share the same problems with study design as the studies evaluating subjective sleep quality and HT. In addition, those studies are rare, and the results conflict. Some PSG studies have observed positive changes in sleep architecture with HT (Montplaisir et al., 2001; Parry et al., 2004; Polo-Kantola et al., 1999; Scharf et al., 1997), mainly decreasing WASO, although some studies have found no improvement (Kalleinen et al., 2008; Purdie et al., 1995; Tansupswatdikul et al., 2015).

2.4 Summary of the previous evidence

The literature shows rather unanimously that subjective sleep disturbances increase in menopausal transition, with the most common complaints being nighttime awakenings resulting in sleep fragmentation (Polo-Kantola, 2011; Shaver et al., 2015). However, most studies have evaluated sleep only with one to three general questions. Instead, sleep architecture during this period has been evaluated in a limited number of studies, and the results have been contradictory (Polo-Kantola, 2011; Shaver et al., 2015). Furthermore, prospective follow-up studies are lacking. HT is shown to alleviate subjective sleep disturbances, particularly if vasomotor symptoms are present (Cintron et al., 2017). However, it is not yet resolved whether sleep disturbances derive from direct female sex steroid effect on sleep regulation, other menopausal symptoms such as vasomotor symptoms, or aging. Further, there is limited evidence in this group of women concerning the associations of sleep with work and common stressful life events in midlife that co-occur with menopausal transition. Strong evidence exists, however, that sleep disturbances are connected with both short- and long-term adverse health consequences, as well as decreased quality of life and work ability (Cappuccio et al., 2010). Symptomatic menopausal transition may last for several years (Avis et al., 2015; Freeman et al., 2011), and after menopause women in industrial countries remain in the paid workforce for approximately 10 years, and in the future even longer. Thus, understanding the causes, as well as prevention and accurate treatment of menopausal sleep disturbances, is essential for better health, quality of life, and work ability during and after menopause.

3 AIMS OF THE STUDY

The overall aim of the study was to evaluate both subjective sleep quality and sleep architecture in climacteric, with a cross-sectional and longitudinal design. In addition, associations of sleep disturbances with other menopausal symptoms, health-related factors, psychosocial and socioeconomic factors, and work were evaluated.

The specific aims were the following:

- I Does subjective sleep length, sleep latency or nighttime awakenings differ during workdays and leisure days in premenopausal and postmenopausal women working regular hours? (Study I)
- II Which sleep disturbances are characteristic for menopause? How does subjective sleep quality change during menopausal transition? (Studies II, III)
- III How does sleep architecture change in menopausal transition during a six-year follow-up? What is the effect of aging and menopausal hormonal changes on sleep architecture changes? (Study IV)
- IV What is the role of possible contributing factors, such as other menopausal symptoms or health-related and socioeconomic factors, in association with menopausal sleep disturbances? Can some premenopausal risk factors for menopausal sleep disturbances be identified prior to menopausal hormonal changes? (Studies I, II, III)

4 MATERIALS AND METHODS

4.1 Participants

Women at the average age of 46 and 56 years were recruited through newspaper announcements for a sleep and cardiovascular study (The Woman 46 Study) in the Turku city area, in Finland (Figure 7). Exclusion criteria included the presence of coronary heart disease, respiratory insufficiency, diagnosed SDB, neurological disease, liver disease, malignancies, and alcohol abuse. Altogether, 228 women were enrolled, of which 81 belonged to the group of women whose age averaged 56 years. All 147 women who were 46 years old at baseline were invited to the follow-up study after approximately five years. The age of 46 years was chosen because the average age of menopause in Finland is 51 years; thus, at follow-up, some of the women were likely to have reached menopause. A total of 21 women were totally missed from follow-up, and 16 women answered the questionnaires without participating in PSG or other measurements at follow-up. After different sub-study-specific exclusion criteria (see later in the text), the sub-studies included a total of 177 women (Figure 8). Basic characteristics of the participants in Studies I–IV are described in Table 2, additional characteristics of the women in Studies II and III in Table 3, and workload variables, screened in Study I, in Table 4.

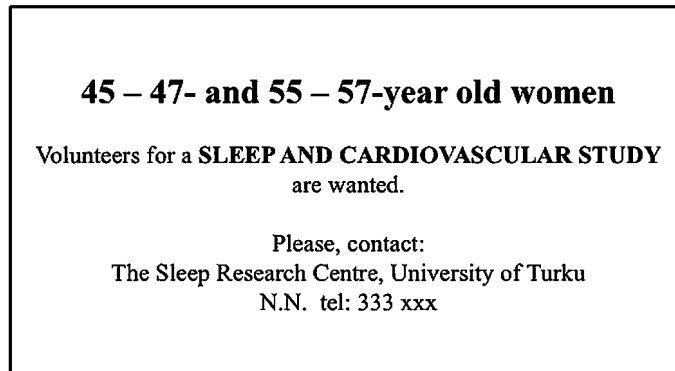


Figure 7. Newspaper announcement used to recruit the participants.

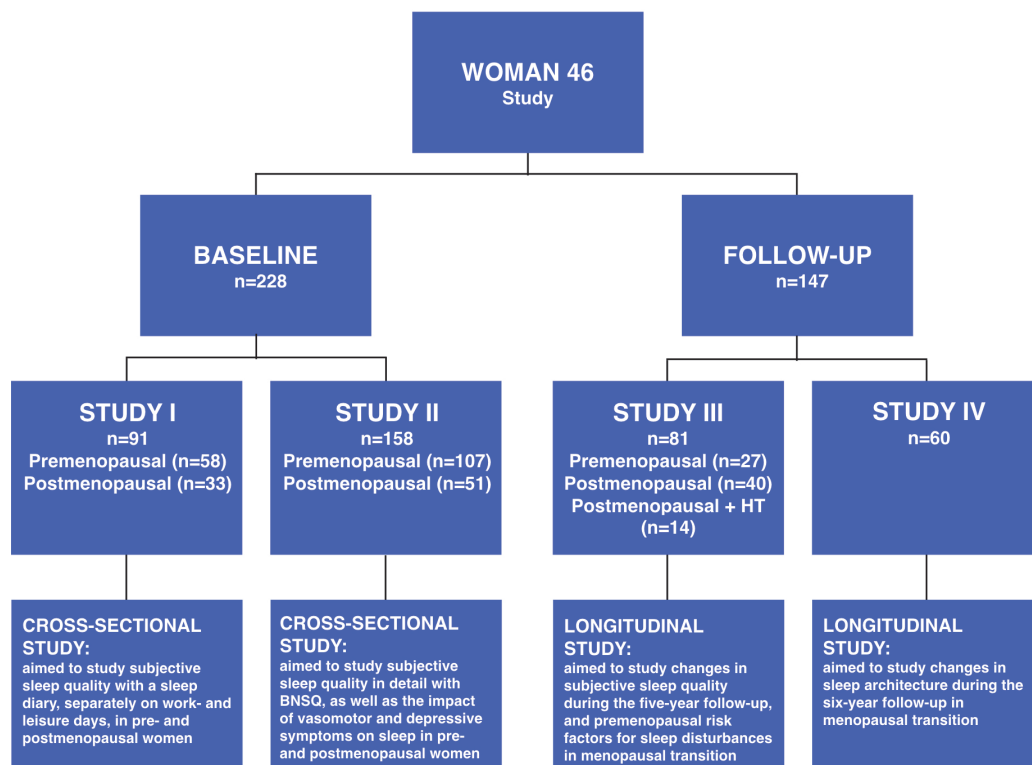


Figure 8. Flow chart of the four sub-studies. HT, hormone therapy; BNSQ, Basic Nordic Sleep Questionnaire.

Studies I and II

Studies I and II were cross-sectional with two study groups: premenopausal and postmenopausal women. Study I included 91 women, of which 58 were premenopausal (aged 44–48 years) and 33 postmenopausal (aged 53–58 years). Women with symptoms of SDB, women with moderate or severe depression, women working in shifts, and unemployed or retired women were not included in this study. Postmenopausal status was defined as a serum FSH (S-FSH) concentration above 30 IU/L.

A total of 158 women were enrolled in Study II. The premenopausal group consisted of 107 women (aged 44–48 years) and the postmenopausal group consisted of 51 women (aged 53–58 years). Exclusion criteria included previous hysterectomy and the use of HT. Premenopausal status was defined as S-FSH concentration below 30 IU/L and postmenopausal status as S-FSH concentration above 30 IU/L, respectively.

Study III

Study III was a prospective follow-up study. At baseline, all women were premenopausal and, on average, were aged 46 years. At the five-year follow-up, some of the women had

reached menopause and transitioned to postmenopause. Using longitudinal study design, it was possible to assess the effects of menopausal hormonal changes and age on sleep. Of 147 women, 21 refused to participate in the follow-up. Exclusion criteria comprised peri- or postmenopausal S-FSH concentration (>20 IU/L) or use of HT at baseline ($n = 24$), and perimenopausal S-FSH concentration (20–30 IU/L) or undefined menopausal status at follow-up ($n = 21$). The remaining 81 women were divided into three groups at follow-up: premenopausal (*pre* group, 27 women), postmenopausal non-HT users (*post* group, 40 women), and postmenopausal HT users (*post+HT* group, 14 women). Premenopause was defined as ongoing menstruation without HT use, or S-FSH concentration lower than 21 IU/L. Postmenopause was defined as amenorrhea for over one year and an age of 51 years or more, or S-FSH concentration over 30 IU/L. In case of a previous hysterectomy or use of an intrauterine hormone device, S-FSH over 30 IU/L was required.

Study IV

Study IV was a longitudinal prospective follow-up study. Of 147 women, 37 refused to participate in the follow-up. Only premenopausal women at baseline (S-FSH < 20 IU/L) were included ($n = 91$). Women using HT ($n = 9$) and women with missing S-FSH ($n = 2$) at follow-up were excluded. In addition, follow-up sleep recordings from 20 women were inadequately recorded due to technical issues, and they were removed from the results, leaving 60 women in the study. In this study, women were not divided into groups but were studied as one group, using S-FSH concentration as a marker of reproductive aging versus chronological aging.

Table 2. Participant characteristics, expressed as means (standard deviations) or percentages.

	Study I			Study II			Study III						Study IV				
	Pre	Post	p	Pre	Post	p	Baseline		Follow-up		Post+HT	Post	Post+HT	p	Baseline	Follow-up	
							n = 58	n = 33	n = 107	n = 51							n = 27
Age (years)	46.0 (1.0)	55.8 (1.1)	<0.001	46.4 (0.8)	56.3 (1.0)	<0.001	45.9 (1.0)	46.1 (0.8)	51.7 (1.0)	52.3 (1.3)	45.9 (0.9)	52.3 (1.3)	52.5 (1.9)	NS	46.0 (0.9)	52.1 (1.3)	<0.001
BMI (kg/m ²)	25.7 (5.4)	26.0 (3.5)	NS	26.2 (5.3)	26.9 (4.6)	NS	25.4 (5.2)	26.6 (5.8)	26.3 (5.8)	28.3 (6.1)	24.4 (2.7)	25.8 (2.6)	25.8 (2.6)	NS	27.0 (6.0)	28.8 (6.6)	<0.001
Serum FSH (IU/L)	8.8 (3.9)	71.8 (29.9)	<0.001	8.5 (5.3)	76.7 (27.8)	<0.001	6.8 (3.6)	7.9 (4.0)	9.1 (3.4)	9.1 (3.4)	9.1 (3.4)	69.4 (25.5)	64.2 (27.2)	<0.001	7.5 (3.6)	44.6 (33.7)	<0.001
Marital status (%)																	
single	5.2	9.1	NS	10.3	15.7	NS	3.7	7.5	7.1	7.1	7.1	7.1	7.1	NS	5.0	5.0	
married	82.8	75.8		72.0	66.7		81.5	70.0	85.7	85.7	85.7	85.7	85.7		73.3	73.3	
divorced	8.6	12.1		16.0	13.7		11.1	20.0	7.1	7.1	7.1	7.1	7.1		18.3	18.3	
widowed	3.4	3.0		1.9	3.9		3.7	2.5	0.0	0.0	0.0	0.0	0.0		3.3	3.3	
Education (%)																	
lower	20.7	54.6	0.001	23.4	49.0	0.001	26.3	7.1	11.1	11.1	11.1	11.1	11.1	NS	18.3	18.3	
higher	79.3	45.5		76.6	51.0		73.7	82.9	88.9	88.9	88.9	88.9	88.9	NS	81.7	81.7	
Night sweats (%)																	
seldom or never	69.0	42.4	<0.001	64.5	45.1	<0.001	66.7	69.2	71.4	71.4	71.4	30.0	42.9	0.003	71.2	45.8	0.007
once a month	19.0	12.1		21.5	13.7		14.8	20.5	7.1	7.1	7.1	15.0	0.0		16.9	18.6	
once a week	8.6	9.1		11.2	9.8		14.8	7.7	21.4	21.4	21.4	20.0	35.7		10.2	11.9	
almost daily	3.4	33.3		2.8	31.4		3.7	2.6	0.0	0.0	0.0	35.0	21.4		1.7	23.7	
Hot flashes (%)																	
seldom or never	91.4	36.4	<0.001	87.9	43.1	<0.001	92.6	94.9	85.7	85.7	85.7	38.5	57.1	0.001	91.4	58.6	0.001
once a month	5.2	15.2		8.4	15.7		7.4	2.6	14.3	14.3	14.3	7.7	7.1		5.2	6.9	
once a week	1.7	24.2		2.8	19.6		0.0	2.6	0.0	0.0	0.0	18.0	28.6		3.4	12.1	
almost daily	1.7	21.2		0.9	21.6		0.0	0.0	0.0	0.0	0.0	35.9	7.1		0.0	22.4	
BDI total score	3.8 (3.6)	6.9 (4.3)	<0.001	4.1 (4.2)	8.1 (5.5)	<0.001	4.2 (2.5)	5.6 (4.6)	4.0 (3.9)	4.0 (3.9)	4.0 (3.9)	7.2 (6.9)	4.7 (3.9)	NS	4.6 (4.3)	5.8 (5.3)	NS

Pre, premenopausal group; Post, postmenopausal group (postmenopausal group without hormone therapy (HT) in Study III); Post+HT, postmenopausal group using HT; n, number; BMI, body mass index; FSH, follicle stimulating hormone; BDI, Beck Depression Inventory; NS, non-significant.

