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CLIMACTERIC-RELATED SYMPTOMS IN MIDLIFE AND BEYOND

Studies Using the Women's Health Questionnaire

Riina Katainen



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Riina Katainen

University of Turku

Faculty of Medicine
Department of Obstetrics and Gynaecology
Doctoral Program in Clinical Research
Turku, Finland

Supervised by

Professor Päivi Polo-Kantola, MD, PhD
Department of Obstetrics and Gynaecology
Turku University Hospital and University of Turku,
Turku, Finland

Reviewed by

Professor Margaret Rees, MD, PhD
Reader Emeritus in Reproductive
Medicine, University of Oxford,
Oxford, United Kingdom

Visiting Professor, Faculty of Medicine,
University of Glasgow, Glasgow,
United Kingdom

Adjunct Associate Professor Robert
Wood Johnson Medical School,
Rutgers University, New Jersey,
United States

Adjunct professor
Hanna Savolainen-Peltonen, MD, PhD
Department of Obstetrics and
Gynaecology, Helsinki University
Hospital and University of Helsinki,
Helsinki, Finland

Opponent

Adjunct professor Eila Suvanto, MD, PhD
Department of Obstetrics and Gynecology,
Oulu University Hospital and University of Oulu,
Oulu, Finland

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They will say you are on the wrong road, if it is your own.
- Antonio Porchia, Voices

*To all my loved ones,
and especially to my Mom with persistent hot flushes*

ABSTRACT

Riina Katainen

Climacteric-Related Symptoms in Midlife and Beyond – Studies Using the Women’s Health Questionnaire

University of Turku, Faculty of Medicine, Department of Obstetrics and Gynaecology, Doctoral Programme in Clinical Research, Turku, Finland

Annales Universitatis Turkuensis, Medica-Odontologica, 2018

This study aimed to evaluate the psychometric properties of the Women’s Health Questionnaire (WHQ) and to investigate whether age, socioeconomic and lifestyle factors, chronic diseases, or cortisol metabolism are associated with the climacteric-related symptoms measured by the WHQ.

The WHQ’s psychometric properties were evaluated in a sample of 3,421 women aged 41–54 years. The same cross-sectional sample was used to investigate associations between climacteric-related symptoms and age, socioeconomic and lifestyle factors, and chronic diseases. The effect of age was also investigated in a 19-year follow-up study of 65 women, who were 47–65 years old and perimenopausal or postmenopausal at baseline. Associations between climacteric-related symptoms and cortisol metabolism were investigated in a sample of 35 perimenopausal and postmenopausal women, aged 45–70 years. Plasma cortisol levels were measured every 20 minutes over 24 hours, and urinary cortisol was analyzed from 24-hour urine collections.

The WHQ is a valid instrument to measure climacteric-related symptoms in Finnish midlife women. In the cross-sectional study, climacteric-related symptoms became more common with age, while in the follow-up study, vasomotor symptoms (VMS), sleep problems, and cognitive difficulties decreased after menopause over time. Higher education, employment, and a healthy lifestyle were associated with fewer symptoms. VMS and sleep problems were relatively independent from chronic diseases, whereas mental and cognitive symptoms were associated with several diseases. Climacteric-related symptoms were not substantially interrelated with cortisol metabolism. To conclude, physicians should pay attention to midlife women’s overall health and to potential concurrent diseases, and encourage women to make healthy lifestyle choices.

Keywords: woman; menopause; premenopause; perimenopause; postmenopause; climacteric; hot flashes; night sweats; sleep; mood; depressive symptoms; anxiety; cognitive; concentration; memory; sexual; sexuality; menstrual; somatic; attractiveness; aging; growing old; prospective

TIIVISTELMÄ

Riina Katainen

Vaihdevuosisoireet keski-ikässä ja sen jälkeen – Tutkimuksia Women’s Health Questionnaire -kyselykaavakkeella

Turun yliopisto, Lääketieteellinen tiedekunta, Synnytys- ja naistentautioppi, Turun kliininen tohtorihjelma, Turku, Suomi

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Tutkimuksen tavoitteena oli selvittää kuinka kyselykaavake Women’s Health Questionnaire (WHQ) toimii vaihdevuosisoireiden mittaamisen välineenä. Lisäksi tutkittiin ovatko vaihdevuosiin liitetyt oireet yhteydessä ikään, sosioekonomisiin ja elämäntapatekijöihin, kroonisiin sairauksiin ja kortisoliaineenvaihduntaan.

WHQ-kyselykaavakkeen toimivuutta tarkasteltiin aineistossa, jossa oli mukana 3421 iältään 41–54-vuotiasta naista. Samaa poikkileikkausaineistoa käytettiin tutkittaessa vaihdevuosisoireina pidettyjen oireiden ja iän, sosioekonomisten ja elämäntapatekijöiden, sekä kroonisten sairauksien välisiä yhteyksiä. Iän vaikutusta oireisiin tutkittiin myös 19 vuoden seurantatutkimuksessa, jossa oli mukana 65 alkutilanteessa 47–65-vuotiasta peri- tai postmenopausaalista naista. Vaihdevuosisoireiden ja kortisoliaineenvaihdunnan välisiä yhteyksiä tutkittiin 35 iältään 45–70-vuotiaan peri- tai postmenopausaalisen naisen aineistossa. Kortisoliaineenvaihdunnan määrittämiseksi naisilta mitattiin plasman kortisolipitoisuus 20 minuutin välein vuorokauden ajan. Lisäksi määritettiin virtsan kokonaiskortisolimäärä vuorokausivirtsanäytteistä.

WHQ-kyselykaavake toimi hyvin suomalaisten keski-ikäisten naisten vaihdevuosisoireiden mittaamisessa. Keski-ikäisillä naisilla vaihdevuosisoireina pidetyt oireet lisääntyivät iän mukana, kun taas seurantatutkimuksessa vasomotoriset oireet (kuumat aallot ja yöhikoilu), unihäiriöt ja kognitiiviset vaikeudet, vähenivät ajan kuluessa menopaussin jälkeen. Korkeampi koulutustaso, työssäkäynti ja terveelliset elämäntavat olivat yhteydessä vähäisempään oireiluun. Vasomotoriset oireet ja unihäiriöt eivät juurikaan liittyneet kroonisiin sairauksiin, kun taas mielialaoireet ja kognitiiviset vaikeudet liittyivät niihin selvästi. Vaihdevuosisoireina pidetyt oireet eivät liittyneet merkittävästi kortisoliaineen-vaihduntaan. Vaihdevuosi-ikäisiä naisia hoitavien terveydenhuollon ammattilaisten on tärkeää kiinnittää huomiota naisten yleiseen terveydentilaan ja arvioida erilaisten sairauksien osuutta vaihdevuosisoireiden aiheuttajana. Lisäksi naisia on syytä kannustaa terveellisiin elämäntapavalintoihin.

Avainsanat: nainen; menopausi, premenopausi; perimenopausi; postmenopausi; vaihdevuodet; kuumat aallot; yöhikoilu, uni; mieliala; masennusoireet; ahdistus; kognitiivinen; keskittyminen; muisti; seksuaalinen; seksuaalisuus; kuukautisoreet; somaattinen; ikääntyminen; vanheneminen; prospektiivinen

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ABBREVIATIONS

α	alpha	IQR	interquartile range
ACTH	adrenocorticotrophic hormone	KMO	Kaiser–Meyer–Olkin
ALSWH	Australian Longitudinal Study on Women’s Health	LC-MS/MS	liquid chromatography- tandem mass spectrometry system
ANOVA	Analysis of variance	MENQOL	Menopause-specific Quality of Life Questionnaire
AUC	area under the curve	MRS	Menopause Rating Scale
AUC _g	area under the curve with respect to ground	PSG	polysomnography
BMI	body mass index	QoL	quality of life
CAR	cortisol awakening response	SD	standard deviation
CI	confidence interval	SMWHS	Seattle Midlife Women’s Health Study
COPD	chronic obstructive pulmonary disease	SRH	self-rated health
CRH	corticotropin-releasing hormone	SWAN	Study of Women's Health Across the Nation
CVD	cardiovascular disease	T ₄	thyroxin
EFA	exploratory factor analysis	TSH	thyroid stimulating hormone
FSH	follicle stimulating hormone	UK	United Kingdom
HPA axis	hypothalamic pituitary adrenal axis	US	United States
HT	hormone therapy (systemic menopausal hormone therapy)	UQOL	Utian Menopause Quality of Life Scale
IU/L	international units per liter	VMS	vasomotor symptoms
		WHI-OS	Women's Health Initiative Observational Study
		WHQ	Women’s Health Questionnaire

LIST OF ORIGINAL PUBLICATIONS

The present thesis is based on the following publications. The publications are referred in the text by Roman numbers (I-VI). Copyright holders of the original publications have permitted the reproduction.

- I **Katainen R**, Engblom J, Vahlberg T, Polo-Kantola P. Psychometric properties of the Finnish version of the Women's Health Questionnaire. *Menopause*. 2017;24(8):923–931.
- II **Katainen R**, Siirtola T, Engblom J, Erkkola R, Polo-Kantola P. A population-based survey of quality of life in middle-aged Finnish women. *Menopause*. 2015;22(4):402–13.
- III **Katainen R**, Engblom J, Siirtola T, Erkkola R, Polo-Kantola P. Climacteric symptoms in middle-aged women with chronic somatic diseases. *Maturitas*. 2016;86(4):17–24.
- IV **Katainen R**, Engblom J, Siirtola T, Erkkola R, Polo-Kantola P. The role of self-rated health on the association between chronic somatic diseases and climacteric symptoms. *Climacteric*. 2017;20(1):80–82.
- V **Katainen R**, Kalleinen N, Teperi S, Vahlberg T, Turpeinen U, Hämäläinen E, Nelimarkka L, Polo-Kantola P. The relationship between diurnal cortisol secretion and climacteric-related symptoms. *Maturitas*. 2018;115:37–44
- VI **Katainen R**, Engblom J, Polo-Kantola P. Climacteric-related symptoms in menopausal transition and beyond: A prospective 19-year follow-up study on previously hysterectomized women. *Menopause*. 2018;25(8):890–896

1 INTRODUCTION

Life expectancy is increasing in the developed world (World Health Statistics, WHO 2016). In Finland, it is 84 years for women (Statistics Finland, 28.10.2016). As the average age for natural menopause is 51 years (Kok et al., 2005; Pakarinen et al., 2010), one third of a woman's life occurs after menopause. However, climacteric-related symptoms may be experienced years before the onset of menopause (Harlow et al., 2012). As most women enter the menopausal transition during their work life, and climacteric-related symptoms decrease their quality of life (QoL) (Avis et al., 2009b; Bachmann, 2005; Savolainen-Peltonen et al., 2014) as well as their capacity to work (Jack et al., 2016), research into the factors linked to these symptoms is warranted. Furthermore, investigations into the duration of climacteric-related symptoms are limited in the literature with mixed results. Therefore, further longitudinal follow-up studies evaluating women's experiences of these symptoms are essential.

Vasomotor symptoms (VMS) are the most typical climacteric symptoms (Avis et al., 2005; Freedman, 2014). Although they have been the focus of intense research, their etiology and pathophysiology are not fully understood (Freedman, 2014). They are linked to decreased reproductive hormone levels, but estrogen levels do not differ between symptomatic and asymptomatic women (Freedman, 2014; Stearns et al., 2002). Other symptoms experienced by climacteric women include sleep problems, diverse mood symptoms, cognitive difficulties, impaired sexual functioning, and various somatic complaints. Their etiology is even more controversial and certainly multifactorial. Climacteric-related symptoms have been connected to various socioeconomic and lifestyle factors. However, the findings of previous studies vary and are somewhat conflicting.

Besides producing various symptoms, decreased reproductive hormone levels increase the risk of various chronic diseases, such as cardiovascular diseases (CVD) (Barton, 2013; Murphy, 2011), diabetes (Barton, 2013), and nocturnal breathing disorders (Bixler et al., 2001). Symptoms of chronic diseases may resemble symptoms that are linked to the climacteric. Yet, associations between chronic diseases and climacteric-related symptoms have not been systematically analyzed.

Climacteric-related symptoms might also be linked to cortisol production and metabolism. Cortisol production is regulated by the hypothalamic pituitary adrenal (HPA) axis (Adam and Kumari, 2009; Hannibal and Bishop, 2014), which is vulnerable to both physical and psychological stress (Hannibal and Bishop, 2014; Miller et al., 2007) and sleep disturbances (Abell et al., 2016; Backhaus et al., 2004; Hartaigh et al., 2012; Polk et al., 2005; Vargas and Lopez-Duran, 2014; Vedhara et al., 2003). Alterations in cortisol secretion may produce symptoms suggestive of climacteric-related symptoms (Adam and Kumari, 2009; Hannibal and Bishop, 2014; McEwen, 2007), and, conversely, climacteric-related symptoms might

generate stress, and thus affect cortisol production. Previous studies investigating associations between cortisol metabolism and climacteric-related symptoms have produced varying and conflicting results (Cagnacci et al., 2011; Cignarelli et al., 1989; Gerber et al., 2017; Gibson et al., 2016; Knight et al., 2010; Mitchell and Woods, 2011; Reed et al., 2016; Rubin et al., 2014; Vedhara et al., 2003; Woods et al., 2006, 2008, 2009; Woods and Mitchell, 2010). Apart from studies investigating VMS, most studies have not specifically addressed symptoms experienced during the female climacteric but have instead included both genders or various age groups. If climacteric-related symptoms were found to be associated with cortisol secretion, these associations might be a link between these symptoms and systemic diseases.

As climacteric-related symptoms considerably influence QoL (Avis et al., 2009b; Bachmann, 2005; Savolainen-Peltonen et al., 2014), in midlife women, QoL is usually measured by instruments assessing such symptoms. In the present thesis, climacteric-related symptoms were measured using the Women's Health Questionnaire (WHQ), which is a climacteric-specific measure of QoL. It evaluates various physical and emotional symptoms and sensations connected to the climacteric (Girod et al., 2004; Hunter, 1992, 2000). A shorter revised version of the WHQ has also been developed (Girod et al., 2006). While the original WHQ includes 36 items, the revised version comprises 23 items (Girod et al., 2004, 2006). Although the original WHQ has been psychometrically validated in various populations (Benzineb et al., 2013; Borud et al., 2009; da Silva Filho et al., 2005; Dotlic et al., 2015; Genazzani et al., 2002a; Hunter, 1992; Shin, 2012; Wiklund et al., 1993; Wool et al., 2000), it has not been validated in the Finnish population (Girod et al., 2004). The revised version is also validated (Benzineb et al., 2013; Girod et al., 2006), but it has not been used as widely as the original WHQ. In addition, cultural factors may influence the symptom experience and reporting (Avis et al., 2005; Gold et al., 2000, 2004; Hall et al., 2007; Lee et al., 2010), further warranting a Finnish validation study.

In the present thesis, associations between climacteric-related symptoms and various factors, including age, socioeconomic and lifestyle factors, chronic somatic diseases, and cortisol metabolism were investigated in cross-sectional study designs among Finnish women populations. To investigate whether climacteric-related symptoms continued to be experienced after menopause over time, a 19-year follow-up study was conducted. In every sub-study, climacteric-related symptoms were measured using the WHQ.

2 REVIEW OF LITERATURE

2.1 General aspects of climacteric

Ovarian function gradually begins to decrease at around 30 to 35 years of age (Perheentupa and Huhtaniemi, 2009; Wallace and Kelsey, 2010). Ovarian aging leads to estrogen withdrawal (Randolph et al., 2011), which in turn makes women vulnerable to different diseases (Armas and Recker, 2012; Barton, 2013; Bixler et al., 2001; Murphy, 2011; Sartori et al., 2011; Simpkins et al., 2012; Talsania and Scofield, 2017; Watt, 2016) and may cause various symptoms (Figure 1). For instance, VMS, sleep disturbances, changes in mood and vitality, decreased sexual desire, and vaginal dryness are often present (Avis et al., 2005; Gartoulla et al., 2014; Thomas and Thurston, 2016). The decrease in estrogen levels culminates in menopause, which is defined as a permanent cessation of menstrual periods. A 12-month period of amenorrhea is required to define the menopausal state (Burger, 1996; Harlow et al., 2012). Menopause occurs on average at a 51 years of age (range: 40–60 years), both worldwide (Kok et al., 2005) and in Finland (Pakarinen et al., 2010). However, the menopausal transition along with climacteric-related symptoms, often begin a few years before the menopausal age, and symptoms may last for years (Harlow et al., 2012). The period preceding menopause is termed premenopause (World Health Organization, 1996). The following period, which begins at the start of the menopausal transition and ends *one year after the final menstrual period*, is termed perimenopause (Harlow et al., 2012). The third and final period from menopause to death is termed postmenopause (Harlow et al., 2012).

As menopause approaches, the number of oocytes and functional follicles in the ovaries declines and menstrual cycles become anovulatory. These changes lead to irregular menstrual cycles before the cessation of menstrual periods. Because of the reduction in functional follicles, smaller amounts of estrogen and inhibin are secreted from the ovaries, which, in turn, result in increased secretion of follicle stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary gland (Burger, 1996). One year after menopause, serum FSH levels are 10–15 times higher and LH levels approximately three times higher than during the early follicular phase of menstrual cycles in young women (Burger, 1996). According to the Stages of Reproductive Aging Workshop (STRAW) criteria, a serum FSH level higher than 25 IU/L may be considered a characteristic of the late menopausal transition (Harlow et al., 2012).

2.2 Climacteric-related symptoms

Women may experience various physical and psychological symptoms during the climacteric. These symptoms include VMS, sleep problems, diverse mood symptoms, cognitive difficulties, impaired sexual functioning, menstrual symptoms, and various somatic complaints. The prevalence of the symptoms varies greatly. VMS are experienced by roughly

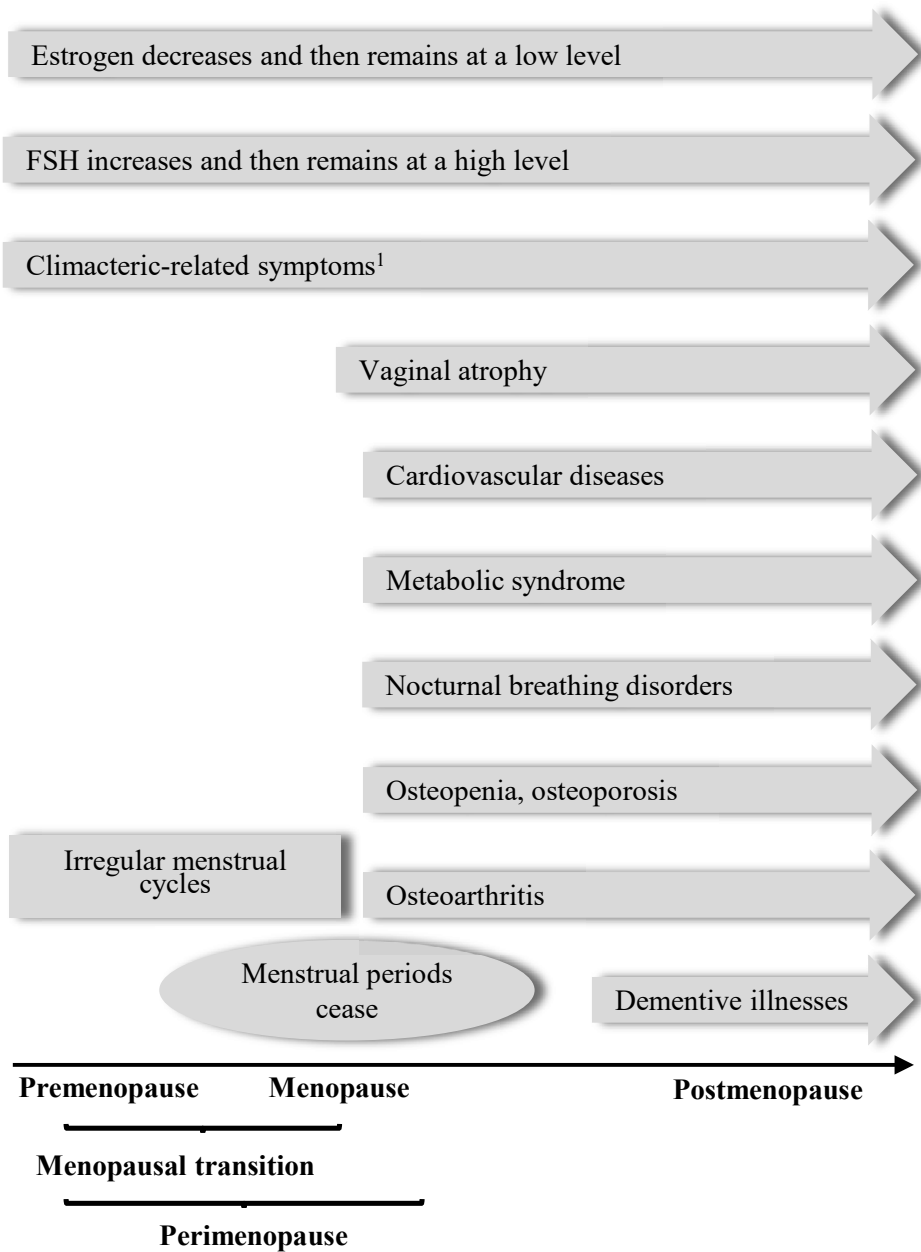


Figure 1. The timing of climacteric-related changes.

The average age for natural menopause is 51 years (Kok et al., 2005; Pakarinen et al., 2010); FSH, follicle stimulating hormone; ¹ The timing of climacteric-related symptoms varies greatly between women.

40%–80% of midlife women (Avis et al., 2005; Dennerstein et al., 2000; Freedman, 2014), sleep problems by approximately 30%–40% (Avis et al., 2005; Dennerstein et al., 2000; Kravitz et al., 2003), mood symptoms by approximately 30%–50% (Avis et al., 2005; Dennerstein et al., 2000), and problems with memory or concentration by approximately 30%–80% (Avis et al., 2005; Dennerstein et al., 2000; Greendale et al., 2011; Schaafsma et al., 2010). VMS are the most typical symptoms (Avis et al., 2005; Freedman, 2014) and although they have gained wide scientific interest during the past decades, their etiology and pathophysiology are not thoroughly understood. VMS result from an alteration in the thermoregulatory system, which regulates body temperature between an upper threshold for sweating and a lower threshold for shivering (Freedman, 2001, 2014; Stearns et al., 2002). In climacteric women, the threshold between sweating and shivering—the thermoneutral zone—is narrowed (Freedman, 2001, 2014; Stearns et al., 2002). The alteration in the thermoregulatory system is induced by an unknown trigger, which initiates an exaggerated heat dissipation response, including peripheral vasodilation, flushing, sweating, and a feeling of intense internal heat (Freedman, 2001, 2014; Stearns et al., 2002). As VMS manifest during the menopausal transition, they are certainly linked to estrogen withdrawal (Freedman, 2001, 2014; Stearns et al., 2002). Yet, no differences in estrogen levels exist between symptomatic and asymptomatic women (Freedman, 2014; Stearns et al., 2002). Blümel et al. (2000) found that women aged 40–59 years old, perimenopausal and postmenopausal women were 12 times more at risk for having VMS, which impaired their QoL, compared to premenopausal women. Interestingly, when they examined the effect of age in the group of postmenopausal women, no association was found between age and VMS. In the present thesis, VMS included hot flashes and night sweats.

Climacteric women often report sleep problems, especially problems with initiating or maintaining sleep (Polo-Kantola, 2011; Shaver and Woods, 2015). Maintenance insomnia leads to sleep fragmentation, which decreases sleep quality and sleep becomes non-restorative (Shaver and Woods, 2015). Climacteric sleep problems are probably initiated by other climacteric-related symptoms (Polo-Kantola, 2011; Shaver and Woods, 2015). However, because estrogen is involved in the metabolism of neurotransmitters, which have an impact on sleep control, and estrogen receptors have been found in areas of the brain that are responsible for sleep regulation (Polo-Kantola, 2011; Shaver and Woods, 2015), estrogen deprivation may also have direct effects on sleep. In the present thesis, sleep problems included waking up early and then sleeping badly for the rest of the night, restlessness, and difficulty initiating sleep.

Mood symptoms experienced by climacteric women include diverse depressive and anxiety symptoms, such as feeling miserable, sad, irritable, anxious or tense, losing interest in things, tearfulness, or a decreased feeling of well-being (Girod et al., 2004; Hunter, 2000; Mishra and Kuh, 2012). As estrogen modulates the serotonergic system (Joffe and Cohen, 1998), it has been hypothesized that the increase in mood symptoms during the climacteric could be related to decreasing estrogen levels or to unstable hormone production (Joffe and Cohen, 1998;

Llaneza et al., 2012). However, previous studies have provided conflicting results on the relationship between mood symptoms and sex hormones, including estrogen (Joffe and Cohen, 1998; Llaneza et al., 2012). A “domino effect” theory, which suggests that mood symptoms are caused by VMS or climacteric-related somatic symptoms, has also been proposed. According to the theory, VMS and somatic symptoms lead to sleep disturbances, which in turn would initiate mood symptoms (Joffe and Cohen, 1998; Llaneza et al., 2012). Although several studies have found an association between mood symptoms and other climacteric-related symptoms, the cause-effect relationship has not been conclusively proved (Joffe and Cohen, 1998; Llaneza et al., 2012; Worsley et al., 2014). Indeed, a 10-year follow-up study of 170 midlife women who did not experience hot flashes or depressive symptoms at baseline, found that in women who later experienced both symptoms, depressive symptoms were more likely to precede hot flashes (Freeman et al., 2009). In the present thesis, mood symptoms were divided into depressive and anxiety symptoms. Depressive symptoms included feeling miserable or sad, losing interest in things, not enjoying the things one usually enjoys, feeling that life is not worth living, a loss of appetite, irritability, and decreased feelings of well-being. Anxiety/fears included feeling frightened or having panicky feelings for no apparent reason, feeling anxious when going out alone, palpitations and a sensation of “butterflies” in the stomach or chest, and feeling tense or wound up.

As estrogen has direct effects on neurotransmitters in the central nervous system, estrogen withdrawal could have an influence on cognitive functions (Greendale et al., 2011). However, the relationship between objectively measured cognitive performance and estrogen depletion is complex (Greendale et al., 2011). Although impaired cognitive performance has not been linked to the menopausal transition with certainty, problems with memory and concentration are a common complaint among climacteric women (Greendale et al., 2011; Schaafsma et al., 2010). The present thesis focused on subjective cognitive difficulties, including problems with memory and concentration and a feeling of clumsiness (Girod et al., 2004; Hunter, 2000).

A decrease in sexual functioning often accompanies the climacteric (Avis et al., 2009a, 2017; Dennerstein et al., 1994; Gracia et al., 2007). In the present thesis, decreased sexual functioning consisted of disinterest in sexual activity, dissatisfaction with the sexual relationship, and distress related to vaginal dryness (Girod et al., 2004; Hunter, 2000). Similar aspects of sexual functioning have been investigated in studies using other questionnaires, but the terms may have been different. For instance, instead of disinterest in sexual activity, some studies have used such terms as a lack of desire or libido (Gracia et al., 2004; Hartmann et al., 2004; Woods et al., 2010). Besides climacteric-related hormonal changes, libido is also sensitive to stress, ongoing life challenges, and to reduced physical or mental well-being (Gracia et al., 2004; Hartmann et al., 2004; Woods et al., 2010). Vaginal dryness in climacteric women is usually caused by vaginal atrophy related to estrogen deprivation. However, unlike other climacteric-related symptoms that tend to decrease over time, vaginal atrophy does not recover spontaneously (Lethaby et al., 2016).

Before menopause, menstrual cycles often become anovulatory, which may lead to heavy menstrual bleeding or irregular menstruation (Sweet et al., 2012). However, once women reach menopause, bleeding ceases entirely. In addition, climacteric women frequently report breast tenderness, which also tend to decrease shortly after menopause (Dennerstein et al., 2000; Guthrie et al., 2004; Mishra and Kuh, 2012). Besides heavy menstrual bleeding and breast tenderness, in the present thesis, menstrual symptoms included abdominal cramps, discomfort, and bloating. Climacteric women also experience diverse somatic symptoms, such as pain in the joints, muscles, or back, headache, numbness, and increased frequency to pass urine (Li et al., 2005; Mishra and Kuh, 2012; Mitchell and Woods, 2010; Moilanen et al., 2010). In the present thesis, somatic symptoms included headaches, tiredness, dizzy spells, backache, pain in the limbs, nausea, pins and needles in the hands and feet, and increased frequency to pass urine.

Climacteric-related symptoms often co-occur and tend to induce or aggravate each other (Burlinson et al., 2010; Gibbs et al., 2013; Greendale et al., 2011; Joffe et al., 2009; Moreno-Frias et al., 2014; Savolainen-Peltonen et al., 2014; Worsley et al., 2014). Strong associations have been found particularly between VMS, sleep problems and mood symptoms. However, the associations are complex, and the directions of cause-effect relationships are not thoroughly understood. VMS and somatic symptoms may disturb sleep, and chronic sleep disturbances further predispose individuals to mood symptoms, which in turn increase the risk of all other symptoms (Bachmann, 2005; Burlinson et al., 2010; Eichling and Sahni, 2005; Gibbs et al., 2013; Greendale et al., 2011; Guidozi, 2013; Joffe et al., 2009; Llaneza et al., 2012; Moreno-Frias et al., 2014; Worsley et al., 2014).

2.3 Measuring QoL in the climacteric

A generally accepted definition of QoL is lacking, which makes measuring QoL challenging and controversial. Regarding QoL as experienced by midlife women, it is typically defined as a health-related concept covering both physical and mental health and various social aspects of life. Climacteric-related symptoms have a considerable impact on midlife women's QoL (Avis et al., 2009b; Bachmann, 2005; Savolainen-Peltonen et al., 2014). Thus, in the climacteric, QoL is usually measured by instruments that assess climacteric-related symptoms. As in all research, it is necessary to use validated instruments. By the end of the 1970s and in the 1980s, studies aimed to clarify the symptoms related to the climacteric. This led to the development of several questionnaires measuring climacteric-related symptoms (Abe et al., 1984; Greene, 1976; Hilditch et al., 1996; Hunter et al., 1986; Kaufert and Syrotuik, 1981). The first questionnaire based on factor analysis was developed by Professor Gerald Greene in 1976 (Greene, 1976). In 1998, Greene further examined his tool and published a modified version, the Greene Climacteric Scale (Greene, 1998), still in use. Other instruments measuring climacteric-related symptoms, which are still in use today include the Kupperman menopausal index (Blatt et al., 1953), the WHQ (Hunter et al., 1986), the Menopause Rating Scale (MRS) (Heinemann et al., 2003, 2004), and the Menopause-Specific

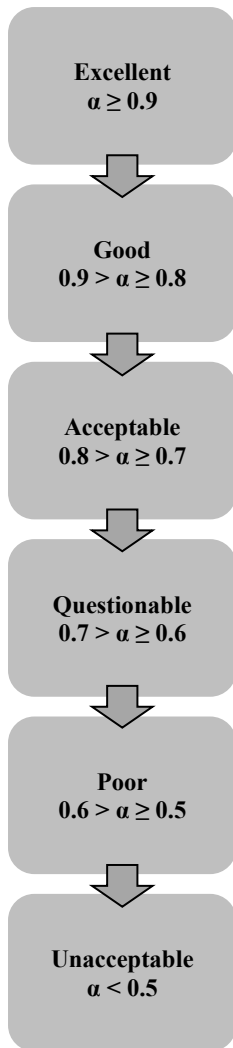


Figure 2. Classification of Cronbach's alpha coefficients (Nunnally, 1978).

Quality of Life (MENQOL) questionnaire (Hilditch et al., 1996). The Utian Quality of Life (UQOL) scale also focuses on midlife women, but instead of climacteric-related symptoms, it assesses general QoL.

The oldest of the instruments still in use is the Kupperman menopausal index (or the Blatt-Kupperman index), which includes 11 symptoms rated on a four-point scale (Blatt et al., 1953). However, the list of symptoms is not based on factor analysis, and the instrument has not been psychometrically validated (Alder, 1998; Cogo-Moreira et al., 2015; Zöllner et al., 2005). The Greene Climacteric Scale includes 21 items rated on a four-point scale (Greene, 1998). The scale includes three symptom domains: VMS, psychological symptoms, and somatic symptoms. Additionally, sexual functioning is assessed by an item termed "loss of interest in sex." Moreover, psychological symptoms may be further divided into depressive symptoms and anxiety. The MRS (<http://www.menopause-rating-scale.info/>) also includes three symptom domains, somato-vegetative symptoms, which include VMS and sleep problems, psychological symptoms, and urogenital symptoms, that encompass both sexual functioning and urinary complaints (Heinemann et al., 2003, 2004). Items are rated on a five-point scale. The MENQOL questionnaire includes 29 items grouped into five domains: vasomotor, psychosocial, sexual, physical, and working life (Hilditch et al., 1996). Respondents are asked to indicate if they have experienced each symptom within the past month and, if so, to rate how bothersome the symptom was on a seven-point scale (Hilditch et al., 1996). A modified version of the MENQOL (the MENQOL-Intervention Questionnaire) was published in 2005 (Lewis et al., 2005).