Table 3. Additional characteristics of the participants in Studies II and III, expressed as percentages.

	Study II			Study III															
	Pre n = 107	Post n = 51	p	Baseline			Follow-up												
				Pre n = 27	Post n = 40	Post+HT n = 14	p	Pre n = 27	Post n = 40	Post+HT n = 14	p								
Quality of life, %			0.012																
very or quite satisfied	91.6	72.6		96.3	87.5	92.9	NS	96.3	87.5	85.1		85.1				NS			
moderate	6.5	21.6		3.7	7.5	7.1		3.7	10.0	0.0		0.0							
quite or very unsatisfied	1.9	5.9		0.0	5.0	0.0		0.0	2.5	14.3		14.3							
Perceived general health, %			0.021														NS		
very or quite good	71.0	58.8		63.0	62.5	78.6		69.2	55.0	71.4		71.4					NS		
tolerable	27.1	27.5		37.0	37.5	14.3		27.1	40.0	28.6		28.6							
quite or very bad	1.9	13.7		0.0	0.0	7.1		3.7	5.0	0.0		0.0							
Perceived mental health, %			NS															NS	
very or quite good	98.1	94.1		100.0	97.5	100.0		96.0	94.9	100.0		100.0						NS	
quite bad	0.9	2.0		0.0	2.5	0.0		0.0	5.1	0.0		0.0							
very bad	0.9	0.0		0.0	0.0	0.0		4.0	0.0	0.0		0.0							
cannot say	0.0	3.9		0.0	0.0	0.0		0.0	0.0	0.0		0.0							
Personal crises during the past year, %	64.5	41.2	0.006	51.9	72.5	64.3	NS	66.7	70.0	57.1		57.1						NS	
Working status, %			0.008																NS
working	90.7	80.4		100.0	85.0	92.9		92.6	89.7	92.3		92.3							
retired	0.9	11.8		0.0	2.5	0.0		0.0	7.7	7.1		7.1							
unemployed	6.5	6.0		0.0	12.5	0.0		7.4	2.5	0.0		0.0							

Pre, premenopausal group; Post, postmenopausal group (postmenopausal group without hormone therapy (HT) in Study III); Post+HT, postmenopausal group using HT; n, number; NS, non-significant.

Table 4. Workload in premenopausal and postmenopausal women in Study I.

	Pre n = 58	Post n = 33	<i>p</i>
Work satisfaction, %			NS
very or quite satisfied	94.8	87.9	
quite or very unsatisfied	5.8	12.1	
Rush to complete one's tasks, %			NS
yes	56.9	51.5	
no	37.9	30.3	
cannot say	5.2	18.2	
Mental load at work, %			NS
yes	22.4	21.2	
no	74.1	75.8	
cannot say	3.5	3.0	
Physical load at work, %			NS
yes	5.4	9.4	
no	91.1	90.1	
cannot say	3.6	0.0	

Pre, premenopausal women; post, postmenopausal women; n, number; NS, non-significant.

4.2 Methods

4.2.1 Questionnaires

Sleep diary

A two-week sleep diary was used to study sleep separately during work and leisure days (Study I, Appendix 3). Bedtime, SL, number of nighttime awakenings, and wake up time were recorded, and total sleep time including naps (TST), nocturnal sleep time (ST), SL, and number of awakenings were calculated.

The Basic Nordic Sleep Questionnaire

In Studies II and III, the BNSQ (Partinen et al., 1995) was used to assess subjective sleep quality in detail. The BNSQ includes 21 questions, of which 14 were included in the present study (Appendix 4). The first item is about general sleep quality, and the items 2–5, 9–10 and 14 refer to insomnia, 6–8 to SDB, and 11–13 to excessive daytime sleepiness. The variables in the BNSQ are categorical, with a low number referring to better sleep quality or to a lower frequency of sleep disturbances. For statistical analyses, the alternative responses for each question were dichotomized. In Study II, sleep disturbances were indicated if the following criteria defined in parentheses were fulfilled: 1) general sleep quality (seldom or never good), 2) difficulties falling asleep (≥ 3 nights per week), 3) sleep latency (> 30 min), 4) nocturnal awakenings (≥ 3 times per night), 5) restless sleep

(quite or very restless sleep) 6) snoring (≥ 3 nights per week), 7) witnessed apnea (≥ 3 times per week), 8) morning headache (≥ 1 times per week), 9) morning tiredness (≥ 3 days per week), 10) daytime tiredness (≥ 3 days per week), 11) unintentional falling asleep at work or during leisure time (≥ 3 days per week), 12) unintentional falling asleep when not active (e.g. watching TV) (frequently or almost every time), 13) naps during the day (≥ 1 times per week), and 14) use of sleep medication (≥ 1 times per week). In Study III, sleep problems were indicated if the following criteria were fulfilled: 1) general sleep quality (seldom or never good), 2) difficulties falling asleep (≥ 1 night per week), 3) sleep latency (>20 min), 4) nocturnal awakenings (≥ 2 times per night), 5) restless sleep (quite or very restless sleep), 6) snoring (≥ 1 night per week), 7) witnessed apnea (≥ 1 night per week), 8) morning headaches (≥ 1 time per week), 9) morning tiredness (≥ 1 time per week), 10) daytime tiredness (≥ 1 time per week), 11) unintentional falling asleep during work or leisure time (≥ 1 time per week), 12) unintentional falling asleep when not active (e.g. watching TV) (sometimes or more frequently), 13) naps during the day (≥ 1 time per week), and 14) use of sleep medication (≥ 1 time per week).

The Beck Depression Inventory

Depressive symptoms were evaluated with the 21-item Beck Depression Inventory (BDI) (Beck et al., 1961). In the BDI, higher scores indicate more severe depressive symptoms, with the following cut off –points: 0–9 for no or minimal depression, 10–18 for mild depression, 19–29 for moderate depression, and 30–63 for severe depression. (Studies I–IV).

Additional questionnaires

For additional questionnaires, see Appendix 5. In addition to Appendix 5, structured questionnaires included questions on marital status, working status, work schedule, lifestyle (smoking, alcohol consumption, physical activity) and current medications. The vasomotor symptom score was the sum of the two questions (night sweats and hot flashes). All questionnaires were completed in the presence of a study nurse.

4.2.2 Measures

A blood sample to test S-FSH concentration was taken in the morning prior to the sleep study, and in premenopausal women at the beginning of the follicular phase (days 1–7 of the menstrual cycle). S-FSH concentration was measured with a time resolved immunofluorometric assay (AutoDELFIA[®], PerkinElmer Life and Analytical Sciences, Wallac Oy, Turku, Finland). The study nurse measured height and weight, and BMI was calculated accordingly.

4.2.3 Sleep recordings

The overnight sleep recordings in Study IV included conventional PSG, SaO₂, and nasal flow pressure measurements. Sleep recordings were performed in the sleep laboratory of the Sleep Research Centre in the Department of Pulmonary Diseases and Clinical Allergology of the University of Turku.

Sleep architecture, including sleep stages, SLs, SE, arousals, and awakenings were evaluated with PSG. PSG recordings included continuous monitoring of the electroencephalogram (EEG, C3/A2, C4/A1, O1/A2, O2/A1), two electro-oculograms (EOG), and two (submental and mandibular) electromyograms (EMG) (Embla®, Medcare Flaga hf. Medical Devices, Reykjavik, Iceland). All recordings were visually scored in 30-second epochs by an experienced sleep technician. For quality control, all recordings were re-scored by an experienced clinical neurophysiologist, certified by the European Sleep Research Society as an Expert Somnologist. Conventional criteria were used to score NREM sleep, consisting of stage 1 (S1), stage 2 (S2), stage 3 (S3), and stage 4 (S4). The latter two stages were combined to SWS. In addition, REM sleep and WASO were scored (Rechtschaffen et al., 1968).

Sleep stages (S1, S2, SWS and REM) were expressed as percentages of TST. REM and SWS periods were calculated. SL was determined as the time in minutes from lights off until an occurrence of three consecutive S1 epochs or as one epoch of any other sleep stage. Sleep onset latencies to S1 and S2 sleep were defined as the times in minutes from lights off to the first 30 seconds of S1 and S2 sleep, and sleep onset latencies to SWS and REM sleep as the times in minutes from sleep onset to the first 30 seconds of the respective sleep stage. WASO and TST were expressed in minutes. TST was equal to awakening latency minus sleep latency minus amount of wakefulness between sleep onset and final awakening. SE was calculated by dividing TST by the time in bed (lights off to lights on), and expressed as a percentage. Sleep stage transitions per one hour, the number of sleep stage transitions from SWS to wake, and the number of awakenings and arousals per one hour were calculated. An awakening was classified as entering wake stage for at least 15 seconds from sleep, and an arousal was classified according to the American Sleep Disorders Association (ASDA) criteria as EEG alpha-activity for at least 3 seconds (Bonnet et al., 1992). Awakenings per hour and arousals per hour were summed up to produce an arousal index (ARI).

Either C3–A2 or C4–A1 EEG derivation was used to calculate SWA, (0.75–4 Hz) during S2, S3, and S4 NREM sleep. First, all EEG artifacts (periods of movements and eye movements) and event triggered slow waves with increased muscle tone were visually identified and removed from the calculations (Heinzer et al., 2001). In six participants, both C3–A2 and C4–A1 channels contained excessive alternating artifacts and thus the recordings from these participants were omitted from the spectral analysis. Forty-three of

all PSGs were initially recorded with a 100 Hz sampling rate, and were up-sampled to 200 Hz before spectral computations. In the up-sampling procedure, a zero was added after each sample of the 100 Hz signal; thereafter, this sequence was filtered with a 401-tap FIR filter (designed to have a pass-band from 0–45 Hz and -3 dB point at 46.7 Hz and stopband from 49.4 to 100 Hz with over 60 dB attenuation in all that range) and the obtained signal samples at 200 Hz were multiplied by two.

EEG signal segmentation of 2-s duration with 50% overlapping was used in the spectral computations. The 2-s long signal segment was centered at the k th second in the recording. After the mean removal, the 2-s long EEG signal segment was windowed with a 400-point long Hanning window function, denoted as w_n , where $n = 1, \dots, L$, and $L = 400$. This sequence was then zero-padded to a length of 1024 and a fast Fourier transform was taken of the entire sequence providing the complex-valued spectrum, denoted as $R(f) = X(f) + jY(f)$, where f denotes the frequency and j denotes the imaginary unit. Thereafter, the spectrum was scaled to the power spectral density, denoted as $P(f)$, as follows (where $\| \cdot \|$ indicates vector norm and f_s the sampling frequency of 200 Hz):

$$P(f) = \frac{2 \cdot \|R(f)\|^2}{f_s \times \sum_{n=1}^L w_n^2}.$$

The mean value of the power spectral density $P(f)$ in the frequency band of 0.75–4 Hz was extracted at each second k (frequency resolution of the $P(f)$ was 0.195 Hz) and multiplied by the SWA band width of 3.25 Hz providing the SWA power (μV^2). Finally, the average value of all the computed SWA power values during the night (excluding artifacts) was extracted, providing the time-average SWA power (μV^2) during the night.

Nasal inspiratory airflow was measured with nasal prongs attached to the pressure transducer. SaO₂ was measured with a finger probe pulse oximeter (Nonin® oximeter built in with Embla® / Somnologica system, MedicareFlaga hf, Reykjavik, Iceland). The overnight mean and minimum of the SaO₂ level, the percentage of SaO₂ under 90%, and the episodes of arterial oxyhemoglobin desaturation of 4% units or more per hour (ODI₄) were calculated automatically with the default settings in Somnologica, after manually removing possible artifacts. AHI was determined visually. Apnea was scored when the amplitude of nasal flow signal decreased at least 90% from the baseline and the event lasted 10 seconds or more. Hypopnea was scored when the amplitude of nasal flow signal decreased at least 30% from the baseline, lasted 10 seconds or more, and was associated with a minimum of 4% desaturation from the baseline before the event.