2.3.1 Women's Health Questionnaire (WHQ)

The WHQ is a climacteric-specific measure of QoL (Appendix 1). It was originally developed by Professor Myra Hunter in 1986. It evaluates various physical and emotional symptoms and sensations related to the climacteric (Girod et al., 2004; Hunter, 1992, 2000). The WHQ has been translated into 27 languages, including Finnish (Appendix 2) (Chevallet, 2000; Girod et al., 2004). Although it has been psychometrically validated in various populations (Benzineb et al., 2013; Borud et al., 2009; da Silva Filho et al., 2005; Dotlic et al., 2015; Genazzani et al., 2002a; Hunter, 1992; Shin, 2012; Wiklund et al., 1993; Wool et al., 2000), it had not been validated in the Finnish population (Girod et al., 2004). Because cultural background may influence women's experienced symptoms and reporting (Avis et al., 2005; Gold et al., 2000,

2004; Hall et al., 2007; Lee et al., 2010), it is important to assess psychometric properties in target populations.

The original WHQ contains 36 items, which are grouped into nine symptom domains, including VMS, sleep problems, depressive symptoms, anxiety/fears, cognitive difficulties, sexual functioning, menstrual symptoms, somatic symptoms, and one's experienced attractiveness, as well as a question concerning worries about growing old (Appendix 1). Thus, the WHQ includes more domains than most climacteric-specific questionnaires. The domains in the WHQ are a product of exploratory factor analysis (EFA) (Hunter, 1992). The developer Professor Hunter, also assessed its test-retest reliability (Hunter, 1992). In order to examine concurrent validity of the depressive symptoms and the anxiety/fears items, she compared the WHQ with the General Health Questionnaire (Hunter, 1992). In later studies, the factor analyses mainly provided quite comparable factor structures to the original (Borud et al., 2009; Dotlic et al., 2015; Girod et al., 2006; Wiklund et al., 1993; Wool et al., 2000). The construct validity of the WHQ was also subsequently confirmed through comparisons with other questionnaires (Borud et al., 2009; Dotlic et al., 2015; Wiklund et al., 1993). Concerning the internal consistency of the WHQ, previous studies have provided incoherent findings (Benzineb et al., 2013; Borud et al., 2009; Dotlic et al., 2015; Girod et al., 2006; Shin, 2012; Wiklund et al., 1993; Wool et al., 2000). To categorize internal consistencies, a classification suggested by Nunnally is commonly used (Figure 2) (Nunnally, 1978). Previous studies investigating the psychometric properties of the WHQ are shown in Table 1.

2.3.2 The revised version of the WHQ

A shorter revised version of the WHQ has also been developed (Girod et al., 2006). Items of depressive symptoms, anxiety/fears, and attractiveness are regrouped into two new domains (i.e., anxiety/depressed mood and well-being), and six items are completely omitted (Appendix 3). Consequently, the revised version includes 23 items, which are grouped into six symptom domains: VMS, sleep problems, anxiety/depressed mood, well-being, cognitive difficulties, and somatic symptoms. The original domains of sexual functioning and menstrual symptoms are also included but as optional domains. The revised version is validated (Benzineb et al., 2013; Girod et al., 2006), but it has not been as widely used as the original WHQ.

2.4 Self-rated health

Self-rated health (SRH) is a single-item measure that assesses a respondent's perception of her health status. It is one of the most widely used measures of general health in population health research. SRH predicts the prognosis of chronic diseases (DeSalvo et al., 2006; Gerber et al., 2009; Miilunpalo et al., 1997; Venskutonyte et al., 2013). Moreover, poor SRH is related to emotional distress (Reile and Leinsalu, 2013), limitations in daily activities and physical functioning (Reile and Leinsalu, 2013), and low life satisfaction (Reile and Leinsalu, 2013).

Table 1. Validation studies of the Women's Health Questionnaire (WHQ)

Author, year, and country	N	Age (range or mean (SD)) ¹	Menopausal status	Included domains	Scale ²	Number of factors ³
Hunter 1992, United Kingdom Development study	682 136	45–65 53 (5)	- All postmenopausal	9	1–4 1–4 (?)	9
Wiklund et al. 1993, Sweden	242	52 (4)	All postmenopausal	Menstrual symptoms excluded	1–4 (?)	8
Wool et al. 2000, Italy	155	40–65	All postmenopausal	9	1–4	10
Genazzani et al. 2002, Italy	416	53 (5)	-	“Worry about growing old” included	-	-
da Silva et al. 2005, Brazil	87	55 (9)	-	9	-	-
Borud et al. 2009, Norway	267	54 (4)	All postmenopausal	7 Sexual functioning and menstrual symptoms excluded “Worry about growing old” included	1–4	5
Shim 2012, the Republic of Korea	304	40–60	30% premenopausal 23% perimenopausal 47% postmenopausal	9 “Worry about growing old” included	1–4	9
Benzineb et al. 2013, Tunisia	1,150	45–65	16% premenopausal 24% perimenopausal 61% postmenopausal	9 “Worry about growing old” included	0–1 (?)	5
Dotlic et al. 2015, Serbia	200	40–65	43% perimenopausal 57% postmenopausal	9	0–1	10
The revised WHQ						
Girod et al. 2006, United Kingdom	1,131	45–65	31% pre- or perimenopausal 69% postmenopausal	7 Sexual functioning and menstrual symptoms excluded	0–100	6
Benzineb et al. 2013, Tunisia	1,150	45–65	16% premenopausal 24% perimenopausal 61% postmenopausal	6	0–1 (?)	6

¹ Age of the participants, years; ² The scale that was used in factor analysis; ³ The number of factors gained in factor analysis.

2.5 Factors contributing to climacteric-related symptoms

2.5.1 Aging and menopause

The majority of women experience climacteric-related symptoms during midlife. Although the etiology of the symptoms is complex, menopause and aging undoubtedly play a significant role. Previous studies have tried to determine which of the two is more important. As the results vary between symptoms, no final conclusion has been reached. Although many symptoms increase around perimenopause, it is difficult to distinguish the effects of age and estrogen withdrawal. Moreover, although estrogen deprivation is permanent, some of the symptoms subside after the menopausal transition.

For VMS, the onset of symptoms typically occurs during perimenopause or postmenopause (Berecki-Gisolf et al., 2009; Blümel et al., 2000; Dennerstein et al., 2007; Gold et al., 2000, 2004; Hunter, 1990; Slaven and Lee, 1998), and the occurrence is more dependent on the woman's menopausal state than her age (Berecki-Gisolf et al., 2009; Blümel et al., 2000; Gold et al., 2000). However, the duration of the symptoms is less clear. In longitudinal studies, average durations from 2.5 to 12 years have been reported (Avis et al., 2015; Col et al., 2009; Freeman et al., 2011, 2014; Smith et al., 2016; Tepper et al., 2016). In a 17-year follow-up study of 1,449 women, a subset of the Study of Women's Health Across the Nation (SWAN), a median duration of 7.4 years was found. However, in women with a symptom debut in premenopause or early perimenopause the median duration was over 11.8 years, whereas in women who experienced their first VMS in postmenopause the median duration was only 3.4 years (Avis et al., 2015). Regarding studies using the WHQ (Table 2), four of them investigated associations between VMS and age (Table 3). The results were incoherent and do not allow for making firm conclusions. However, the results give reason to assume that age and the menopausal state are not the only factors to impact the symptomatology.

In sleep problems, an increase during the climacteric is also well documented (Blümel et al., 2012; Kravitz et al., 2003; Polo-Kantola, 2011). A meta-analysis of over 60,000 midlife women found that compared to premenopausal women, the odds ratio of sleep problems was 1.6 for perimenopausal women and 1.7 for postmenopausal women (Xu et al., 2014). However, aging *per se* may also impair general sleep quality and predispose individuals to sleep-onset insomnia or difficulty maintaining sleep (Ancoli-Israel, 2005; Guidozzi, 2015; Lampio et al., 2017; Ohayon et al., 2004). Three studies investigating associations between the WHQ symptom domains and age found that more frequent sleep problems were associated with older age (Table 3), while an Italian study, in which all women were postmenopausal, found no difference between women aged 45–54 years and women aged 55 years or older (Genazzani et al., 2002b).

Although the Baltimore Longitudinal Study of Aging found that depressive symptoms were most prevalent in young adulthood in both genders, and that they decreased across midlife

Table 2. Previous studies that used the Women's Health Questionnaire (WHQ)

Author, year, and country	N	Age ¹	Method of interview ²	Scale	WHQ domains	Investigated variables ³
Slaven and Lee 1998 Australia	304	NR	NR	0–1	All	Menopausal state (3-class), hysterectomy, educational level (3-class), employment (yes/no) ⁴
Genazzani et al. 2002 Italy	2160	NR	Postal	1–4 ⁵	All	Age (2-class), years since menopause (≤ 3 / > 3 years), education level (4-class), socioeconomic score (according to employment/partner's employment, 6-class), marital status (4-class), the geographic area (North, Centre, South), chronic disease (yes/no), and the use of HT (yes/no)
Amore et al. 2004 Italy	1,434	45–56	Postal	1–4	All items were included, but regrouped according to factor analysis	Age, menopausal state (3-class), educational level (6-class), employment, marital status, a number of life events over the past year, the place of residence (urban/rural), number of children, the use of HT (yes/no), and past affective symptoms
Daley et al. 2007 United Kingdom	1,206	46–55	Postal	0–1	All	A BMI (3-class) and exercise (yes/no) ⁶
Zolnierczuk-Kieliszek et al. 2011 Poland	2,143	45–65	Postal	NR	All	Menopausal state (4-class), educational level, employment (8-class), pension (yes/no), marital status (yes/no), the use of HT (yes/no), SRH (3-class), permanent specialist health care (yes/no), pension for disabled (yes/no), chronic disease (yes/no), gynecologic disease (yes/no)
Ferrand et al. 2013	1,040	45–64	Personal in Tunisia	0–1	Sexual functioning,	Menopausal state, educational level (4-class), employment (ever worked: yes/no), occupational

Tunisia and France	774	48–53	Postal in France		menstrual symptoms, and attractiveness were excluded	grade (3-class), marital status (yes/no), a number of children (3-class), exercise (yes or no), country (Tunisia or France), and the place of residence (urban/rural)
Zolnierczuk-Kieliszek et al. 2014 Poland	2,143	45–65	Postal	NR	All	Age (45-49/50-65), educational level (5-class), employment (8-class), pension, financial situation (3-class), marital status (yes/no), housing conditions (3-class), and the place of residence (urban/rural)
Kanadys et al. 2016 Poland	268	45–55	NR	0–1	All Also whole score	Educational level (3-class), marital status (2-class), SRH (2-class), menopausal symptoms (yes/no), and a BDI score
Jarecka et al. 2017 Poland	200	45–68	NR	0–1	All	Menopausal state (3-class), marital status (marital/cohabiting), and a length of relationship
Dotlic et al. 2018 Serbia	500	40–65	Personal	0–1	All	Age, educational level (3-class), employment (yes/no), recreation, professional activity (3-class), household income, marital status (yes/no), a number of children, the place of residence (city center/outskirts), a BMI, alcohol use (yes/no), smoking (yes/no), exercise (3-class), the use of HT (yes/no), chronic disease (yes/no), gynecologic disease (yes/no), menopausal symptoms, and the number of induced abortions and miscarriages ⁷

Previous studies are presented only if the analyses have included factors that were investigated in **Studies II–IV** (i.e., age, educational level, employment, marital status, body mass index [BMI], alcohol use, or smoking); studies that focused merely on the effects of hormone therapy (HT) are not shown. In some of the studies, several statistical models including different combinations of the variables were performed. Results were not systematically reported for all variables, including both dependent and independent variables. NR, Not reported; SRH, self-rated health; The number of classes in each variable is shown if reported in the publication. ¹ Age of the participants, years; ² Personal or postal interview; ³ Variables included in statistical analyses; ⁴ Analyses were adjusted for age; ⁵ Dichotomized with respect to the upper tertile value; ⁶ Analyses were adjusted for age, alcohol consumption (4-class), menopausal state (3-class), and smoking (yes/no); ⁷ The analyses were adjusted for age, menopausal state (2-class), and the Beck Depression Inventory (BDI) score.

Table 3. Associations between climacteric-related symptoms and age in previous studies that used the Women's Health Questionnaire (WHQ)

Age		
	Genazzani et al. 2002 Italy Age of the participants: not reported	Younger women had more VMS and menstrual symptoms than older women (women aged 45–54 years were compared to women aged \geq 55 years). ¹ Age was not associated with sleep problems, depressive symptoms, anxiety/fears, cognitive difficulties, sexual functioning, somatic symptoms, and attractiveness.
	Amore et al. 2004 Italy Age of the participants: 45–56 years	Older women had more VMS and sleep problems (correlation, Fisher's F). ² Age was not associated with depressive symptoms, depressive/anxiety symptoms, anxiety, cognitive difficulties, sexual functioning, and somatic symptoms. ³
	Zolnierczuk-Kieliszek et al. 2014 Poland Age of the participants: 45–65 years	Older women had more VMS, sleep problems, cognitive difficulties, and somatic symptoms (women aged 45–49 years were compared to women aged 50–65 years). ⁴ Older women had lower sexual functioning and they felt they were less attractive. Younger women had more menstrual symptoms. Age was not associated with depressive symptoms and anxiety/fears.
	Dotlic et al. 2018 Serbia Age of the participants: 40–65 years	Older women had more sleep problems and anxiety/fears (correlation). ² Age was not associated with VMS, depressive symptoms, cognitive difficulties, sexual functioning, menstrual symptoms, somatic symptoms, and attractiveness.

Previous studies are presented only if the analyses included factors that were investigated in **Studies II–IV** (i.e., age, educational level, employment, marital status, body mass index [BMI]), alcohol use, or smoking); studies that focused merely on the effects of hormone therapy are not shown; VMS, vasomotor symptoms; If a symptom domain is not mentioned in the table, it was excluded from the analyses; ¹All women were postmenopausal; ²Menopausal state was considered; ³Items of the WHQ were partially regrouped into new symptom domains. For instance, the items of menstrual symptoms and attractiveness were included in other symptom domains; ⁴Menopausal state was not considered.

and then increased again in older adulthood (Sutin et al., 2013), previous studies investigating midlife women have suggested that depressive symptoms increase during the menopausal transition (Bromberger et al., 2010; Bromberger and Kravitz, 2011; Campbell et al., 2017; Cohen et al., 2006; Freeman et al., 2004; Llana et al., 2012; Maartens et al., 2002; Woods et al., 2008). However, whether depressive symptoms increase (Bromberger and Kravitz, 2011; Maartens et al., 2002) or decrease (Campbell et al., 2017; Freeman et al., 2004; Hickey et al., 2016) after the menopausal transition is debatable. As depressive and anxiety symptoms encompass various feelings and emotions, controversial findings between previous studies may be due to inconsistent methods of symptom assessment. Moreover, while some studies have focused on depressive or anxiety symptoms, others have focused on actual depressive or anxiety disorders. In the present thesis, the focus was on symptoms instead of disorders. In longitudinal subsets of the SWAN, depressive symptoms and anxiety were both more frequent during perimenopause and postmenopause than during premenopause (Bromberger et al., 2010, 2013). Interestingly, in anxiety, the increase was seen only among women with no anxiety at baseline, whereas in women with anxiety, the experience of anxiety remained at the original level (Bromberger et al., 2013). Regarding age, in studies using the WHQ, no associations have been found between age and depressive symptoms (Table 3). However, a Serbian study found that older women had more anxiety/fears than younger women (Dotlic et al., 2018).

As to cognitive functioning, it has remained unresolved whether cognitive difficulties experienced by midlife women are directly related to menopause or age or are rather a consequence of night sweats or climacteric-related sleep problems (Amore et al., 2007; Drogos et al., 2013; Maki et al., 2008; Mitchell and Woods, 2011; Polo-Kantola et al., 1997; Portin et al., 1999). A large cross-sectional subset of the SWAN found that forgetfulness was associated with the menopausal state; it was more common among perimenopausal and postmenopausal women than among premenopausal women (Gold et al., 2000). Moreover, among four age groups, 40–43 years, 44–47 years, 48–51 years, and ≥ 52 years, forgetfulness was most frequent among women aged 48–51 years (Gold et al., 2000). Instead, in the Seattle Midlife Women's Health Study (SMWHS), in which the association between menopausal state and problems with concentration was also investigated, no association was found (Mitchell and Woods, 2011). Both studies included hot flashes and sleep problems as covariates. During a 6.5 years follow-up period in women with a median age of 54 years at baseline (Karlama et al., 2017), several climacteric-related symptoms were also included as covariates in a longitudinal subset of the SWAN investigating changes in objectively measured cognitive performance. Here, they found that cognitive performance decreased. However, in a Finnish 6-year follow-up study of 60 postmenopausal women, objectively measured cognitive performance did not change during the follow-up period (Alhola et al., 2006). Previous studies have used diverse tests to assess cognitive functioning. As different tests may measure entirely different components of cognitive functioning, comparing the outcomes is complicated. Of the studies using the WHQ, one found an association between

cognitive difficulties and age; women aged 50–65 years had more cognitive difficulties than women aged 45–49 years (Table 3).

A decrease in sexual functioning has been linked both to menopause and aging (Avis et al., 2009a; Blümel et al., 2000; Gracia et al., 2007; Guthrie et al., 2004; Mishra and Kuh, 2006; Prairie et al., 2011; Woods et al., 2010). In a longitudinal subset of the SWAN investigating sexual functioning through the menopausal transition, the importance of sex, sexual desire, arousal, frequency of sexual intercourse, and physical pleasure decreased with age. Yet, no age-related changes in pelvic pain or emotional satisfaction were found. However, of the various variables only sexual desire and vaginal/pelvic pain were associated with the menopausal state: perimenopausal and postmenopausal women had lower sexual desire and more vaginal/pelvic pain than premenopausal women (Avis et al., 2009a). Regarding older age, a study in the United States (US) found that in women aged 62 years or older, among numerous variables related to sexual functioning, only two were associated with age: older women were more likely to be unreceptive to their partner's sexual initiatives and less likely to find an unknown person sexually attractive (Galinsky et al., 2014). As to studies using the WHQ, Zolnierczuk-Kieliszek et al. (2014) found that older women had lower sexual functioning than younger women (Table 3).

In the WHQ, the somatic symptoms domain includes a group of various symptoms that have been connected to the climacteric (Appendix 1) (Girod et al., 2004; Hunter, 2000). Although often reported by climacteric women, the symptoms are quite unspecific and possibly not directly related to menopause or aging. Zolnierczuk-Kieliszek et al. (2014) found that older women had more somatic symptoms than younger women, while other studies using the WHQ failed to find any associations (Table 3).

Not all women suffer from climacteric-related symptoms and the severity of the symptoms varies widely from one woman to another. Thus, besides climacteric hormonal changes or age, other factors certainly affect the manifestation of symptoms.

2.5.2 Socioeconomic factors

Socio-economic factors refer to various components of social and financial standing. In the present thesis, socio-economic factors included educational level, employment, and marital status. In other studies, additional factors have included for instance financial situation, occupational grade, place of residence (e.g., urban/rural), number of children, and number of life events. Compared to higher education, a lower educational level is usually linked to more frequent climacteric-related symptoms (Blümel et al., 2012; Bromberger et al., 2010; Dennerstein et al., 2007; Ferrand et al., 2013; Gold et al., 2000; Kanadys et al., 2016; Mitchell and Woods, 2010; Williams et al., 2009; Zolnierczuk-Kieliszek et al., 2011, 2014). Moilanen et al. (2010) investigated associations between climacteric-related symptoms and socio-economic and lifestyle factors in 1,427 Finnish women, aged 45–64 years. In line with some

previous studies (Ferrand et al., 2013; Gold et al., 2000; Kanadys et al., 2016; Li et al., 2003; Williams et al., 2009; Zolnierczuk-Kieliszek et al., 2014), they found that women with lower educational level (primary/secondary) had more VMS than women with higher educational level (tertiary). However, in psychological (i.e., depressive/anxiety symptoms, sleep problems, tiredness, and memory problems) and somatic symptoms (i.e., various pain symptoms, heaviness in arms or legs, weakness, numbness, dizziness, nausea, and swollen feet), no differences emerged related to the educational levels (Moilanen et al., 2010). In a study of nearly 7,000 Swedish midlife women, Li et al. (2003) found that women with a lower educational level had more VMS, joint problems, and pain in their legs or back than women with a higher educational level. In contrast, interestingly, women with a higher educational level had higher odds for suffering from tiredness, headaches, and overstress. However, educational level was not associated with sleep problems, irritability, depressive symptoms, dizziness, or gastrointestinal symptoms (Li et al., 2005).

Previous studies examining associations between the WHQ symptom domains and socioeconomic factors (i.e., educational level, employment, or marital status) are shown in Table 2, and their results are shown in Table 4. Eight of these studies included educational level as a variable. Most of them found that some symptoms were more frequent among women with a lower educational level, but the symptom domains in which the differences were found varied between the studies (Amore et al., 2004; Ferrand et al., 2013; Genazzani et al., 2002b; Kanadys et al., 2016; Zolnierczuk-Kieliszek et al., 2011, 2014). The oldest of the studies, a study of 304 Australian women, did not find any association between educational levels and the WHQ symptom domains (Slaven and Lee, 1998). Additionally, in the most recent study, a Serbian study of 500 women, only cognitive difficulties and anxiety/fears were associated with educational level; cognitive difficulties were more frequent among women with a lower educational level, but, conversely, anxiety/fears were more frequent in women with a higher educational level (Dotlic et al., 2018). In Poland, two research groups have investigated associations between climacteric-related symptoms and educational level. Both found that all symptoms, except menstrual symptoms, were more frequent among women with a lower educational level (Kanadys et al., 2016; Zolnierczuk-Kieliszek et al., 2011, 2014). Ferrand et al. (2013) assessed VMS, sleep problems, depressive symptoms, anxiety/fears, cognitive difficulties, and somatic symptoms using the WHQ in a Tunisian population of 1,040 women and in a French population of 774 women. They found that among Tunisian women, all investigated symptoms were associated with educational levels; women with lower educational level had more symptoms. In contrast, among French women, educational levels were not associated with any of the symptoms (Ferrand et al., 2013). The cultural or ethnicity dependence of the association was also found in the SWAN, whereby ethnic differences in VMS, including hot flashes, cold sweats, and night sweats, were investigated in women living in the US. A lower educational level was linked to more frequent VMS in Caucasian, African American, Chinese, and Japanese women, but, in Hispanics no associations were found between educational levels and VMS (Gold et al., 2006). Besides cultural factors, differences between previous studies may be related to

Table 4. Associations between climacteric-related symptoms and socioeconomic factors (i.e., educational level, employment, and marital status) in previous studies that used the Women's Health Questionnaire (WHQ)

Educational level		
	Slaven and Lee 1998 Australia	Educational level was not associated with the WHQ symptom domains.
	Genazzani et al. 2002 Italy	Women with a lower educational level had more VMS and somatic symptoms. Educational level was not associated with sleep problems, depressive symptoms, anxiety/fears, cognitive difficulties, sexual functioning, menstrual symptoms, and attractiveness.
	Amore et al. 2004 Italy	Women with a lower educational level had more VMS, sleep problems, depressive symptoms, anxiety/fears, and somatic symptoms than women with a higher educational level. Educational level was not associated with cognitive difficulties, sexual functioning, and a new domain, which included depressive and anxiety symptoms. ¹
	Zolnierczuk-Kieliszek et al. 2011 Poland	Women with a lower educational level had more VMS, sleep problems, depressive symptoms, anxiety/fears, cognitive difficulties, and somatic symptoms than women with a higher educational level. Women with a lower educational level had also lower sexual functioning and they felt they were less attractive. Educational level was not associated with menstrual symptoms.
	Ferrand et al. 2013 Tunisia and France	Tunisian population: women with a lower educational level had more VMS, sleep problems, depressive symptoms, anxiety/fears, cognitive difficulties, and somatic symptoms. French population: educational level was not associated with the symptoms (VMS, sleep problems, depressive symptoms, anxiety/fears, cognitive difficulties, and somatic symptoms).
	Zolnierczuk-Kieliszek et al. 2014 Poland	Women with a lower educational level had more VMS, sleep problems, depressive symptoms, anxiety/fears, cognitive difficulties, and somatic symptoms than women with a higher educational level. Women with a lower educational level had also lower sexual functioning and they felt they were less attractive. Educational level was not associated with menstrual symptoms.
	Kanadys et al. 2016 Poland	Women with a lower educational level had more VMS, sleep problems, depressive symptoms, anxiety/fears, cognitive difficulties, and somatic symptoms than women with a higher educational level. Women with a lower educational level had

		also a lower sexual functioning and they felt they were less attractive. Educational level was not associated with menstrual symptoms.
Employment	Dotlic et al. 2018 Serbia	Women with a lower educational level had more cognitive difficulties, whereas women with a higher educational level had more anxiety/fears. Educational level was not associated with VMS, sleep problems, depressive symptoms, sexual functioning, menstrual symptoms, somatic symptoms, and attractiveness.
	Slaven and Lee 1998 Australia	Employment (yes/no) was not associated with the WHQ symptom domains.
	Amore et al. 2004 Italy	Employment (classification not reported) was not associated with the symptom domains. ¹
	Zolnierczuk-Kieliszek et al. 2011 Poland	Unemployed and retired women had more symptoms than employed women, but it was not defined in which symptom domains the differences were found.
	Ferrand et al. 2013 Tunisia and France	Employment (ever worked: yes/no) was not associated with the WHQ symptom domains.
	Zolnierczuk-Kieliszek et al. 2014 Poland	Unemployed and retired women had more VMS, sleep problems, depressive symptoms, anxiety/fears, cognitive difficulties, and somatic symptoms than employed women. Unemployed and retired women had lower sexual functioning and they felt they were less attractive. Employment was not associated with menstrual symptoms.
Marital status	Dotlic et al. 2018 Serbia	Unemployed women had more anxiety/fears than employed women. Employment was not associated with VMS, sleep problems, depressive symptoms, cognitive difficulties, sexual functioning, menstrual symptoms, somatic symptoms, and attractiveness.
	Genazzani et al. 2002 Italy	Married women had lower sexual functioning than single/divorced/widowed women. Marital status was not associated with VMS, sleep problems, depressive symptoms, anxiety/fears, cognitive difficulties, menstrual symptoms, somatic symptoms, and attractiveness.
	Amore et al. 2004 Italy	Marital status (classification for the correlation analysis was not reported) was not associated with the symptoms. ¹
	Zolnierczuk-Kieliszek et al. 2011 Poland	Single/divorced/widowed women had more symptoms than married/coupled women, but it was not defined in which symptoms the differences were found.

Table 4 continues

Ferrand et al. 2013 Tunisia and France	Tunisian population: women living alone had more sleep problems, anxiety/fears, cognitive difficulties, and somatic symptoms than married/cohabiting women. Marital status was not associated with VMS and depressive symptoms. French population: women living alone had more anxiety/fears than married/cohabiting women. Marital status was not associated with VMS, sleep problems, depressive symptoms, cognitive difficulties, and somatic symptoms.
Zolnierczuk-Kieliszek et al. 2014 Poland	Single/divorced/widowed women had more depressive symptoms and they felt they were less attractive than married/coupled women. Marital status was not associated with VMS, sleep problems, anxiety/fears, cognitive difficulties, sexual functioning, menstrual symptoms, and somatic symptoms.
Kanadys et al. 2016 Poland	Married women had more anxiety/fears than single/divorced/widowed women. Marital status was not associated with VMS, sleep problems, depressive symptoms, cognitive difficulties, sexual functioning, menstrual symptoms, somatic symptom, and attractiveness.
Jarecka et al. 2017 Poland	Marital status (married/cohabiting) was not associated with the WHQ symptom domains.
Dotlic et al. 2018 Serbia	Single/divorced/widowed women had lower sexual functioning than married/coupled women. Marital status was not associated with VMS, sleep problems, depressive symptoms, anxiety/fears, cognitive difficulties, menstrual symptoms, somatic symptoms, and attractiveness.

Previous studies are presented only if the analyses included factors that were investigated in **Studies II–IV** (age, educational level, employment, marital status, body mass index [BMI], alcohol use, or smoking); studies that focused merely on the effects of hormone therapy are not shown. VMS, vasomotor symptoms. If a symptom domain is not mentioned in the table, it was excluded from the analyses. ¹ Items of the WHQ were partially regrouped into new symptom domains. For instance, the items of menstrual symptoms and attractiveness were included in other symptom domains.

divergent school systems between countries. Moreover, it must be noted that substantial changes in school systems and in women's educational levels have also taken place over the years. Unlike educational level, employment status has not been principally associated with VMS in previous studies in the 2000s (Amore et al., 2004; Ferrand et al., 2013; Gold et al., 2000; Slaven and Lee, 1998; Williams et al., 2009). Additionally, findings on the association between employment and other climacteric-related symptoms have been incoherent. In the previously mentioned Swedish study, Li et al. (2003 and 2005) found that although VMS did not differ between employed and unemployed women, part-time employed women had more VMS than full-time employed women (Li et al., 2003). As the study was cross-sectional, the direction of cause-effect relationships could not be determined. However, the burden related to severe VMS might have been the cause for part-time employment. As to somatic and psychological symptoms, unemployed women had more symptoms (Li et al., 2005). Similar results were obtained in a US study of nearly 3,000 postmenopausal women: unemployed women had more somatic and psychological symptoms than employed women, but, VMS were not associated with employment status (Williams et al., 2009). In these studies, psychological symptoms included cognitive difficulties in addition to depressive and anxiety symptoms (Li et al., 2005; Williams et al., 2009), and in the Swedish study, also sleep problems and tiredness (Li et al., 2005). As to depressive symptoms, a Dutch study of nearly 5,000 midlife women found that employment outside the home was protective against symptoms (Maartens et al., 2002). In the SWAN, unemployed women had more sleep problems, and forgetfulness than employed women, but in terms of VMS or pain symptoms, no differences were found (Gold et al., 2000). A neutral association between pain symptoms and employment was also found in the SMWHS (Mitchell and Woods, 2010). However, in contrast to the results of the SWAN, forgetfulness was not associated with employment, although unemployed women reported more difficulties with concentration (Mitchell and Woods, 2011). Of the studies using the WHQ, six have included employment as a variable (Amore et al., 2004; Dotlic et al., 2018; Ferrand et al., 2013; Slaven and Lee, 1998; Zolnierczuk-Kieliszek et al., 2011, 2014). Three of them failed to find any associations (Table 4). In the aforementioned Serbian study, one of the WHQ symptom domains, anxiety/fears, was associated with employment, in which unemployed women had more symptoms (Dotlic et al., 2018). However, in a Polish study of over 2,000 women, unemployed and retired women reported more of all other WHQ symptoms except menstrual symptoms (Zolnierczuk-Kieliszek et al., 2014). Different professions were also compared to each other: agricultural workers had more somatic symptoms, but fewer sleep problems than women with intellectual work or other types of physical work (Zolnierczuk-Kieliszek et al., 2012). The concept of not being employed has varied between studies; for example retirement, being a homemaker, or being self-employed may have been included in the same cluster with unemployment (Dotlic et al., 2018; Gold et al., 2000; Li et al., 2003, 2005; Mitchell and Woods, 2010; Williams et al., 2009). Moreover, the distribution of reasons for not being employed is partly culturally dependent.

Another socioeconomic factor playing a major role in life is marital or relationship status. Studies have reported both less (Ferrand et al., 2013; Giannouli et al., 2012; Li et al., 2005; Zolnierczuk-Kieliszek et al., 2011, 2014) and more frequent (Gold et al., 2000; Kanadys et al., 2016; Monterrosa-Castro et al., 2012) climacteric-related symptoms in married women. However, several studies have failed to find any associations (Amore et al., 2004; Avis et al., 2009b; Gold et al., 2006; Maartens et al., 2002; Mishra and Kuh, 2012). In studies using the WHQ, some associations have been found (Table 4). Ferrand et al. (2013), who enrolled both Tunisian and French women in their study, found that among Tunisian women, several symptoms were more frequent in women living alone than in women living with a partner. However, among French women, only anxiety/fears were associated with relationship status. The Polish studies reported conflicting findings (Kanadys et al., 2016; Zolnierczuk-Kieliszek et al., 2014). Zolnierczuk-Kieliszek et al. (2014) found that unmarried women had more depressive symptoms and they felt they were less attractive, whereas Kanadys et al. (2016) found that married women had more anxiety/fears. In a study by a third Polish research group (Jarecka and Bielawska-Batorowicz, 2017), none of the 200 women were living alone. Thus, they were able to investigate differences only between married and cohabiting women. Two of the studies using the WHQ found an association between marital/relationship status and sexual functioning. Genazzani et al. (2002a) found that married women had lower sexual functioning, whereas in the study by Dotlic et al. (2008) unmarried women had lower sexual functioning. This association of unmarried women having lower sexual functioning has also been found in studies assessing sexual functioning using other questionnaires (Avis et al., 2009a; Giannouli et al., 2012; McCall-Hosenfeld et al., 2008), while also opposing (Mishra and Kuh, 2006; Valadares et al., 2008) and neutral (Gallicchio et al., 2007; Gracia et al., 2004; Thomas et al., 2011) findings have been reported. A United Kingdom (UK) follow-up study of 1,525 midlife women found that married or cohabiting women had more difficulties with intercourses than single/divorced/widowed women (Mishra and Kuh, 2006). The term “difficulties with intercourses” was not defined more precisely. Moreover, sexually inactive women were possibly included. In the SWAN, married/cohabiting women reported more pelvic pain during sexual intercourse, but they experienced more sexual desire, arousal, emotional satisfaction, and physical pleasure than single/divorced/widowed women. However, it is important to note that arousal, emotional satisfaction, physical pleasure, and pelvic pain during sexual intercourses were only answered by women who had engaged in sexual activity with a partner during the past six months (Avis et al., 2009a).

2.5.3 Lifestyle factors

A healthy lifestyle comprises various components, such as a sufficient amount of good quality sleep, balanced nutrition, regular exercise, non-smoking, and restricted alcohol consumption. In the present thesis, lifestyle factors included the body mass index (BMI), alcohol consumption, and smoking. As androgen precursors are converted to estrogens in adipose tissue (Simpson, 2003) and estrogen levels are higher in obese than in normal weight climacteric women (Whiteman et al., 2003a), obesity could prevent climacteric-related

symptoms (Whiteman et al., 2003a). However, besides forming estrogens, adipose tissue produces hormones (leptin and tumor necrosis factor- α) that may reduce ovarian steroid production (Whiteman et al., 2003a). Adipose tissue also acts as a thermal insulator (Anderson, 1999; Petrofsky and Laymon, 2009) and could therefore increase the frequency and intensity of hot flashes and sweating by reducing the heat dissipating function. Moreover, as obesity increases the risk of nocturnal breathing disorders, especially of obstructive sleep apnea, which further increases the risk of night sweats and sleep problems (Arnardottir et al., 2013), it could be expected that these symptoms would be more prevalent among obese women. In studies published after the millennium, overweight has as a general rule been associated with more frequent VMS (Berecki-Gisolf et al., 2009; Gold et al., 2000; Moilanen et al., 2010; Whiteman et al., 2003b; Williams et al., 2009). There is also some evidence that overweight or obese women would have more psychological (Bromberger et al., 2010; Dotlic et al., 2018; Moilanen et al., 2010; Williams et al., 2009) and somatic (Berecki-Gisolf et al., 2009; Gold et al., 2000; Williams et al., 2009) symptoms. Moreover, although some studies have yielded a connection between overweight and impaired sexual functioning (McCall-Hosenfeld et al., 2008; Williams et al., 2009), in most studies, sexual functioning has not been related to the BMI (Dotlic et al., 2018; Gallicchio et al., 2007; Giannouli et al., 2012; Gracia et al., 2004; Nackers et al., 2015). In the SWAN, women with a BMI of 27 kg/m² or higher had more frequent VMS, urinary incontinence, and pain symptoms than women with lower BMI. However, sleep problems and vaginal dryness were not associated with the BMI (Gold et al., 2000). Almost identical associations were found in the Australian Longitudinal Study on Women's Health (ALSWH), a large 15-year follow-up study of over 10,000 women, aged 45–50 years at baseline. Although women with a BMI over 25 kg/m² had more VMS, urinary incontinence, and joint pain than women with a normal BMI, sleep problems and headaches were not associated with the BMI (Berecki-Gisolf et al., 2009). In both the SWAN and the ALSWH, women with a higher BMI were more often diagnosed with depression (Berecki-Gisolf et al., 2009; Bromberger et al., 2011). Furthermore, Moilanen et al. (2010) found that in Finnish women, a BMI of 25 kg/m² or higher was associated with more frequent VMS and psychological symptoms, including sleep problems, tiredness, nervousness, depressive symptoms, irritability, burnout, and memory problems than a BMI of less than 25 kg/m². In contrast, somatic symptoms were not associated with the BMI (Moilanen et al., 2010).

Previous studies examining associations between the WHQ symptom domains and lifestyle factors (i.e., BMI, alcohol consumption, or smoking) are shown in Table 2, and their results are shown in Table 5. Two of the studies have included the BMI as a variable (Daley et al., 2007; Dotlic et al., 2018). Daley et al. (2007) found that women with a BMI of 30 kg/m² or higher had more VMS and somatic symptoms, and they felt themselves less attractive than women with a lower BMI. A similar association between the BMI and attractiveness was found by Dotlic et al. (2018). However, they found no other associations between the BMI and the domains of the WHQ.

Table 5. Associations between climacteric-related symptoms and lifestyle factors (i.e., body mass index, alcohol use, and smoking) in previous studies that used the Women's Health Questionnaire (WHQ)

BMI	Daley et al. 2007 United Kingdom	Women with a BMI of ≥ 30 kg/m ² had more VMS and somatic symptoms and they felt they were less attractive than women with a lower BMI. The BMI was not associated with sleep problems, depressive symptoms, anxiety/fears, cognitive difficulties, sexual functioning, and menstrual symptoms.
	Dotlic et al. 2018 Serbia	Women with a higher BMI felt they were less attractive than women with a lower BMI. The BMI was not associated with VMS, sleep problems, depressive symptoms, anxiety/fears, cognitive difficulties, sexual functioning, menstrual symptoms, and somatic symptoms.
Alcohol use	Dotlic et al. 2018 Serbia	Abstainers had more VMS, sleep problems, and anxiety/fears than women who used alcohol. Alcohol use was not associated with depressive symptoms, cognitive difficulties, sexual functioning, menstrual symptoms, somatic symptoms, and attractiveness.
Smoking	Dotlic et al. 2018 Serbia	Smoking was not associated with the WHQ symptom domains.
HT use	Genazzani et al. 2002 Italy	Nonusers of HT had more VMS and anxiety/fears and lower sexual functioning than current users. The use of HT was not associated with sleep problems, depressive symptoms, cognitive difficulties, menstrual symptoms, somatic symptoms, and attractiveness.
	Amore et al. 2004 Italy	The use of HT was not associated with the WHQ symptom domains. ¹
	Zolnierczuk-Kieliszek et al. 2011 Poland	Nonusers and former HT users had more sleep problems than current HT users. The use of HT was not associated with VMS, depressive symptoms, anxiety/fears, cognitive difficulties, sexual functioning, menstrual symptoms, somatic symptoms, and attractiveness.
	Dotlic et al. 2018 Serbia	The use of HT was not associated with the WHQ symptom domains.

Previous studies are presented only if the analyses included factors that were investigated in **Studies II–IV** (i.e., age, educational level, employment, marital status, body mass index [BMI], alcohol use, or smoking); studies that focused merely on the effects of HT are not shown. VMS, vasomotor symptoms. If a symptom domain is not mentioned in the table, it was excluded from the analyses.¹ Items of the WHQ were partially regrouped into new symptom domains. For instance, items of menstrual symptoms and attractiveness were included in other symptom domains.

Alcohol may reduce the risk of climacteric-related symptoms by increasing the levels of estrogen (Liu et al., 2015; Playdon et al., 2018). However, the association between alcohol intake and estrogen metabolism is complex and it has not been thoroughly investigated (Liu et al., 2015). One study found that alcohol consumption increased estrogen levels in postmenopausal women using hormone therapy (HT), yet no change was found in non-HT-users (Ginsburg et al., 1996). Alcohol's association with sleep problems has been widely investigated in general populations (Colrain et al., 2014). Because alcohol acts as a sedative and shortens sleep latency, it is commonly used as a hypnotic agent to self-medicate sleep problems (Colrain et al., 2014). Thus, those having sleep problems may be more likely to use alcohol. However, later during the night, alcohol decreases sleep quality (Colrain et al., 2014), induces daytime tiredness, and, consequently may also cause a deterioration of cognitive functioning (Maki et al., 2008; Mitchell and Woods, 2011). Alcohol's direct effects on the brain are dose-dependent and not entirely understood (Ilomäki et al., 2015; Mukherjee, 2013). While excessive drinking over a prolonged period may cause serious problems with cognition (Mukherjee, 2013), light to moderate drinking may protect against dementing illnesses (Ilomäki et al., 2015).

Alcohol consumption has been linked to both increased (Blümel et al., 2012; Herber-Gast et al., 2013; Li et al., 2003, 2005; Moilanen et al., 2010; Wang et al., 2013; Worsley et al., 2017) and decreased (Hunter and Chilcot, 2013; Mitchell and Woods, 2011; Woods et al., 2010; Woods and Mitchell, 2010) climacteric-related symptoms. In the SMWHS, problems with falling asleep and waking during the night decreased and sexual desire increased with increasing alcohol consumption (Woods et al., 2010; Woods and Mitchell, 2010). However, cognitive difficulties were not associated with alcohol consumption (classified as yes/no) (Mitchell and Woods, 2011). In the Swedish study by Li et al. (2003, 2005), climacteric-related symptoms did not differ between abstainers and women using alcohol in small amounts (less than 15 ml of 100% alcohol per week). However, women using large amounts of alcohol (15 ml of 100% alcohol per week or more) had more hot flashes, fatigue, overstress, joint problems, and pain in their legs and back. However, sleep problems, depressive symptoms, irritability, headaches, and gastrointestinal symptoms were not associated with alcohol consumption. Moreover, dizziness was more common in abstainers (Li et al., 2003, 2005). The association between excessive drinking and more frequent symptoms was also found in the ALSWH. Women who consumed three or more alcoholic drinks per day had more night sweats than abstainers, while the frequency of night sweats in women who used alcohol occasionally or in smaller amounts did not differ from abstainers (Herber-Gast et al., 2013). Interestingly, alcohol consumption was not associated with hot flashes or depressive symptoms (Herber-Gast et al., 2013; Hickey et al., 2016). Other studies connecting excessive alcohol consumption to more frequent climacteric-related symptoms have also been published (Blümel et al., 2012; Moilanen et al., 2010; Worsley et al., 2017). Of the previous studies using the WHQ, only Dotlic et al. (2018) have included alcohol consumption as a variable (Table 5). Abstainers had more VMS, sleep problems, and anxiety/fears than other women (the consumption of alcohol was classified as yes/no); the remaining domains were not

associated with alcohol consumption (Dotlic et al., 2018). Thus, the possible beneficial effects of alcohol consumption are obviously restricted to small alcohol amounts or to occasional use, which could explain controversial findings between previous studies.

Smoking advances the onset of menopause by 1.5–2.0 years (McKinlay, 1996) and has been connected to most climacteric-related symptoms (Berecki-Gisolf et al., 2009; Gold et al., 2000; Hunter and Chilcot, 2013; Li et al., 2003, 2005; Whiteman et al., 2003b; Williams et al., 2009). Associations between smoking and climacteric-related symptoms may result from reduced estrogen levels caused by smoking. Reduced estrogen levels may be produced by direct ovarian damages (Hoyer, 2005; Kapoor and Jones, 2005; Plante et al., 2010) or changes in estrogen metabolism (Kapoor and Jones, 2005; Whiteman et al., 2003a). Smoking affects the cytochrome P450 enzyme system, which is responsible for the metabolism of estrogen (Whiteman et al., 2003a), reducing the conversion of androgens to estrogens by inhibiting aromatase activity (Whiteman et al., 2003a), and decreasing the production of biologically active estrogen metabolites (Kapoor and Jones, 2005). In the SWAN, smokers had more VMS (Gold et al., 2000, 2006), sleep problems (Gold et al., 2000; Kravitz et al., 2003), urinary incontinence (Gold et al., 2000), and pain symptoms (Gold et al., 2000) than non-smokers, but smoking was not associated with forgetfulness (Gold et al., 2000), sexual functioning (Avis et al., 2009a), or vaginal dryness (Gold et al., 2000). However, in the SMWHS, smoking was only associated with decreased sexual desire (Woods et al., 2010), and not with sleep problems (Woods and Mitchell, 2010), cognitive difficulties (Mitchell and Woods, 2011), or pain symptoms (Mitchell and Woods, 2010). The ALSWH found that smokers had more VMS, both hot flashes and night sweats, sleep problems, psychological symptoms (measured by the Mental Health Inventory), and pain symptoms than non-smokers. Moreover, smokers were more often diagnosed with major depression, but no differences were found in urinary incontinence or headaches (Berecki-Gisolf et al., 2009). In the previous Finnish study, Moilanen et al. (2010) found no association between smoking and the investigated symptoms, which were VMS and psychological and somatic symptoms. Regarding studies using the WHQ, only Dotlic et al. (2018) included smoking as a variable; smoking was not associated with the WHQ symptom domains (Table 5).

2.5.4 Hormone therapy

Menopausal HT is used to treat climacteric-related symptoms (Marjoribanks et al., 2017). The treatment consists of estrogen alone or estrogen combined with progestin (Marjoribanks et al., 2017). Progestin is needed to prevent endometrial hyperplasia if a woman has an intact uterus (Marjoribanks et al., 2017). In addition, vaginal symptoms related to estrogen deprivation may be treated with local HT (Lethaby et al., 2016). Besides alleviating climacteric-related symptoms, systemic HT protects against osteoporosis and bone fractures (Marjoribanks et al., 2017). If initiated within 10 years after menopause, HT may also be protective against CVD (Boardman et al., 2015; Savolainen-Peltonen et al., 2016). If administered orally, HT increases the risk of venous thromboembolism (Marjoribanks et al.,

2017). In addition, long-term use of HT, especially the combined treatment of estrogen and progestin, is connected to an increased risk of breast cancer (Marjoribanks et al., 2017). Before initiating HT use, individual benefits and risk factors must be thoroughly considered. Absolute contraindications include a history of breast cancer, deep venous thrombosis, or pulmonary embolism, a diagnosed clotting disorder, and unexplained gynecological bleeding (Boardman et al., 2015).

HT is the most effective treatment for VMS (Bachmann, 2005; Williams and Cho, 2017). It also alleviates climacteric sleep problems (Bachmann, 2005; Polo-Kantola, 2011; Williams and Cho, 2017). Regarding other climacteric-related symptoms, the results of previous studies have been controversial (Bachmann, 2005; Rudolph et al., 2004; Williams and Cho, 2017). Several studies have used the WHQ to investigate the effects of HT compared to placebo treatment (Gambacciani et al., 2003; Nielsen et al., 2006; Polisseni et al., 2013; Savolainen-Peltonen et al., 2014; Strickler et al., 2000; Veerus et al., 2012; Welton et al., 2008; Wiklund et al., 1993). All of these studies found that HT was an effective treatment for VMS and sleep problems. Furthermore, in most studies, HT was also beneficial for sexual functioning (Gambacciani et al., 2003; Nielsen et al., 2006; Polisseni et al., 2013; Veerus et al., 2012; Welton et al., 2008; Wiklund et al., 1993). Wiklund et al. (1993) found that HT was effective in alleviating all investigated symptoms (menstrual symptoms were excluded), while other studies have found it effective for only a part of the symptoms. The beneficial effects on symptoms other than VMS, sleep problems, and sexual functioning have been sporadic. Symptoms that have been alleviated by using HT include depressive symptoms (Gambacciani et al., 2003), anxiety/fears (Gambacciani et al., 2003), cognitive difficulties (Nielsen et al., 2006), and somatic symptoms (Gambacciani et al., 2003). Polisseni et al. (2013) found that all investigated symptoms (menstrual symptoms were excluded) decreased during the three-month treatment period, but for all other symptoms except VMS, a similar decrease was found in women using a placebo. Furthermore, Savolainen-Peltonen et al. (2014) found that HT was effective for alleviating VMS, sleep problems, anxiety/fears, and cognitive difficulties only in women who had disturbing hot flashes at baseline. Thus, HT had no effect on symptoms in women without baseline hot flashes. Besides beneficial effects, disadvantageous effects were found in two studies, whereby the use of HT increased menstrual symptoms (Nielsen et al., 2006; Strickler et al., 2000).

Previously, four population-based cross-sectional studies have investigated associations between the WHQ symptom domains and the use of HT (Table 5). Genazzani et al. (2002a) found that nonusers had more VMS and anxiety/fears and lower sexual functioning, while Zolnierczuk-Kieliszek et al. (2011) found that nonusers and former HT users had more sleep problems. In contrast, Amore et al. (2004) and Dotlic et al. (2018) did not find any differences between HT users and nonusers.

2.6 Climacteric-related symptoms and chronic somatic diseases

The prevalence of various chronic diseases, such as CVD (Barton, 2013; Murphy, 2011), diabetes (Barton, 2013), dyslipidemia (Barton, 2013), nocturnal breathing disorders (Bixler et al., 2001), osteoporosis (Armas and Recker, 2012; Finkelstein et al., 2008; Talsania and Scofield, 2017), osteoarthritis (Talsania and Scofield, 2017; Watt, 2016), and urinary incontinence (Sartori et al., 2011), increase after menopause. Several chronic diseases or their medications may produce symptoms that resemble climacteric-related symptoms (Anderson, 2011; Badgio and Worden, 2007; Cazzola et al., 2012; Herber-Gast et al., 2013; Plotkin, 2010; Provini et al., 2010; Saaresranta et al., 2010; Santonicola et al., 2011; Vance et al., 2011; Viera et al., 2003). In the present thesis, chronic somatic diseases were addressed within wider disease groups, which included CVD, diabetes, neurological, sensory organ, bronchopulmonary, musculoskeletal, gastrointestinal, urological, dermatological, thyroid disease, and cancer. Although two previous studies using the WHQ have included the presence of a chronic disease as a variable (Genazzani et al., 2002b; Zolnierczuk-Kieliszek et al., 2011), no previous studies have investigated associations between the WHQ symptom domains and specific diseases or disease groups.

2.6.1 Climacteric-related symptoms and cardiovascular diseases

VMS have been linked to an increased risk of CVD (Andrikoula et al., 2009; Gast et al., 2008; Herber-Gast et al., 2015; Tuomikoski et al., 2011). Risk factors connected to more frequent VMS include higher BMI (Gast et al., 2008), blood pressure (Andrikoula et al., 2009; Gast et al., 2008; Tuomikoski and Savolainen-Peltonen, 2017), and heart rate (Andrikoula et al., 2009); poorer endothelial function (Thurston et al., 2008); greater aortic calcification (Thurston et al., 2008); higher carotid intima media thickness (Thurston et al., 2011); increased cholesterol levels (Gast et al., 2008); lower concentration of antioxidants (Andrikoula et al., 2009); and higher concentration of lipoperoxides (Andrikoula et al., 2009). Moreover, the association between hot flashes and an increased risk of CVD might be mediated by an increase in sympathetic activity related to VMS (Freedman, 2014; Low et al., 2011). In a longitudinal subset of the ALSWH, women with frequent VMS had almost a two-fold increased risk of developing coronary heart disease over a period of 14 years compared to women without VMS (Herber-Gast et al., 2015). However, not all studies have found associations between VMS and CVD risk profiles (Tuomikoski and Savolainen-Peltonen, 2017). The Women's Health Initiative Observational Study (WHI-OS) found that while VMS occurring during the late menopausal transition were associated with an increased risk of future CVD events, VMS occurring during the early menopausal transition were associated with a reduced risk (Szmuiłowicz et al., 2011). Sleep problems are also linked to an increased risk of CVD (Matthews et al., 2013; Thurston et al., 2017). In the SWAN, problems falling asleep, waking early in the morning, poor sleep quality, short sleep duration, and snoring were associated with calcification of the aorta but not with calcification in the coronary arteries (Matthews et al., 2013). In another study investigating midlife women, short sleep time and

poor sleep quality were associated with increased carotid atherosclerosis (Thurston et al., 2017). The association between sleep problems and an increased risk of CVD might be mediated by increased sympathetic activity related to sleep disturbances (Farina et al., 2014). Moreover, CVD often coincide with nocturnal breathing disorders (Bruyneel, 2015; Luyster et al., 2014; Neilan et al., 2013; Quan, 2009; Xu et al., 2015), which in turn increase sleep problems and tiredness (Saareanta et al., 2016; Taylor et al., 2007).

Women with depressive symptoms or major depression are more likely to have CVD (Da Silva et al., 2014; Llaneza et al., 2012; Matthews et al., 2007; Sobel and Markov, 2005; Windle and Windle, 2013). Several links have been suggested, which include sleep disturbances (Da Silva et al., 2014), stress (Steiner, 2011), an increase in visceral fat (Llaneza et al., 2012), metabolic syndrome (Llaneza et al., 2012), chronic inflammation (Matthews et al., 2007), and imbalanced coagulation (Matthews et al., 2007). In addition, overactivity of a sympathetic nervous system and the HPA axis are also linked to both conditions (connections between the HPA axis and climacteric-related symptoms are described in Sub-section 2.7.3) (Steiner, 2011). Moreover, difficulties in coping with the disease may also lead to depressive symptoms (Dash, 2013). As to cognitive difficulties, previous literature emphasizes the role of underlying vascular diseases in the origin of the symptoms (Warsch and Wright, 2010). CVD may produce microangiographic changes and minor infarcts in the brain and are therefore associated with compromised cognitive functioning (Vance et al., 2011).

Associations between CVD and sexual functioning have been examined mainly in populations that include only men or both genders. A recent US study of 105 participants, of which 52 were women with an average age of 32 years, found that atrial arrhythmias in women were associated with decreased sexual functioning. Yet, hypertension or the use of beta blockers were not (Neiman et al., 2017). Moreover, another US study that included 376 postmenopausal women with metabolic syndrome, aged 64–82 years, found that CVD as a diabetic complication (i.e., heart attack, coronary artery bypass, or angina) were only associated with decreased sexual activity, but not with sexual desire or satisfaction. Furthermore, a history of heart failure, poor circulation, or stroke was not associated with sexual functioning (Trompeter et al., 2016).

2.6.2 Climacteric-related symptoms and diabetes

In the ALSWH, women with severe VMS, particularly with early symptom onset, were more likely to have diabetes than women with mild VMS (Herber-Gast and Mishra, 2014). However, in another subset of the ALSWH, diabetes was only associated with night sweats and not with hot flashes (Herber-Gast et al., 2013). Whether the increased sweating in climacteric diabetic women is related to the climacteric, diabetes, or hypoglycemia is uncertain (Herber-Gast et al., 2013; Mold, 2004). On one hand, insulin resistance and decreased glucose uptake are linked to sympathetic nerve activity (Tuomikoski and Savolainen-Peltonen, 2017), but on the other hand, diabetes harms sympathetic nerves and

sweat glands and may, therefore, also decrease sweating (Murota, 2016; Petrofsky et al., 2012). Furthermore, findings concerning the relationship between VMS and insulin resistance have been contradictory. Although some studies have linked insulin resistance to more frequent VMS (Kwon et al., 2016; Thurston et al., 2012), others have reported neutral results (Ryu et al., 2015; Tuomikoski et al., 2012).

In women, diabetes is associated with both short and long sleep duration (Ayas et al., 2003; Shadyab et al., 2015; Tuomilehto et al., 2008), daytime napping (Shadyab et al., 2015; Sun et al., 2016), and tiredness (Fritschi et al., 2012; Hayley et al., 2015), but probably not with other types of sleep problems (Björkelund et al., 2005; Monterrosa-Castro et al., 2013). In an Australian study, the association between diabetes and tiredness was not related to sleep duration (Hayley et al., 2015). Instead, the association attenuated when the BMI was considered (Hayley et al., 2015). Thus, tiredness and daytime napping might be a consequence of often co-occurring nocturnal breathing disorders (Harper et al., 2012; Saaresranta et al., 2016; Vgontzas et al., 2003).

Concerning the association between diabetes and depressive symptoms, the results of previous studies have conflicted (Demmer et al., 2015; Hasan et al., 2016; Monterrosa-Castro et al., 2013). Diabetes has been connected to more frequent depressive symptoms (Demmer et al., 2015), and the existence of depression may even predict a future risk of diabetes (Demmer et al., 2015). However, not all studies have confirmed the association (Hasan et al., 2016). Regarding anxiety, an association with diabetes seems unlikely (Demmer et al., 2015; Hasan et al., 2016; Monterrosa-Castro et al., 2013). Besides being a consequence of having difficulties coping with chronic disease, depressive symptoms might result from vascular damages in the brain (Dash, 2013), abnormalities in the neurotransmitter levels related to metabolic consequences of diabetes (Dash, 2013), or from coinciding sleep disturbances (Eichling and Sahni, 2005). Moreover, depressive symptoms may increase the risk of cognitive decline (Dash, 2013), which, in diabetics, may also be caused by hyperglycemia or hypoglycemia, insulin resistance, alterations in the HPA axis functioning (the involvement of the HPA axis in cognitive functioning is described in Sub-section 2.7.3), or by neurodegeneration or vascular damage (Dash, 2013; Warsch and Wright, 2010).

Depressive symptoms also play a major role in the association between diabetes and impaired sexual functioning (Bargiotta et al., 2011; Cortelazzi et al., 2013; Enzlin et al., 2002). According to a meta-analysis of 26 studies, the odds ratio for female sexual dysfunction was 2.3 in women with type 1 diabetes and 2.5 in women with type 2 diabetes (Pontiroli et al., 2013). Diabetic vascular and nerve dysfunction might impair the sexual response and lead to functional changes in genitalia (Bargiotta et al., 2011). Moreover, impaired sexual functioning may be related to a hormonal imbalance, disturbances of the sympathetic nervous system, or to hyperglycemia, which can lead to dyspareunia by reducing vaginal hydration and lubrication and increasing exposure to genitourinary infections (Bargiotta et al., 2011).

However, the decline in sexual functioning is not related to the duration of diabetes or the presence of diabetic complications (Cortelazzi et al., 2013; Enzlin et al., 2002).

2.6.3 Climacteric-related symptoms and neurological diseases

Neurological diseases include a wide range of different conditions. Associations between neurological diseases and climacteric-related symptoms have not gained interest in previous literature. Excessive sweating could be a symptom of an underlying neurological disease (Ohshima and Tamada, 2016). In addition, many diseases, such as migraine, epilepsy, Parkinson's disease, neuromuscular diseases, brain or spinal cord injuries, and Alzheimer's disease, are linked to sleep disturbances (Anderson, 2011; Cevoli et al., 2012; Peter-Derex et al., 2015), depressive symptoms (Anderson, 2011; Frediani and Villani, 2007), cognitive decline (Anderson, 2011; Peter-Derex et al., 2015; Wang et al., 2014), and impaired sexual functioning (Bronner et al., 2015; Linstow et al., 2014; Vodušek, 2014).

2.6.4 Climacteric-related symptoms and diseases of the eye, ear, and lungs

In the present thesis, sensory organ diseases included diseases of the eyes and ears. They are probably not directly associated with climacteric-related symptoms. However, various symptoms of sensory organ diseases, such as pain, tinnitus, or dizziness, may increase the risk of sleep problems and mood symptoms (Bittar and von Söhsten Lins, 2015; Guidozi, 2013; Schecklmann et al., 2015; Sobel and Markov, 2005). As to bronchopulmonary diseases, an Icelandic study found that in individuals with untreated obstructive sleep apnea, the prevalence of frequent nocturnal sweating was threefold higher than in the general population (Arnardottir et al., 2013). Moreover, some bronchopulmonary diseases, such as asthma, chronic obstructive pulmonary disease (COPD), obstructive sleep apnea, and other nocturnal breathing disorders, are linked to sleep disturbances (Blümel et al., 2012; Plotkin, 2010; Saaresranta et al., 2016). The most common sleep problems in relation to these diseases are tiredness (Kapsimalis and Kryger, 2002), daytime sleepiness (Blümel et al., 2012; Kapsimalis and Kryger, 2002), and decreased sleep quality (Provini et al., 2010). Bronchopulmonary diseases are also linked to more frequent depressive and anxiety symptoms (Di Marco et al., 2011; Fan and Meek, 2014; Guidozi, 2013; Lavoie et al., 2009; Sobel and Markov, 2005) and decreased cognitive functioning (Fan and Meek, 2014; Lavoie et al., 2009; Panossian and Daley, 2013). Depressive symptoms and anxiety typically reflect poor disease control (Di Marco et al., 2011; Fan and Meek, 2014; Lavoie et al., 2009), but they may also increase symptom awareness (Di Marco et al., 2011; Fan and Meek, 2014; Lavoie et al., 2009). Obstructive sleep apnea is associated with impaired sexual functioning (Steinke et al., 2016). However, regarding other bronchopulmonary diseases, knowledge is limited to male sexual functioning (Goodell, 2007; Steinke, 2005).

2.6.5 Climacteric-related symptoms and musculoskeletal diseases

Pain related to any disease may cause sleep problems (Guidozzi, 2013). Thus, musculoskeletal diseases, which commonly manifest as pain are a common source of poor sleep (Bruyneel, 2015; Guidozzi, 2013). Musculoskeletal pain is also associated with depressive symptoms and anxiety (Crofford, 2015; Sobel and Markov, 2005). The causal relationship is bidirectional: pain itself predisposes to mood symptoms, and mood symptoms increase the risk of chronic pain (Crofford, 2015; Sobel and Markov, 2005). Moreover, mood symptoms and pain may partly share the same biological pathways (Crofford, 2015; Sobel and Markov, 2005).

2.6.6 Climacteric-related symptoms and gastrointestinal diseases

Some gastrointestinal diseases have been connected to VMS (Santonicola et al., 2011; Singh et al., 2011; Viera et al., 2003). Santonicola et al. (2011) found that untreated postmenopausal celiac women had more hot flashes than women without celiac diseases or celiac women consuming a gluten-free diet (Santonicola et al., 2011). Moreover, inflammatory bowel disease (Singh et al., 2011) and gastroesophageal reflux (Viera et al., 2003) are known to cause night sweats in both genders. In addition to gastrointestinal symptoms, women with irritable bowel syndrome are also susceptible to various other symptoms, including diverse mood symptoms and somatic symptoms (Mulak et al., 2014). However, other gastrointestinal diseases are also associated with more frequent sleep problems (Ali et al., 2013; Mårild et al., 2015), depressive symptoms (Bokemeyer et al., 2013; Sobel and Markov, 2005; Zingone et al., 2015), and anxiety (Sobel and Markov, 2005; Zingone et al., 2015), and with decreased cognitive (Berrill et al., 2013; Lichtwark et al., 2014) and sexual (Bokemeyer et al., 2013) functioning. Sleep may be disturbed by diverse gastrointestinal symptoms (Ali et al., 2013), or, in individuals with inflammatory bowel disease, by an activated immune system (Ali et al., 2013). In addition, sleep disturbances may contribute to gastrointestinal diseases, possibly through their effect on inflammation (Ali et al., 2013). Furthermore, the association between gastrointestinal diseases and decreased cognitive functioning is probably mediated by co-occurring mood symptoms (Berrill et al., 2013).

2.6.7 Climacteric-related symptoms and urological diseases

Diseases of the urological system include diseases of the kidneys and lower urinary tract. Of these, advanced renal diseases may lead to excessive sweating (Murota, 2016). Renal diseases and diseases of the lower urinary tract are both associated with sleep problems and mood symptoms (Finkelstein et al., 2010; Maung et al., 2016; Sakakibara et al., 2013; Troxel et al., 2014). Diseases of the lower urinary tract may disturb sleep through various symptoms, such as nocturnal feelings of urgency, bladder pain, or nocturia (Troxel et al., 2014), while in advanced renal diseases, insomnia is thought to be related to chronic pain, physical stress, decreased levels of melatonin, or to restless legs syndrome caused by an iron deficiency

(Maung et al., 2016). Moreover, urological diseases may compromise sexual functioning (Castagna et al., 2015; Chen et al., 2013; Vecchio et al., 2010), in most cases, due to fear of urinary incontinence (Castagna et al., 2015; Chen et al., 2013).