4.2.4 Statistical analyses

Statistical analyses were carried out with SAS System for Windows, versions 9.1 and 9.3 (SAS Institute, Cary, NC), and with IBM SPSS version 23 with standard packages. In all the tests, a p -value < 0.05 was considered as statistically significant. Group distributions in categorical variables were studied with the Chi-Square test or the McNemar-Bowker test, and in continuous variables with the T-test for independent samples and analysis of variance (ANOVA). ORs were calculated and reported with 95% confidence intervals (CI). Correlations were assessed with the Pearson correlation coefficient.

In Study I, sleep diary variables were adjusted with BDI score, vasomotor symptom score, and education, and ANOVA was carried out. The cutoff point in the BDI score was between 8 and 9. In the post-hoc analysis, nine HT users from the postmenopausal group were excluded. In Study II, associations of significant independent variables with sleep variables, together with interactions (between menopausal group, independent variables and sleep variables), were studied in models using a binary logistic regression model with backward selection. Model 1 included menopausal group, night sweats, hot flashes, and BDI, and the Model 2 included menopausal group, quality of life, perceived physical health, reported personal crises, education, and working status. In Model 1, seven BNSQ variables (snoring, witnessed apnea, use of sleep medication, morning headache, unintentional falling asleep at work or during leisure time, unintentional falling asleep when not active, and frequency of naps) and five BNSQ variables in Model 2 (witnessed apnea, use of sleep medication, morning headache, unintentional falling asleep at work or during leisure time, and unintentional falling asleep when not active) were left out from the analysis because of joint distribution characteristics.

In Study III, a univariate ANOVA was conducted for each menopausal group and each independent variable with sleep variables separately at baseline and at follow-up. Thereafter, a multivariable analysis using a binary logistic regression model with backward selection was conducted to analyze group and time effects together with interactions (interaction refers to unequal group differences at different time points) adjusted for other independent variables, which remained significant in the analysis (BDI total score, night sweats, perceived general health, personal crises, use of CNS medication, and BMI). Because of joint distribution characteristics, it was not possible to conduct multivariable analyses for four sleep variables (restless sleep, morning headache, falling asleep at work or during leisure time, and use of sleep medication). Further, the effects of predisposing factors at baseline (significant independent variables from ANOVA analyses) on sleep variables at five-year follow-up were studied using multivariable analysis with binary logistic regression with stepwise selection. In addition, the effects of changes (deltas) in independent variables from baseline to five-year follow-up on sleep variables were studied using a similar approach. Methods were chosen based on levels of measurement of dependent variables together with descriptive analysis.

In order to study the within-patient changes in PSG variables in Study IV, an ordinary least squares linear regression model was fitted for each PSG variable using change in time (six years, constant) and change in S-FSH concentration (continuous) as covariates. Effect sizes were given by the regression models as unstandardized B coefficients, which signify how much a given PSG variable changes when time is increased by six years or when S-FSH concentration is increased by 1 IU/L. Adjusted regression coefficients were obtained by including changes in BMI, night sweats, hot flashes, and BDI total score as covariates in the regression models.

4.3 Ethical aspects

The study protocol was approved by the Ethics Committee of the Hospital District of Southwest Finland. Written informed consent was obtained from all the participants after given oral and written information.

5 RESULTS

5.1 Subjective sleep quality

5.1.1 Sleep during work and leisure days

TST and ST were shorter and awakenings were more frequent in postmenopausal women compared to premenopausal women during workdays, as well as for the entire 14-day period, but no differences were found during leisure days. Postmenopausal women reported longer SL during the entire 14-day period, as well as both during work and leisure days. After adjusting for the BDI score, TST and ST remained shorter during the 14-day period and during workdays in postmenopausal women. In addition, SL tended to be longer ($p = 0.070$) in postmenopausal women on workdays. There was an interaction between the menopausal group and BDI. During workdays, TST and ST were shorter in premenopausal women who scored higher in BDI compared to premenopausal women who had lower BDI scores. Postmenopausal women scoring higher in BDI had longer TST and ST during workdays compared to those postmenopausal women whose BDI scores were lower. After adjusting for the vasomotor symptom score, TST and ST remained shorter during the 14-day period in postmenopausal women and there was a tendency toward shorter TST ($p = 0.078$) and ST ($p = 0.073$) during workdays in postmenopausal women. When adjusting for education, TST and ST remained shorter during the 14-day period and during workdays, and SL remained longer during the 14-day period and during leisure days in postmenopausal women. Further, a group and education interaction was found. Higher-educated premenopausal women had longer TST and ST during workdays when compared to lower-educated premenopausal women, whereas higher-educated postmenopausal women had shorter TST and ST during workdays compared to lower-educated postmenopausal women. (Table 5).

The mean differences in TST, ST, and SL between work and leisure days were calculated separately in pre- and postmenopausal women. In premenopausal women, the mean difference in TST was -71 minutes during workdays compared to leisure days, and in postmenopausal women -100 minutes respectively ($p = \text{NS}$). The mean difference in ST was -68 minutes and -89 minutes, respectively ($p = \text{NS}$). The mean differences in SL were essentially similar in both groups.

Table 5. Sleep diary results between the premenopausal and postmenopausal groups in Study I. Data are presented as crude data and after adjustment for depressive mood, vasomotor symptoms, or education.

	Unadjusted		Adjusted for BDI (<i>p</i>)		Adjusted for VMS (<i>p</i>)		Adjusted for education (<i>p</i>)		
	Pre	Post	Group	Interaction	Group	Interaction	Group	Interaction	
	n = 58	n = 33	n = 91	n = 91	n = 91	n = 91	n = 91	n = 91	
	Mean (SD)	Mean (SD)	<i>p</i>	Group	Interaction	Group	Interaction	Group	Interaction
TST									
TST 14 days (min)	473.7 (34.2)	447.1 (46.0)	0.002	0.006	NS	0.048	NS	0.009	NS
TST workday (min)	444.9 (32.8)	406.5 (51.2)	<0.001	<0.001	0.032	NS	NS	<0.001	0.046
TST leisure day (min)	515.8 (51.5)	506.8 (57.1)	NS	NS	NS	NS	NS	NS	NS
ST									
ST 14 days (min)	467.3 (35.5)	435.3 (44.4)	<0.001	0.004	NS	0.037	NS	0.003	NS
ST workday (min)	439.9 (35.8)	397.6 (53.5)	<0.001	<0.001	0.04	NS	NS	<0.001	0.014
ST leisure day (min)	507.8 (49.8)	486.4 (56.0)	NS	NS	NS	NS	NS	NS	NS
Latency									
Latency 14 days (min)	10.8 (8.7)	19.5 (17.7)	0.011	NS	NS	NS	NS	0.019	NS
Latency workday (min)	11.0 (10.3)	18.0 (16.9)	0.04	NS	NS	NS	NS	NS	NS
Latency leisure day (min)	10.4 (8.3)	20.5 (20.3)	0.01	NS	NS	NS	NS	0.012	NS
Awakenings									
Awakenings 14 days (per night)	1.4 (1.0)	1.9 (1.3)	0.033	NS	NS	NS	NS	NS	NS
Awakenings workday (per night)	1.4 (1.2)	1.9 (1.4)	0.043	NS	NS	NS	NS	NS	NS
Awakenings leisure day (per night)	1.5 (1.2)	1.9 (1.4)	NS	NS	NS	NS	NS	NS	NS

Pre, premenopausal women; post, postmenopausal women; n, number; TST, total sleep time including naps; ST, nocturnal sleep time; Latency, sleep latency; Awakenings, nocturnal awakenings; BDI, Beck Depression Inventory (score); VMS, vasomotor symptoms; Group, menopausal group (premenopausal or postmenopausal); SD, standard deviation; NS, non-significant.

According to the post-hoc analysis that excluded HT users, latency during workdays and awakenings during the 14-day period did not differ between the groups. Otherwise, the results remained unchanged.

5.1.2 Symptoms of insomnia, sleep-disordered breathing, and excessive daytime sleepiness

According to Study II, postmenopausal women (aged on average 56 years) perceived their general sleep quality as worse compared to premenopausal women about 10 years younger ($p < 0.001$). Of postmenopausal women, 51.0 % considered their general sleep quality seldom or never good, which was approximately double the proportion of 24.3 % reported by the premenopausal group. Postmenopausal women had more nocturnal awakenings ($p = 0.015$), they slept more restlessly ($p = 0.020$), and they dozed off more easily when not active (e.g. watching TV) ($p < 0.001$) compared to premenopausal women. Difficulty falling asleep, SL, frequency of snoring and witnessed apnea, morning headache, morning and daytime tiredness, tendency to fall asleep unintentionally during work or leisure time, the frequency of daytime napping, or the use of sleep medication did not differ between the groups. (Figure 9). After adjustment for night sweats, hot flashes, and BDI score, only morning tiredness differed between the groups; postmenopausal women felt themselves less often tired in the morning compared to premenopausal women (OR 0.2, 95% CI 0.1–0.7, $p = 0.006$).

In Study III, the three study groups of 46-year-old women were similar according to the BNSQ sleep variables at baseline, when all women were premenopausal. At the five-year follow-up, difficulty falling asleep was more frequent in postmenopausal non-HT users and less frequent in postmenopausal HT users. Morning headache was more frequent in postmenopausal non-HT users and less frequent in women who remained premenopausal. General sleep quality tended to be worse ($p = 0.052$) and nocturnal awakenings more frequent ($p = 0.053$) in postmenopausal non-HT users. (Table 6.) After adjusting for BDI total score, night sweats, perceived general health, personal crises, use of CNS medication, and BMI, only one difference was found; the risk of difficulty falling asleep was higher in postmenopausal non-HT users compared to postmenopausal HT users (OR 14.6 (95% CI 1.4–156.4), $p = 0.027$).

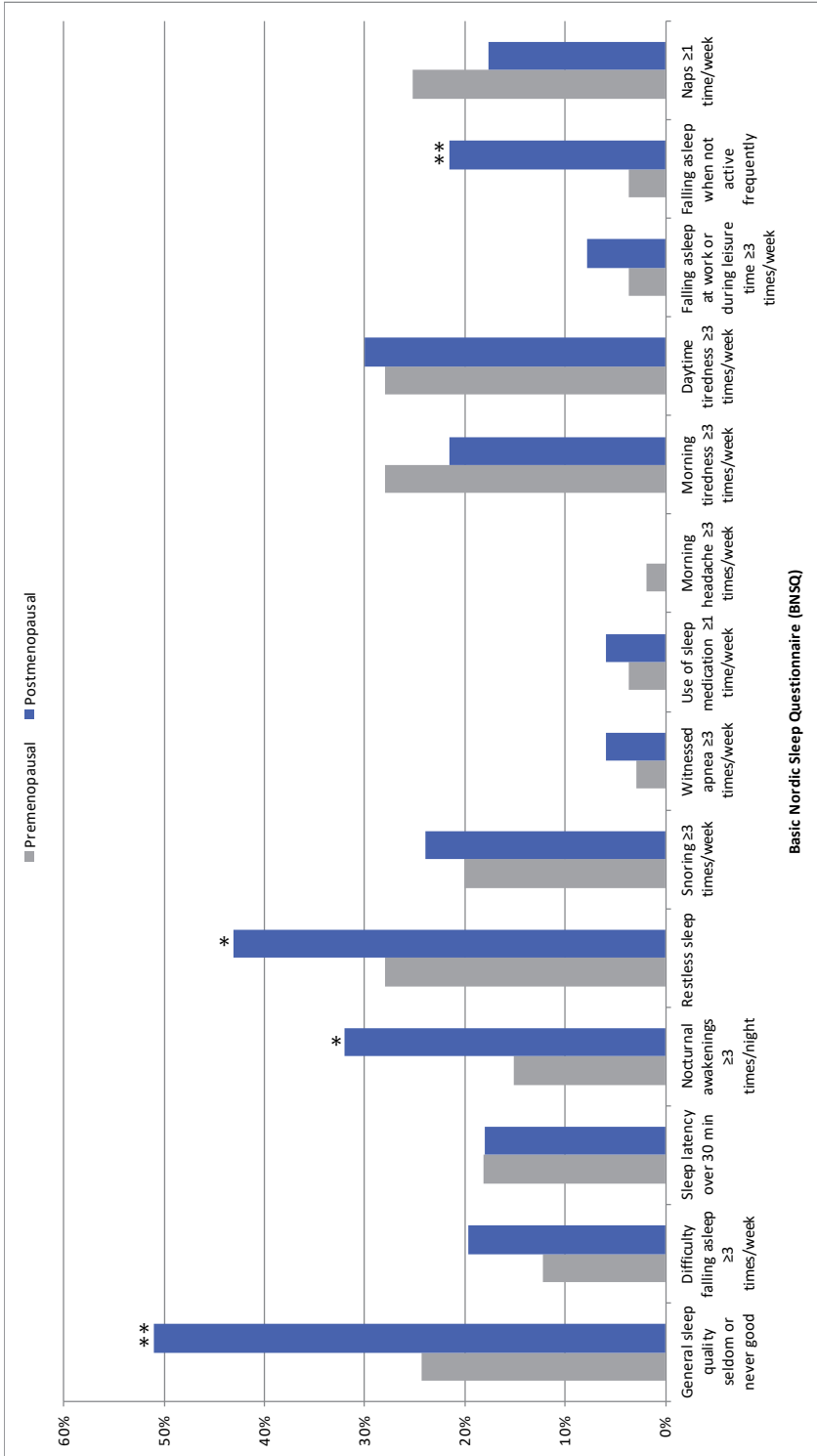


Figure 9. Sleep assessment in premenopausal and postmenopausal women using the Basic Nordic Sleep Questionnaire in Study II. Values are expressed in percentages. * $p < 0.05$, ** $p < 0.001$. (Reprinted with permission from the North American Menopause Society.)