2.6.8 Climacteric-related symptoms and dermatological diseases

Dermatological diseases may induce symptoms that resemble those of the climacteric. Although some of the diseases are connected to reduced sweating (Bito et al., 2012; Shiohara et al., 2011), at least rosacea may cause flushing (Katsambas and Nicolaidou). Moreover, pruritus, a frequent symptom in dermatological diseases, disturbs sleep and is associated with depressive symptoms and anxiety (Thorburn and Riha, 2010). Dermatological diseases may also lead to mood symptoms through decreased self-image or self-esteem, social isolation, or difficulties with forming relationships (Barankin and DeKoven, 2002). The same factors have detrimental effects on sexual functioning (Molina-Leyva et al., 2014), which may also be compromised by genital presentation of dermatological diseases (Kellogg Spadt and Kusturiss, 2015; Molina-Leyva et al., 2014).

2.6.9 Climacteric-related symptoms and thyroid diseases

Thyroid diseases commonly present as overproduction or underproduction of thyroid hormones (Almandoz and Gharib, 2012; Blick and Jialal, 2018; del Ghianda et al., 2014). Symptoms in both conditions are often similar to symptoms of climacteric (del Ghianda et al., 2014). Overproduction (hyperthyroidism) may manifest as hot flashes, intolerance to heat, sweating, palpitations, insomnia, irritability, mood changes, muscle weakness, or abdominal tenderness (Blick and Jialal, 2018; del Ghianda et al., 2014), whereas underproduction (hypothyroidism) is connected to cold intolerance, fatigue, depressive symptoms, anxiety, dry skin, constipation, and muscle aches (Almandoz and Gharib, 2012; del Ghianda et al., 2014). Moreover, hyperthyroidism and hypothyroidism may both lead to heavy menstrual bleeding, irregular menstruation, or amenorrhea (Blick and Jialal, 2018; del Ghianda et al., 2014; Mansourian, 2013).

2.6.10 Climacteric-related symptoms and cancer

Cancer diseases often produce systemic symptoms along with local manifestations. Some cancers, such as brain tumors, carcinoid syndrome, pheochromocytoma, and renal, thyroid, and pancreatic carcinoma may cause flushing or increased sweating (Stearns et al., 2002; Zhukovsky, 2002). Cancer diagnosis is often followed by sleep problems (Artherholt and Fann, 2012) and diverse mood symptoms (Artherholt and Fann, 2012). Among patients with advanced cancer, the burden of physical illness, low self-esteem, hopelessness, and proximity to death contribute especially to depressive symptoms, and major depression is common (Artherholt and Fann, 2012). Aside from co-occurring sleep problems and mood symptoms,

the impact of cancer on cognitive and sexual functioning depends on diverse disease and treatment factors (Artherholt and Fann, 2012; Falk and Dizon, 2013).

Besides the associations that have been described here, many diseases may affect sleep, mood, and cognitive or sexual functioning through various symptoms or medications. Moreover, it must be noted that the causal relationship between somatic diseases and some of the climacteric-related symptoms, particularly sleep problems and mood symptoms, may be bidirectional (Sobel and Markov, 2005).

2.7 Climacteric-related symptoms and cortisol

2.7.1 Cortisol metabolism

Cortisol has vital physical functions. It binds to glucocorticoid receptors, which exist in almost all tissues in the body (Fries et al., 2009). Cortisol provides energy for the brain and muscles by mobilizing glucose from tissues, enhances cerebral blood flow, cardiovascular output, and respiration, and modulates immune responses, preventing tissue and nerve damage associated with inflammation (Fries et al., 2009; Hannibal and Bishop, 2014). It is an end product of a major endocrine system called the HPA axis (Adam and Kumari, 2009; Hannibal and Bishop, 2014). The HPA axis regulates homeostasis by adapting responses to physical and environmental challenges (Fries et al., 2009). It is activated by the amygdala, which promotes the release of corticotropin-releasing hormone (CRH) from the hypothalamus. In turn, CRH stimulates the anterior pituitary to release adrenocorticotrophic hormone (ACTH), which triggers the release of cortisol in the cortex of the adrenal glands (Fries et al., 2009). Cortisol is produced and secreted in a diurnal rhythm and as a response to stressful stimuli (Adam and Kumari, 2009; Fries et al., 2009; Hannibal and Bishop, 2014; Miller et al., 2007). Blood levels of cortisol rise early in the morning to facilitate awakening, peak sharply within 20–30 minutes after awakening, and then gradually decline towards evening (Adam and Kumari, 2009; Hannibal and Bishop, 2014; Miller et al., 2007). The sharp peak in the cortisol levels after awakening is termed the cortisol awakening response (CAR) (Fries et al., 2009).

The HPA axis is vulnerable to both physical and psychological stress (Hannibal and Bishop, 2014; Miller et al., 2007). The response depends on the duration of exposure to the stressful stimuli. The response to acute stress is a rapid increase in cortisol secretion, while chronic stress may result in either an increase or a decrease (Hannibal and Bishop, 2014; Miller et al., 2007). Moreover, stress leads to disturbances in the diurnal variation, for instance, to an increase or decrease of the CAR (Adam and Kumari, 2009; Fries et al., 2009; Kudielka and Wüst, 2010) or to flattening of the decline from morning to evening (Adam and Kumari, 2009). Correct functioning of cortisol secretion is crucial for health. Excessive production increases the risk of CVD (Adam and Kumari, 2009) and metabolic syndrome (Adam and Kumari, 2009), and compromises mental health (Adam and Kumari, 2009; Hannibal and

Bishop, 2014; McEwen, 2007) and cognitive functions (Adam and Kumari, 2009; Hannibal and Bishop, 2014; McEwen, 2007).

Cortisol levels increase during aging in both genders (Van Cauter et al., 1996; Yen and Laughlin, 1998). However, the increase is more remarkable in women (Van Cauter et al., 1996). In a study of 163 participants, premenopausal women had slightly lower 24-hour mean plasma cortisol levels than men of the same age (blood samples were collected every 20–30 minutes). However, after menopause, the differences disappeared (Van Cauter et al., 1996). In the SMWHS, overnight urinary cortisol excretion increased during the late menopausal transition, but as women entered the postmenopausal state, cortisol levels returned to the premenopausal levels (Woods et al., 2006). Some gender differences have been found also related to the CAR. Compared to men, women have a stronger and more prolonged increase in cortisol levels after awakening (Fries et al., 2009). Moreover, a study investigating associations between cortisol secretion and work-related recovery and fatigue found that women who needed more than three days to recover after a work week had a higher salivary CAR than women who recovered in less than three days, whereas men who needed more than three days to recover had a lower CAR than men who recovered in a shorter time. In addition, among women, a higher CAR was correlated with a greater lack of energy and greater physical exertion, while no correlation was found among men (Eek et al., 2012). By contrast, cortisol responses to acute stress are weaker in women than in men (Kirschbaum and Hellhammer, 1994).

2.7.2 Measuring cortisol secretion

Cortisol levels can be measured from blood (plasma or serum) (Kirschbaum and Hellhammer, 1994), saliva (Kirschbaum and Hellhammer, 1994; Miller et al., 2007), urine (Kirschbaum and Hellhammer, 1994; Miller et al., 2007), cerebrospinal fluid (Miller et al., 2007), or hair (Gibson et al., 2016; Miller et al., 2007). Cortisol levels measured from blood or saliva represent cortisol levels at specific time points (Russell et al., 2012), whereas urinary cortisol provides information on the total cortisol production and secretion during the sampling period (Russell et al., 2012), and hair cortisol levels represent long-term cortisol production (Russell et al., 2012). Cortisol levels measured from serum comprise both protein-bounded and unbounded cortisol and, thus, are dependent on the concentration of cortisol-binding globulin, while salivary cortisol levels represent levels of unbounded cortisol. However, salivary cortisol levels correlate well with both total and free cortisol levels measured from blood (Kirschbaum and Hellhammer, 1994).

Various variables may be used to define cortisol secretion. As cortisol levels are dependent on the time of awakening, levels measured at specific clock times are rather uninformative (Adam and Kumari, 2009). To identify average cortisol levels, mean cortisol levels or the area under the curve (AUC) can be calculated. However, more essential elements of diurnal cortisol secretion are the CAR and the decline from early morning to late evening (Adam and

Kumari, 2009). To define the decline from morning to evening, a diurnal cortisol slope is usually calculated (Adam and Kumari, 2009), which represents the decrease in cortisol levels during the day at a certain time.

2.7.3 The relationship between cortisol and climacteric-related symptoms

As cortisol secretion is vulnerable to both physical and mental stress (Hannibal and Bishop, 2014; McEwen, 2007) as well as to sleep disturbances (Abell et al., 2016; Backhaus et al., 2004; Hagger-Johnson et al., 2010; Hartaigh et al., 2012; Polk et al., 2005; Vargas and Lopez-Duran, 2014; Vedhara et al., 2003; Woods et al., 2006; Woods and Mitchell, 2010), cortisol secretion might be influenced by the burden caused by climacteric-related symptoms or directly by climacteric sleep problems. However, the results of previous studies investigating the relationship between cortisol secretion and climacteric-related symptoms have been varying and conflicting (Table 6). As VMS deteriorate sleep (Lampio et al., 2014) and are linked to perceived stress (Avis et al., 2015; Gold et al., 2004), it could be hypothesized that VMS would have an impact on cortisol secretion. However, quite a few associations have been found (Gerber et al., 2017; Gibson et al., 2016; Reed et al., 2016; Rubin et al., 2014). The subset of the SMWHS found that women who had an increase in overnight urine cortisol secretions during the menopausal transition ($n = 15$) experienced more VMS and hot flashes than women who had stable cortisol secretions ($n = 7$) (Woods et al., 2006). In another subset of the same study, a lower overnight urinary cortisol excretion predicted the occurrence of more hot flashes over the following two days (Woods et al., 2009). By contrast, an Italian study found that more frequent VMS were associated with higher 24-hour urinary cortisol excretions (Cagnacci et al., 2011). Gibson et al. (2016) investigated associations between VMS and cortisol secretions in women who reported having daily hot flashes (Gibson et al., 2016). VMS were assessed with diaries over seven days. More frequent VMS were associated with higher hair cortisol levels and flatter diurnal cortisol slopes (Gibson et al., 2016). Moreover, a US study found that more frequent VMS were associated with lower salivary cortisol levels 30 minutes after awakening and higher cortisol levels in the early afternoon, but not with the rest of the investigated cortisol variables (Reed et al., 2016). In a recent study, also of US origin, VMS were not associated with cortisol levels at different time points nor with the calculated cortisol variables (Gerber et al., 2017).

The CAR has not been associated with subjective VMS (Gerber et al., 2017; Reed et al., 2016; Rubin et al., 2014). However, in a US study of 40 women, salivary CAR was higher in women with objective VMS, assessed with an ambulatory hot flash monitor, than in women without VMS (Rubin et al., 2014). Yet, neither objective or subjective VMS were associated with the cortisol AUC (Rubin et al., 2014). Although, in a study from the 1980s that measured changes in finger temperature and skin resistance, serum cortisol levels peaked 15 minutes after a hot flash (Meldrum et al., 1984).

Sleep problems have been linked to cortisol metabolism (Abell et al., 2016; Backhaus et al., 2004; Hagger-Johnson et al., 2010; Hartaigh et al., 2012; Polk et al., 2005; Vargas and Lopez-Duran, 2014; Vedhara et al., 2003; Woods et al., 2006; Woods and Mitchell, 2010). However, few studies have investigated associations between cortisol secretion and symptoms experienced by climacteric women (Gerber et al., 2017; Woods et al., 2006, 2009; Woods and Mitchell, 2010). In the SMWHS, associations between sleep problems and cortisol secretion were investigated in three subsets (Woods et al., 2006, 2009; Woods and Mitchell, 2010). In the two first subsets, no associations were found between sleep problems and overnight urinary cortisol excretion (Woods et al., 2006, 2009). However, in the third subset, difficulties falling asleep, but not waking during the night or too early in the morning, were associated with lower overnight urinary cortisol excretions (Woods and Mitchell, 2010). Gerber et al. (2017) found that more frequent sleep problems were associated with higher cortisol levels at bedtime but not with other investigated cortisol variables (Gerber et al., 2017).

Depressive and anxiety symptoms have also been found to be associated with cortisol secretion, particularly with hypercortisolism and flattening of the rhythm of cortisol secretion (Cagnacci et al., 2011; Hartaigh et al., 2012; Knight et al., 2010; Kudielka and Wüst, 2010; Maletic and Raison, 2009). However, most previous studies have included both women and men. Studies including only midlife women have mainly failed to find associations between depressive or anxiety symptoms and cortisol secretion (Gerber et al., 2017; Vedhara et al., 2003; Woods et al., 2006, 2008). In the SWAN, salivary cortisol levels were measured at 18:00h and at 21:00h and again the following day upon the awakening. Although the cortisol slope represents the decline during the day, in the SWAN, the slope was calculated using the cortisol values from two consecutive days; morning cortisol values were treated as if they were from the same day as the evening cortisol values. Cortisol slopes were flatter in women with more frequent depressive symptoms, but depressive symptoms were not associated with cortisol levels at specific time points (Knight et al., 2010). Vedhara et al. (2003) investigated associations between cortisol levels and three different mood symptoms—depressive symptoms, anxiety, and stress. Cortisol levels were measured at five different time points during one day. In line with the results of the SWAN, none of the symptoms were associated with cortisol levels. However, a nonlinear association was found between anxiety and stress and cortisol levels; the form of cortisol curves differed according to the symptomatology. In women with anxiety or stress, cortisol levels were higher in the morning and in the evening, but lower during the day (Vedhara et al., 2003). In the SMWHS, depressive symptoms or mood symptoms (including panicky feelings, nervousness, mood changes, depressive symptoms, irritability, tearfulness, difficulty concentrating, forgetfulness, and tiredness) were not associated with overnight urinary cortisol excretion or with the increase in cortisol secretion during the menopausal transition (Woods et al., 2006, 2008). Furthermore, neutral associations were also reported by Gerber et al. (2017).

Regarding cognitive functioning, the SMWHS did not find associations between cognitive difficulties and cortisol secretion (Mitchell and Woods, 2011; Woods et al., 2006, 2009).

Table 6. Associations between climacteric-related symptoms and cortisol secretions in previous studies

Authors, year, and country	N	Age, mean (SD), (range)	Cortisol measures	Investigated symptoms	Results
Meldrum et al. 1984, United states	18	NR ²	Serum cortisol Samples were collected every 15 min and additionally every 5 min for 20 min beginning with the onset of each hot flash (duration of the sampling was not reported)	Objectively measured and subjectively reported hot flashes	Cortisol levels increased 15 min after hot flashes, which were both objectively measured and subjectively reported
Cignarelli et al. 1989, Italy	6	49 (3) (-)	Plasma cortisol Samples were collected during 11 hot flashes	Objectively measured hot flashes	Cortisol levels increased during hot flashes, but did not reach statistical significance
Vedhara et al. 2003, United Kingdom	54	44 (-) (-)	Salivary cortisol Samples were collected at 07:00h–08:00h, 60 min after the first measurement, at 12:00h–13:00h, at 16:00h–17:00h, and at 23:00h–24:00h over one day	Subjective depressive symptoms, anxiety, and stress	Nonlinear association was found between anxiety and stress and cortisol secretions No associations between depressive symptoms and cortisol levels
Woods et al. 2006, United states	169	47 (4) ³ (35–55)	Overnight urinary cortisol Samples were collected monthly (8–12 times per year) over seven years Increase in cortisol levels during the menopausal transition was assessed	Hot flashes, VMS, sleep problems, cognitive difficulties, and mood symptoms	More frequent hot flashes and VMS were associated with a higher increase in overnight urinary cortisol levels during menopausal transition Sleep problems, cognitive difficulties, and mood symptoms were not associated with the increase in overnight urinary cortisol

Woods et al. 2008, United states	302	41 (4) ³ (35–55)	Overnight urinary cortisol Samples were collected monthly over four years and then four times per year over next five years	Depressive symptoms	Depressive symptoms were not associated with overnight urinary cortisol levels
Woods et al. 2009, United states	132	40 (4) ³ (35–55)	Overnight urinary cortisol Samples were collected monthly (8–12 times per year) over four years and then four times per year over next five years, but one sample was enough to be included in the study	Hot flashes, sleep problems, depressive symptoms, and cognitive difficulties	More frequent hot flashes were associated with lower overnight urinary cortisol levels Sleep problems, depressive symptoms, and cognitive difficulties were not associated with overnight urinary cortisol levels
Knight et al. 2010, United states	408	50 (4) (35–55)	Salivary cortisol Samples were collected at 18:00h and 21:00h and again the following day at the time of awakening	Depressive symptoms	More frequent depressive symptoms were associated with flatter cortisol slopes (although salivary samples were collected over two consecutive days, to calculate the slope, they were treated as if they were all collected on the same day) Depressive symptoms were not associated with cortisol levels measured at specific time points
Mitchell and Woods 2010, United states	292	41 (4) ³ (35–55)	Overnight urinary cortisol Samples were collected monthly (8–12 times per year) over four years and then four times per year over next five years	Back pain and joint pain	More severe back pain was associated with lower overnight urinary cortisol levels Joint pain was not associated with overnight urinary cortisol levels

Table continues at the next page

Table 6 continues

Authors, year, and country	N	Age, mean (SD), (range)	Cortisol measures	Investigated symptoms	Results
Woods and Mitchell 2010, United states	286	41 (4) ³ (35–55)	Overnight urinary cortisol Samples were collected monthly (8–12 times per year) over four years and then four times per year over next five years	Difficulty getting off to sleep, awakening during the night, and early morning awakening	More frequent difficulties getting off to sleep were associated with lower overnight urinary cortisol levels Awakening during the night and early morning awakening were not associated with overnight urinary cortisol levels
Cagnacci et al. 2011, Italy	85	53 (6) (-)	24-hour urinary cortisol	VMS, depressive symptoms, anxiety, sexual functioning, and somatic symptoms	More frequent VMS, depressive symptoms, anxiety, and somatic symptoms were associated with higher 24-hour urinary cortisol excretions Sexual functioning was not associated with 24-hour urinary cortisol excretions
Mitchell and Woods 2011, United states	292	41 (4) ³ (35–55)	Overnight urinary cortisol Samples were collected monthly (8–12 times per year) over four years and then four times per year over next five years	Difficulties concentrating and forgetfulness	Difficulties concentrating and forgetfulness were not associated with overnight urinary cortisol levels
Rubin et al. 2014, United states	40	52 (-) (-)	Salivary cortisol Samples were collected at the time of awakening, and 15, 30, and 45 min and 3, 6, 9, and 12 h after awakening on three days	Objectively measured and subjectively reported VMS	Women with objective VMS had a higher CAR than women without objective VMS Neither objective or subjective VMS were associated with the cortisol AUC

Gibson et al. 2016, United states	44	53 (5) (NR)	Salivary cortisol and hair cortisol Salivary samples were collected at the time of awakening and at bedtime on three consecutive days Hair samples were collected once	Hot flashes	More frequent hot flashes were associated with flatter diurnal cortisol slopes and higher hair cortisol levels
Reed et al. 2016, United states	306	55 (4) (40–62)	Salivary cortisol Samples were collected at the time of awakening, 30 min after waking, in early afternoon, and at bedtime on two consecutive days	Hot flashes	More frequent hot flashes were associated with lower cortisol levels 30 min after awakening and higher cortisol levels in the early afternoon Hot flashes were not associated with total daytime cortisol, awakening response (cortisol at the time of awakening + cortisol 30 min after awakening), diurnal variation (cortisol at the time of awakening - cortisol at bedtime), and bedtime cortisol
Gerber et al. 2017, United states	109	49 (6) (18–65)	Salivary cortisol Samples were collected at the time of awakening, 30 min after waking, 1 h before bedtime, and at bedtime	Hot flashes, sleep problems, depressive symptoms	More frequent sleep problems were associated with higher cortisol levels at bedtime Hot flashes and depressive symptoms were not associated with cortisol variables

VMS, vasomotor symptoms; CAR, cortisol awakening response; AUC, area under the curve; ¹ Age of the participants, years; ² All women were postmenopausal, but ages were not reported; ³ Age at baseline.

Another study found that climacteric women with higher serum cortisol levels performed worse in some of the tests measuring cognitive functioning. However, cortisol levels were measured from serum samples that were collected at 7:00–8:00h in the morning regardless of the time of awakening (Rackiewicz et al., 2017). In studies including both genders, instead of subjective cognitive difficulties, the focus has been on cognitive performance measured with neuropsychological tests (Bennion et al., 2015; Ebner et al., 2015; Singh-Manoux et al., 2014). There is some evidence that a short-term increase in cortisol levels improves cognitive functioning (Bennion et al., 2015; Ebner et al., 2015), whereas persistent or excessively high levels are harmful (Ebner et al., 2015; Greendale et al., 2000).

Since somatic symptoms are not specific to the climacteric and the domain of somatic symptoms in the WHQ consists of several diverse symptoms (Girod et al., 2004; Hunter, 2000), it is unfeasible to define associations between various somatic symptoms and cortisol metabolism. However, alike depressive and anxiety symptoms, conditions associated with chronic pain and fatigue are linked to the flattening of the diurnal rhythm of cortisol secretion (Maletic and Raison, 2009). Moreover, chronic pain and fatigue have been mainly linked to a decrease in cortisol secretion (Fries et al., 2009; Kumari et al., 2009; Maletic and Raison, 2009; Mitchell and Woods, 2010), rather than hypercortisolism.

3 AIMS OF THE STUDY

This study was designed to evaluate the validity and reliability of the WHQ and to investigate climacteric-related symptoms and their associations with various factors, including age, socioeconomic and lifestyle factors, chronic somatic diseases, and cortisol metabolism. In every sub-study, climacteric-related symptoms were measured with the WHQ.

The specific aims were:

1. To evaluate the psychometric properties of the original and revised versions of the WHQ in a Finnish population. The psychometric properties of the original WHQ were examined on both the 1–4 scale and the binary scale (**Study I**).
2. To evaluate climacteric-related symptoms experienced by midlife Finnish women, and to investigate associations between climacteric-related symptoms and age, and socioeconomic and lifestyle factors (**Study II**).
3. To investigate which climacteric-related symptoms are linked with chronic somatic diseases and whether these associations are dependent upon SRH (**Studies III and IV**).
4. To investigate associations between climacteric-related symptoms and cortisol levels and metabolism (**Study V**).
5. To evaluate whether climacteric-related symptoms continue over time after menopause (**Study VI**).

4 MATERIALS AND METHODS

4.1 Participants

The studies included three different samples (Figure 3). The participants' characteristics are shown in Table 7, and the use of HT in different age groups in **Sample I** is shown in Table 8.

4.1.1 Recruitment

Inclusion and exclusion criteria for all studies are shown in Table 9.

4.1.1.1 *Studies I–IV*

In Finland, all women aged 50–69 years are invited every second year to a nationwide breast cancer screening mammography. However, in Turku, Finland, a study also inviting women aged 40–49 years (invited annually or every third year depending on the year of birth) and women aged 70–74 years (invited every second year) was conducted from 1987 to 2009 in order to investigate the effectiveness of mammography screening in the prevention of breast cancer. All women irrespective of their previous cancer history or familial background were invited to the screening. The participants for the cross-sectional studies presented in the present thesis (**Studies I–IV**) were women who were called for the mammography screening in Turku in 1999–2000. The participation rate in the screening program was 87.0%. A total of 6,408 women, aged 41–54 years, received a postal questionnaire concerning their health-related issues; 3,421 women (53.4%) returned the questionnaire.

4.1.1.2 *Study V*

The participants for **Study V** were originally recruited through announcements in local newspapers for a larger study investigating the effects of menopause and HT on sleep and cognition (Alhola, 2007; Kalleinen, 2008). A total of 35 women were recruited, of whom 17 were perimenopausal and 18 postmenopausal. Women defined as perimenopausal had ongoing regular or irregular menstrual cycles (except for one woman who had previously had a hysterectomy), and their serum FSH level was < 23 IU/L. Women defined as postmenopausal were 58 years or older and had long-lasting amenorrhea (mean time since menopause: 11.5 years, range: 6–22 years). The mean age of perimenopausal women was 47.9 years (standard deviation [SD] 1.7, range: 45–51 years), and the mean age of postmenopausal women was 62.8 years (SD 2.9, range: 58–70 years). There were no differences in cortisol variables or in the WHQ symptom domain means between perimenopausal and postmenopausal women ($p > 0.50$); thus, the two groups were combined to form one group. Women were required to have a regular sleep-wake schedule from 22:00–

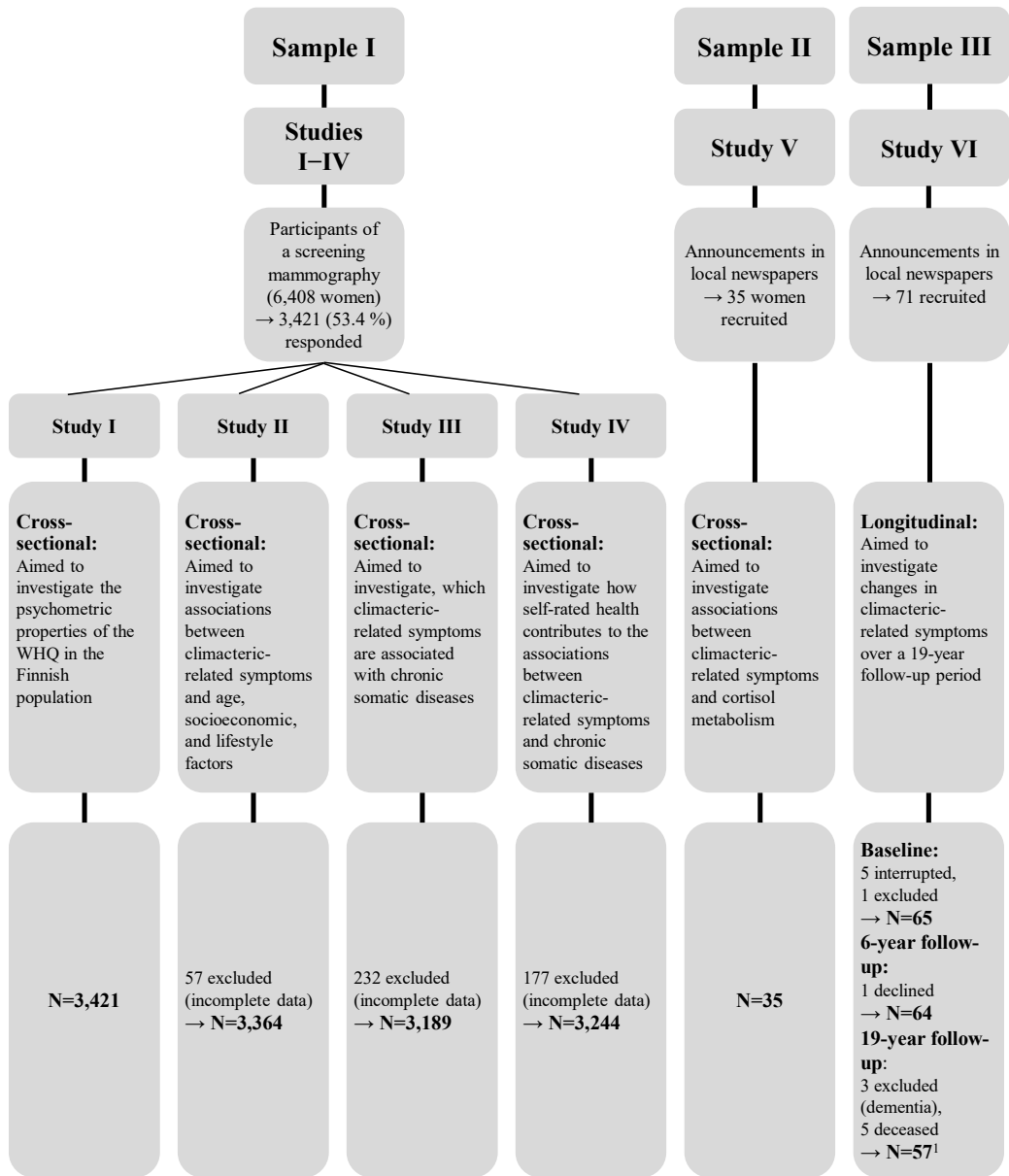


Figure 3. Study samples and aims.

The WHQ, the Women's Health Questionnaire; ¹The one who declined to participate at the 6-year follow-up, participated at the 19-year follow-up.

Table 7. Characteristics of the participants

	Sample I	Sample II	Sample III		
			Baseline	6-year follow-up	19-year follow-up
N	3421	35	65	64	57
Median (SD, range)					
Age (years)	48.9 (4.2, 40–59)	55.2 (7.9, 45–70)	56.2 (4.4, 47–65)	61.9 (4.3, 53–71)	74.9 (4.5, 66–85)
BMI	25.6 (4.5, 15–60)	26.0 (4.2, 21–38)	26.9 (4.0, 20–39)	27.3 (4.0, 20–38)	
%					
Educational level					
Lower ^a	83.4	80.0	90.8	90.6	87.7
Higher ^b	16.6	20.0	9.2	9.4	12.3
Employment					
Employed	85.7	51.4	47.7	21.9 ^c	3.5 ^c
Unemployed	9.1	40.0	9.2	1.6	3.5
Retired	5.2	8.6	43.1	90.6	96.5
Marital status					
Single	8.9	8.6	6.2	6.3	5.3
Married/cohabiting	69.0	71.4	67.7	62.5	54.4
Divorced	19.0	14.3	15.4	15.6	12.3
Widowed	3.1	5.7	10.8	15.6	28.1
Smoking					
No/occasionally	77.2	97.1	93.8	95.3	94.7
Yes, regularly	22.8	2.9	6.2	4.7	5.3
Systemic HT					
No	65.6	57.1	26.2	9.4	8.8
Previously	30.6	0	0	50.0	7.0
Yes	3.8	40.0	73.8	40.6	84.2
Local HT					
No		74.3	83.1	70.3	45.6
Previously		8.6	15.4	14.1	26.3
Yes		17.1	1.5	15.6	28.1
Ongoing menstruations					
Yes	49.0	45.7 ^c	0		
No	47.3 ^d	54.3 ^c	100		
Hysterectomized					
Perimenopausal	22.1	11.4	100		
Postmenopausal		2.9			
Peri- or postmenopausal		8.6			
			100 ^f		
One ovary removed	6.8	2.9	13.8		
Both ovaries removed	4.7	2.9	24.6		

HT, hormone therapy; ^a Lower than university; ^b University diploma; ^c At the 6-year follow-up nine and at the 19-year follow-up two women were both employed and retired; ^d Of those with no menstruations, 872 (53.9%) were either hysterectomized or used some hormonal contraceptives or intrauterine device ([IUD] including both copper and hormonal IUD); ^e One of the premenopausal women was hysterectomized. Thus, the total number of premenopausal women was 17 and the number of postmenopausal women was 18; ^f Serum follicle stimulating hormone (s-FSH) was ≥ 28 IU/L in all women.

Table 8. Use of hormone therapy (HT) in the different age groups in Sample I

Age (years)	Nonuser (%)	Current HT user (%)	Former HT user (%)
41–42	98.9	0.7	0.4
45–46	93.3	5.3	1.4
49–50	63.4	32.7	3.9
51–52	56.4	39.2	4.4
53–54	39.2	54.6	6.2

23:00h to 06:00–07:00h, which was confirmed by sleep diaries completed three weeks before and one week after the study period.

4.1.1.3 Study VI

Study VI was a prospective longitudinal study, which included three interviews. Changes in climacteric-related symptoms

during the follow-up period were investigated. The participants were originally recruited for a trial studying the effects of HT on sleep and cognition (Kalleinen et al., 2008; Polo-Kantola, 1999; Polo-Kantola et al., 1997, 1998). The recruitment was carried out through announcements in local newspapers. The original study was a prospective randomized placebo-controlled cross-over study and included two 3-month treatment periods (HT and placebo). A total of 71 women were accepted, of whom five were interrupted and one was excluded because of an initiation of antidepressant use. Thus, 65 perimenopausal or postmenopausal women constituted the final baseline study population. The mean time interval between the baseline and the second interview (later referred to as “the 6-year follow-up”) was 5.8 years (SD 0.5 years, range 5.0–6.6 years), and the interval between the baseline and the third interview (later referred to as “the 19-year follow-up”) was 19.2 years (SD 0.4 years, range 18.5–19.8 years).

At the baseline and at the 6-year follow-up, questionnaires were completed by women in the presence of a researcher. To gain a good participation rate for the 19-year follow-up, the researcher who was familiar with the women (P P-K) contacted them by phone. The women were asked if they were interested in participating in the follow-up and whether they wanted to choose a personal or a postal interview. An appointment time was booked for those who chose to be interviewed personally (28 women), and the questionnaires were posted to the remaining participants (29 women). Of the original 65 women, one (1.5%) declined to participate in the second interview (the 6-year follow-up). At the time of the third interview (the 19-year follow-up), three (4.6%) could not participate because of severe dementia and five (7.7%) were deceased. Thus, the third follow-up was completed by the remaining 57 women (including the one who declined at the second follow-up).

Even though there were only a few missing answers in the questionnaires completed independently, the women whose questionnaires were missing answers were re-contacted and asked to complete those items over the phone. The women interviewed personally and those interviewed by a postal questionnaire did not differ by age ($p = 0.813$). Systemic HT was used by four (7.0%) women, all of whom chose to be interviewed by a postal questionnaire.

Table 9. Inclusion and exclusion criteria

Sample I (Studies I–IV)**Inclusion criteria:**

Participation to a screening mammography

Exclusion criteria:

No exclusion criteria but depending on the missing answers some women were excluded from sub-studies

Sample II (Study V)**Inclusion criteria:**

Age 45–51 years or ≥ 59 years

Laboratory values: normal blood hemoglobin, leukocytes, thrombocytes, and serum thyroid stimulating hormone (s-TSH) and negative urine drug screen

Exclusion criteria:

Diseases: malignancies, neurological (except mild migraine), cardiovascular (except treated hypertension), endocrinological (except treated hyperlipidemia), and mental diseases, previously diagnosed and treated nocturnal breathing disorder, fibromyalgia, and restless legs syndrome

Medications: current use of hormone therapy (HT) and medications possibly affecting sleep

Life style factors: abuse of alcohol or drugs, smoking, excessive use of caffeine (more than five cups per day)

Sample III (Study VI)**Inclusion criteria at the baseline:**

Peri- or postmenopausal state (serum follicle stimulating hormone (s-FSH) ≥ 28 IU/L) and previous hysterectomy for benign indication

Laboratory values: normal blood hemoglobin, leucocytes, sedimentation rate, s-TSH, free thyroxin (T₄), vitamin B₁₂, creatinine, glucose, and cholesterol levels

Exclusion criteria at the baseline:

Diseases: malignancies, neurological (except migraine), cardiovascular (except treated hypertension), endocrinological (except treated hyperlipidemia), and mental diseases

Medications: current use of HT, central nervous system medications (including sleep medications)

Life style factors: abuse of alcohol or drugs and smoking (more than 10 cigarettes per day)

4.1.2 Ethics

In **Studies I–IV**, the return of the questionnaire implied consent. The Joint Ethics Committee of the University of Turku and Turku University Hospital (Record number: 9/1998), and the City of Turku (Record number: 6/98) approved the study.

In **Study V**, written informed consent was obtained from all participants. The study was approved by the Joint Ethics Committee of the University of Turku and Turku University Hospital (Record number: 9/2001).

In **Study VI**, written informed consent was obtained both at the baseline and at the follow-ups. The study was approved by the Joint Ethics Committee of the University of Turku and Turku University Hospital (Record numbers: 2/1993, 5/2000, and 2/2013).

4.2 Methods

4.2.1 Questionnaires

4.2.1.1 *The WHQ*

The WHQ was used to assess climacteric-related symptoms in every sub-study (Appendixes 1 and 2). The WHQ had been previously translated into Finnish, and the translation had been validated (Chevallet, 2000; Girod et al., 2004). Thirty-five items of the original WHQ are grouped into nine symptom domains as follows: VMS (two items), sleep problems (three items), depressive symptoms (seven items), anxiety/fears (four items), cognitive difficulties (three items), sexual functioning (three items), menstrual symptoms (four items), somatic symptoms (seven items), and one's experienced attractiveness (two items). The item of worries about growing old is not included in the domains. Because some of the items are expressed positively and others negatively, the scoring is reversed for certain items (a total of six items, #7, #10, #21, #25, #31, and #32). The items are rated on a 4-point scale (yes, definitely; yes, sometimes; no, not much; no, not at all). The developer of the WHQ, Professor Hunter recommends reducing the item scores to a binary scale (0–1). Even though, the factor structure of the questionnaire is based on factor analysis, which was conducted on the 1–4 scale (Hunter, 1992). The 1–4 scale was also used in the factor analyses of the majority of the subsequent validation studies (Table 1). In the present thesis, the use of the 1–4 scale was considered to offer more dynamics. Thus, analyses were performed on the 1–4 scale. However, in **Studies I–IV**, the 0–1 scale was also calculated (Table 10). In **Study I**, the psychometric properties of the WHQ were examined on both the 1–4 scale and on the binary scale. To obtain the major factor scale scores, the item scores were summed and then divided by the number of items in each domain. Thus, the scores ranged from 0 to 1 or from 1 to 4 in every symptom domain. Because the attractiveness domain accounted for only 2.8% of the total variance when the WHQ was originally developed (Hunter, 1992), this domain is often

Table 10. Scales and domains in the sub-studies

	Study I	Study II	Study III	Study IV	Study V	Study VI
Used scale	0–1 and 1–4	0–1 and 1–4	0–1 and 1–4	0–1 and 1–4	1–4	1–4
Included domains	Vasomotor Sleep Depressive Anxiety/fears Cognitive Sexual Menstrual Somatic Attractiveness	Vasomotor Sleep Depressive Anxiety/fears Cognitive Sexual Menstrual Somatic	Vasomotor Sleep Depressive Anxiety/fears Cognitive Sexual Menstrual	Vasomotor Sleep Depressive Anxiety/fears Cognitive Sexual Menstrual	Vasomotor Sleep Depressive Anxiety/fears Cognitive Sexual Menstrual Somatic	Vasomotor Sleep Depressive Anxiety/fears Cognitive Sexual Somatic
Excluded domains		Attractiveness	Somatic Attractiveness	Somatic Attractiveness	Attractiveness	Menstrual Attractiveness
Exceptions	Menstrual symptoms: women who had previously had hysterectomy were excluded	Menstrual symptoms: women who had previously had hysterectomy were excluded	Menstrual symptoms: women who had previously had hysterectomy were excluded	Menstrual symptoms: women who had previously had hysterectomy were excluded	Menstrual symptoms: Postmenopausal women were excluded	

omitted (Hunter, 2000). Accordingly, the attractiveness domain was excluded from all other sub-studies except **Study I**. As described above, the item of worries about growing old is not part of any domain; thus, the item was excluded from all analyses. In **Study VI**, at the baseline, item #18. was formed as *I suffer from pain in my limbs*, instead of the original, *I suffer from backache or pain in my limbs*; the question was retained unchanged at the follow-ups.

Missing data was handled as described in the user manual of the questionnaire (Girod et al., 2004). In depressive and somatic symptoms, each of which included seven items, two missing answers were allowed; in VMS and attractiveness each of which included two items, no missing answers were allowed; and in the remaining domains each of which included 3–4 items, one missing answer was allowed. Concerning the domain of sexual functioning, the women were instructed to reply to two of the three items (#31: *I am satisfied with my current sexual relationship*, and #34: *As a result of vaginal dryness, sexual intercourse has become uncomfortable*) only if they were sexually active. Because only one missing answer was accepted (Girod et al., 2004), the domain included only sexually active women. Moreover, in the menstrual symptoms domain, women who had no menstrual periods were instructed to skip one of the items (#26. *I have heavy periods*). However, as one missing answer was accepted, the domain included women who were not menstruating. In **Studies I–IV**, women who had previously had a hysterectomy were excluded from the analyses concerning the domain of menstrual symptoms. In addition, in **Study V**, postmenopausal women were excluded from the analyses concerning that domain. In **Study VI**, the domain of menstrual symptoms was totally excluded since all women had previously had a hysterectomy. As to missing answers, the number of answers for each item/domain is shown in Table 11. In **Study V**, there were no missing answers in the WHQ apart from the items in sexual functioning and

menstrual symptoms. For **Study VI**, at the baseline, apart from the items of sexual functioning, there were only three missing answers: in depressive symptoms, one woman had one missing answer and in somatic symptoms two women had one missing answer each. In these symptom domains, two missing answers would have been accepted (Girod et al., 2004); thus, the domains included all women. At the follow-ups, with the exception of sexual functioning, there were no missing answers.

4.2.1.2 *The revised version of the WHQ*

On the revised 23-item version of the WHQ, the items of depressive symptoms, anxiety/fears, and attractiveness are regrouped into domains “anxiety/depressed mood” and “well-being” (Appendix 3). Moreover, six items, #11: *I am restless and can't keep still* (sleep problems), #1: *I am more irritable than usual* (depressive symptoms), #13: *I worry about growing old* (an independent item), #21: *I feel rather lively and excitable* (attractiveness), #30: *I often notice pins and needles in my hands and feet* (somatic symptoms), and #35: *I need to pass urine/water more frequently than usual* (somatic symptoms), are completely omitted. Thus, the revised 23-item version of the WHQ includes six domains: VMS (two items), sleep problems (two items), anxiety/depressed mood (seven items), well-being (four items), cognitive difficulties (three items), and somatic symptoms (five items). Additionally, items in the domains of sexual functioning (three items) and menstrual symptoms (four items), which are included as optional domains, are separated from the other items, and a question, “*Are you currently having menstrual periods?*” is inserted before the items of menstrual symptoms (Girod et al., 2004, 2006). Items are rated on a 4-point scale, and the scores are summed and divided similarly as in the original questionnaire. However, the scoring is transformed into a 0–100 scale (Girod et al., 2004). The value 0 corresponds to the original value 1 and the value 100 to the original value 4. In **Study I**, to investigate the psychometric properties in the revised 23-item version, the original 36-item WHQ was used. Some of the questions were removed, and the remaining questions were re-grouped to obtain the symptom domains included in the revised version. To make it easier to read and to compare the results, a higher number corresponded to more symptoms in every scale for every sub-study.

4.2.1.3 *Additional questionnaires*

Besides the WHQ, the participants filled in questionnaires regarding various background factors, including age, educational level, employment, marital status, body height and weight, consumption of alcohol, smoking, use of HT, diagnosed diseases, and medications (the questionnaires used for different study samples had some differences). In **Study II**, the women were grouped into five age groups (41–42, 45–46, 49–50, 51–52, and 53–54 years). Educational level (low [no education or vocational training], intermediate, or high [university]), employment (employed, unemployed, or retired), and marital status (single, married/cohabiting, divorced, or widowed) were included as socioeconomic variables. The

Table 11. Means in the symptom domains and distinct items in the different study populations on the 1–4 scale

	Sample I			Sample II			Sample III							
	N	Mean	SD	N	Mean	SD	Baseline		6-year follow-up		19-year follow-up			
							Mean	SD	Mean	SD	Mean	SD		
Vasomotor symptoms domain	3231	1.94	0.95	35	2.04	0.93	2.90	0.98	64	1.90	0.97	54	1.64	0.91
19. I have hot flushes	3245	1.98	1.03	35	2.06	1.06	3.08	1.05	64	1.91	1.03	57	1.63	1.01
27. I suffer from night sweats	3330	1.91	1.05	35	1.94	0.94	2.72	1.05	64	1.89	1.01	57	1.65	0.97
Sleep problems domain	3328	1.84	0.73	35	2.11	0.66	2.24	0.78	64	2.02	0.66	57	1.98	0.74
1. I wake early and then sleep badly for the rest of the night	3293	2.04	1.03	35	2.51	1.01	2.69	1.12	64	2.41	0.95	57	2.18	1.05
11. I am restless and can't keep still	3324	1.59	0.83	35	1.51	0.74	1.57	0.85	64	1.50	0.82	57	1.40	0.80
29. I have difficulty in getting off to sleep	3235	1.89	1.05	35	2.29	1.13	2.45	1.19	64	2.14	1.08	57	2.35	1.25
Depressive symptoms domain	3332	1.69	0.56	35	1.54	0.43	1.68	0.53	64	1.52	0.43	57	1.54	0.50
3. I feel miserable and sad	3309	1.63	0.83	35	1.51	0.66	1.55	0.73	64	1.36	0.65	57	1.40	0.80
5. I have lost interest in things	3328	1.62	0.84	35	1.51	0.66	1.78	0.87	64	1.59	0.79	57	1.47	0.68
7. I still enjoy the things I used to ^a	3321	1.96	0.94	35	1.77	0.88	1.85	0.92	64	1.69	0.73	57	1.63	0.84
8. I feel life is not worth living	3318	1.38	0.75	35	1.34	0.80	1.42	0.77	64	1.22	0.58	57	1.40	0.86
10. I have a good appetite ^a	3327	1.46	0.84	35	1.20	0.41	1.32	0.73	64	1.53	0.96	57	1.39	0.73
12. I am more irritable than usual	3321	1.91	0.92	35	1.57	0.82	2.02	0.98	64	1.59	0.81	57	1.75	1.02
25. I have feelings of well-being ^a	3252	1.84	0.92	35	1.46	0.56	1.83	0.79	64	1.66	0.70	57	1.75	0.99
Anxiety/fears domain	3322	1.57	0.59	35	1.44	0.43	1.47	0.48	64	1.41	0.49	57	1.45	0.64
2. I get very frightened or panic feelings for apparently no reason at all	3323	1.40	0.73	35	1.31	0.63	1.28	0.57	64	1.23	0.50	57	1.35	0.69
4. I feel anxious when I go out of the house on my own	3319	1.25	0.62	35	1.20	0.47	1.29	0.61	64	1.33	0.67	57	1.37	0.79
6. I get palpitations or a sensation of "butterflies" in my stomach or chest	3307	1.76	0.88	35	1.54	0.70	1.88	0.88	64	1.67	0.84	57	1.70	0.98
9. I feel tense or "wound up"	3311	1.86	0.90	35	1.69	0.87	1.43	0.66	64	1.39	0.68	57	1.37	0.77

Cognitive difficulties domain	3299	1.96	0.75	35	2.14	0.78	65	2.58	0.72	64	2.37	0.65	56	2.20	0.70
20. I am more clumsy than usual	3315	1.82	0.91	35	1.83	0.95	65	2.66	0.92	64	2.42	0.94	57	2.67	1.04
33. I have difficulty concentrating	3262	1.92	0.95	35	2.26	0.98	65	2.32	0.94	64	2.13	0.86	57	1.70	0.91
36. My memory is poor	3218	2.07	0.93	35	2.34	0.94	65	2.75	0.81	64	2.56	0.79	57	2.23	0.91
Sexual functioning domain	2768	1.86	0.72	26	1.94	0.67	48	2.40	0.78	35	2.04	0.68	19	2.35	0.90
24. I have lost interest in sexual activity	3283	2.09	1.02	35	2.11	1.05	65	2.58	0.95	64	2.28	1.02	57	2.89	1.06
31. I am satisfied with my current sexual relationship ^a	2702	1.92	0.92	26	1.92	0.84	48	2.15	0.92	35	1.83	0.98	19	1.95	1.08
34. As a result of vaginal dryness, sexual intercourse has become uncomfortable	2679	1.64	0.90	26	1.85	0.83	48	2.48	1.07	35	2.63	1.03	19	2.47	1.26
Menstrual symptoms domain^b	3221	1.86	0.65	16	2.16	0.60									
17. My breasts feel tender or uncomfortable	2574	1.56	0.83	35	1.46	0.78	65	1.35	0.69	64	1.30	0.68	57	1.39	0.84
22. I have abdominal cramps or discomfort	2577	1.55	0.85	35	1.63	0.97	65	1.69	0.83	64	1.47	0.82	57	1.67	0.87
26. I have heavy periods	1843	2.43	1.09	16	2.63	1.20									
28. My stomach feels bloated	2533	2.86	1.00	35	2.06	1.08	65	2.29	1.06	64	2.08	1.04	57	2.02	1.04
Somatic symptoms domain	3323	1.91	0.61	35	1.83	0.51	65	2.13	0.57	64	2.05	0.52	54	2.00	0.61
14. I have headaches	3319	1.95	1.01	35	2.11	1.05	65	2.26	0.99	64	2.09	0.95	57	1.74	0.92
15. I feel more tired than usual	3325	2.33	1.00	35	2.40	0.95	65	2.32	0.94	64	2.06	0.89	57	1.75	0.95
16. I have dizzy spells	3307	1.65	0.90	35	1.43	0.70	64	1.67	0.87	64	1.78	0.90	57	1.86	1.06
18. I suffer from pain in my limbs	3321	2.36	1.10	35	2.37	1.11	64	2.36	1.07	64	2.38	1.19	57	2.19	1.16
23. I feel sick or nauseous	3315	1.37	0.72	35	1.14	0.55	65	1.45	0.71	64	1.20	0.44	57	1.60	0.88
30. I often notice pins and needles in my hands and feet	3179	1.74	0.96	35	1.37	0.69	65	2.17	1.04	64	2.13	1.13	57	1.79	0.92
35. I need to pass urine/water more frequently than usual	3204	1.99	1.03	35	1.83	0.98	65	2.42	1.18	64	2.44	1.14	57	2.47	1.10

To calculate symptom domain means, scale items were summated and divided by the number of the items in each symptom domain. A higher number refers to more symptoms. ^a Reversed scoring; ^b In Study VI, all women were hysterectomized, thus no response for the item #26: *I have heavy periods.*

BMI was calculated according to the heights and weights reported by the women. The BMI was divided into three categories ($< 25 \text{ kg/m}^2$, $25\text{--}30 \text{ kg/m}^2$, and $>30 \text{ kg/m}^2$). Lifestyle variables included consumption of alcohol (never, occasionally/rarely/a few times per month, weekly, and daily), smoking (never/occasionally, stopped, smoking < 10 cigarettes daily, or smoking > 10 cigarettes daily), and use of HT (non-users, current HT users, and former HT users). The occurrence of chronic diseases (CVD; diabetes; neurological diseases; a disease of the sensory organs, e.g. diseases of the eye or ear; bronchopulmonary disease; musculoskeletal disease, e.g. rheumatoid arthritis or arthrosis; serious liver disease; gastrointestinal diseases, e.g. esophageal, gastric, or bowel disease; urological disease; dermatological disease; hypothyroidism; hyperthyroidism; a mental health problem; or any cancer) was recorded as reported by the women. For the analyses, hypothyroidism (in 205 women, 6.4%) and hyperthyroidism (in 53 women, 1.7%) were combined to form a group “thyroid disease”, and serious liver disease (in 19 women, 0.6%) was included in gastrointestinal diseases. The occurrence of diseases in the different samples is shown in Table 12.

Table 12. Prevalence of diseases

	Sample I	Sample II	Sample III		
			Baseline	6-year follow-up	19-year follow-up
N	3421	35	65	64	57
	%	%	%	%	%
Cardiovascular disease	9.3	20.0	13.8	23.1	86.0
Diabetes	2.1	0	0	1.6	15.8
Neurological disease	3.2	2.9	7.7	7.8	7.0
Sensory organ disease	7.4	0	0	0	0
Bronchopulmonary disease	7.5	5.7	4.6	7.8	22.8
Musculoskeletal disease	14.3	2.9	33.8	10.9	31.6
Gastrointestinal disease	9.7	0	6.2	3.1	5.3
Urological disease	2.8	0	0	0	1.8
Dermatological disease	8.9	2.9	3.1	1.6	0
Thyroid disease	7.0	0	0	4.7	19.3
Cancer	3.4	2.9	0	0	14.0
Mental health problem	6.8	0	0	0	3.5

4.2.1.3.1 *Self-rated health (SRH)*

SRH was assessed with the question: “*In your own opinion, do you consider your health state good, moderate, or poor?*” (**Sample I**). Thus, it included three categories.

4.2.1.3.2 *QoL satisfaction*

QoL satisfaction was assessed with the question, “*How satisfied are you with your current QoL?*” (**Sample I**). It included five categories (i.e., very satisfied, quite satisfied, cannot say, quite unsatisfied, and very unsatisfied). In the analyses, the response “cannot say” was handled as a missing answer; thus, the item included four categories instead of the original five.

4.2.1.3.3 *Frequency and duration of climacteric symptoms*

In **Sample III**, besides the WHQ, the frequency of climacteric symptoms in general during the past six months and the duration of climacteric symptoms during one’s life span were asked at every follow-up without defining climacteric symptoms more precisely (later referred to as “climacteric symptoms [unspecified]”). The frequency of these unspecified climacteric symptoms during the past six months was recorded as never, seldom, or often, and the duration during one’s life span as never, less than a month, more than a month but less than six months, or more than six months.

4.2.1.3.4 *Sexual life*

Sexual life details were assessed in **Sample I**. These details included information on when the latest sexual intercourse occurred, reasons for not being sexually active, satisfaction with the frequency of sexual activities, and the quality of sexual life after the climacteric (the term climacteric was unspecified).

4.2.2 **Cortisol measurements**

Plasma cortisol levels and urinary cortisol excretion were assessed to investigate associations between climacteric-related symptoms and cortisol production (**Study V, Sample II**). The women spent three consecutive nights in the sleep laboratory at the Sleep Research Unit, Department of Physiology, University of Turku, Finland. The first night was for adaptation. During the second day, 24-hour urine samples were collected to assess total 24-hour urinary cortisol excretion. Blood sampling started at 21:00h on the third evening. An intravenous stationary cannula was placed into the forearm two hours before the start of the blood sampling. Blood samples were drawn every 20 minutes over 24 hours. Thus, the total number of blood samples was 73. Throughout the night, 23:00–07:00h, in order to draw blood samples with minimal sleep disturbance, the cannula was connected to a plastic tube running through

a soundproof lock into an adjoining room. The cannula was kept patent with a slow heparinized saline infusion. Polysomnography (PSG) was performed during all three study nights. On the third evening, the women went to bed (lights-off) at 23:00h and were awakened (lights-on) in the morning at 07:00h. However, PSG indicated that 19 women woke up before lights-on (05:15–06:59h). According to the study protocol they stayed in bed until lights-on. Only a red light was allowed for illumination overnight (23:00–07:00h) if needed. On the mornings of the third and fourth days, because of the original study, cognitive tests were performed. The day structure and program were similar for each participant.

The blood samples were analyzed in a laboratory of PerkinElmer Life and Analytical Sciences, Wallac Oy, Turku, Finland and the urine samples in the laboratory of Women's Clinic, HUSLAB, Helsinki, Finland. Blood samples were drawn into Li-Heparin tubes, placed in the refrigerator for 20 minutes, centrifuged, and frozen immediately. Plasma cortisol levels were measured with AutoDELFIA assays. The analytical sensitivity was 15 nmol/L. The 24-hour urine samples were collected without any preservatives and stored at -70°C before analysis. Urinary cortisol concentrations were measured with liquid chromatography-tandem mass spectrometry (LC-MS/MS). One milliliter of urine spiked with D₃-cortisol as internal standard was extracted with 5 ml of dichlormethane. The organic phase was washed with 0.1 mol/L sodium hydroxide and 0.1 mol/L hydrochloride and evaporated to dryness. The residue was dissolved in 1 ml of 40% methanol and analyzed by AB Sciex API 3000™ LC-MS/MS with electrospray ionization interface in the negative mode. The detection limit was 1 nmol/L.

Mean plasma cortisol levels (nmol/L) were calculated for 24 hours, night (23:00–07:00h), and day (07:20–21:00h). Morning baseline cortisol levels (nearest cortisol levels to awakening) were based on the PSG recordings. The CAR was calculated by subtracting the morning baseline levels from the highest levels within one hour after awakening. Cortisol slopes were calculated from the morning baseline to 21:00h (slope 1) and from the morning maximum to 21:00h (slope 2). Data on the wake-up time was lacking for one woman, a morning baseline value was lacking for another, and one other had a negative CAR. These women were excluded from corresponding analyses. AUC with respect to ground (AUC_g), including all 73 plasma cortisol measurements, was calculated with the formula, m_i = an individual measurement and n = a total number of measurements (Pruessner et al., 2003):

$$AUC_g = \sum_{i=1}^{n-1} \frac{m_{(i+1)} + m_i}{2}$$

In total, cortisol variables in the analyses included: 24-hour, night, day, maximum, minimum, morning baseline, CAR, AUC_g, slope 1, slope 2, and 24-hour urine cortisol.

4.2.3 Statistical analyses

The main aspects of the statistical analyses in the sub-studies are described in Table 13. Symptom domains of the WHQ and independent variables were first submitted for descriptive analyses. Means, medians, SDs, and interquartile ranges (IQR) were used to define the data in the symptom domains. To examine the internal consistency of the symptom domains in each sample, Cronbach's alpha (α) coefficients were used. Correlations between the WHQ symptom domains were determined using Spearman's correlation coefficients. P-values less than 0.05 were considered statistically significant. In every sub-study, hysterectomized women were excluded from the analyses of the menstrual symptoms domain.

In **Study I**, all analyses were conducted for all three versions of the questionnaire (i.e., the original WHQ on the 1–4 scale, the original WHQ on the 0–1 scale, and the revised WHQ on the 0–100 scale). For the revised version of the WHQ, EFA was conducted with and without the items of sexual functioning and menstrual symptoms. As these items are optional in the revised WHQ, and as this was not similarly considered in the original WHQ used in this study (Appendixes 1 and 3), only the results from the EFA without these items are presented in this summary (the results from the EFA with these items were presented in **Study I**). Moreover, because the item “worries about growing old” is not part of any domain, and because it has been commonly omitted in previous studies (Dotlic et al., 2015; Girod et al., 2006; Hunter, 1992; Wiklund et al., 1993), the item was not included in either the EFA or other analyses. Since the WHQ is considered to be a measure of QoL (Girod et al., 2004), the correlation analysis between the domains of the different versions of the WHQ and the women's own estimations of QoL satisfaction were carried out.

In **Study II**, univariate analysis of variance (ANOVA) was performed for the WHQ symptom domains and various variables, which was conducted for each independent variable separately. Then, two multivariable analyses were performed. The first included all independent variables and the second included only independent variables that were significantly ($p < 0.05$) associated with the dependent variables in the univariate analyses. Associations between the WHQ symptom domains and the independent variables were quantified with means (and 95% confidence intervals [CI]) of symptom domain differences between categories of independencies. In **Study III**, associations between the WHQ symptom domains and chronic somatic diseases were investigated with multivariable analyses. Independent variables (chronic somatic diseases) were selected with a stepwise method using p-values; only independent variables that were significantly associated ($p < 0.05$) with the dependent variables were included in the analyses. Multivariable analyses were repeated, adjusting for age, education, employment, BMI, smoking, use of HT, and mental health problems. Mental health problems were included as a covariate because they are linked to various symptoms (Bixo et al., 2001; Llaneza et al., 2012), and they would probably have mediated associations between climacteric-related symptoms and chronic somatic diseases. As somatic symptoms related to each chronic somatic disease are well documented, the

Table 13. Statistical analyses

Study I: Psychometric properties of the Women's Health Questionnaire (WHQ)

Variables:

The symptom domains of the WHQ

Statistical analyses:

SAS system for Windows, release 9.4

1. Correlations between the symptom domains of the WHQ were determined using **Spearman's correlation coefficients**.
 2. Correlations between the symptom domains of the WHQ and the question "How satisfied are you with your current quality of life (QoL)?" were determined using **Spearman's correlation coefficients**.
 3. **Cronbach's alpha (α) coefficients** were used to analyze **the internal consistency** of the symptom domains.
 4. **Exploratory factor analysis** using the principal components extraction method with varimax rotation was conducted to establish factors (subscales) and factor loadings for items.
 - Factors were required to have eigenvalues greater than 1.
 - To select items for the factors, the highest factor loadings were used; the item was considered a part of the factor if the factor loading was greater than 0.40.
 5. **KMO-test** was used to measure **sampling adequacy**.
-

Study II: Associations between climacteric-related symptoms and age and socioeconomic and lifestyle factors

Variables:

Independent variables: age, educational level, employment status, marital status, body mass index (BMI), consumption of alcohol, smoking, and the use of hormone therapy (HT).

Dependent variables: the domains of the WHQ

Statistical analyses:

SAS system for Windows, release 9.2

1. Associations between dependent and the independent variables were investigated using the **univariate analysis of variance**, which was conducted for each independent variable separately.
 2. Two **multivariable analyses of variance** were performed:
 - The first included all independent variables.
 - The second included only the independent variables that were significant in the univariate analyses
-

Study III: Associations between climacteric-related symptoms and chronic somatic diseases

Variables:

Independent variables: chronic somatic diseases (cardiovascular disease (CVD), diabetes, neurological, sensory organ, bronchopulmonary, musculoskeletal, gastrointestinal, urological, dermatological, thyroid disease, and cancer)

Dependent variables: the domains of the WHQ

Adjusted for: age, education, employment, BMI, smoking, the use of HT, and mental health problems

Statistical analyses:

SAS system for Windows, release 9.2

Multivariable analyses of variance were conducted to assess associations between the dependent and independent variables. Independent variables were selected with a stepwise

method using p-values; the independent variables that were significantly associated with the dependent variables were included in the analyses.

Study IV: Associations between climacteric-related symptoms and chronic somatic diseases adjusted for self-rated health (SRH)

Variables:

Independent variables: chronic somatic diseases (CVD, diabetes, neurological, sensory organ, bronchopulmonary, musculoskeletal, gastrointestinal, urological, dermatological, thyroid disease, and cancer)

Dependent variables: the domains of the WHQ

Adjusted for: age, education, employment, BMI, smoking, the use of HT, mental health problems, and SRH

Statistical analyses:

SAS system for Windows, release 9.4

1. The **multivariable analyses** of Study III were repeated, adjusting for SRH
-

Study V: Associations between climacteric-related symptoms and cortisol metabolism

Variables:

1. Cortisol variables including 24-hour mean, night mean (23:00-07:00h), day mean (07:20-21:00h), maximum, minimum, morning baseline, cortisol awakening response (CAR), area under the curve with respect to ground (AUCg), slope 1, slope 2, and 24-hour urinary cortisol
2. The domains of the WHQ

Statistical analyses:

SAS system for Windows, release 9.4

1. Normality of the variables was examined by the **Shapiro-Wilk test**.
 2. Depending on the normality of the distribution, **the Pearson's or Spearman's correlation coefficient analysis** was used to investigate the correlations between the WHQ symptom domain means and cortisol variables.
 3. Accordingly, **independent samples t-tests or Mann-Whitney U-tests** were conducted to assess differences in the cortisol variables between women with the WHQ domain score above the median and those with the score below the median
-

Study VI: Changes in climacteric-related symptoms during the 19-year follow-up period

Variables:

Independent variables: three time points: baseline, 6-year follow-up, and 19-year follow-up

Dependent variables: the domains of the WHQ

Adjusted for: baseline age, baseline BMI, baseline employment, and the use of systemic HT

- Concerning the domain of sexual functioning, the analyses were adjusted also for the use of local HT

Statistical analyses:

SAS system for Windows, release 9.4

The **repeated measures analysis of variance** with time as the independent variable was performed to analyze changes in the WHQ symptom domains

domain of somatic symptoms was excluded in this sub-study. In **Study IV**, the analyses of **Study III** were adjusted for SRH in order to investigate its role in the association between climacteric-related symptoms and chronic somatic diseases.

In **Study V**, to demonstrate the 24-hour cortisol secretion profile, a cortisol curve was graphed. The normality of the variables was examined using the Shapiro-Wilk test. VMS, anxiety/fears, minimum cortisol levels, and 24-hour urinary cortisol were not normally distributed. Thus, they were analyzed with non-parametric tests. Depending on the normality of the distribution, correlations between the WHQ symptom domain means and cortisol variables were investigated by Pearson's or Spearman's correlation coefficient analyses. Subsequently, the women were divided into two groups according to their symptomatology. The division was done separately for each WHQ symptom domain. One group was formed by women with scores above the median (more symptoms) and the other by those with scores below the median (fewer symptoms). Again, depending on the normality of the distribution, independent samples t-tests or the Mann-Whitney U-tests were conducted separately for each WHQ symptom domain to assess differences in the cortisol variables between the two groups.

In the follow-up study, **Study VI**, changes in the WHQ symptom domains during the follow-up period were investigated by repeated measures ANOVA with time as an independent variable. Analyses were adjusted for baseline age, baseline BMI, baseline employment (classified as "working" or "not-working"), and the use of HT (classified as "yes" or "no" according to the participant's current use). Concerning the domain of sexual functioning and its items, the analyses were also adjusted for the use of local HT (classified as "yes" or "no" according to the participant's current use). Associations were quantified with means (and SDs) of symptom domain differences between categories of independencies. An additional cross-sectional independent samples t-test was carried out to examine differences in age and symptom domain means between women who were interviewed personally and women who were interviewed by a postal questionnaire at the 19-year follow-up.

The probability of making false discoveries when performing multiple comparisons was considered. Thus, for the multivariable analyses in **Studies II, III, and IV** and for repeated measures ANOVA in **Study VI**, Tukey's multiple comparison tests were used to identify significant differences. The results of **Studies II–VI** are only shown on the 1–4 scale.