Table 6. Results of the Basic Nordic Sleep Questionnaire at baseline and at follow-up in Study III, expressed as percentages.

	Baseline			<i>p</i>	Five-year follow-up			<i>p</i>
	Pre n = 27	Post n = 40	Post+HT n = 14		Pre n = 27	Post n = 40	Post+HT n = 14	
General sleep quality seldom or never good (%)	11.1	25.0	15.4	NS	11.1	35.0	14.3	NS
Difficulties falling asleep \geq 1 night per week (%)	25.9	32.5	7.7	NS	18.5	42.5	7.1	0.016
Sleep latency over 20 min (%)	30.8	35.9	7.7	NS	14.8	30.0	7.1	NS
Nocturnal awakenings \geq 2 times per night (%)	37.0	50.0	46.2	NS	25.9	55.0	35.7	NS
Restless sleep (%)	25.9	25.0	0.0	NS	18.5	41.0	28.6	NS
Snoring \geq 1 night per week (%)	37.0	33.3	38.5	NS	42.3	48.7	46.1	NS
Witnessed apneas \geq 1 night per week (%)	0.0	5.3	7.7	NS	4.0	7.9	0.0	NS
Morning headache \geq 1 time per week (%)	7.4	12.5	7.7	NS	0.0	20.0	7.1	0.033
Morning tiredness \geq 1 time per week (%)	51.9	52.5	15.4	NS	44.4	60.0	35.7	NS
Daytime tiredness \geq 1 time per week (%)	63.0	52.5	46.2	NS	55.6	62.5	57.1	NS
Falling asleep at work or during leisure time \geq 1 time / week (%)	14.8	5.0	0.0	NS	11.1	22.5	14.3	NS
Falling asleep when not active sometimes or often (%)	37.0	22.5	23.1	NS	18.5	30.0	42.9	NS
Naps \geq 1 time per week (%)	33.3	42.5	30.8	NS	40.7	27.5	28.6	NS
Use of sleep medication \geq 1 time per week (%)	0.0	10.0	0.0	NS	7.4	12.5	0.0	NS

Pre, premenopausal women; Post, postmenopausal women not using hormone therapy; Post+HT, postmenopausal women using hormone therapy; NS, non-significant.

5.2 Sleep architecture

In the entire cohort of Study IV, SL, sleep onset latencies to S1 and S2 and sleep stage transitions per hour decreased, whereas sleep onset latency to REM, transitions from SWS to wake, WASO, awakenings, and ARI increased during the follow-up period. In addition, AHI and ODI₄ increased during the follow-up period. (Table 7.)

Both aging and S-FSH concentration influenced PSG variables in the regression analysis. Aging six years decreased SL by 12.2 minutes, sleep onset latency to S2 by 12.8 minutes, and increased transitions from SWS to wake by 0.9 per night, WASO by 27.3 minutes, awakenings by 1.4 times per hour, ARI by 2.4 units, and AHI by 5.6 units. An increase of ten units in S-FSH concentration increased SWS by 0.9% and SWS periods by 0.2 per night. However, neither aging nor S-FSH concentration were associated with SWA. (Table 8.)

After adjusting the regression analysis with BMI, night sweats, hot flashes, and BDI total score, aging and S-FSH concentration still had an effect on PSG variables. After adjusting, aging six years decreased TST by 37.4 minutes (95% CI -71.5 – (-3.3), $p = 0.032$) and SE by 6.5% (95% CI -12.7 – (-0.2), $p = 0.043$), and increased transitions from SWS to wake by 1.0 per night (95% CI 0.1–1.9, $p = 0.035$), WASO by 37.7 minutes (95% CI 12.5–63.0, $p = 0.004$), awakenings by 1.8 per hour (95% CI 0.8–2.8, $p = 0.001$) and ARI by 2.3 units (95% CI 0.1–4.4, $p = 0.045$). An increase of ten units (IU/L) in S-FSH concentration increased SWS by 0.9% (95% CI 0.01–0.2, $p = 0.035$). (Table 8, Figure 10)

5.3 Associative and predictive factors for climacteric sleep disturbances

In Study II, the frequency of night sweats and hot flashes, depressive symptoms, and lower education were associated with poorer sleep quality. (Figure 11.) More frequent night sweats increased the risk for poorer general sleep quality (OR 5.0 (95% CI 2.0–11.1), $p < 0.001$). An interaction was found between the menopausal group and night sweats in general sleep quality, restless sleep, and morning tiredness. In postmenopausal women, those sleep variables did not differ according to the frequency of the symptoms. In premenopausal women, those who reported more frequent night sweats had poorer general sleep quality (OR 11.1 (95% CI 3.3–50.0, $p < 0.001$), more restless sleep (OR 5.0 (95% CI 1.3–12.5), $p = 0.020$) and more morning tiredness (OR 5.0 (95% CI 1.7–16.7), $p = 0.004$) than those seldom reporting night sweats. More frequent hot flashes increased the risk for nighttime awakenings (OR 5.0 (95% CI 2.0–12.5), $p < 0.001$).

Table 7. Polysomnography results in Study IV at baseline and at the six-year follow-up, expressed as means (SD).

	Baseline n = 60	Follow-up n = 60	Mean difference (SD)	<i>p</i>
TST (min)	370.8 (66.0)	362.2 (70.2)	-8.6 (73.6)	NS
SE (%)	81.2 (13.0)	78.6 (14.2)	-2.6 (13.2)	NS
SL (min)	30.7 (22.8)	20.0 (16.5)	-10.7 (25.3)	0.002
Lat onset S1 (min)	28.8 (27.6)	19.1 (16.8)	-9.7 (30.8)	0.018
Lat onset S2 (min)	35.8 (29.9)	24.0 (16.8)	-11.8 (30.9)	0.004
Lat onset SWS (min)	37.9 (50.2)	41.2 (72.8)	3.3 (62.0)	NS
Lat onset REM (min)	125.8 (61.0)	147.0 (75.8)	21.2 (73.5)	0.030
S1 (%)	8.3 (5.0)	9.0 (4.9)	0.8 (5.2)	NS
S2 (%)	58.2 (8.1)	57.0 (10.5)	-1.2 (10.3)	NS
SWS (%)	15.0 (9.0)	16.6 (9.5)	1.6 (8.9)	NS
SWS periods	3.4 (2.2)	4.0 (2.3)	0.6 (2.5)	NS
SWA (μ V2)	50.7 (38.4)	49.5 (26.2)	-1.2 (35.3)	NS
REM (%)	18.6 (5.6)	17.0 (5.2)	-1.5 (6.5)	NS
REM periods	4.2 (1.6)	4.2 (1.6)	0.02 (1.9)	NS
Sleep stage transitions / h	20.5 (7.5)	17.9 (3.9)	-2.6 (8.6)	0.023
Transitions from SWS to wake	0.9 (1.1)	2.3 (1.9)	1.4 (1.9)	<0.001
WASO (min)	55.5 (49.1)	79.5 (60.0)	24.0 (51.7)	0.001
Awakenings / h	2.8 (1.9)	4.2 (2.3)	1.3 (2.0)	<0.001
Arousals / h	9.0 (4.5)	9.8 (5.5)	0.8 (3.6)	NS
ARI / h	11.8 (5.2)	13.9 (6.5)	2.1 (4.5)	<0.001
AHI / h	5.1 (6.5)	10.6 (15.1)	5.5 (13.0)	0.003
Mean SaO ₂ (%)	95.4 (1.5)	95.4 (1.7)	-0.02 (1.1)	NS
Min SaO ₂ (%)	87.6 (4.6)	87.5 (5.5)	-0.1 (5.3)	NS
Sat<90%	0.8 (2.6)	1.6 (5.2)	0.7 (5.4)	NS
ODI ₄ / h	4.9 (7.3)	8.8 (14.0)	3.9 (10.7)	0.009

SD, standard deviation; min, minutes; TST, total sleep time; SE, sleep efficiency; SL, sleep latency; S1, stage 1 NREM sleep; NREM, non-rapid eye movement sleep; S2, stage 2 NREM sleep; SWS, slow wave sleep; REM, rapid eye movement sleep; Lat onset S1/S2/SWS/REM; sleep onset latency to S1/S2/SWS/REM sleep; SWA, slow wave activity; h, hour; WASO, wake after sleep onset; ARI, arousal index; AHI, apnea-hypopnea index; SaO₂, oxygen saturation; Min SaO₂, minimum oxygen saturation; ODI₄, episodes of arterial oxyhemoglobin desaturation of 4% units or more per hour; NS, non-significant.

Table 8. The results of linear regression analyses in Study IV, expressing the effects of time and S-FSH on sleep variables. The results are presented both unadjusted and adjusted for BMI, night sweats, hot flashes and BDI total score (p-values only), and expressed as Coefficient beta (B).

	Effect of time				Effect of S-FSH			
	B	95% CI	<i>p</i>	Adj <i>p</i>	B	95% CI	<i>p</i>	Adj <i>p</i>
TST (min)	-22.9	(-51.3 - 5.6)	NS	0.032	0.39	(-0.19 - 0.96)	NS	NS
SE (%)	-3.2	(-8.4 - 2.0)	NS	0.043	0.02	(-0.09 - 0.12)	NS	NS
SL (min)	-12.2	(-22.1 - (-2.3))	0.017	NS	0.04	(-0.16 - 0.24)	NS	NS
Lat onset S1 (min)	-6.9	(-19.0 - 5.2)	NS	NS	-0.08	(-0.32 - 0.17)	NS	NS
Lat onset S2 (min)	-12.8	(-24.9 - (-0.7))	0.039	NS	0.03	(-0.22 - 0.27)	NS	NS
Lat onset SWS (min)	6.3	(-18.5 - 31.2)	NS	NS	-0.08	(-0.58 - 0.42)	NS	NS
Lat onset REM (min)	22.8	(-6.0 - 51.6)	NS	NS	-0.04	(-0.63 - 0.54)	NS	NS
S1 (%)	1.2	(-0.9 - 3.2)	NS	NS	-0.01	(-0.05 - 0.03)	NS	NS
S2 (%)	0.3	(-3.7 - 4.3)	NS	NS	-0.04	(-0.12 - 0.04)	NS	NS
SWS (%)	-1.8	(-5.1 - 1.4)	NS	NS	0.09	(0.03 - 0.16)	0.008	0.035
SWS periods	-0.1	(-1.1 - 0.8)	NS	NS	0.02	(0.0 - 0.04)	0.037	NS
SWA (μ V ₂)	-8.1	(-22.3 - 6.1)	NS	NS	0.21	(-0.11 - 0.53)	NS	NS
REM (%)	-0.4	(-3.0 - 2.1)	NS	NS	-0.03	(-0.08 - 0.02)	NS	NS
REM periods	-0.4	(-1.1 - 0.3)	NS	NS	0.01	(0.0 - 0.03)	NS	NS
Sleep stage transitions / h	-2.7	(-6.1 - 0.6)	NS	NS	0.004	(-0.06 - 0.07)	NS	NS
Transitions from SWS to wake	0.9	(0.2 - 1.6)	0.016	0.035	0.01	(0.0 - 0.03)	NS	NS
WASO (min)	27.3	(7.0 - 47.5)	0.009	0.004	-0.09	(-0.5 - 0.32)	NS	NS
Awakenings / h	1.4	(0.6 - 2.2)	0.001	0.001	-0.003	(-0.02 - 0.01)	NS	NS
Arousals / h	0.9	(-0.5 - 2.3)	NS	NS	-0.004	(-0.03 - 0.02)	NS	NS
ARI / h	2.4	(0.6 - 4.1)	0.009	0.045	-0.01	(-0.04 - 0.03)	NS	NS
AHI / h	5.6	(0.2 - 11.0)	0.041	NS	-0.003	(-0.11 - 0.11)	NS	NS
Mean SaO ₂ (%)	0.2	(-0.3 - 0.6)	NS	NS	-0.01	(-0.01 - 0.0)	NS	NS
Min SaO ₂ (%)	-0.4	(-2.5 - 1.8)	NS	NS	0.01	(-0.04 - 0.05)	NS	NS
Sat<90%	0.4	(-1.8 - 2.6)	NS	NS	0.01	(-0.04 - 0.06)	NS	NS
ODI ₄ / h	3.7	(-0.7 - 8.1)	NS	NS	0.01	(-0.08 - 0.1)	NS	NS

The effect of time, aging of six years; the effect of S-FSH, one unit (IU/L) increase in S-FSH concentration. BMI, body mass index; BDI, Beck Depression Inventory; S-FSH, serum follicle stimulating hormone; 95% CI, 95 percent confidential interval; min, minutes; TST, total sleep time; SE, sleep efficiency; SL, sleep latency; S1, stage 1 NREM sleep; NREM, non-rapid eye movement sleep; S2, stage 2 NREM sleep; SWS, slow wave sleep; REM, rapid eye movement sleep; Lat onset S1/S2/SWS/REM; sleep onset latency to S1/S2/SWS/REM sleep; SWA, slow wave activity; h, hour; WASO, wake after sleep onset; ARI, arousal index; AHI, apnea-hypopnea index; SaO₂, oxygen saturation; Min SaO₂, minimum oxygen saturation; ODI₄, episodes of arterial oxyhemoglobin desaturation of 4% units or more per hour; IU/L, international units per liter; NS, non-significant.