5 RESULTS

5.1 Occurrence of climacteric-related symptoms in different study samples

The means (SDs) for the symptom domains and for the distinct items in all three samples are shown in Table 11 and in Figure 4. The domain and item means were moderately comparable between the samples. However, as seen in Figure 4, VMS, cognitive difficulties, and impaired sexual functioning tended to be more frequent in **Sample III** (only visual comparisons, no statistical comparisons performed), which was probably related to the fact that all women in Sample III were peri- or postmenopausal, whereas the other samples also included premenopausal women.

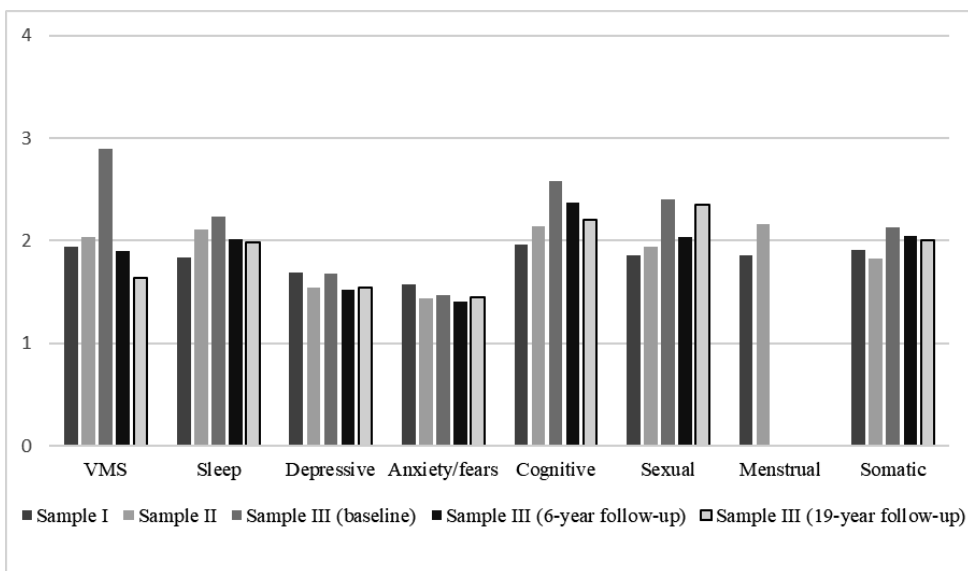


Figure 4. WHQ symptom domain means in the different study samples.

In **Sample III**, at the baseline, the majority of the women had experienced climacteric symptoms (unspecified) during the past six months (Table 14). At the 6-year follow-up, a minority had experienced climacteric symptoms often, one-third seldom, and over half of the women not at all. At the 19-year follow-up, only one woman was still experiencing climacteric symptoms often, 10.5% seldom, and the majority of the women not at all. The women's reports concerning the duration of climacteric symptoms over the life span were inconsistent between the follow-ups (Table 14). At the baseline, 89.3% of the women answered that they had experienced climacteric symptoms for more than one month. At the 6-year follow-up, the corresponding percentage was 79.7%, while 17.2% of the women answered that they had never experienced climacteric symptoms. At the 19-year follow-up, only half of the women (49.1%) answered that they had experienced climacteric symptoms for more than one month, while over one-third answered that they had never experienced

climacteric symptoms. Furthermore, at the 19-year follow-up, in **Sample III**, the women interviewed by a postal questionnaire had more somatic ($p = 0.040$) and depressive ($p = 0.003$) symptoms and anxiety/fears ($p = 0.003$) than women interviewed personally.

Table 14. The frequency and duration of climacteric symptoms in Sample III

	Baseline	6-year follow-up	19-year follow-up
Age (years)	56.2 (4.4, 47–65)	61.9 (4.3, 53–71)	74.9 (4.5, 66–85)
	N (%)	N (%)	N (%)
Frequency of climacteric symptoms during the past six months			
Not at all	16 (24.6)	37 (57.8)	47 (82.5)
Seldom	19 (29.2)	21 (32.8)	6 (10.5)
Often	29 (44.6)	6 (9.4)	1 (1.8)
Duration of climacteric symptoms over one's life span			
Never	3 (4.6)	11 (17.2)	20 (35.1)
Less than one month	3 (4.6)	2 (3.1)	3 (5.3)
More than one month but less than six months	20 (30.8)	12 (18.8)	6 (10.5)
More than six months	38 (58.5)	39 (60.9)	25 (38.6)

Climacteric symptoms were asked without defining climacteric symptoms more precisely. In the text referred to as “climacteric symptoms (unspecified)”.

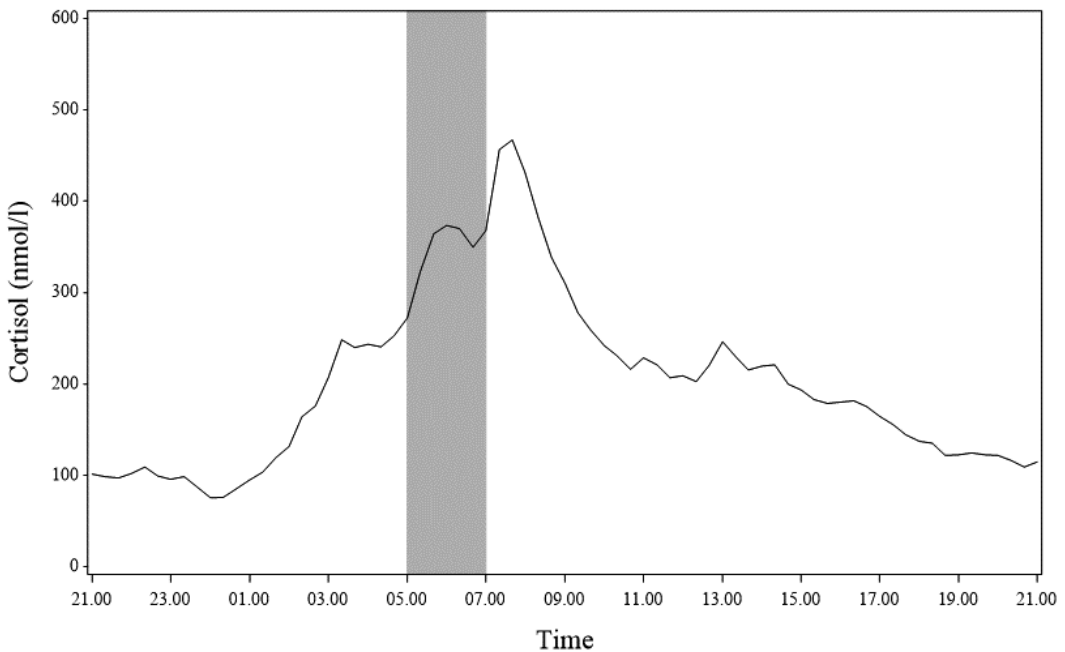


Figure 5. The 24-hour cortisol curve.

The grey area indicates the time of awakening, which varied between women.

The sexual life details in **Sample I** are shown in Table 15. Most women had been sexually active during the past week or during the past month. The most common reason for not being sexually active was the lack of a partner, followed by the lack of sexual desire. Most women were satisfied with the frequency of sexual activities, but almost one-third answered “not often enough.” The item concerning quality of sexual life after the climacteric was answered by 44.3% of the women. Approximately half of the women had a similar quality of sexual life after the climacteric as before, while according to the replies the quality of sexual life was worse than before for one-third and better than before for 13.6%.

Table 15. Sexual life details of women in Sample I

	N (%)
The most recent sexual intercourse	3353
During the past week	1848 (55.1)
During the past month	748 (22.3)
During the past year	327 (9.8)
More than a year ago, but less than 10 years ago	338 (10.1)
More than 10 years ago	69 (2.1)
Never experienced sexual intercourse	23 (0.7)
Reasons for not being sexually active	1298
The lack of a partner	454 (35.0)
The lack of sexual desire (own)	393 (30.3)
Partner's lack of sexual desire	221 (17.0)
Painful intercourse	94 (7.2)
Own disease	21 (1.6)
Partner's disease	115 (8.9)
Satisfaction with the frequency of sexual activities	3135
Satisfied with the frequency	2014 (64.2)
Not often enough	934 (29.8)
Too often	187 (6.0)
Quality of sexual life after climacteric	1514
Similar as before	823 (54.4)
Worse than before	485 (32.0)
Better than before	206 (13.6)

5.2 Cortisol secretion

The mean values for different cortisol variables (**Study V**) are shown in Table 16, and the 24-hour plasma cortisol curve is shown in Figure 5. There were only a few associations between cortisol variables and the WHQ symptom domains. These associations are described in Figure 6 and in Section 5.4.

5.3 Psychometric properties of the WHQ

5.3.1 Internal consistency and sampling adequacy

Cronbach's α coefficients for the different samples are shown in Figure 7. In **Sample I**, Cronbach's α coefficients were highest for the revised version of the WHQ, second highest for the original WHQ on the 1–4 scale, and lowest for the original WHQ on the 0–1 scale. On the 1–4 scale, coefficients varied between 0.51 and 0.79, and were acceptable (> 0.70) for five domains (VMS, depressive symptoms, anxiety/fears, cognitive difficulties, and somatic

symptoms). On the 0–1 scale, Cronbach's α coefficients varied between 0.44 and 0.71; coefficients were acceptable (≥ 0.70) for only two domains (VMS and depressive symptoms). For the revised WHQ, Cronbach's α coefficients varied between 0.54 and 0.85 and were acceptable (0.71–0.80) for three domains (VMS, cognitive difficulties, and somatic symptoms) and good (> 0.80) for one domain (anxiety/depressed mood). The Kaiser–Meyer–Olkin (KMO) value was > 0.90 for every version of the WHQ indicating high sampling adequacy. In **Sample II**, Cronbach's α coefficients varied between 0.70 and 0.75, and in **Sample III** between 0.56 and 0.84.

Table 16. Mean values in the cortisol variables

	N	Mean (nmol/l)	SD (nmol/l)	Min (nmol/l)	Max (nmol/l)
Serum cortisol levels					
24-h mean	35	202.7	36.2	148.4	314.6
Night mean ^a	35	207.3	40.9	144.2	299.1
Day mean ^b	35	214.5	42.6	152.6	346.5
Maximum	35	515.3	87.1	369.0	738.1
Minimum	35	50.7	24.6	19.9	133.0
Morning baseline ^c	33	367.2	82.6	224.0	564.0
CAR ^d	33	144.0	146.0	-15.0	452.1
AUC _g ^e	35	4885.7	877.5	3471.8	7675.3
24-h urine cortisol					
	N	Mean (nmol/l/h)	SD (nmol/l/h)	Min (nmol/l/h)	Max (nmol/l/h)
Slope 1 ^f	32	-17.7	6.0	-29.7	-5.1
Slope 2 ^g	32	-29.0	7.0	-42.8	-17.1

^a 23:00–07:00h; ^b 07:20–21:00h; ^c The nearest value to awakening, which was determined by polysomnography; ^d The cortisol awakening response (CAR) was calculated by subtracting the morning baseline levels from the highest levels within one hour after awakening (morning maximum); ^e Area under the curve with respect to ground (AUC_g) was calculated including all 73 cortisol measurements; ^f Slope 1 was calculated from the morning baseline to 21:00h; ^g Slope 2 was calculated from the morning maximum to 21:00h.

5.3.2 Construct validity and item convergent validity

On the 1–4 scale, the EFA resulted in seven factors explaining 52.1% of the total variance; on the 0–1 scale in eight factors, explaining 48.1% of the variance; and in the revised version of the WHQ, in five factors, explaining 54.4% of the total variance. The factors in the different scales are shown in Table 17.

5.3.3 Correlations between the WHQ symptom domains

The correlations between the WHQ symptom domains in the different samples are shown in Table 18. In **Sample I**, all correlations between the symptom domains on the different

versions of the WHQ were statistically significant ($p < 0.05$), but most coefficients were below 0.50. In **Samples II** and **III**, the correlations were divergent and not all correlations were significant.

5.3.4 Correlations between the WHQ symptom domains and QoL satisfaction

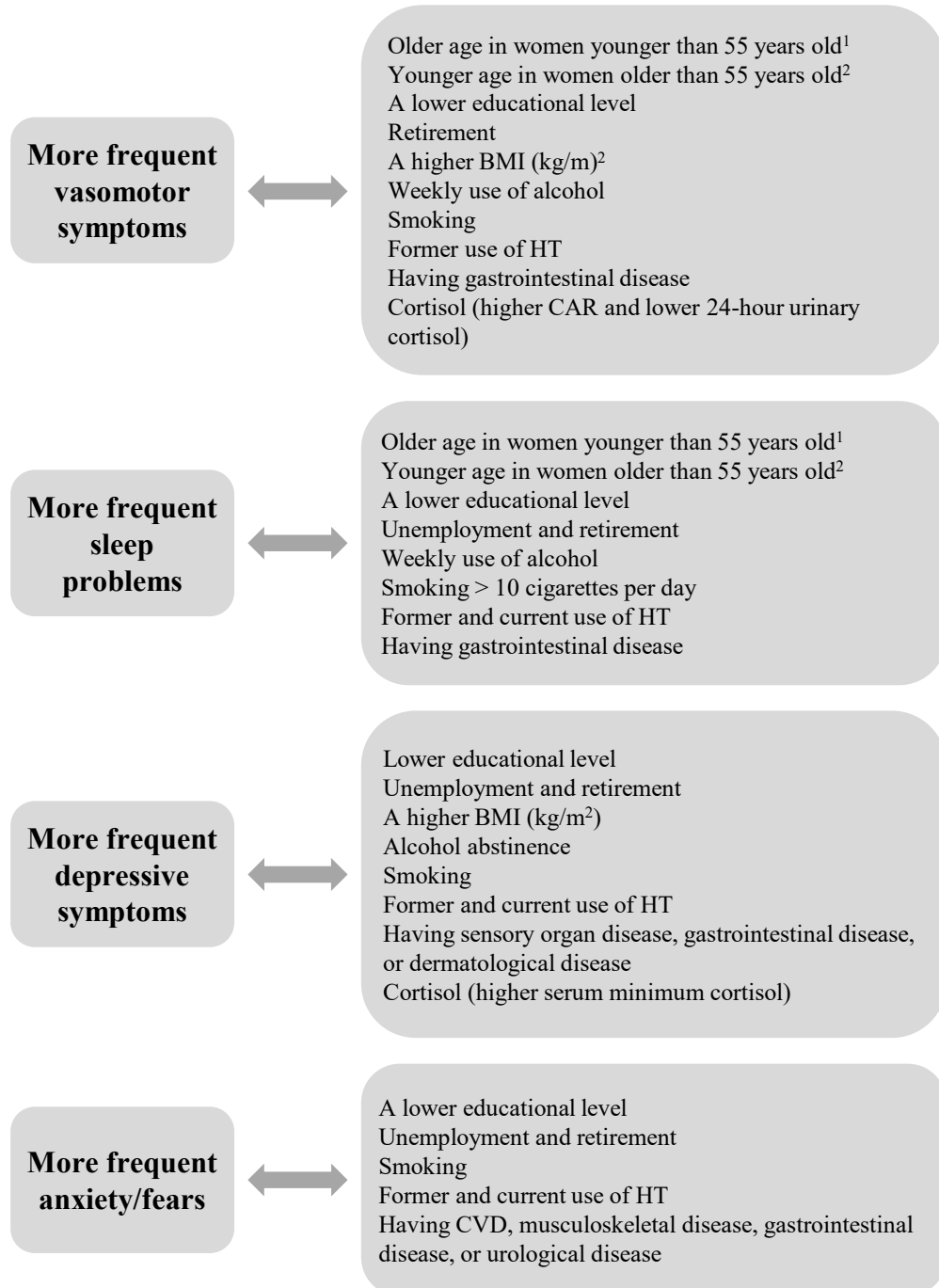
In **Sample I**, 24.8% ($n=798$) of the women were very satisfied with their QoL, 62.3% ($n=2002$) were quite satisfied, 6.4% ($n=207$) were quite unsatisfied, and 0.8% ($n=25$) were very unsatisfied; the frequency of missing answers was 207 and 5.7% ($n=182$) replied “cannot say” (omitted from the statistics). The correlations between the various symptom domains of the WHQ and QoL satisfaction are described in Table 19. All correlations were statistically significant, but apart from two correlation coefficients, they were lower than 0.50; the correlation coefficients between QoL satisfaction and depressive symptoms on the 1–4 scale and between QoL satisfaction and anxiety/depressed mood in the revised WHQ were 0.50. The correlations were fairly stronger on the 1–4 scale (range 0.26–0.50) and on the revised version (range 0.26–0.50) than on the binary scale (range 0.25–0.39).

5.4 Climacteric-related symptoms and associated factors

Statically significant associations between climacteric-related symptoms and investigated factors are described in Figure 6. Details of differences, 95% CIs, and p-values are presented in **Studies II–V**.

5.4.1 Vasomotor symptoms

In the cross-sectional study (**Study II**), which only included women younger than 55 years old, older women had more VMS than younger women (49–54 years vs. 41–42 years, 49–54 years vs. 45–46 years, and 51–54 years vs. 49–50 years). By contrast, in the longitudinal study, which included only perimenopausal and postmenopausal women (**Study VI**), VMS decreased over time (between all interviews) as the women aged. Among the socioeconomic factors, VMS were associated with educational level and employment status but not with marital status. Women with a lower educational level had more symptoms than women with a higher educational level (intermediate and low vs. high). As to employment, retirement was associated with having more VMS (compared to employment or unemployment). Women with a BMI of 25–30 kg/m² had more VMS than women with a BMI less than 25 kg/m². Regarding alcohol consumption, weekly use of alcohol was associated with having more VMS when compared occasional use or abstinence. Smokers had more VMS than both non-smokers and former smokers regardless of the number of cigarettes the smokers smoked. VMS were also more frequent among former HT users than among women who had never used it or who were currently using HT.



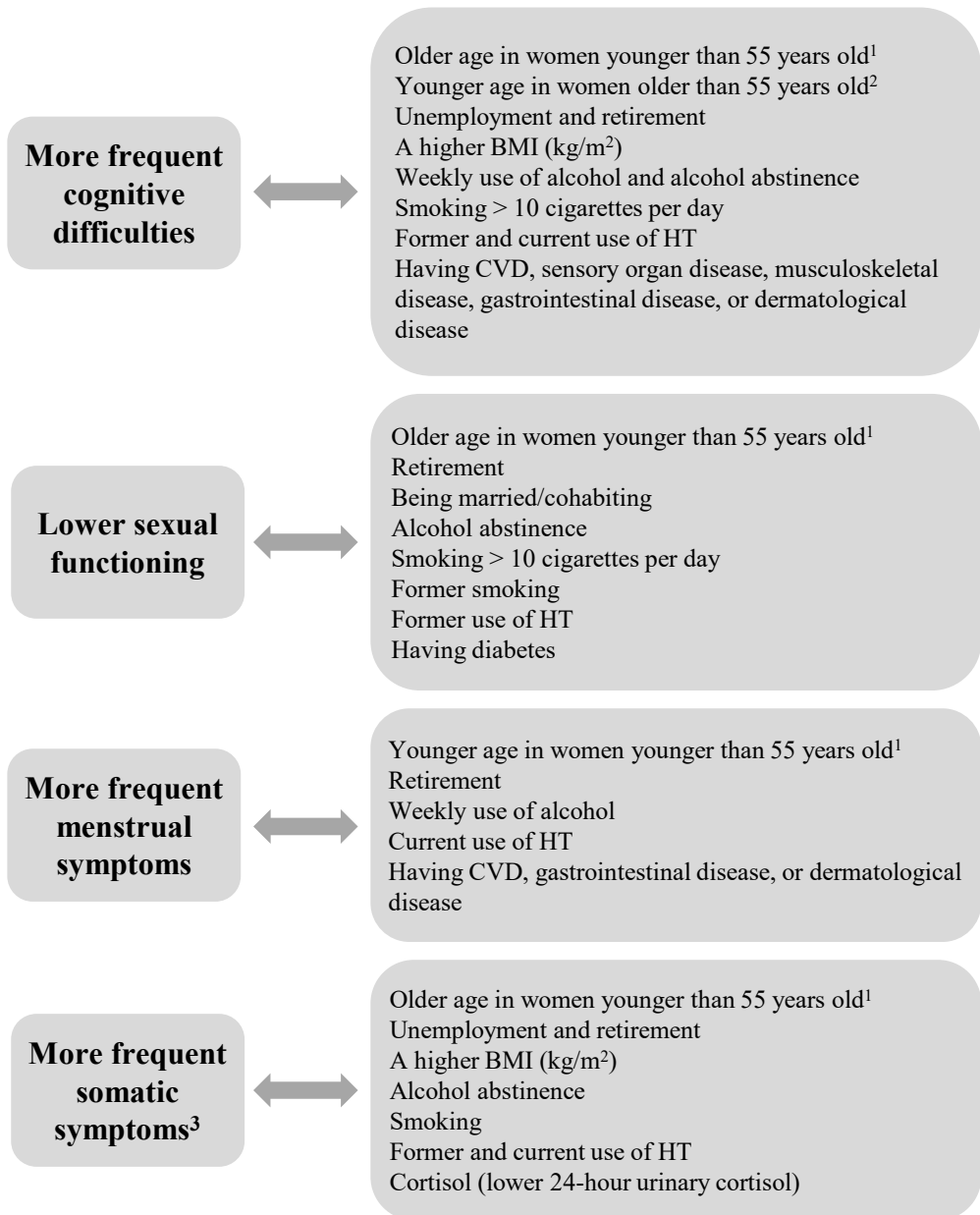


Figure 6. Associations between climacteric-related symptoms and the investigated factors. BMI, body mass index; HT, hormone therapy; CVD, cardiovascular disease ¹ Age in Study II; ² Aging in Study VI; ³ Associations between somatic symptoms and chronic somatic diseases were not investigated.

Table 17. Factors in the exploratory factor analyses

The 1-4 scale			The 0-1 scale			The revised WHQ		
Factors	% VE ¹	The original domain ²	Factors	% VE ¹	The original domain ²	Factors	% VE ¹	The original domain ²
Factor 1	13.4		Factor 1	11.4		Factor 1	15.6	
2. I get very frightened or panic feelings for apparently no reason at all		Anxiety/fears	2. I get very frightened or panic feelings for apparently no reason at all		Anxiety/fears	2. I get very frightened or panic feelings for apparently no reason at all		Anxiety/fears
3. I feel miserable and sad		Depressive	3. I feel miserable and sad		Depressive	3. I feel miserable and sad		Depressive
4. I feel anxious when I go out of the house on my own		Anxiety/fears	4. I feel anxious when I go out of the house on my own		Anxiety/fears	4. I feel anxious when I go out of the house on my own		Anxiety/fears
5. I have lost interest in things		Depressive	5. I have lost interest in things		Depressive	5. I have lost interest in things		Depressive
8. I feel life is not worth living		Depressive	6. I get palpitations or a sensation of "butterflies" in my stomach or chest		Anxiety/fears	6. I get palpitations or a sensation of "butterflies" in my stomach or chest		Anxiety/fears
9. I feel tense or "wound up"		Anxiety/fears	8. I feel life is not worth living		Depressive	8. I feel life is not worth living		Depressive
11. I am restless and can't keep still		Sleep	9. I feel tense or "wound up"		Anxiety/fears	9. I feel tense or "wound up"		Anxiety/fears
12. I am more irritable than usual		Depressive	11. I am restless and can't keep still		Sleep			
33. I have difficulty concentrating		Cognitive	12. I am more irritable than usual		Depressive			
			33. I have difficulty concentrating		Cognitive			
Factor 2	11.7		Factor 2	8.8		Factor 2	11.2	
6. I get palpitations or a sensation of "butterflies" in my stomach or chest		Anxiety/fears	6. I get palpitations or a sensation of "butterflies" in my stomach or chest		Anxiety/fears	5. I have lost interest in things		Depressive
14. I have headaches		Somatic	14. I have headaches		Somatic			

16. I have dizzy spells	Somatic	15. I feel more tired than usual	Somatic	15. I feel more tired than usual	Somatic
17. My breasts feel tender or uncomfortable	Menstrual	16. I have dizzy spells	Somatic	20. I am more clumsy than usual	Cognitive
18. I suffer from backache or pain in my limbs	Somatic	17. My breasts feel tender or uncomfortable	Menstrual	32. I feel physically attractive ^e	Attractiveness
20. I am more clumsy than usual	Cognitive	18. I suffer from backache or pain in my limbs	Somatic	33. I have difficulty concentrating	Cognitive
22. I have abdominal cramps or discomfort	Menstrual	22. I have abdominal cramps or discomfort	Menstrual	36. My memory is poor	Cognitive
23. I feel sick or nauseous	Somatic	23. I feel sick or nauseous	Somatic		
28. My stomach feels bloated	Menstrual	28. My stomach feels bloated	Menstrual		
30. I often notice pins and needles in my hands and feet	Somatic	30. I often notice pins and needles in my hands and feet	Somatic		
Factor 3	6.6	Factor 3	5.4	Factor 3	10.4
1. I wake early and then sleep badly for the rest of the night	Sleep	24. I have lost interest in sexual activity	Sexual	6. I get palpitations or a sensation of "butterflies" in my stomach or chest	Anxiety/fears
19. I have hot flushes	Vasomotor	31. I am satisfied with my current sexual relationship ³	Sexual	14. I have headaches	Somatic
27. I suffer from night sweats	Vasomotor	34. As a result of vaginal dryness, sexual intercourse has become uncomfortable	Sexual	15. I feel more tired than usual	Somatic
29. I have difficulty in getting off to sleep	Sleep	35. I need to pass urine/water more frequently than usual	Somatic	16. I have dizzy spells	Somatic
				18. I suffer from backache or pain in my limbs	Somatic
				23. I feel sick or nauseous	Somatic

Table continues at the next page

Table 17 continues

The 1-4 scale			The 0-1 scale			The revised WHQ		
Factors	% VE ¹	The original domain ²	Factors	% VE ¹	The original domain ²	Factors	% VE ¹	The original domain ²
Factor 4 7. I still enjoy the things I used to ³ 21. I feel rather lively and excitable ² 25. I have feelings of well-being ³ 32. I feel physically attractive ³	6.5	Depressive Attractiveness Depressive Attractiveness	Factor 4 20. I am more clumsy than usual 21. I feel rather lively and excitable ² 32. I feel physically attractive ³	4.9	Cognitive Attractiveness Attractiveness	Factor 4 1. I wake early and then sleep badly for the rest of the night 19. I have hot flushes 27. I suffer from night sweats 29. I have difficulty in getting off to sleep	9.4	Sleep Vasomotor Vasomotor Sleep
Factor 5 24. I have lost interest in sexual activity 31. I am satisfied with my current sexual relationship ³ 34. As a result of vaginal dryness, sexual intercourse has become uncomfortable	5.9	Sexual Sexual Sexual	Factor 5 1. I wake early and then sleep badly for the rest of the night 29. I have difficulty in getting off to sleep	4.8	Sleep Sleep	Factor 5 7. I still enjoy the things I used to ³ 10. I have a good appetite ³ 25. I have feelings of well-being ³ 32. I feel physically attractive ³	7.6	Depressive Depressive Depressive Attractiveness
Factor 6 15. I feel more tired than usual 33. I have difficulty concentrating	5.0	Somatic Cognitive	Factor 6 7. I still enjoy the things I used to ³ 10. I have a good appetite ³	4.8	Depressive Depressive			

Table 18. Spearman's correlation coefficients between the symptom domains in the different samples

	Vasomotor	Sleep	Depressive	Anxiety/fears	Cognitive	Sexual	Menstrual	Somatic
Vasomotor	1.0 1.0 <i>1.0</i>	0.39*** 0.48** 0.40**	0.34*** NS 0.37**	0.35*** NS 0.25*	0.40*** NS 0.25*	0.28*** NS NS	0.26*** NS -	0.42*** NS 0.29*
Sleep	1.0 1.0 <i>1.0</i>	1.0 1.0 <i>1.0</i>	0.51*** NS 0.45***	0.55*** NS 0.49***	0.49*** NS 0.42***	0.31*** NS NS	0.35*** NS -	0.51*** NS 0.34**
Depressive	1.0 1.0 <i>1.0</i>	1.0 1.0 <i>1.0</i>	1.0 1.0 <i>1.0</i>	0.64*** 0.40* 0.52***	0.56*** NS 0.58***	0.44*** NS 0.32*	0.31*** NS -	0.52*** 0.37* 0.59***
Anxiety/fears	1.0 1.0 <i>1.0</i>	1.0 1.0 <i>1.0</i>	1.0 1.0 <i>1.0</i>	1.0 1.0 <i>1.0</i>	0.56*** 0.37* 0.39***	0.34*** NS 0.29*	0.43*** 0.53* -	0.58*** 0.40* 0.45***
Cognitive	1.0 1.0 <i>1.0</i>	1.0 1.0 <i>1.0</i>	1.0 1.0 <i>1.0</i>	1.0 1.0 <i>1.0</i>	1.0 1.0 <i>1.0</i>	0.36*** NS NS	0.39*** 0.53* -	0.61*** 0.39* 0.62***
Sexual	1.0 1.0 <i>1.0</i>	1.0 1.0 <i>1.0</i>	1.0 1.0 <i>1.0</i>	1.0 1.0 <i>1.0</i>	1.0 1.0 <i>1.0</i>	1.0 1.0 <i>1.0</i>	0.18*** NS -	0.34*** NS NS
Menstrual	1.0 1.0 <i>1.0</i>	1.0 1.0 <i>1.0</i>	1.0 1.0 <i>1.0</i>	1.0 1.0 <i>1.0</i>	1.0 1.0 <i>1.0</i>	1.0 1.0 <i>1.0</i>	1.0 1.0 <i>1.0</i>	0.51*** NS -
Somatic	1.0 1.0 <i>1.0</i>	1.0 1.0 <i>1.0</i>	1.0 1.0 <i>1.0</i>	1.0 1.0 <i>1.0</i>	1.0 1.0 <i>1.0</i>	1.0 1.0 <i>1.0</i>	1.0 1.0 <i>1.0</i>	1.0 1.0 <i>1.0</i>

On the first row, the correlations in **Sample I** on the original WHQ are shown in **bold**; On the second row, the correlations in **Sample II**; On the third row, the correlations in **Sample III** (at the baseline) are shown in *italic*; * p < 0.05; ** p < 0.01; *** p < 0.001; NS, non-significant; The domain of attractiveness was omitted.

Of the chronic somatic diseases, VMS were, before adjusting for confounding factors, associated with bronchopulmonary, musculoskeletal, and gastrointestinal diseases, and cancer. After adjusting for confounding factors (age, education, employment, BMI, smoking, use of HT, and mental health problems), VMS were only associated with gastrointestinal diseases. Even this association disappeared, when SRH was included in the analyses.

When associations between VMS and cortisol variables were investigated as correlations, VMS were associated with the CAR and 24-hour urinary cortisol excretion; the CAR was higher and the 24-hour urinary cortisol excretion lower among women with more frequent VMS. When the women were divided into two groups according to their VMS, women with a VMS score above the median (more symptoms) had lower 24-hour urinary cortisol excretion than women with a VMS score below the median. There were no other associations between VMS and cortisol variables.

Table 19. Spearman's correlation coefficients for the associations between the WHQ symptom domains in the different versions of the WHQ and the question "How satisfied are you with your current quality of life?"