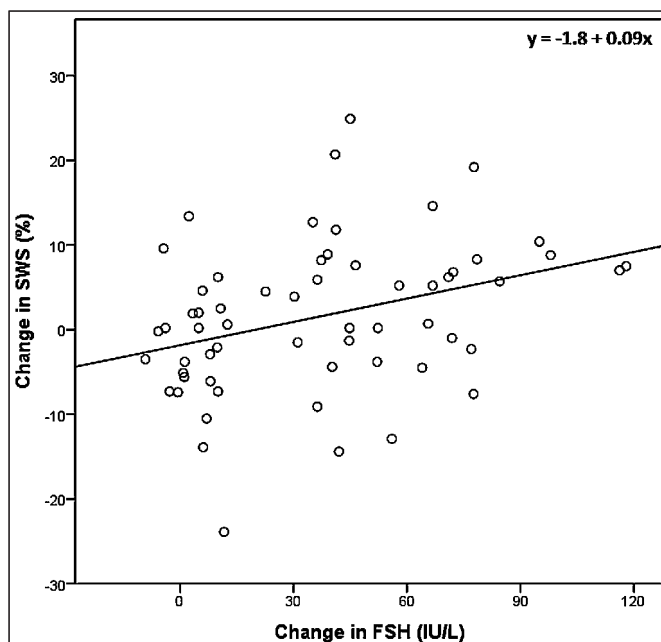


Figure 10. The relationship between the change in S-FSH (IU/L) and SWS (%). The regression line is given by ordinary least squares linear regression. The regression coefficients, their 95% confidence intervals, and their *p*-values are shown in Table 8. SWS, slow wave sleep; FSH, follicle stimulating hormone level. (Reprinted with permission from The Oxford University Press.)

Higher BDI scores increased the risk for poor general sleep quality (OR 6.2 (95% CI 2.4–16.0), $p < 0.001$), restless sleep (OR 6.7 (95% CI 2.5–18.2), $p < 0.001$), and morning (OR 4.5 (95% CI 1.7–11.8), $p = 0.002$) and daytime tiredness (OR 2.5 (95% CI 1.1–5.9), $p = 0.035$).

Lower education level increased the risk for poor general sleep quality (OR 2.2 (95% CI 1.03–4.6), $p = 0.042$), longer SL (OR 2.5 (95% CI 1.01–6.1), $p = 0.047$), and more restless sleep (OR 2.5 (95% CI 1.2–5.4), $p = 0.018$). An interaction was found between the menopausal group and education on SL and frequency of naps. In postmenopausal women, education had no effect on SL, whereas lower-educated premenopausal women had longer SL than those with a higher education level (OR 4.3 (95% CI 1.5–12.3), $p = 0.007$). Lower-educated postmenopausal women took fewer naps than those with a higher education level (OR 0.09 (95% CI 0.01–0.8), $p = 0.032$) whereas, in premenopausal women, there was a tendency to the opposite direction (OR 2.5, 95% CI 1.0–6.7, $p = 0.057$).

In Study III, several predictors for sleep disturbances during menopausal transition were found in longitudinal analysis. Women with a higher BDI score at baseline had increased risk for nighttime awakenings (OR 1.2 (95% CI 1.02–1.3), $p = 0.025$), morning (OR 1.2 (95% CI 1.06–1.4), $p = 0.007$) and daytime (OR 1.2 (95% CI 1.1–1.4), $p = 0.007$) tiredness, and tendency to fall asleep during work or leisure time (OR 1.2 (95% CI 1.01–1.4), $p = 0.036$) at follow-up. Women who had experienced personal crises at baseline had increased

risk for longer SL (OR 5.5 (95% CI 1.1–26.3), $p = 0.035$) and tendency to fall asleep when not active (OR 5.4 (95% CI 1.4–20.8), $p = 0.014$) at follow-up. Women who reported poor perceived health at baseline had increased risk for difficulty falling asleep at follow-up (OR 2.9 (95% CI 1.04–7.9), $p = 0.043$). Women using CNS medication at baseline had increased risk for worse general sleep quality at follow-up (OR 11.4 (95% CI 1.1–121.8), $p = 0.044$). Women with night sweats already at baseline had increased risk for difficulty falling asleep at follow-up (OR 10.5 (95% CI 2.3–49.0), $p = 0.003$). (Figure 11.)

In Study III, the effects of changes (deltas) in independent variables from baseline to follow-up on sleep were evaluated, and associations with increasing night sweats, BMI, and alcohol consumption with sleep disturbances were found. For exact p-values, see the original article. (Figure 11.)

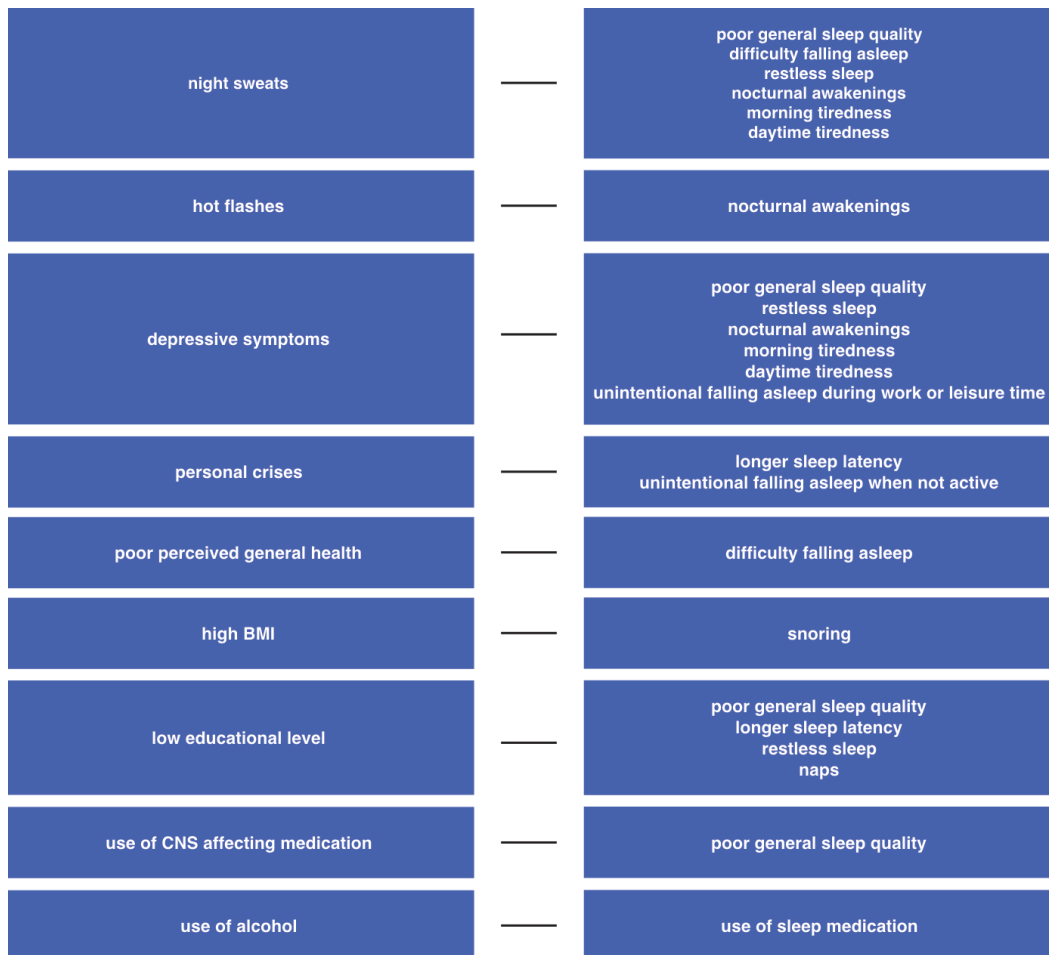


Figure 11. Associative and predictive factors for sleep disturbances in menopausal transition according to Studies II and III. The exact p-values are presented in the original articles.

6 DISCUSSION

The objectives of this observational study were to assess both subjective sleep quality and sleep architecture in menopausal transition, with both cross-sectional and longitudinal design. The purpose was to understand the influence of age and menopausal hormonal changes, as well as to study the association of other menopausal symptoms, health-related factors, and work, with sleep disturbances during this period of life. Furthermore, the possible predictors for sleep disturbances in menopausal transition, identifiable already in premenopause, were examined. In cross-sectional and longitudinal analyses, postmenopausal women reported more sleep disturbances compared to premenopausal women. When studied in more detail, insomnia symptoms, such as difficulty in initiating and maintaining sleep and, and to a lesser extent symptoms of SDB and excessive daytime sleepiness, accounted for most perceived sleep disturbances. According to the longitudinal PSG study, sleep architecture became impaired as a result of aging; sleep became more fragmented, and both SE and TST decreased. Menopausal hormonal changes, however, seemed to restore some SWS. Predictably, vasomotor symptoms played an important role in explaining difficulty to maintain sleep in subjective analyses. Several premenopausal health-related factors, such as depressive symptoms, personal crises, and perceived impaired general health predicted impaired subjective sleep quality in menopausal transition.

6.1 Subjective sleep quality in menopausal transition

The present study (Studies I and II) emphasizes the previous findings from cross-sectional studies asserting that postmenopausal women are less satisfied with their sleep than premenopausal women (Cheng et al., 2008; Hung et al., 2014; Kravitz et al., 2003; Shin et al., 2005; Sun et al., 2014; Timur et al., 2009; Young et al., 2003). In the current sample, 51% of postmenopausal women perceived their sleep quality as seldom or never good, which is in line with the literature of the prevalence of menopausal sleep disturbances (Nelson, 2008). According to the longitudinal study (Study III), the prevalence of sleep disturbances increased somewhat after menopause, in line with most previous longitudinal studies (Berecki-Gisolf et al., 2009; Kravitz et al., 2008; Tom et al., 2010; Woods et al., 2010). When evaluated more in detail, using cross-sectional analyses (Study II), poorer general sleep quality was attributed to difficulty in maintaining sleep, since awakenings were more frequent and sleep more restless in postmenopausal women. Perception of restless sleep presumably corresponds to awakenings/arousals or frequent transitions from deeper sleep stages to lighter ones. In addition, daytime propensity to fall asleep when not active, referring to excessive daytime sleepiness, was more common in postmenopausal women than in premenopausal women. In the five-year follow-up study (Study III), difficulty falling asleep was more frequent in postmenopausal women compared to

postmenopausal women using HT, and morning headache, possibly indicating SDB, was more frequent in postmenopausal women compared to premenopausal women. In addition, general sleep quality tended to be worse and awakenings more frequent in postmenopausal women not on HT at the follow-up time-point. Difficulty falling asleep remained significant after adjusting with confounding factors. Excessive daytime sleepiness in the current study may suggest symptoms of SDB or sleep deprivation, as those are the most common causes of excessive daytime sleepiness (Pagel, 2009; Roth et al., 1996). Excessive daytime sleepiness, however, must be differentiated from daytime tiredness, which is usually caused by insomnia (Riemann et al., 2014).

To sum up, the present study found that after menopause, participants mostly reported insomnia symptoms (difficulty initiating and maintaining sleep) but, interestingly, also reported symptoms related to SDB, as well as an increase in excessive daytime sleepiness. The previous literature from cross-sectional (Cheng et al., 2008; Moreno-Frias et al., 2014; Shin et al., 2005) and longitudinal studies (Kravitz et al., 2008; Woods et al., 2010) supports the present finding that reduced sleep quality is mostly related to difficulty maintaining sleep. However, a few studies have found difficulty initiating sleep to account for impaired sleep quality, two cross-sectional studies (Cheng et al., 2008; Young et al., 2003) and one longitudinal study (Kravitz et al., 2008). Studies addressing excessive daytime sleepiness during menopause are sparse (Chedraui et al., 2010; Cheng et al., 2008; Young et al., 2003). Cheng and co-workers found that excessive daytime sleepiness was more prevalent in post- and perimenopausal women compared to premenopausal women (Cheng et al., 2008), but the study of Young et al. did not find any difference in daytime sleepiness between menopausal groups (Young et al., 2003). The majority of the existing studies have evaluated sleep only by asking one general question about sleep quality (Berecki-Gisolf et al., 2009; Freeman et al., 2015; Kravitz et al., 2003; Tom et al., 2010), or with a few questions about insomnia (Kravitz et al., 2008; Shin et al., 2005; Woods et al., 2010). Evaluating sleep disturbances so restrictively does not allow a full understanding of the overall picture of the problem, and might over- or underestimate the prevalence.