Domains	The original WHQ on the 1–4 scale	The original WHQ on the 0–1 scale	The revised WHQ on the 0–100 scale
Somatic	0.39	0.37	0.37
Vasomotor	0.28	0.25	0.28
Sleep	0.38	0.34	0.33
Depressive	0.50	0.39	
Anxiety/fears	0.44	0.38	
Anxiety/depressed mood			0.50
Well-being			0.41
Cognitive	0.37	0.33	0.37
Sexual	0.34	0.28	0.34
Menstrual	0.26	0.25	0.26

For all correlations $p < 0.0001$

5.4.2 Sleep problems

In the cross-sectional study (**Study II**), which only included women younger than 55 years old, sleep problems were more common in older age but only when women aged 49–50 years were compared to women aged 41–42 years. In the longitudinal study (**Study VI**), sleep problems decreased over time, from the baseline to the 19-year follow-up. Women with a lower educational level had more sleep problems than women with higher educational level (intermediate and low vs. high). Unemployed and retired women had more sleep problems than employed women, and retired women had more sleep problems than unemployed women. Sleep problems were not associated with marital status or with the BMI. Instead, they were associated with alcohol consumption; those using alcohol weekly had more sleep problems than those using alcohol occasionally. Smokers had more sleep problems than non-smokers, but only if they smoked more than 10 cigarettes per day. Sleep problems were more

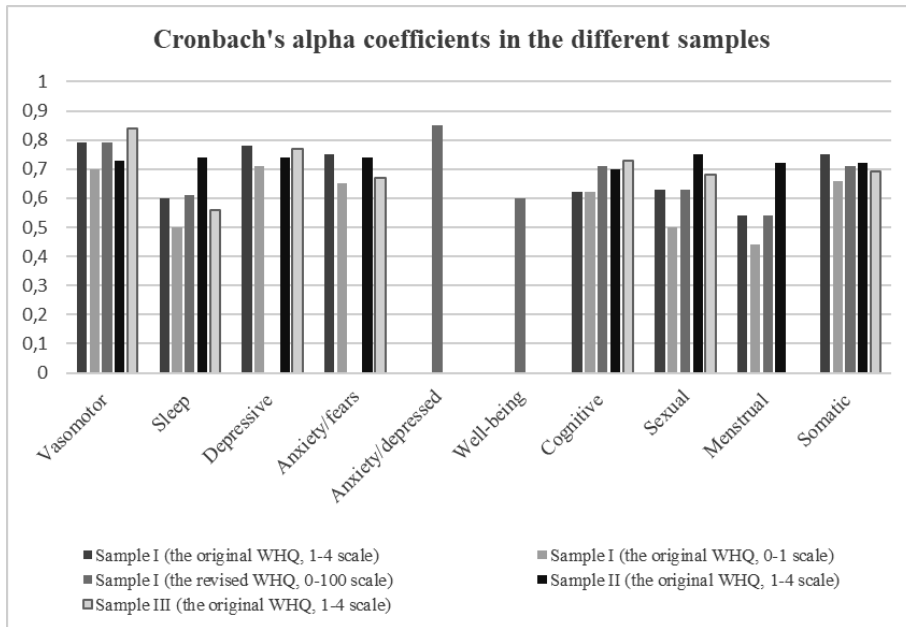


Figure 7. Internal consistencies in different samples.

The depressive symptom domain and the anxiety/fears domain are in the revised WHQ replaced with the anxiety/depressed mood domain and the well-being domain. Cronbach's alpha coefficients in Sample III are shown only for the baseline.

frequent among former and current HT users compared to women who had never used it. When former and current HT users were compared to each other, former users had more sleep problems.

Of the chronic somatic diseases, sleep problems were, before adjustments, associated with CVD and neurological, musculoskeletal, gastrointestinal, and dermatological diseases. After adjusting for confounding factors, sleep problems were only associated with gastrointestinal diseases; the association disappeared when SRH was included into the analyses. Sleep problems were not associated with cortisol variables.

5.4.3 Mood symptoms

Depressive symptoms and anxiety/fears were not associated with age in either the cross-sectional or the longitudinal study. In **Study II**, depressive symptoms and anxiety/fears were associated with both educational level and employment status but not with marital status. Women with a lower educational level had more depressive symptoms and anxiety/fears than women with a higher educational level (low vs. high), and unemployed and retired women had more symptoms than employed women. Moreover, for anxiety/fears, retired women had more symptoms than unemployed women. As to the BMI, women with a BMI higher than 30 kg/m² had more depressive symptoms than women with a lower BMI (> 30 kg/m² vs. < 25 kg/m², > 30 kg/m² vs. ≤ 25–30 kg/m²). However, anxiety/fears were not associated with the

BMI. Alcohol abstainers had more depressive symptoms than women using alcohol occasionally; anxiety/fears were not associated with alcohol use. Smokers had more depressive symptoms and anxiety/fears than non-smokers and former smokers, regardless of the number of cigarettes the smokers smoked. Former and current HT users had more depressive symptoms and anxiety/fears than women who had never used HT. Moreover, former users had more depressive symptoms than current users.

Of the chronic diseases, depressive symptoms were, before adjustments, associated with CVD and sensory organ, musculoskeletal, gastrointestinal, urological, and dermatological diseases, and after adjusting for confounding factors, with sensory organ, gastrointestinal, and dermatological diseases. However, all of these associations disappeared when SRH was included in the analyses. Anxiety/fears were, before adjustments, associated with CVD and neurological, musculoskeletal, gastrointestinal, urological, and dermatological diseases; after adjusting for confounding factors, the associations with neurological and dermatological diseases were no longer significant. After including SRH into the analyses, anxiety/fears were only associated with gastrointestinal diseases.

In **Study V**, in the Spearman's correlation coefficient analysis, depressive symptoms were associated with higher minimum plasma cortisol levels. However, the association was not found in the Mann-Whitney U-test. No other associations were found between mood symptoms and cortisol variables.

5.4.4 Cognitive difficulties

In the cross-sectional study (**Study II**), which only included women younger than 55 years old, older women had more cognitive symptoms than younger women (49–54 years vs. 41–42 years and 49–52 years vs. 45–46 years). However, in the longitudinal study (**Study VI**), cognitive difficulties decreased from the baseline to the 19-year follow-up. Of the socioeconomic factors, cognitive difficulties were associated with employment status but not with educational level or marital status. Unemployed and retired women had more cognitive difficulties than employed women, and retired women had more than unemployed women. Women with a BMI higher than 30 kg/m² had more cognitive difficulties than women with a BMI lower than 25 kg/m². For cognitive difficulties, alcohol abstainers and those using alcohol weekly had more symptoms than those using alcohol occasionally. Smokers had more difficulties than non-smokers, but only if they smoked more than 10 cigarettes per day. As to the use of HT, former and current users had more symptoms than those who had never used HT.

Cognitive difficulties were, before adjustments, associated with CVD and neurological, sensory organ, musculoskeletal, gastrointestinal, urological, and dermatological diseases, and cancer, and after adjusting for confounding factors, with CVD and sensory organ, musculoskeletal, gastrointestinal, and dermatological diseases. None of these associations

remained significant after including SRH in the analyses. Cognitive difficulties were not associated with cortisol variables.

5.4.5 Sexual functioning

In the cross-sectional study (**Study II**), which only included women younger than 55 years old, sexual functioning was lower in older women than in younger women (49–54 years vs. 41–42 years and 53–54 years vs. 45–46 years). However, in the longitudinal study (**Study VI**), no change was found in sexual functioning during the follow-up period. Engagement in sexual activities decreased during the follow-up period: 73.8% of the women were sexually active at the baseline, 54.7% at the 6-year follow-up, and only 33.3% at the 19-year follow-up.

Sexual functioning was not associated with educational level, but retired women had lower sexual functioning than employed or unemployed women. Sexual functioning was the only domain that was associated with marital status; married/cohabiting women had lower sexual functioning than divorced and widowed women (divorced and widowed women did not differ from each other). However, sexual functioning was not associated with the BMI. Alcohol abstainers had lower sexual functioning than women using alcohol occasionally. Smoking more than 10 cigarettes per day was associated with lower sexual functioning, but even women who had stopped smoking had lower sexual functioning than those who had never smoked. Former smokers did not differ from current smokers. Former HT users had lower sexual functioning than women who had never used HT, but no other differences were found concerning the use of HT. Moreover, in the longitudinal study (**Study VI**), the adjustment for the use of local HT did not alter the results; during the follow-up period, no changes were found in sexual functioning.

Of the chronic diseases, sexual functioning was, before adjustments, associated with diabetes and bronchopulmonary, musculoskeletal, and gastrointestinal diseases. However, after adjusting for confounding factors, sexual functioning was only associated with diabetes; the association disappeared when SRH was included into the analysis. Sexual functioning was not associated with cortisol variables.

5.4.6 Menstrual and somatic symptoms

Menstrual symptoms were the only domain, in which younger women had more symptoms than older women in the cross-sectional study (**Study II**), which only included women younger than 55 years old (41–42 years vs. 53–54 years, 45–46 years vs. 51–54 years, and 49–52 years vs. 53–54 years). Somatic symptoms were more frequent in older women, but only when women aged 49–50 were compared to women aged 41–42 (**Study II**). Because all women were previously hysterectomized in the longitudinal study (**Study VI**), changes in menstrual symptoms were not analyzed. Somatic symptoms remained unchanged during the

follow-up period. Menstrual and somatic symptoms were not associated with educational level or marital status. Retired women had more of both symptoms than employed or unemployed women. Furthermore, unemployed women had more somatic symptoms than employed women. Menstrual symptoms were not associated with the BMI, but women with a higher BMI had more somatic symptoms than women with a lower BMI (differences were significant between all comparisons). Both menstrual and somatic symptoms were associated with alcohol consumption. Women who used alcohol weekly had more menstrual symptoms than abstainers, but abstainers had more somatic symptoms than women who used alcohol occasionally. Menstrual symptoms were not associated with smoking. Instead, somatic symptoms were more common in women who smoked more than 10 cigarettes per day (compared to non-smokers and former smokers). Menstrual and somatic symptoms were both associated with the use of HT. Current HT users had more menstrual symptoms than those who had never used HT. Regarding somatic symptoms, these were more frequent among former and current HT users than women who had never used it. Moreover, when former and current users were compared to each other, former users had more somatic symptoms.

Menstrual symptoms were, before adjustments, associated with CVD and neurological, gastrointestinal, and dermatological diseases, and after adjusting for confounding factors, with CVD and gastrointestinal and dermatological disease. After including SRH into the analyses, menstrual symptoms were associated with CVD and gastrointestinal diseases. Associations between somatic symptoms and chronic diseases were not investigated.

Menstrual symptoms were not associated with cortisol variables. However, one association was found between somatic symptoms and cortisol variables: in the t-tests, women with a WHQ symptom domain score above the median (more symptoms) had lower 24-hour urinary cortisol excretion than women with a score below the median. The association was not, however, found in the Spearman's correlation coefficient analysis.

6 DISCUSSION

The present thesis had two main objectives: to validate the WHQ in a Finnish population and to better understand associations between climacteric-related symptoms and various factors that have been linked to them. The psychometric properties of the WHQ were evaluated by several statistical analyses. The WHQ proved to be a valid instrument for measuring climacteric-related symptoms in Finnish midlife women. The relationships between climacteric-related symptoms and aging were examined in cross-sectional and longitudinal analyses. In the cross-sectional study of midlife women, older women had more symptoms than younger women, while in the longitudinal study, VMS, sleep problems, and cognitive difficulties decreased after menopause over time. Higher education, employment and healthy lifestyles were associated with fewer symptoms. Climacteric-related symptoms were also linked to chronic somatic diseases. Most symptoms had several associations with chronic diseases. However, VMS and sleep problems were only associated with gastrointestinal diseases, and lower sexual functioning was only associated with diabetes. Moreover, most diseases appeared to be associated with experienced climacteric-related symptoms only with deteriorating SRH. As to associations between climacteric-related symptoms and cortisol metabolism, only a few weak associations were found.

6.1 Methodological considerations and study limitations

6.1.1 Participants

The studies' advantages and limitations are shown in Table 20. In studies investigating **Sample I**, consideration of the impact of the menopausal state would have been of interest. Although the questionnaire included a question "*Do you still have natural menstruations and if not, at what age did they end?*", the lack of FSH measurements and several sources for errors, such as previous hysterectomy without oophorectomy or the use of a hormonal spiral (intrauterine device [IUD]), oral contraceptives, or HT, which may cause either amenorrhea or lead to an extension of menstrual bleedings beyond menopause, meant that the menopausal state could not be reliably determined. However, as the sample was large and menopause usually occurs around the age of 51 (Kok et al., 2005; Pakarinen et al., 2010), the different age groups most likely represented the different menopausal states moderately well also, the two youngest groups consisted mainly of premenopausal women; the third group, 49–50 years, mainly of women in early perimenopause; the fourth, 51–52 years, of perimenopausal women currently reaching the menopause; and the oldest group, 53–54 years, of postmenopausal women. **Sample II** was too small to separately examine women in perimenopausal and postmenopausal states. If these two groups had been separated, the results could have been different. However, no statistical differences in cortisol variables or in the WHQ symptom domain means were found between perimenopausal and postmenopausal women. In **Sample III**, the aim was to study time-dependent changes in

climacteric-related symptoms in older age after menopause. Therefore, at least the perimenopausal state was required at the baseline.

6.1.2 Method of interview

For a large sample, such as **Sample I**, the postal questionnaire was the most practical way to collect the data. However, in lieu of a personal interview, the postal questionnaire probably resulted in a higher number of missing replies or limited information. Information concerning diseases was based on the women's self-reports, which may have resulted in both under- and over-reporting. It must be noted that only previously diagnosed and, consequently, probably treated diseases were considered in the analyses. Moreover, mental health problems often remain undiagnosed [16], which may have impacted the results, since only diagnosed mental health problems were considered in the adjustment. Some issues may be challenging to express verbally. Thus, the participants may have been more honest when interviewed anonymously using the postal survey. Supporting this point of view, at the 19-year follow-up in **Sample III**, the women interviewed using the postal questionnaire reported more symptoms than the women interviewed personally. On one hand, the women interviewed through the postal questionnaire were possibly more honest, especially as regards mood symptoms. On the other hand, some of the women may have been unable to attend the personal interview due to their symptomatology and, therefore, chose to be interviewed using the postal questionnaire.

In **Sample II** and at the baseline and at the 6-year follow-up in **Sample III**, the women filled in the questionnaires in the presence of a researcher, which led to a minuscule number of missing answers. Missing answers were also remarkably rare also at the 19-year follow-up as women with missing answers were re-contacted and asked to complete these items over the phone.

In **Sample III**, recalling the duration of climacteric symptoms (unspecified) during one's life span varied in the follow-up period. Although the majority of the women had experienced climacteric symptoms (unspecific), according to their reports at the baseline, at the 19-year follow-up, the percentage was much lower, and one-third of the women stated that they had never experienced climacteric symptoms (unspecified). This indicates that retrospective interviews concerning climacteric symptoms are not reliable. Moreover, the dampening of the participant's recollection of symptom duration may indicate that women are not permanently traumatized by the symptoms.

6.1.3 The WHQ

Although the WHQ was previously validated and widely used (Girod et al., 2004; Hunter, 2000), even in the Finnish studies (Hautamäki et al., 2014; Luoto et al., 2012; Mansikkamäki et al., 2015; Penttinen et al., 2011; Savolainen-Peltonen et al., 2014), the questionnaire had

Table 20. Advantages and limitations

Study I

Advantages:

- A high number of participants
- Use of exploratory factor analysis to investigate the factor structure

Limitations:

- The recruitment was prone to participation bias¹
 - The menopausal state could not be assessed
 - The use of a postal questionnaire: a probability for a higher number of missing replies
 - Symptoms were assessed only using the Women's Health Questionnaire (WHQ): no comparisons to other questionnaires were conducted
 - Lack of the follow-up: the test-retest reliability could not be examined
-

Study II

Advantages:

- A high number of participants
- A comparable response rate with previous studies
- The use of a validated instrument to assess climacteric-related symptoms
- The use of multivariable analyses, adjusting for several confounding factors to investigate independent associations between the symptoms and independent variables

Limitations:

- The recruitment was prone to participation bias¹
 - The use of a postal questionnaire: a risk for a higher number of missing replies
 - Cross-sectional study design: no possibility to define the direction of cause-effect relationships
 - The correlations between the symptom domains may have produced or reduced associations
 - A high number of comparisons: false-positive results were possible (Tukey's multiple comparison tests were performed)
-

Study III

Advantages:

- A high number of participants
- A comparable response rate with previous studies
- The use of a validated instrument to assess climacteric-related symptoms
- The use of multivariable analyses, adjusting for several confounding factors to investigate the independent associations between the symptoms and independent variables

Limitations:

- The recruitment was prone to participation bias¹
 - The use of a postal questionnaire: a probability for a higher number of missing replies
 - Information concerning diseases was based on the participants' self-reports
 - Cross-sectional study design: no possibility to define the direction of cause-effect relationships
 - The correlations between the symptom domains may have produced or reduced associations
 - A high number of comparisons: false-positive results were possible (Tukey's multiple comparison tests were performed)
-

Study IV

Advantages:

- A high number of participants
- A comparable response rate with previous studies
- The use of a validated instrument to assess climacteric-related symptoms
- The use of multivariable analyses, adjusting for several confounding factors to investigate the independent associations between the symptoms and independent variables

Limitations:

- The recruitment was prone to participation bias¹
 - The use of a postal questionnaire: a probability for a higher number of missing replies
 - Cross-sectional study design: no possibility to define the direction of cause-effect relationships
 - The correlations between the symptom domains may have produced or reduced associations
 - A high number of the comparisons: false-positive results were possible (Tukey's multiple comparison tests were performed)
-

Study V

Advantages:

- The use of a validated instrument to assess climacteric-related symptoms
- No missing answers in the WHQ
- Personal contact with the participants
- Cortisol levels were assessed from a high number of blood samples
- Wake-up times were based on the polysomnography recordings
- Day schedules and contents and study environment were precisely analogous for all participants
- The curves for 24-hour cortisol production, based on frequent measures with short intervals, were obtained

Limitations:

- A low number of participants
 - The recruitment was prone to participation bias²
 - The correlations between the symptom domains may have produced or reduced associations
 - Cortisol levels were only measured over one day
 - A high number of comparisons: false-positive results were possible
-

Study VI

Advantages:

- The long follow-up periods
- A high follow-up participation rate
- The use of a validated instrument to assess climacteric-related symptoms
- A low number of missing answers
- Personal contact with the participants

Limitations:

- A low number of participants
 - The recruitment was prone to participation bias²
 - Long time-intervals between the interviews: impossible to investigate the duration of symptoms
 - The correlations between the symptom domains may have produced or reduced associations
 - A high number of comparisons: false-positive results were possible (Tukey's multiple comparison tests were performed)
-

¹ The participants had possibly better psychological well-being than those who declined to participate; ² Because the participants were originally recruited to participate in a study that investigated sleep and cognition, these symptoms were possibly overrepresented. In addition, because the study required an own initiation to participate, participants also were presumably more interested on their health and well-being. Due to strict exclusion criteria the study population was highly selected.

not been validated in a Finnish population. Previous studies have provided varying results concerning the internal consistencies of the WHQ symptom domains (Benzineb et al., 2013; Borud et al., 2009; Dotlic et al., 2015; Girod et al., 2006; Wiklund et al., 1993; Wool et al., 2000). In **Study I**, on the binary scale, only two domains had Cronbach's α values, which could be classified as acceptable (a classification suggested by Nunnally is shown in Figure 2). On the 1–4 scale and on the revised WHQ, the internal consistencies were substantially higher. Moreover, compared to the binary scale, on the 1–4 scale and on the revised WHQ the sampling adequacy was also slightly superior and the factors in the EFA explained a larger proportion of the total variance. Furthermore, besides statistical aspects, the 1–4 scale offered more dynamics. A discrepancy between “yes, definitely” and “yes, sometimes” may be considered equal to the discrepancy between “yes, sometimes” and “no, not much.” Thus, by combining the answers “yes, definitely” and “yes, sometimes,” as done on the binary scale, the content is significantly reduced. Supporting the functionality of the symptom domains, the magnitudes of the WHQ symptom domain means were relatively comparable between the different study samples.

As the WHQ is a measure of QoL, correlations between the symptom domains and the question “*How satisfied are you with your current QoL?*” were investigated. All domains correlated with the question. The strongest correlations were found with mood symptoms. Thus, mood symptoms obviously deteriorate QoL more than other symptoms included in the WHQ. Additionally, women with mood symptoms may have a generally more negative view of life.

All WHQ symptom domains correlated with each other. However, the original symptom domains were somewhat distinguishable from the factors in the EFA, particularly on the revised WHQ. Although VMS in the WHQ comprise only two items, the internal consistency of the domain was rather good, especially in **Sample III**. The domain could benefit from additional items, but, besides hot flashes and night sweats, other VMS, such as general sweating or palpitations, would be quite unspecific. VMS typically co-occur with sleep problems (Polo-Kantola, 2011), which was also seen in the EFA as one of the factors was formed by VMS and sleep problems. However, from a clinical point of view, they are different symptoms. Thus, it is feasible to separate these two types of symptoms in clinical studies as well as in clinical practice. The internal consistency of the sleep problems domain was poor in **Samples I** and **III** but acceptable in **Sample II**. Besides a low number of items, another weakness is that the domain includes an item that is not directly related to sleep problems. In line with findings of previous studies (Borud et al., 2009; Girod et al., 2006; Wiklund et al., 1993; Wool et al., 2000), this item, “*I am restless and can't keep still,*” had the highest factor loadings on the factor of anxiety/depressed mood. On the revised WHQ, the item is omitted (Girod et al., 2004, 2006). The sleep problems domain would probably benefit from replacing the item with an item targeting restless sleep. Furthermore, the item “*I feel more tired than usual*” from the domain of somatic symptoms could be regarded as a sleep problem. However, the item had the highest factor loadings on the factor that included mainly somatic symptoms.

Items of the depressive symptoms and anxiety/fears domains formed the first factor in the EFA on both scales on the original version of the WHQ, as well as on the revised version, which is consistent with the findings from previous studies (Borud et al., 2009; Girod et al., 2006; Greene, 1976; Wool et al., 2000). Moreover, the internal consistency for the anxiety/depressed mood domain on the revised WHQ was considerably higher than for the two original separate domains. Thus, the findings supported combining the domains of depressive symptoms and anxiety/fears as done on the revised version. A separate factor was formed by the items of the domains of depressive symptoms and attractiveness, which in the revised version are regrouped into the domain of well-being. Yet, the internal consistency of the well-being domain was questionable (Nunnally, 1978). Although the expression “butterflies in my stomach” also exist in Finnish, the “*I get palpitations or a sensation of ‘butterflies’ in my stomach or chest*” item could be understood as a somatic symptom. This probably explains why, in addition to the factor that includes items from its original domain (anxiety/fears), the item was also found in the factor that included somatic symptoms.

In all study samples, the internal consistency of the cognitive difficulties domain was barely acceptable; on the binary scale (**Sample I**), it was even lower. On the 1–4 scale, the items “*I have difficulty concentrating*” and “*My memory is poor*” were found in the same factors. However, the factors were contaminated by other items. The third item of the cognitive difficulties domain, “*I am more clumsy than usual,*” was only found in the same factor with other cognitive difficulties in the EFA of the revised WHQ. However, the Finnish translation of the item (“*Olen kömpelömpi kuin yleensä*”) is understood as a physical rather than a cognitive problem. Indeed, on the 1–4 scale in the original WHQ, the item had the highest factor loading on the factor, which included several items from the domain of somatic symptoms. The cognitive difficulties domain could be improved by adding an item that would assess the ability to learn new things.

Although the internal consistency of the sexual functioning domain was rather poor, its items emerged as an independent factor that included all three original items. However, on the binary scale, the factor also included an item “*I need to pass urine/water more frequently than usual.*” This finding is probably explained by vaginal atrophy, which is linked to both more frequent urination and to decreased sexual functioning (Goldstein et al., 2013). On the 1–4 scale, the item did not load on any of the factors, and on the revised version, the item is omitted (Girod et al., 2004, 2006). As the domain of sexual functioning includes only sexually active women, the domain may underestimate the dissatisfaction and distress caused by vaginal dryness. The domain does not consider the fact that women may involuntarily become sexually inactive because of these symptoms. Moreover, women who have lost interest in sexual activity may still be satisfied with their sexual relationships, which may weaken the internal consistency of the domain.

In **Sample I**, the internal consistency of the menstrual symptoms domain was poor (Nunnally, 1978). However, in **Sample II**, which included only 16 menstruating women, the internal

consistency was comparable to the internal consistency of other domains. In the EFA, the items of the menstrual symptoms domain were found in the factor, which included several items from the domain of somatic symptoms. Three menstrual symptoms items, “*My breasts feel tender or uncomfortable,*” “*I have abdominal cramps or discomfort,*” and “*My stomach feels bloated,*” do not relate directly to the menstrual cycle, and may even occur in women who are not menstruating at all. Items in the menstrual symptoms domain could thus be moved to the somatic symptoms domain. Or, to assess as a separate domain, a clarification should be added as done on the revised WHQ, in which women are instructed to answer whether they experienced these symptoms during their last menstrual period (Girod et al., 2004). Because the somatic symptoms domain includes various totally different symptoms, some of the items may cancel each other’s effect. However, the internal consistency of the domain was at least near to acceptable in every sample. The domain probably identifies individuals with a general tendency to experience physical symptoms quite well.

Although it would be tempting to complete some of the domains with additional items, it is certainly beneficial to include as few items as possible to obtain high response rates and a low number of missing answers. Furthermore, the psychometric properties of the revised version of the WHQ were just as good or even better than those of the original WHQ. Thus, the findings of the present thesis endorse the use of the revised WHQ. Bearing in mind that the WHQ is a measure of overall QoL, if the interest is on a certain symptom group, such as sleep problems, cognitive difficulties, mood symptoms, or sexual functioning, the use of specific instruments should be considered.

6.1.4 Cortisol measurements

The day-to-day variations in cortisol production and responses are vast and linked to various factors, including sleep-wake rhythm (Adam and Kumari, 2009; Vargas and Lopez-Duran, 2014), eating (Adam and Kumari, 2009), and other possible stressors (Adam and Kumari, 2009). Therefore, in **Study V**, the day structure and the study environment were precisely analogous for all participants, and blood collection was not initiated before the women were familiar with the laboratory environment. Moreover, a two-hour time interval between the insertion of the blood sampling cannula and the start of the sampling diminished the possible stress induced by the placement of the cannula. Regardless, the laboratory environment was undoubtedly stressful; thus, the cortisol levels were certainly not comparable to those experienced at home. To minimize the disturbance associated with blood collection, repeated blood samples were drawn using an intravenous stationary cannula. However, instead of investigating cortisol levels at each collecting time point, the aim of the study was to investigate differences in the cortisol variables according to the climacteric-related symptoms experienced and to demonstrate the profile of cortisol production over 24 hours. As day-to-day variations in cortisol secretion are substantial, the study would have benefited from including cortisol measures over several days. However, due to the blood loss caused by gathering blood samples every 20 minutes, it would not have been ethically acceptable to

continue collecting blood for more than one day. Blood samples were the only suitable method to assess 24-hour cortisol profiles and to collect the morning samples from those who woke up spontaneously (i.e., the nearest samples to awakening). Furthermore, without the PSG recordings, the assessment of actual wake-up times would not have been possible. The wake-up times were essential for the calculation of the CAR and cortisol slope.

6.1.5 Statistical analyses

In **Study I**, EFA instead of confirmatory factor analysis was chosen as it allowed for examining the limitations of the factor structure. EFA was also used by the developers of the original WHQ and the revised WHQ (Girod et al., 2006; Hunter, 2000). As the KMO values were high for all versions of the questionnaire, indicating substantial common variance among groups of variables, the data were suitable for EFA. In **Studies II–IV**, all investigated variables were included in the multivariable analyses. Thus, although it was not possible to define the direction of the cause-effect relationships, the results represented independent associations between the symptoms and the variables. In **Study V**, the low number of participants did not allow for any adjustments. For the same reason, in **Study VI**, the number of confounding factors was limited (age, baseline BMI, baseline employment, and the use of HT).

6.2 Climacteric-related symptoms and associated factors

Because of the broad topic, which is concerned with the associations between climacteric-related symptoms and age, socioeconomic and lifestyle factors, and the use of HT, the discussion is mainly restricted to studies that have used the WHQ. An additional motivation was to exclude the effects of diverse methods of symptom assessment as sources of discrepancies between the results of previous studies. All previous studies included some additional variables that were not considered in the present thesis. Moreover, multivariable models included different combinations of the variables (Amore et al., 2004; Dotlic et al., 2018; Ferrand et al., 2013) or variables were only included in univariable analyses (Kanadys et al., 2016). Thus, the results are not fully comparable. In addition, in some studies, the description of the statistical methods was unclear, or the results were not systematically shown for all WHQ symptom domains or for all independent variables (Jarecka and Bielawska-Batorowicz, 2017; Kanadys et al., 2016; Slaven and Lee, 1998; Zolnierczuk-Kieliszek et al., 2011, 2014). No previous studies investigating associations between climacteric-related symptoms measured by the WHQ and chronic somatic diseases or cortisol secretion were found.

6.2.1 Vasomotor symptoms

As the average age for menopause is 51 years (Kok et al., 2005; Pakarinen et al., 2010), the finding that women older than 50 years had more VMS than younger women (**Study II**) was

in line with the general assumption that VMS become more common during perimenopause (Berecki-Gisolf et al., 2009; Blümel et al., 2000; Dennerstein et al., 2007; Gold et al., 2004). As expected, based on the findings of previous studies (Avis et al., 2015; Col et al., 2009; Freeman et al., 2011, 2014; Genazzani et al., 2002b; Smith et al., 2016; Tepper et al., 2016), in the longitudinal study (**Study VI**), the decrease in VMS was more remarkable from the baseline to the 6-year follow-up than from the 6-year follow-up to the 19-year follow-up. VMS were uncommon at the 19-year follow-up, but not totally absent. Besides being related to the climacteric, in older women, VMS, especially sweating, may be related to other factors, such as obesity (Whiteman et al., 2003b) or chronic diseases, such as diabetes (Herber-Gast et al., 2013; Mold, 2004), obstructive sleep apnea (Arnardottir et al., 2013), or gastroesophageal reflux (Viera et al., 2003).

In line with most studies using the WHQ (Amore et al., 2004; Ferrand et al., 2013; Genazzani et al., 2002b; Kanadys et al., 2016; Zolnierczuk-Kieliszek et al., 2014), lower educational level was associated with more frequent VMS (**Study II**). Educated women may have been more committed to a healthy lifestyle, thereby reducing their symptoms (Hunter and Chilcot, 2013; Li et al., 2003; Moilanen et al., 2010). Moreover, Zolnierczuk-Kieliszek et al. (2014) found that agricultural workers and other manual workers had more VMS than women who performed intellectual work (Zolnierczuk-Kieliszek et al., 2014). Thus, another explanation could be that sweating or hot flashes were initiated by more physical work in lower educated women.

VMS were also more frequent in women with a higher BMI (**Study II**). However, the difference was small and found only when comparing women with a BMI of 25–30 kg/m² to women with a BMI under 25 kg/m². In the previous study, which found an association between VMS and the BMI, the BMI classification corresponded to the present thesis (Daley et al., 2007), whereas in the other study, which did not find an association, the BMI was a continuous variable (Dotlic et al., 2018).

Women who used alcohol on a weekly basis had more VMS than abstainers and women who used alcohol occasionally (**Study II**). No other associations were found between VMS and alcohol consumption. Only a few women consumed alcohol daily, which probably explained the neutral findings concerning daily consumption. Although Dotlic et al. (2018) found that alcohol consumption might even have beneficial effects on VMS, in the present thesis, no beneficial effects were found. However, occasional use was not harmful either. Alcohol consumption habits differ between cultures, which possibly explains the incoherent findings between studies. As tobacco deteriorates ovaries (Hoyer, 2005; Kapoor and Jones, 2005) and reduces estrogen levels (Kapoor and Jones, 2005), the finding of more frequent VMS in daily smokers was expected (**Study II**).

Former HT users had more VMS than nonusers and current users (**Study II**). In the three oldest age groups, one-third to one-half of the women used HT, whereas nonusers belonged

mainly to the two youngest age groups. Thus, most nonusers were obviously still asymptomatic. As VMS did not differ between nonusers and current users, HT was undoubtedly an effective treatment against VMS. Moreover, the finding of former HT users having more VMS indicated that, in some women, VMS persisted after the cessation of the treatment.

Of the investigated diseases, VMS were only associated with gastrointestinal diseases (**Study III**). This association might be related to night sweats caused by inflammatory bowel diseases (Singh et al., 2011) or gastroesophageal reflux (Viera et al., 2003), or it may reflect poor diet control in celiac women (Santonicola et al., 2011). Based on the previous literature, associations between VMS and chronic somatic diseases are sporadic. Thus, as diseases were included as wide disease groups, the lack of associations was not surprising. VMS are linked to an increased risk of CVD (Andrikoula et al., 2009; Gast et al., 2008; Herber-Gast et al., 2015; Tuomikoski et al., 2011), but hot flashes and night sweats may have different associations with risk factors (Hitchcock et al., 2012). This might partly explain the neutral findings in the present thesis since the VMS domain does not allow for investigating these symptoms separately (Girod et al., 2004). Another explanation was certainly the rather young age of the participants, as the occurrence of CVD, which have been connected to VMS (Andrikoula et al., 2009; Gast et al., 2008; Herber-Gast et al., 2015; Tuomikoski et al., 2011), is low before menopause (Barton, 2013; Murphy, 2011).