6.2 Sleep architecture in menopausal transition

A limited number of studies have evaluated sleep architecture in pre- and postmenopausal women, all with cross-sectional design. These studies have not found an association between the changes in sleep architecture and perceived sleep disturbances in peri- and postmenopausal women. Four studies found no differences in sleep architecture between pre- and postmenopausal women (Campbell et al., 2011; Freedman et al., 2004; Kalleinen et al., 2008; Shaver et al., 1988). An interesting observation from the two large studies was that postmenopausal women had more SWS compared to premenopausal women (Hachul et al., 2015; Young et al., 2003). The study of Young et al. also found higher SE

and less S2 sleep in postmenopausal women compared to premenopausal women; nevertheless, postmenopausal women were more dissatisfied with their sleep (Young et al., 2003). However, another study reported worse sleep architecture in peri- and postmenopausal women compared to premenopausal women (lower SE and longer total wake time), but the study participants were insomnia patients (Xu et al., 2011). The present study (Study IV) was the first longitudinal study evaluating sleep architecture in normal menopausal transition. The effect of menopause on sleep architecture was studied using S-FSH as a marker of entering to menopause, and higher S-FSH concentration was observed to be associated with more SWS after controlling with BMI, vasomotor, and depressive symptoms. No other sleep parameter was altered along the change in S-FSH concentration. The finding of increased SWS during the menopausal transition is in line with the two previous studies (Hachul et al., 2015; Young et al., 2003). Sowers and co-workers measured S-FSH longitudinally and PSG cross-sectionally, and found that more rapid rate of S-FSH change was associated with higher percentage of SWS, as well as longer TST (Sowers et al., 2008). In contrast, in another cross-sectional study, higher S-FSH concentration was connected to poorer sleep architecture after adjusting with age, BMI, and hot flashes (de Zambotti et al., 2015). To make this even more complex, in the same study, S-FSH was not associated with any PSG parameter in perimenopausal women with insomnia (de Zambotti et al., 2015).

The physiology behind increasing SWS in menopausal transition is not known. The phenomenon could be explained by the increase in body temperature in women with higher S-FSH concentration. It has been suggested that an increase in core body temperature is associated with increased SWS (Horne et al., 1985; Horne et al., 1987). During menopausal transition (Freedman, 2005; Freedman et al., 2006), and by aging (Pandolf, 1997), a change in thermoregulation has been proposed. Sleep deprivation increases SWS (Gaudreau et al., 2001), but in the current study there was no decrease in SL to SWS, thus sleep deprivation is unlikely to explain the finding. Sowers et al. found a more rapid rate of S-FSH change to be connected to more SWS. They suggested that S-FSH change could be considered as an indicator of rebalance of hormones during the menopausal transition, influencing chronobiological rhythms which are synchronized by the gonadotropins, LH and FSH (Sowers et al., 2008). In addition, the increase in SWS could reflect a coping mechanism in menopausal women with increased sleep fragmentation due to aging. Nonetheless, the increase of SWS in the current study was very marginal, and probably does not have substantial clinical importance. Despite the FSH-effect on SWS, S-FSH or aging did not impact SWA. This is in line with two previous cross-sectional studies, where delta EEG power or SWA were not associated with menopausal status (Campbell et al., 2011; Kalleinen et al., 2008). In the study by Kalleinen et al., however, SWA was higher in young women (aged 22-26 years) compared to pre- and postmenopausal women (Kalleinen et al., 2008). There are also other reports in the literature showing that SWA decreases with age (Carrier et al., 2001; Schwarz et al., 2017).

In the present study, the deterioration of sleep architecture was explained more by aging than by menopausal hormonal changes (Study IV). After controlling for BMI, vasomotor, and depressive symptoms, aging six years resulted in shorter TST, lower SE, and more fragmented sleep, since transitions from SWS to wake were more frequent and there was an increase in WASO, awakenings, and ARI. These findings reinforce the earlier findings of effects of aging on sleep architecture (Harmell et al., 2011). However, the age effects on sleep do not solely explain why peri- and postmenopausal women have more perceived sleep disturbances than premenopausal women (Kravitz et al., 2008; Woods et al., 2010).

6.3 Contributors and predictive factors for sleep disturbances in menopausal transition

6.3.1 Associations with vasomotor symptoms

It is easy to understand that sleep is disturbed if a woman wakes up several times during the night covered with perspiration. Indeed, vasomotor symptoms undoubtedly impair subjective sleep quality (Burlinson et al., 2010; de Zambotti et al., 2014; Ohayon, 2006; Xu et al., 2012). However, according to the literature, the presence of vasomotor symptoms does not automatically result in sleep disturbances. It has been proposed that only symptoms occurring at nighttime (Joffe et al., 2013), being severe (Ohayon, 2006), or bothersome (interfering with work, social or leisure activities) (Xu et al., 2012) are associated with sleep disturbances. Vasomotor symptoms were linked to sleep disturbances in the present study as well, particularly with difficulty maintaining sleep (Study II). Furthermore, nighttime sweating was somewhat more harmful to sleep than hot flashes (Study II). Night sweats were associated with sleep quality differently depending on menopausal status; in postmenopausal women, even sparse sweats disturbed sleep whereas, in premenopausal women, only frequent sweats were perceived as detrimental (Study II). This may reflect the overall vulnerability of sleep in menopausal transition, as is also shown regarding workload (see later in Discussion). Further, experience of night sweats during premenopause and an increasing frequency of night sweats during the five-year follow-up increased the risk for sleep disturbances later in the transition period (Study III).

Nevertheless, hot flashes and night sweats did not solely account for sleep impairment. After controlling for vasomotor symptoms, postmenopausal women further reported shorter ST and TST (including naps) (Study I) and increased difficulty falling asleep (Study III) compared to premenopausal women. In Study II, however, the differences in sleep parameters disappeared after adjusting with vasomotor symptoms and BDI score and, instead, postmenopausal women felt more tired in the morning than premenopausal women.

Concerning sleep architecture, aging was the most important contributor for alterations during the follow-up. These findings were independent of the occurrence of vasomotor symptoms. Neither did the occurrence of vasomotor symptoms abolish the positive effect of increasing S-FSH on SWS% (Study IV). This is in line with a few studies finding no relationship between vasomotor symptoms and sleep architecture (Freedman et al., 2004; Young et al., 2003), whereas other studies have demonstrated an association between vasomotor symptoms and sleep disruption (de Zambotti et al., 2014; Joffe et al., 2013; Thurston et al., 2012).

The main indication for HT is the treatment of bothersome climacteric symptoms, and it is the most effective treatment for vasomotor symptoms (de Villiers et al., 2016; MacLennan et al., 2004). HT has found to improve subjective sleep quality with co-occurring vasomotor symptoms (Cintron et al., 2017; Shaver et al., 2015). The impact of HT on sleep quality in women without vasomotor symptoms is obscure, although a beneficial effect has been proposed in these women (Polo-Kantola et al., 1998). In the present follow-up study, postmenopausal women using HT did not report more frequent sleep disturbances compared to premenopausal women at the same age, but postmenopausal women without HT did. After adjustment of vasomotor symptoms and various other confounding factors, the risk for difficulty falling asleep was further increased in postmenopausal women without HT compared to postmenopausal women using HT. Therefore, in the present study, one could suggest that the better sleep quality in women using HT did not result solely from alleviation of vasomotor symptoms.

In conclusion, one could assume that perception of poor sleep quality, especially difficulty maintaining sleep in menopausal transition, was at least partly contributed by vasomotor symptoms, but the influence of vasomotor symptoms on sleep architecture was minimal. Nevertheless, HT provided benefit for subjective sleep quality, in line with previous studies. Thus, in the management of menopausal sleep disturbances, HT should be considered as the first line treatment, especially if vasomotor symptoms are present. However, possible contraindications should be evaluated carefully before the initiation of HT.

6.3.2 Associations with depressive symptoms

The prevalence of depressive symptoms and clinical depression increases during menopausal transition, verified both in cross-sectional and longitudinal studies (Bromberger et al., 2007; Cohen et al., 2006; Freeman et al., 2006). The same finding was seen in the present cross-sectional analyses (Studies I and II), where postmenopausal women reported more depressive symptoms in BDI compared to premenopausal women. However, the longitudinal analysis did not support the increase in depressive symptoms after menopause (Study III). Addressing depressive symptoms in sleep studies is essential,

since there is a close relationship between depressive symptoms and sleep problems. According to the current knowledge, the association is bidirectional (Kahn et al., 2013; Sivertsen et al., 2012). In menopausal women, depressive symptoms associate negatively with subjective sleep quality (Brown et al., 2009; Burleson et al., 2010; Pien et al., 2008; Toffol et al., 2014). However, the effects on sleep architecture have been to some extent contradictory in this group (Kravitz et al., 2011; Toffol et al., 2014). The negative association of depressive symptoms with subjective sleep quality was significant. In Study II, higher scores on the BDI increased the risk for poor general sleep quality and restless sleep, as well as morning and daytime tiredness regardless of menopausal state. Furthermore, the unfavorable relationship between depressive symptoms and sleep seemed rather persistent and strong, since higher BDI scores at premenopause predicted sleep disturbances, including awakenings and daytime symptoms, even after five years, in menopausal transition (Study III), which is in line with another prospective study assessing predictors for menopausal sleep disturbances (Tom et al., 2009).

6.3.3 Associations with nocturnal breathing problems

The prevalence of SDB increases during menopausal transition (Anttalainen et al., 2006; Mirer et al., 2017; Polesel et al., 2015; Young et al., 2003), and thus the possibility of SDB must be considered when evaluating sleep disturbances of women in menopausal transition, especially in overweight women. It should be noted that the clinical picture of SDB in women differs from that of men; women are more symptomatic with lower AHI than men, have more prolonged partial upper airway obstruction, and more frequently report insomnia as a symptom of SDB (Anttalainen et al., 2016; Saaresranta et al., 2016), possibly leading to mis- or underdiagnosis of SDB in women (Lindberg et al., 2017). In the current study, women with a previous diagnosis of SDB were excluded. However, it is possible that women had some symptoms of SDB, although the mean AHI of 5.1 (SD 6.5) at baseline at the age of 46 years was only borderline to SDB (Study IV). At the six-year follow-up, the mean AHI was 10.6 (SD 15.1). Thus, the mean AHIs are comparable with the values in the recent study of Mirer et al., where mean AHI was 6.9 (SD 7.9) in premenopausal women (mean age 47.5 years), 9.3 (SD 13.7) in perimenopausal women (mean age 49.6) and 10.9 (SD 14.4) in postmenopausal women (mean age 53.2 years) (Mirer et al., 2017). A cross-sectional study of Hachul et al. found that AHI was higher and SaO₂ lower in postmenopausal women compared to premenopausal after adjustment of age, BMI and other confounding factors (Hachul et al., 2015). In the present study, however, the increase in AHI was age-dependent, and this finding lost significance when adjusted with BMI and other confounding factors. This supports the fact that obesity plays an important role in the pathogenesis of SDB (Young et al., 2002). In subjective sleep evaluations (Studies II and III), excessive daytime sleepiness and morning headache, possibly indicating SDB, were more frequent in postmenopausal women without HT compared to premenopausal women or postmenopausal women using HT. However, no

differences in nighttime symptoms of SDB (snoring, witnessed apneas) or other daytime symptoms (morning/daytime tiredness, naps) were found. The present study confirms the current view that SDB must be considered in differential diagnostics of sleep disturbances in midlife women.

6.3.4 Associations with work

In a few recent evaluations, menopausal symptoms (Geukes et al., 2012; Griffiths et al., 2013; Jack et al., 2016; Whiteley et al., 2013a), and menopausal sleep disturbances (Hammam et al., 2012; Simon et al., 2009) as well, have been found to decrease work ability. Further, menopausal symptoms have been associated with increased costs related to decreased productivity, increased health care costs, and work absenteeism (Bolge et al., 2010; Kleinman et al., 2013; Whiteley et al., 2013a). Some studies have demonstrated that, among menopausal symptoms, sleep disturbances are the most harmful in regard to work performance (Hammam et al., 2012; Simon et al., 2009). In turn, work stress and other psychosocial factors in the working environment have been associated with negative experience of menopausal symptoms (Hammam et al., 2012; Mishra et al., 2006). The current study strengthens the previous findings. In Study I, postmenopausal women reported poorer sleep quality on workdays compared to their premenopausal counterparts. However, sleep quality of postmenopausal women approached that of premenopausal women on leisure days. However, the difference on workdays disappeared after controlling for vasomotor symptoms but remained significant after controlling for depressive symptoms and education in terms of TST and ST. These observations support the hypothesis that sleep of postmenopausal women is more vulnerable to external stressors, including job strain and work-related stress. Nevertheless, since subjective sleep quality was better during leisure days in postmenopausal women, in terms of sleep duration, they appeared to have capacity to recover from the influence of their workload. In the general population, disappearance of job strain has shown to decrease sleep disturbances in a prospective study (Halonen et al., 2017) and, in menopausal women, positive work-related psychosocial factors, such as high supervisor support, have been associated with fewer reports of menopausal symptoms (Bariola et al., 2017). Consequently, it seems important to guarantee adequate recovery and make arrangements to reduce work-related stress in the workplace in order to maintain sufficient work ability after menopause. However, more studies about menopause, work and sleep are definitely needed.

6.3.5 Psychosocial, health-related, and socioeconomic factors

Personal crises experienced in the premenopausal state predicted sleep disturbances in the five-year follow-up (Study III). Menopausal transition takes place in midlife, which is often characterized by a variety of life stressors that women struggle with, in addition to

physical changes and symptoms due to menopause. In addition, perimenopausal women have been shown to report more psychological distress compared to premenopausal women (Bromberger et al., 2001). This period in women's lives has been considered as a turning point with new social and family roles and experiences (Helson et al., 2005). In addition to new roles and expectations in the family, possibly due to children gaining independence and leaving home, these stressors might include marital problems, illnesses or death of a partner or parents, or worries about getting old (Darling et al., 2012). These midlife-stressors have been linked with lower quality of life (Avis et al., 2004; Avis et al., 2009), and recently with sleep disturbances as well (Cuadros et al., 2012; Darling et al., 2012; Saaresranta et al. 2013; Woods et al., 2010) in menopausal women. In addition to the present study, few longitudinal studies concerning the association of stressful life events with sleep in menopause exist. A prospective study by Hall and colleagues showed that chronic stress, measured by the presence of very upsetting life events, predicted subjective sleep disturbances and more nighttime awakenings in PSG relative to women with lower stress profiles (Hall et al., 2015), in line with the results of the present study. In general populations, it has been demonstrated that particularly stressful family events may predict insomnia (Bernert et al., 2007), and that an individual's vulnerability to stress-related temporary sleep problems may be a risk factor for chronic insomnia (Harvey et al., 2014; Yang et al., 2014). These factors, which to some extent are part of normal midlife, must be taken into account when evaluating sleep disturbances in menopausal transition.

In addition, some other health-related predictors for sleep disturbances in menopausal transition were found, including poor perceived general health and use of CNS-affecting medication (mostly antidepressants and medication for chronic pain). The use of CNS medications partly reflects the depressive symptoms discussed before, but possibly also the prevalence of chronic pain problems in this sample. The relationship of chronic pain to sleep disturbances is generally known (Ohayon, 2005; Plotkin, 2010). Partly in line with the present study, Tom et al. found in their prospective study that the use of prescription medication and medical diseases predicted sleep disturbances later in menopausal transition (Tom et al., 2009). In general populations, it is well documented that other medical diseases might cause or contribute to sleep disturbances (Ancoli-Israel, 2006; Plotkin, 2010), and that sleep disturbances secondary to other medical diseases might be more severe and persistent than primary sleep disturbances (Ancoli-Israel, 2006). However, the perception of physical and mental health is shown to be an even more important contributor to sleep disturbances in midlife women than the existence of chronic diseases or medications used (Polo-Kantola et al., 2014). In the present study, women with severe medical diseases were excluded but, despite that, perception of poor health was associated with sleep disturbances in the longitudinal analysis. Consistent with the present study, a cross-sectional analysis of the Seattle Midlife Women's Health Study observed that poor perceived health was associated with more severe problems in initiating and

maintaining sleep, as well as in early morning awakenings in midlife women (Woods et al., 2010).

Lower levels of education were associated with increased risk of sleep disturbances in cross-sectional analyses (Study II), confirming the commonly held view that lower-educated individuals report more sleep disturbances (Arber et al., 2009; Gellis et al., 2005; Leng et al., 2014). The association has been found in menopausal women as well (Blümel et al., 2012). The relationship between educational profile and sleep differed somewhat between pre- and postmenopausal women, as the association was more pronounced in premenopausal women. The finding might be explained by the fact that premenopausal women were higher educated than postmenopausal women about 10 years older in Study II, both groups representing typical education levels in their age cohorts.

It could be hypothesized that the sleep of menopausal women is already vulnerable, due partly to long-effective risk factors, partly to the effect of aging, and partly due to the challenging life changes in midlife. Finally, when hormonal fluctuations and associated symptoms occur, it may be the last straw, and sleep disturbances manifest. Considering the burden of menopausal sleep disturbances on quality of life (Avis et al., 2009; Bolge et al., 2010) and other adverse health consequences (Cappuccio et al., 2010; Stranges et al., 2012), it would be essential to identify women with these known risk factors well beforehand, in premenopause. This would enable timely interventions, such as adequate psychosocial support and treatment, in order to prevent future sleep disturbances. Psychosocial support is justified by the previous reports that women with positive attitudes toward menopause have less menopausal symptoms (Ayers et al., 2010; Nosek et al., 2010).

6.4 Strengths and weaknesses of the study

The major strengths of the study include both cross-sectional, in two age and menopausal state groups, and prospective analyses of subjective sleep quality. To the best knowledge, Study IV was the first prospective follow-up study focusing on the influence of menopause on PSG-measured sleep architecture in menopausal transition. In that study, S-FSH concentration was analyzed continuously, using it as a marker of reproductive aging. This uniquely enabled to distinguish the effects of menopausal hormonal changes and aging on sleep architecture. The longitudinal design also permitted evaluation of predictors for sleep disturbances in menopausal transition. The same associative factors have previously been assessed cross-sectionally, but the evidence from prospective studies is sparse (Hall et al., 2015; Tom et al., 2009).

The strongest element of the study was the use of both subjective and objective measures of sleep. Perception of sleep is clinically more relevant, as it guides diagnosis and treatment. The measurements of sleep quality, sleep diary, and the validated BNSQ are

practical tools, commonly used in both scientific research and clinical practice (Carney et al., 2012; Partinen et al., 1995). The strength of the BNSQ includes the wide range of sleep questions, including questions regarding insomnia, SDB, and excessive daytime sleepiness. One general question asked about sleep quality does not specify the nature of a problem, and asking only a few questions about insomnia ignore the other sleep disorders impairing sleep. Several previous sleep studies in menopausal women, both cross-sectional and longitudinal, have included only 1–3 general questions of sleep quality or insomnia (Kravitz et al., 2003; Kravitz et al., 2008; Shin et al., 2005; Woods et al., 2010). When studied more in detail, not all aspects of subjective sleep were impaired in postmenopausal women and, in addition to insomnia symptoms, symptoms of SDB and excessive daytime sleepiness were observed after menopause (Studies II and III).

In addition to subjective measures, PSG, the golden standard used to study sleep architecture, was also used in this study. There are few PSG studies in menopausal women, and prospective follow-up designs are lacking. Knowledge of the physiological changes in sleep architecture helps to understand the mechanisms and causes of poor sleep quality experienced by menopausal women. For quality control, the sleep recordings were double-scored in order to decrease bias resulting from subjective evaluations. Besides sleep architecture and continuity, SWA analysis, seldom studied in this group, was performed.

Furthermore, the study was also strengthened by the homogeneity of the study population, since both culture and ethnicity have been documented to be associated with the severity of sleep disturbances at various stages of menopausal transition (Xu et al., 2014). The participants were relatively healthy, as women with a history of major medical diseases were excluded from the study, reducing the effect of comorbidities on sleep.

In addition, the study encompassed the evaluation of the association of work, sleep, and menopause. Since there is an increasing number of working menopausal women, research focusing on the complex relationship between menopausal symptoms, work stress, and ability has recently received increasing interest. Menopausal symptoms have been connected to decreased work productivity and increased associated costs (Bolge et al., 2010; Geukes et al., 2012; Jack et al., 2016; Kleinman et al., 2013) and vice versa; work-related factors may influence the experience of menopausal symptoms (Bariola et al., 2017; Hammam et al., 2012; Mishra et al., 2006). Furthermore, the current study was one of the first conducted with menopausal women who worked regular hours.

The main limitation of the present study was the small sample size, and thus the results should be repeated in larger cohorts. The problem of small sample size is especially pronounced in connection with small sub-groups and with multivariable analyses consisting of several explanatory factors. In the studies with small sample size, it is difficult to find significant associations due to the low power and increased level of uncertainty in the statistical tests. Further, study characteristics limit the generalizability

of the current findings. First, this was not a random population cohort, as the participants were recruited with newspaper announcements. The recruitment strategy could appeal more to poor sleepers than good sleepers, which might overestimate the effect of menopause on sleep. In addition, the recruitment strategy used might allow more women with severe menopausal symptoms to participate, possibly overestimating the role of vasomotor symptoms, for example. Second, the participants of the study probably were somewhat healthier compared to their age-matched counterparts, since all major medical diseases were excluded. A total of 21 women refused to participate at all in the follow-up study, and 37 women in the PSG study. One could suggest that the drop-outs slept so poorly in the sleep laboratory at baseline that they refused to participate any more, while the better sleepers remained in the study.

Another obvious limitation was the lack of use of the STRAW criteria (Harlow et al., 2012) in defining the menopausal stages. This was not possible in the present study because of the missing bleeding characteristics of many participants due to the use of an intrauterine hormone device, causing amenorrhea. However, menopausal state was defined by using S-FSH concentrations, except in Study III, where also amenorrhea over one year and the age of 51 or more were used to define postmenopausal status in some women, if S-FSH measurement was lacking. When S-FSH is measured only once, there is a possibility that the postmenopausal group includes perimenopausal women as well. The most reliable method to define menopausal status would be the combination of bleeding characteristics and repeated S-FSH measurements. However, the recall of bleeding characteristics may not be accurate. In addition, hormonal intrauterine device, causing amenorrhea, is widely used in Finnish midlife women, which complicates the defining of recent bleeding patterns. The grouping issue was solved in Study IV, as S-FSH was analyzed continuously. A weakness concerning PSG recordings included the lack of an adaptation night before the sleep recording. The first night's effect on sleep is well-known in the literature (Agnew et al., 1966) and is also shown in menopausal women (Virtanen et al., 2016), whereas it has been hypothesized that the phenomenon involves up to four consecutive nights (Le Bon et al., 2001).

6.5 Future aspects

Menopausal sleep disturbances are a common public health problem affecting large numbers of women globally, and causing a notable economic burden to the society. From an individual's point of view, sleep disturbances have considerable adverse effects on women's overall health, quality of life, and work ability. Therefore, recognition of these problems, preventive measures, and awareness of treatment options are crucial.

Regarding the current findings concerning premenopausal predictors for the development of sleep disturbances later in menopausal transition, future longitudinal studies with larger

cohorts are warranted in order to confirm these preliminary results. In addition, it would be important to study the association of these factors with sleep architecture. There is little evidence of factors associated with longer duration of menopausal sleep disturbances (Tom et al., 2009). However, more studies about the duration of climacteric sleep disturbances and associative factors are needed. Globally, the current trend is to extend work careers and to increase work productivity. When taking into account the marginal number of existing literature concerning the association between work and sleep in context of menopause, there is definitely a need to explore the effects of work on menopausal sleep disturbances in more depth, as well as to perform prospective assessments of the impact of reduced workload and provided support for sleep quality.

In regard to the previous confounding data adopted from the few PSG studies of menopausal transition, there is an urge for future studies with larger cohorts and longitudinal designs with repeated measures on menopausal transition to better understand the effects of menopause on sleep architecture and the causes of perception of diminished sleep quality. In addition to PSG, spectral analyses might be helpful.

Nevertheless, with the knowledge of all the adverse effects of poor sleep, the assessment of sleep and risk factors should be part of routine clinical examinations of midlife women. Based on the previous findings about the associations of psychosocial factors, work stress, and menopausal symptoms, as well as the vulnerability of sleep in menopausal women, workplace adjustments should also be made. Increasing awareness of menopause among both employees and employers, providing sufficient support and appropriate health care services, and generating a positive working culture and environment are essential. Finding high-risk women in time, intervening in a timely manner, and providing appropriate treatment is vital in order to prevent chronic sleep disturbances, as well as to maintain a good quality of life and sufficient work performance in menopausal transition and beyond.

7 CONCLUSIONS

In this thesis, the sleep of midlife women in climacteric was studied, both with subjective measures and objectively by using PSG. Sleep was assessed with a cross-sectional design and prospectively. Further, contributors and predictors for sleep disturbances in menopausal transition were evaluated. The main conclusions were the following:

- I Postmenopausal women reported impaired subjective sleep quality on workdays compared to premenopausal women, but the difference diminished during leisure days. This finding suggests that sleep in postmenopausal women is more vulnerable to job strain or work stress. Thus, adequate support and leisure time to recover from workload should be provided to menopausal women in order to sustain work ability during menopause.
- II Menopausal sleep disturbances were mainly attributed to insomnia symptoms (difficulty to initiate and maintain sleep), but also to symptoms of SDB and excessive daytime sleepiness. When diagnosing and treating menopausal sleep disturbances, different causes for sleep disturbances must be considered, including the possibility of SDB.
- III After controlling for BMI, vasomotor, and depressive symptoms, aging six years resulted in a decline in TST and SE, as well as deterioration of sleep continuity. However, an increase in S-FSH concentration, reflecting transition from premenopause to the menopausal state, was paradoxically associated with increased time spent in SWS. The increase in SWS might relate to a coping mechanism.
- IV Vasomotor symptoms were strongly linked with difficulty to maintain sleep and, in postmenopausal women, even a low frequency of vasomotor symptoms was associated with disturbed sleep. Depressive symptoms had negative effects on sleep quality and daytime symptoms regardless of menopausal state. Several risk factors at premenopause, such as depressive symptoms, experience of personal crises, and poor perceived health predicted poor sleep quality in later phases of menopausal transition. These data emphasize the importance of recognizing these high-risk women in advance and providing them timely interventions.

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APPENDICES

Appendix 1. Prospective studies on subjective sleep quality in menopausal transition.

Authors	Sample characteristics	Sleep measures	Follow-up period	Findings	Comments
Kravitz et al. 2008	The SWAN study: Pre- or perimenopausal women aged 42-52y at baseline (n = 3045)	The frequency of difficulty falling asleep, staying asleep, and early morning awakening during the past 2 weeks	7y	Adjusted OR for difficulty falling and staying asleep ↑ through menopausal transition, but adjusted OR for early morning awakening ↓ from late perimenopause to postmenopause	FSH ↑ was associated with higher OR of difficulty staying asleep, and E2 ↓ with higher OR of difficulty falling and staying asleep
Berecki-Gisolf et al. 2009	The Australian Longitudinal Study on Women's Health: Age 45-50y at baseline (n = 8649)	Difficulty sleeping during the past 12 months	5y	Adjusted OR for difficulty sleeping was increased in all menopausal transition stages compared to premenopause, being most increased after 1-4y after menopause	Study evaluated various other menopausal symptoms as well
Woods and Mitchell 2010	The Seattle Midlife Women's Health Study: Late reproductive, early or late transition and early postmenopausal at baseline, mean age 41.4, SD 4.3 (n = 286)	A health diary from three consecutive days that included three sleep questions (difficulty falling asleep, awakening during the night and early morning awakening), severity of the symptoms ranged from 0 to 4	17y	After adjustment only awakening during the night ↑ during the late menopausal transition and early postmenopause, difficulty falling asleep ↓ during early postmenopause	Awakening during the night was associated with increased FSH and decreased estrone levels, and early morning awakening with decreased estrone levels
Tom et al. 2010	A birth cohort study: Aged 48y at baseline (n= 962)	Trouble sleep during the past 12 months, rated none, moderate, severe	7y	Age-adjusted OR for severe sleep difficulty was higher in all menopausal transition groups compared to women who remained premenopausal	Moderate sleep difficulty was studied as well: relationship between menopausal transition status and moderate sleep difficulty was not as strong as with the severe sleep difficulty
Freeman et al. 2015	Penn Ovarian Aging Study: Mean age 42.2, SD 3.4 at baseline (n = 255)	Trouble sleeping in the past month, rated mild, moderate, severe	14 y	No association of sleep disturbances with final menstrual period	Sleep disturbances at premenopause and concurrent hot flashes were associated with sleep disturbances after menopause

y, year; n, number; FSH, follicle stimulating hormone level; BMI, body mass index; OR, odds ratio; E2, estradiol; SD, standard deviation.

Appendix 2. Polysomnography sleep studies in menopausal transition.

Authors	Study design	Sample characteristics	Findings	Comments
Shaver et al. 1988	cross-sectional	Pre-, peri-, and postmenopausal women aged 40-59y (n = 76)	No differences in sleep parameters between the groups	Peri- and postmenopausal women experiencing hot flashes had longer REM latency and tended to have lower SE compared to women without hot flashes
Young et al. 2003	observational epidemiology study	Pre-, peri-, and postmenopausal women, mean age 46.3y, SD 8.1 (n = 589)	Peri- and postmenopausal women had more SWS, and postmenopausal women had less S2, and higher SE compared to premenopausal women	Peri- and postmenopausal women were more dissatisfied with their sleep quality compared to premenopausal women. No adaptation night.
Sharkey et al. 2003	cross-sectional	Pre- and postmenopausal women aged 45-56y (n = 25)	Postmenopausal women had more SWS and less S1	No difference in subjective sleep quality. Two consecutive laboratory nights.
Freedman et al. 2004	cross-sectional	Pre- and postmenopausal women with and without hot flashes, aged 46-51y (n = 31)	No differences in sleep parameters	Most awakenings preceded a hot flash, not vice versa. Three consecutive laboratory nights.
Kalleinen et al. 2008	cross-sectional	Young (aged 20-26y), premenopausal (aged 45-51y) and postmenopausal (aged 59-71y) (n = 61)	No differences between pre- and postmenopausal women. Young women had longer TST, higher SE and SWA, more SWS, and less WASO compared to pre- and postmenopausal women.	Postmenopausal women were less satisfied with their sleep quality compared to premenopausal women. Two consecutive laboratory nights
Sowers et al. 2008	sleep was studied cross-sectionally and FSH annually 7 y prior the sleep study	At the time of the sleep study, women were pre-, early, or late perimenopausal and postmenopausal, median age 52y (n = 365)	More rapid rate of FSH change was associated with more SWS and longer TST	More rapid rate of FSH change was associated with poorer subjective sleep quality. Two night of in-home PSG.
Hachul et al. 2009	cross-sectional	Early and late postmenopausal women aged 50-65y (n = 30)	No differences in sleep parameters	2 consecutive laboratory nights
Hachul et al. 2010	cross-sectional	Reproductive (mean age 38.8y (SD 10.4)) and postmenopausal (55.9y (7.9)) women (n = 931)	More SWS, less S2 and REM in postmenopausal women compared to reproductive women, after adjustment of age and BMI, only greater chance of having AHI >5 for postmenopausal	No adaptation night
Campbell et al. 2011	cross-sectional	Pre-, early peri-, late peri- and postmenopausal women aged 48-59y (n = 321)	No differences in PSG measures. Beta EEG power, indicating arousal, ↑ in late peri- and postmenopausal women, but no difference in delta EEG power	Beta EEG power was related to hot flash frequency, three consecutive in-home PSG-measurement nights, results adjusted with age and other covariates
Xu et al. 2011	cross-sectional	Pre-, peri-, and postmenopausal women aged 40-59y (n = 74)	Longer total wake time and lower SE in peri- and postmenopausal women compared to premenopausal women	All subjects were insomnia patients. No differences in subjective sleep quality. Three consecutive laboratory nights.
de Zambotti et al. 2015	cross-sectional	Young (aged 18-27y) and perimenopausal women with and without insomnia (aged 43-52y) (n = 44)	FSH ↑ was associated with WASO, awakenings and arousals ↑ in perimenopausal non-insomniacs, but not in insomnia patients. In young women, FSH ↑ was related to WASO and N1 ↑.	In perimenopausal insomniacs TST correlated with anxiety and depression. No adaptation night.
Hachul et al. 2015	cross-sectional	Reproductive (mean age 34.6y, (SD 8.4)), early (52.2y (5.3)) and late (63.3y (8.6)) postmenopausal women (n = 535)	More N3, higher AHI ja lower SaO2 in postmenopausal women compared to premenopausal, no difference between early and late postmenopausal women	Wide age range (20-80y), results were adjusted with age, BMI, blood pressure. No adaptation night.

n, number; y, year; REM, rapid eye movement sleep; SD, standard deviation; SWS, slow wave sleep; S2, stage 2 non-rapid eye movement (NREM) sleep; SE, sleep efficiency; S1, stage 1 NREM sleep; FSH, follicle stimulating hormone; TST, total sleep time; PSG, polysomnography; WASO, wake after sleep onset; N1, stage 1 NREM sleep; N3, stage 3 NREM sleep; SD, standard deviation; EEG, electroencephalogram; AHI, apnea-hypopnea -index.

Appendix 3. Sleep diary.

Day	Work/Leisure day	Wake up time	Bedtime	Sleep latency (min)	Number of awakenings	Naps (min)
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						

Appendix 4. Selected questions of The Basic Nordic Sleep Questionnaire (BNSQ) used in the study.

- (1) Have you slept well during the past three months?
 1. Always
 2. Usually
 3. Seldom
 4. Never
- (2) How often have you had difficulties in falling asleep during the past three months?
 1. Never or less than once a month
 2. Less than once a week
 3. On 1–2 nights a week
 4. On 3–5 nights a week
 5. Every night or almost every night
- (3) How quickly have you fallen asleep during the past three months?
 1. In 10 minutes
 2. In 10–20 minutes
 3. In 20–30 minutes
 4. In 30–40 minutes
 5. In over 40 minutes
- (4) If you usually wake up at night, how many times did you wake up in the course of the night during the past three months?
 1. Usually I do not wake up at night
 2. Once a night
 3. 2 times a night
 4. 3–4 times a night
 5. At least 5 times a night
- (5) After you have fallen asleep, how restful has your sleep been during the past three months?
 1. Very restful
 2. Quite restful
 3. Quite restless
 4. Very restless
 5. Cannot say
- (6) Have been snoring while sleeping during the past three months?
 1. Never or less than once a month
 2. Less than once a week
 3. On 1–2 nights a week
 4. On 3–4 nights a week
 5. Every night or almost every night
- (7) Have you had nocturnal apneas during the past three months?
 1. Never or less than once per month
 2. Less than once a week
 3. On 1–2 nights a week
 4. On 3–4 nights a week
 5. Always or almost always while asleep
- (8) Have you had morning headache during the past three months?
 1. Never or less than once per month
 2. Less than once a week
 3. On 1–2 mornings a week

4. On 3–4 mornings a week
 5. Every or almost every morning
- (9) Have you felt disturbingly tired in the mornings during the past three months?
1. Never or less than once per month
 2. Less than once a week
 3. On 1–2 mornings a week
 4. On 3–4 mornings a week
 5. Every morning or almost every morning
- (10) Have you felt disturbingly tired during the daytime during the past three months?
1. Never or less than once per month
 2. Less than once a week
 3. On 1–2 days a week
 4. On 3–4 days a week
 5. Daily or almost daily
- (11) Have you suffered from unintentional falling asleep at work or during leisure time during the past three months?
1. Never or less than once per month
 2. Less than once a week
 3. On 1–2 days a week
 4. On 3–4 days a week
 5. Daily or almost daily
- (12) Have you suffered from unintentional falling asleep when not active (e.g. watching TV) during the past three months?
1. Never
 2. Seldom
 3. Sometimes
 4. Frequently
 5. Almost every time
- (13) How often have you taken a daytime nap during the past three months?
1. Never or less than once a month
 2. Less than once a week
 3. On 1–2 days a week
 4. On 3–4 days a week
 5. Daily or almost daily
- (14) Have you used sleep medication during the past three months?
1. Never or less than once a week
 2. Less than once a week
 3. On 1–2 nights a week
 4. On 3–4 nights a week
 5. Every night or almost every night

Appendix 5. Additional questionnaires.

1. Vasomotor symptoms

During the past six months, have you experienced?

- a. Night sweats
 1. Seldom or never
 2. Once a month
 3. Once a week
 4. Almost daily
- b. Hot flashes
 1. Seldom or never
 2. Once a month
 3. Once a week
 4. Almost daily

2. Quality of life

How satisfied are you with your quality of life?

1. Very satisfied
2. Quite satisfied
3. Moderately satisfied
4. Quite unsatisfied
5. Unsatisfied
6. Very unsatisfied
7. Cannot say

3. Perceived general health

What is your own perception of your current general health?

1. Very good
2. Quite good
3. Tolerable
4. Quite bad
5. Very bad
6. Cannot say

4. Perceived mental health

What is your own perception of your current mental health?

1. Very good
2. Quite good
3. Quite bad
4. Very bad
5. Cannot say

5. Personal crises

Have you encountered 1) No, 2) Yes, within a year or 3) Yes, earlier

- a) Change of habitation 1 2 3
- b) Death of a spouse 1 2 3
- c) Death of some other close person 1 2 3
- d) Illness of a close person 1 2 3
- e) Financial difficulties 1 2 3

- f) Loss of a job 1 2 3
- g) Empty nest syndrome 1 2 3
- h) Conflicts in family 1 2 3
- i) Some other hard event? 1 2 3

6. Workload

How much do you like your present work?

- 1. Very much
- 2. Somewhat
- 3. Not especially
- 4. Not at all

Do you feel rushed to complete your tasks at work?

- 1. No
- 2. Yes
- 3. Cannot say

Do you suffer from excessive mental load at work?

- 1. No
- 2. Yes
- 3. Cannot say

Do you suffer from excessive physical load at work?

- 1. No
- 2. Yes
- 3. Cannot say

7. Education

What is your educational level?

- 1. Elementary school or less
- 2. Elementary school + at least one year some other education
- 3. Middle school
- 4. Middle school + institute level education
- 5. High school
- 6. High school + institute level education
- 7. Academic education

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