6.2.2 Sleep problems

Sleep problems are known to increase during the climacteric (Blümel et al., 2012; Kravitz et al., 2003; Polo-Kantola, 2011). In studies using the WHQ, older women had more sleep problems (Amore et al., 2004; Dotlic et al., 2018; Zolnierczuk-Kieliszek et al., 2014). Thus, in **Study II**, it would have been expected that women in the two or three oldest age groups would have more symptoms than women in the younger age groups. However, sleep problems only differed between women aged 41–42 years and women aged 49–50 years, in which the older women had more sleep problems. Using the Basic Nordic Sleep Questionnaire, a previous study evaluated sleep problems in more detail with the same study population as in **Sample I** of the present thesis (Vaari et al., 2008). Indeed, no differences were found between different age groups for problems falling asleep or the frequency of nocturnal awakenings. The only differences were in morning tiredness and snoring; morning tiredness was more frequent in the youngest age group, while snoring was more frequent in the older age groups (Vaari et al., 2008). In the longitudinal study, the decrease in sleep problems during the 19-year follow-up period was quite minor (**Study VI**). Thus, taken together, several other factors can presumably explain the experience of sleep problems, besides climacteric hormonal changes.

Women with a high educational level had fewer sleep problems than women with low or intermediate educational levels (**Study II**). However, no differences emerged between low

and intermediate educational levels. As the previous studies using the WHQ have offered conflicting findings on associations between sleep problems and educational levels (Amore et al., 2004; Dotlic et al., 2018; Ferrand et al., 2013; Genazzani et al., 2002b; Kanadys et al., 2016; Slaven and Lee, 1998; Zolnierczuk-Kieliszek et al., 2011, 2014), the discrepancy cannot be dependent on differing methods of symptom assessment. Instead, cultural factors and differences in school systems as well as in the classification of educational levels may play a major role.

In line with the previous studies using the WHQ (Daley et al., 2007; Dotlic et al., 2018), the present thesis failed to find associations between sleep problems and the BMI (**Study II**). A higher BMI increases the risk of nocturnal breathing disorders (Arnardottir et al., 2013) and, therefore, could be associated with more frequent sleep problems (Blümel et al., 2012; Kapsimalis and Kryger, 2002; Plotkin, 2010). However, typical sleep problems in relation to nocturnal breathing disorders are tiredness (Kapsimalis and Kryger, 2002), daytime sleepiness (Blümel et al., 2012; Kapsimalis and Kryger, 2002), and decreased sleep quality (Provini et al., 2010), symptoms that are not included in the sleep problems domain of the WHQ (Girod et al., 2004; Hunter, 2000).

Regarding alcohol consumption, the only difference was found between occasional and weekly consumption; weekly consumption was associated with more frequent sleep problems (**Study II**). Since Dotlic et al. (2018) classified the consumption of alcohol as yes/no, the results cannot be compared (Dotlic et al., 2018). The finding of the present thesis argues that alcohol should not be used as a sleep aid. However, occasional use does not seem to be disadvantageous either. Smoking was associated with more frequent sleep problems (**Study II**), but the association was dose-dependent. Women who smoked fewer than 10 cigarettes per day did not differ from non-smokers. This may explain why Dotlic et al. (2018) did not find any associations, as in their study smoking was also classified as simply yes/no.

Like VMS, sleep problems were also more frequent among former HT users than among nonusers or current users (**Study II**). However, current HT users had more sleep problems than nonusers. Even though, placebo-controlled studies have found that HT is an effective treatment for sleep problems as measured by the WHQ (Gambacciani et al., 2003; Nielsen et al., 2006; Polisseni et al., 2013; Savolainen-Peltonen et al., 2014; Strickler et al., 2000; Veerus et al., 2012; Welton et al., 2008; Wiklund et al., 1993). The finding of the present thesis endorses the assumption that sleep problems experienced by climacteric women are multifactorial, rather than solely dependent on hormonal alterations.

Before adjusting for confounding factors, several associations were found between sleep problems and chronic diseases. However, although chronic diseases are commonly linked to sleep problems (Ali et al., 2013; Anderson, 2011; Artherholt and Fann, 2012; Blümel et al., 2012; Bruyneel, 2015; del Ghianda et al., 2014; Fritschi et al., 2012; Hayley et al., 2015; Matthews et al., 2013; Plotkin, 2010), in the present thesis, after adjusting for confounding

factors, sleep problems were only associated with gastrointestinal diseases (**Study III**). Thus, some of the confounding factors certainly mediate associations between sleep problems and chronic diseases. Another explanation for the lack of associations is certainly the content of the sleep problems domain, since symptoms such as tiredness, poor sleep quality, or night-time restlessness are not included (Girod et al., 2004; Hunter, 2000).

6.2.3 Mood symptoms

Although several studies have found that depressive symptoms increase during the menopausal transition (Bromberger et al., 2010; Bromberger and Kravitz, 2011; Campbell et al., 2017; Cohen et al., 2006; Freeman et al., 2004; Llana et al., 2012; Maartens et al., 2002; Woods et al., 2008), in the present thesis, as in other studies using the WHQ (Amore et al., 2004; Dotlic et al., 2018; Genazzani et al., 2002b; Zolnierczuk-Kieliszek et al., 2014), depressive symptoms were not associated with age (**Study II**). No changes were found during the 19-year follow-up period either (**Study VI**). Thus, incoherent outcomes between studies using the WHQ and studies using other questionnaires are probably a consequence of different methods of symptom assessment.

Although previous Nordic studies have not found associations between mood symptoms and educational level (Li et al., 2005; Moilanen et al., 2010), in the present thesis, depressive symptoms and anxiety/fears were both more frequent among lower educated women (**Study II**). This finding is in line with the findings of most studies that have used the WHQ (Amore et al., 2004; Ferrand et al., 2013; Kanadys et al., 2016; Zolnierczuk-Kieliszek et al., 2011, 2014). Thus, again, as outcomes differ between studies using the WHQ and studies using other questionnaires, the method of symptom assessment appears to play an even more important role than cultural factors. As to the association between mood symptoms and employment, previous studies that have used the WHQ yielded incoherent findings (Amore et al., 2004; Dotlic et al., 2018; Ferrand et al., 2013; Slaven and Lee, 1998; Zolnierczuk-Kieliszek et al., 2014). Yet, the finding of the protective effect of employment was anticipated (**Study II**) (Li et al., 2005; Maartens et al., 2002; Williams et al., 2009). Retired women were most likely on disability pensions, since in Finland, the average age for the old age pension for women is 63.9 years (Finnish Centre for Pensions, 19.4.2018), and the highest age of the women in **Study II** was 54 years. Furthermore, the main reasons for disability pension are major depression, other mental health problems, and musculoskeletal disorders (The Finnish Pension Alliance TELA 4.12.2012), which explains more frequent mood symptoms in the retired women compared to the employed women. Still, depressive symptoms did not differ between retired and unemployed women. Thus, unemployment potentially has a detrimental impact on mental wellbeing.

Although other studies (Bromberger et al., 2010; Moilanen et al., 2010; Williams et al., 2009), including the previous Finnish study (Moilanen et al., 2010), have suggested that a high BMI increases the risk of depressive symptoms, previous studies that have used the WHQ failed to

find any associations between mood symptoms and the BMI (Daley et al., 2007; Dotlic et al., 2018). Despite the use of the same questionnaire, in the present thesis, depressive symptoms were more frequent among women with a BMI over 30 kg/m² (**Study II**). The biological pathways between obesity and depressive symptoms are probably independent from cultural factors (Luppino et al., 2010). Instead, psychological pathways might be culture-related (Luppino et al., 2010). In general, thinness is a beauty ideal in Europe. Thus, the difference between the European studies using the WHQ might indicate that Finnish women are more susceptible to feelings of body dissatisfaction or low self-esteem, which increase the risk of depressive symptoms (Luppino et al., 2010).

Previous studies investigating climacteric women have mainly failed to find associations between mood symptoms and alcohol consumption (Herber-Gast et al., 2013; Hickey et al., 2016; Li et al., 2005; Moilanen et al., 2010). In the present thesis (**Study II**), as in the previous study using the WHQ (Dotlic et al., 2018), more frequent mood symptoms were associated with abstinence from alcohol rather than alcohol use. This might be related to the reasons behind their abstinence, since women with major depression, generalized anxiety, or a history of alcohol abuse are less likely to use alcohol (Colenda et al., 2010).

Smokers often list alleviating depressive feelings and anxiety, stabilizing one's mood, and relieving stress as reasons to smoke (Taylor et al., 2014). Then again, it has also been hypothesized that poor mental health and smoking might have common causes and that smoking might cause or aggravate mental health problems (Taylor et al., 2014). Thus, the finding of more frequent mood symptoms among smokers was reasonable (**Study II**). However, Dotlic et al. (2018) did not find associations.

As to the use of HT, only two of the previous placebo-controlled studies that used the WHQ found that HT could alleviate mood symptoms (Gambacciani et al., 2003; Genazzani et al., 2002b). Furthermore, in the present thesis, current HT users had more mood symptoms than nonusers (**Study II**). Therefore, HT cannot be considered a drug of choice to treat depressive or anxiety symptoms in midlife women.

As expected based on the previous literature (Crofford, 2015; Finkelstein et al., 2010; Sakakibara et al., 2013; Sobel and Markov, 2005), several chronic diseases were associated with mood symptoms. However, after including SRH in the analyses, only one association was found: women with gastrointestinal diseases had more anxiety/fears. Thus, diseases that do not impair SRH apparently do not contribute to mood symptoms either. As to the association between anxiety/fears and gastrointestinal diseases, the association might be related to the co-occurrence of anxiety and irritable bowel syndrome (Mulak et al., 2014), as irritable bowel syndrome has no detrimental effects on overall health.

6.2.4 Cognitive difficulties

Although most of the studies using the WHQ did not find associations between cognitive difficulties and age (Amore et al., 2004; Dotlic et al., 2018; Genazzani et al., 2002b), in the cross-sectional study (**Study II**), cognitive difficulties were more frequent in older age groups (**Study II**), and in the longitudinal study, cognitive difficulties decreased during the 19-year follow-up period (**Study VI**). The findings support the assumption that the climacteric is accompanied by cognitive difficulties (Amore et al., 2007; Drogos et al., 2013; Gold et al., 2000; Maki et al., 2008; Mitchell and Woods, 2011; Polo-Kantola et al., 1997; Portin et al., 1999). However, given that three (4.6%) women were excluded from the 19-year follow-up because of severe dementia, the decrease instead of an increase could also be related to an increased risk of developing dementia among women with cognitive difficulties at the baseline (Amariglio et al., 2012; Deary et al., 2009). Moreover, underestimation of symptoms at the 19-year follow-up must be considered as older women may be habituated to their cognitive difficulties.

Although cognitive difficulties were not associated with educational level (**Study II**), an association was found between cognitive difficulties and employment; unemployed and retired women had more cognitive difficulties than employed women (**Study II**). As most previous studies investigating associations between cognitive difficulties and employment, as measured by the WHQ, failed to find an association (Amore et al., 2004; Dotlic et al., 2018; Ferrand et al., 2013; Slaven and Lee, 1998), the association was certainly dependent on cultural factors or on the differences in the concepts of “employed” and “unemployed.”

In opposition to the neutral findings of Dotlic et al. (2018), in the present thesis, cognitive difficulties were more frequent among both abstainers and women who used alcohol weekly than among women who used alcohol occasionally (**Study II**). The incoherent findings may be due to different classifications, as neither the amounts nor the frequency were specified by Dotlic et al. The findings of the present thesis support the understanding that alcohol’s effects on the brain are dose-dependent (Ilomäki et al., 2015; Mukherjee, 2013).

Smoking may have detrimental effects on cognitive functioning (Pines, 2011). In the present thesis, smokers had more cognitive difficulties than non-smokers, but only if they smoked more than 10 cigarettes per day (**Study II**). The neutral association between cognitive difficulties and smoking fewer than 10 cigarettes per day may be related to the age of the participants. As the highest age of the women was 54 years, the effects of light smoking may not yet have been apparent. The dose-dependence might explain why Dotlic et al. (2018) did not find associations between smoking and cognitive difficulties.

In most previous placebo-controlled studies using the WHQ, HT has not been shown to have beneficial effects on cognitive functioning (Gambacciani et al., 2003; Polisseni et al., 2013; Strickler et al., 2000; Veerus et al., 2012; Welton et al., 2008; Wiklund et al., 1993). In the

present thesis, current and former users had more cognitive difficulties than nonusers (**Study II**). Although HT could alleviate cognitive difficulties indirectly by reducing VMS (Bachmann, 2005; Williams and Cho, 2017) and sleep problems (Bachmann, 2005; Polo-Kantola, 2011; Williams and Cho, 2017), and thereby daytime tiredness, studies using the WHQ do not support the use of HT as a treatment for cognitive difficulties.

All diseases that were associated with cognitive difficulties were also associated with depressive symptoms or anxiety/fears (**Study III**). Thus, as cognitive functioning may be compromised by mood symptoms (Greendale et al., 2011), at least some of the associations found between cognitive difficulties and chronic somatic diseases were possibly mediated by depressive or anxiety symptoms. Surprisingly, diabetes (Dash, 2013) and neurological diseases (Peter-Derex et al., 2015; Videnovic and Golombek, 2013; Wang et al., 2014), which might have direct negative effects on cognitive functioning, were not associated with cognitive difficulties. In diabetes, cognitive difficulties are mainly connected to advanced disease (Dash, 2013), and in neurological diseases to diseases characterized by late disease onset (Peter-Derex et al., 2015; Videnovic and Golombek, 2013). Thus, in the present thesis, the women were perhaps too young to have developed cognitive difficulties related to these diseases (**Study III**).

6.2.5 Sexual functioning

The findings of the present thesis (**Study II**) together with the findings of the previous studies that have used the WHQ, give reason to suggest that sexual functioning is dependent on the menopausal state. Besides the decrease in sexual functioning seen at 49–50 years of age, as measured by the WHQ, one-third of the women replied to the additional item that the quality of their sexual life was worse than before the climacteric. However, the majority had not experienced negative changes. In the follow-up study of the present thesis, most women discontinued sexual activity (**Study VI**). While three-quarters of the women were sexually active at the baseline, only one-third were sexually active at the 19-year follow-up. A similar decrease has been found in previous studies (Avis et al., 2009a; Lee et al., 2016; Lonnèe-Hoffmann et al., 2014). The decrease may be linked to several factors, such as widowhood, distress related to vaginal dryness, partner's age-related sexual dysfunctions (Araujo et al., 2004; Lee et al., 2016), or a loss of interest in sexual activity due to habituation or routines related to a long shared history with a partner (Klusmann, 2002). The decrease in sexual activity certainly explained why sexual functioning remained unchanged during the follow-up period (**Study VI**), as the items were answered only by sexually active women. In addition, compared to women in two other study samples (**Samples I and II**), among the women in **Sample III**, sexual functioning appeared to be lower already at the baseline (Figure 4, visual comparison only, no statistical comparisons performed).

Lower sexual functioning among retired women (**Study II**) may be based on the same factors as the connection between retirement and mood symptoms described above. Sexual

functioning was the only domain in which marital status had importance. In line with the findings of Genazzani et al. (2002a), married/cohabiting women had poorer sexual functioning than divorced or widowed women (**Study II**). Supporting that finding, a previous study found that sexual functioning in midlife women was impaired by living with a sexual partner and by relationship of 20 years or more (Valadares et al., 2008). Thus, a change of a partner may also have a favorable impact on sexual functioning (Avis et al., 2009a; Dennerstein and Lehert, 2004). Among married/cohabiting women, decreased sexual functioning might be related to diverse relationship factors or to habituation and routines (Klusmann, 2002).

Although Dotlic et al. (2018) did not find associations between sexual functioning and alcohol consumption or smoking, in the present thesis lower sexual functioning was associated with alcohol abstinence and smoking. As the association between sexual functioning and alcohol consumption was found only when abstainers were compared to women who used alcohol occasionally, and the association between sexual functioning and smoking was only linked to smoking more than 10 cigarettes per day, the explanation for the different findings between the two studies was likely, as with other symptom domains, the diverse categorization of alcohol consumption and smoking. As low estrogen levels are linked to impaired sexual functioning (Dennerstein et al., 2002), the association between lower sexual functioning and smoking might be related to tobacco's harmful effects on the ovaries and estrogen metabolism (Hoyer, 2005; Kapoor and Jones, 2005; Plante et al., 2010; Whiteman et al., 2003a). However, smoking also has negative effects on the genital blood flow (Battaglia et al., 2011). Given that the difference was found even between non-smokers and former smokers, unlike in other symptom domains, the effects on the genital blood flow may be irreversible.

Sexual functioning did not differ between current HT users and nonusers (**Study II**). As previous placebo-controlled studies have rather unanimously shown that HT has beneficial effects on sexual functioning (Gambacciani et al., 2003; Nielsen et al., 2006; Polisseni et al., 2013; Veerus et al., 2012; Welton et al., 2008; Wiklund et al., 1993), the lack of difference was likely related to the young age of the nonusers. In the longitudinal study, the use of local HT increased during the follow-up period (**Study VI**). At the 19-year follow-up, local HT was used by almost one-third of the women, whereas at the baseline, only one woman used it. Yet, the adjustment for the use of local HT did not alter the results. Thus, factors other than vaginal dryness or atrophy can probably explain dissatisfaction and a lack of interest in sexual activity.

Of the chronic diseases, sexual functioning was only associated with diabetes. As diabetes was not associated with other symptoms, and the highest age of the women in **Study III** was 54 years old, diabetic complications were possibly rare. Thus, the finding might support the postulation that diabetes compromises sexual functioning regardless of the disease duration or complications (Cortelazzi et al., 2013; Enzlin et al., 2002). However, the association disappeared when SRH was included in the analysis.

6.2.6 Menstrual and somatic symptoms

As menstrual bleeding ceases as a consequence of menopause, the finding that menstrual symptoms were more frequent among younger women was anticipated (**Study II**). Genazzani et al. (2002a) also found that younger women had more menstrual symptoms, even though all the women in their study were postmenopausal. Moreover, Dotlic et al. (2018) failed to find any associations between menstrual symptoms and age or with the menopausal state. Thus, it is warranted to add a clarification that items in the menstrual symptoms domain concern symptoms experienced during menstrual periods as done in the revised WHQ. Somatic symptoms were more frequent in older women but only when comparing women aged 49–50 years to women aged 41–42 years (**Study II**). This might indicate that somatic symptoms included in the WHQ are indeed more frequent during perimenopause but not thereafter. In the follow-up study, somatic symptoms remained unchanged (**Study VI**). Neutral findings may have been related to the broad content of the somatic symptoms domain.

The finding of more frequent somatic symptoms in women with a lower educational level (**Study II**) was consistent with the findings of several previous studies that used the WHQ (Amore et al., 2004; Ferrand et al., 2013; Genazzani et al., 2002b; Kanadys et al., 2016; Zolnierczuk-Kieliszek et al., 2011, 2014). Given that Zolnierczuk-Kieliszek et al. (2012) found that agricultural workers had more somatic symptoms than women who performed intellectual work, the association might be related to different types of work. Moreover, like all other symptoms, somatic symptoms were also associated with employment. As mentioned above, all of the women in **Study II** were under the average age for the old age pension (Finnish Centre for Pensions, 19.4.2018). Thus, more frequent symptoms among retired women were certainly related to their reasons for early retirement.

Menstrual symptoms were not associated with the BMI or smoking, but women who consumed alcohol weekly had more menstrual symptoms than abstainers. Excessive alcohol consumption has been linked to menstrual disorders (Portoletto et al., 2017; Sarkola, 2001), but the typical disorders are anovulation and amenorrhea (Portoletto et al., 2017; Sarkola, 2001). Thus, as excessive alcohol consumption may induce various abdominal symptoms (Bode and Bode, 1997), the association between alcohol consumption and menstrual symptoms was probably produced by items that were not directly related to menstruation. Somatic symptoms were associated with all investigated lifestyle factors. A high BMI and smoking more than 10 cigarettes per day were harmful, whereas occasional alcohol consumption was beneficial. As to previous studies that used the WHQ, Dotlic et al. (2018) found no associations between somatic symptoms and the socioeconomic factors that were included in the present thesis. Instead, Daley et al. (2007) found that women with a higher BMI had more somatic symptoms, which is in line with the findings of the present thesis. The different results between the studies that have used the WHQ are probably due to the broad content of the somatic symptoms domain and the diverse methods used for the assessment of lifestyle factors.

According to previous studies, menstrual symptoms measured by the WHQ may present as side effects of HT use (Nielsen et al., 2006; Strickler et al., 2000). Regarding somatic symptoms, two previous studies that used the WHQ found that HT had beneficial effects on symptoms (Gambacciani et al., 2003; Wiklund et al., 1993), while most studies found no effects (Nielsen et al., 2006; Savolainen-Peltonen et al., 2014; Strickler et al., 2000; Veerus et al., 2012; Welton et al., 2008). It must be noted that some of the somatic symptoms, such as headaches or nausea, might also be a consequence of HT use (Barnabei et al., 2002; Jalava-Broman et al., 2011). In the present thesis, current HT users had more menstrual and somatic symptoms than nonusers (**Study II**).

The association between more frequent menstrual symptoms and CVD (**Study III**) was possibly related to the use of anticoagulants or menorrhagia caused by irregular menstrual cycles connected to CVD (de Kleijn et al., 1999). As the menstrual symptoms domain includes items concerning abdominal cramps, discomfort, and bloating—symptoms that are likely to be caused by gastrointestinal diseases—the association with gastrointestinal diseases was expected. The associations between menstrual symptoms and CVD and gastrointestinal diseases were two of the few associations that were found even after including SRH in the analyses, meaning that the associations were probably not dependent on the severity of the diseases.

6.3 Climacteric-related symptoms and cortisol metabolism

Only a few associations were found between climacteric-related symptoms and cortisol variables (**Study V**). Although previous studies have failed to find associations between subjective VMS and the CAR, in the present thesis, more frequent VMS were associated with a higher CAR. The CAR was calculated using the highest value within one hour after waking, whereas Gerber et al. (2017) and Reed et al. (2016) measured cortisol levels for the CAR from salivary samples that were collected at awakening and 30 minutes later (Gerber et al., 2017; Reed et al., 2016). Rubin et al. (2014) collected samples at awakening and every 15 minutes thereafter. Although they did not find associations between subjective VMS and the CAR, the CAR was higher among women with objective VMS (Rubin et al., 2014). Thus, different methods for calculating the CAR might at least partially explain the different results. Moreover, in the present thesis, the timing of the morning baseline samples was based on the PSG recordings, while in other studies the awakening times were subjective and the samples were collected by the participants (Gerber et al., 2017; Reed et al., 2016; Rubin et al., 2014). As increases in the CAR have been observed in relation to elevated burden, such as chronic stress, worrying, or work overload (Fries et al., 2009), the association between more frequent VMS and a higher CAR was rational. However, it must be noted that the association was rather weak.

More frequent VMS were associated with lower 24-hour urinary cortisol excretion (**Study V**). Thus far, the association between VMS and 24-hour urinary cortisol excretion has been

only examined in one study with contrasting results (Cagnacci et al., 2011). However, the result of the present thesis gets support from the SMWHS, in which hot flashes were associated with lower cortisol levels in overnight urine samples (Woods et al., 2009). Incoherent findings between studies may be related to the fact that chronic stress may result in an increase as well as a decrease of cortisol secretion (Hannibal and Bishop, 2014; Miller et al., 2007). Moreover, as nighttime cortisol levels are difficult to investigate, the knowledge on nighttime cortisol secretion is limited.

Various distinct sleep problems have been linked to cortisol levels in previous studies (Backhaus et al., 2004; Vargas and Lopez-Duran, 2014; Woods et al., 2006; Woods and Mitchell, 2010). Yet, in line with the findings of the present thesis (**Study V**), neutral outcomes have been reported when sleep problems were assessed as a domain of several symptoms (Hartaigh et al., 2012; Vargas and Lopez-Duran, 2014; Woods et al., 2006). The present thesis endorses neutral findings reported by previous studies on associations between climacteric mood symptoms and cortisol secretion (Gerber et al., 2017; Vedhara et al., 2003; Woods et al., 2006, 2008). It must be noted that in **Study V**, a floor-effect was possible since the scores in mood symptoms were low. As to cognitive functioning, in line with neutral findings of the SMWHS, no associations were found between cognitive difficulties and cortisol secretion (Mitchell and Woods, 2011; Woods et al., 2006, 2009). As described in the literature review in the present thesis, the relationship between cognitive functioning and cortisol metabolism is complex (Bennion et al., 2015; Ebner et al., 2015; Greendale et al., 2000). In addition, the findings of studies using neuropsychological tests cannot be generalized to subjective cognitive difficulties.

In spite of the high number of items in the somatic symptoms domain, the low number of participants in **Study V**, and the rarity of somatic symptoms, lower 24-hour urinary cortisol excretion was found in women with more frequent somatic symptoms. This finding is in line with the assumption that chronic pain, fatigue, and other somatic symptoms are associated with decreased rather than increased cortisol secretion (Fries et al., 2009; Kumari et al., 2009; Maletic and Raison, 2009; Mitchell and Woods, 2010).

The varied findings between studies may be related to the broad day-to-day variations in cortisol secretion. Moreover, it must be considered that the correlations and differences were small in the present thesis. Thus, the clinical significance of the associations is uncertain. Nevertheless, it can be concluded that the hypothesis that climacteric-related symptoms may be linked to cortisol secretion was only weakly supported and only for certain symptoms.

6.4 Future aspects

Climacteric-related symptoms often have a substantial negative effect on QoL. However, symptoms experienced vary greatly between women. Various symptoms become more common as women transition from the premenopausal state to perimenopause or postmenopause. Associations between climacteric-related symptoms and socioeconomic and lifestyle factors have been thoroughly investigated. Knowledge about the essential relationship between healthy lifestyles and fewer symptoms can be used to motivate women to exercise, maintain or reach normal body weight, quit smoking, and use alcohol only in moderation. As lower educated, unemployed, and abnormally early retired women have a higher risk for climacteric-related symptoms, special consideration should be given to these women.

Regarding associations between climacteric-related symptoms and chronic diseases, physicians should pay attention to women's overall health and to potential concurrent diseases, instead of merely assuming that various symptoms in midlife women are the result from a hormonal imbalance. Regarding previously diagnosed chronic diseases investigated in the present thesis, they appear to contribute to climacteric-related symptoms only if they impair SRH. Future studies with longitudinal study designs are mandatory to assess the causal relationships between chronic diseases and climacteric-related symptoms.

As cortisol secretion is vulnerable to both physical and mental stress, it can be hypothesized that cortisol secretion is altered by climacteric-related symptoms. If climacteric-related symptoms were associated with cortisol secretion, it could indicate a link between climacteric-related symptoms and several systemic diseases, such as an increased risk of CVD. However, in the present thesis, only a few weak associations between climacteric-related symptoms and cortisol secretion were found. Because of the broad day-to-day variations in cortisol secretion, future studies with larger study populations are needed, including cortisol measurements on consecutive days.

Measuring climacteric-related symptoms with validated instruments is essential. The present thesis, along with previous studies, favors the use of the WHQ. As the psychometric properties of the revised version of the WHQ were equal to or even better than those of the original WHQ and as it is beneficial to include as few items as possible in questionnaires to ensure a good response rate, the use of the revised WHQ should be preferred.

7 CONCLUSIONS

In the present thesis, several statistical analyses were applied to evaluate the psychometric properties of the WHQ. The relationships between climacteric-related symptoms and aging were examined with both a cross-sectional study design and, prospectively, in a longitudinal setting. The associations between climacteric-related symptoms and various other factors were also investigated.

The main conclusions were:

1. The WHQ is a valid instrument for measuring climacteric-related symptoms in Finnish midlife women. The psychometric properties of the revised version of the WHQ were as good as or even better than those of the original WHQ. In addition, the psychometric properties on the 1–4 scale were better than those on the original binary scale. These findings support the use of the revised WHQ with an analogous scale to the 1–4 scale.
2. Of the climacteric-related symptoms, QoL was decreased most by VMS, cognitive difficulties, and impaired sexual functioning. In midlife women, climacteric-related symptoms became more common during aging. Higher education and employment along with a healthy lifestyle were associated with fewer symptoms. This information helps to distinguish populations and women at risk and can be used in health education.
3. All climacteric-related symptoms included in the WHQ were linked to at least some chronic somatic diseases. Apart from VMS and sleep problems, which were only associated with gastrointestinal diseases and impaired sexual functioning, which was only associated with diabetes, the remaining symptoms were associated with several diseases. It must be noted that only previously diagnosed diseases were considered in the present thesis. When treating climacteric women, it is important that physicians pay attention to overall health and to potential concurrent diseases, along with the consideration that hormonal depletion may be behind the symptoms. SRH seemed to be an important mediator for associations between climacteric-related symptoms and chronic somatic diseases: most diseases appeared to be associated with experienced climacteric-related symptoms only with deteriorating SRH.
4. Although previous studies have reported various associations between climacteric-related symptoms and components of cortisol secretion, in the present thesis, the hypothesis that climacteric-related symptoms may be linked with cortisol secretion was only weakly supported and only for certain symptoms.
5. VMS, the most typical symptoms of the climacteric, decreased as time passed after menopause. This supported previous findings that VMS seldom last for life, but instead diminish over time. A slight decrease was also found in sleep problems and cognitive

difficulties. As these symptoms have been linked to VMS, it can be hypothesized that the decrease was at least partly related to the decrease of VMS. No changes were found in mood and somatic symptoms, indicating that the reasons for these symptoms are probably multifactorial and not entirely dependent on climacteric-related hormonal changes.

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APPENDICES

Appendix 1. The Original Women's Health Questionnaire

Vasomotor symptoms (2 items)

(No missing answers allowed)

- 19. I have hot flushes
- 27. I suffer from night sweats

Sleeping problems (3 items)

(One missing answer allowed)

- 1. I wake early and then sleep badly for the rest of the night
- 11. I am restless and can't keep still
- 29. I have difficulty in getting off to sleep

Depressive symptoms (7 items)

(Two missing answers allowed)

- 3. I feel miserable and sad
- 5. I have lost interest in things
- 7. I still enjoy the things I used to
- 8. I feel life is not worth living
- 10. I have a good appetite
- 12. I am more irritable than usual
- 25. I have feelings of well-being

Anxiety and fears (4 items)

(One missing answer allowed)

- 2. I get very frightened or panic feelings for apparently no reason at all
- 4. I feel anxious when I go out of the house on my own
- 6. I get palpitations or a sensation of "butterflies" in my stomach or chest
- 9. I feel tense or "wound up"

Cognitive difficulties (3 items)

(One missing answer allowed)

- 20. I am more clumsy than usual
- 33. I have difficulty concentrating
- 36. My memory is poor

Sexual functioning (3 items)

(One missing answer allowed)

- 24. I have lost interest in sexual activity
- 31. I am satisfied with my current sexual relationship (please omit if not sexually active)
- 34. As a result of vaginal dryness, sexual intercourse has become uncomfortable (please omit if not sexually active)

Menstrual symptoms (4 items)

(One missing answer allowed)

- 17. My breasts feel tender or uncomfortable
- 22. I have abdominal cramps or discomfort
- 26. I have heavy periods (please omit if no periods at all)
- 28. My stomach feels bloated

Somatic symptoms (7 items)

(Two missing answers allowed)

- 14. I have headaches
- 15. I feel more tired than usual
- 16. I have dizzy spells
- 18. I suffer from backache or pain in my limbs
- 23. I feel sick or nauseous
- 30. I often notice pins and needles in my hands and feet
- 35. I need to pass urine/water more frequently than usual

Attractiveness (2 items)

(No missing answers allowed)

- 21. I feel rather lively and excitable
- 32. I feel physically attractive

An independent item:

- 13. I worry about growing old

Appendix 2. The Women's Health Questionnaire in Finnish

Alla esitetään terveyteen liittyviä väitteitä. Arvioikaa niiden paikkansapitävyyttä kohdallanne tällä hetkellä tai lähimpien viikkojen aikana numeroiden 1-4 avulla

1 =pitää täysin paikkansa, 2 = pitää osittain paikkansa, 3 = pitää hyvin vähän paikkaansa, 4 = ei pidä ollenkaan paikkaansa

1. Herään aikaisin ja nukun sen jälkeen huonosti lopun yötä.	1	2	3	4
2. Tunnen itseni pelokkaaksi ilman syytä.	1	2	3	4
3. Tunnen itseni epätoivoiseksi ja surulliseksi.	1	2	3	4
4. Tunnen itseni levottomaksi, jos lähdän yksin pois kotoa.	1	2	3	4
5. Olen menettänyt mielenkiinnon useimpiin asioihin.	1	2	3	4
6. Minulla on sydämentykytystä tai tunnen "perhoseja mahassani".	1	2	3	4
7. Nautin yhä samoista asioista kuin ennenkin.	1	2	3	4
8. Elämä ei tunnu elämisen arvoiselta.	1	2	3	4
9. Tunnen oloni kireäksi tai pingottuneeksi.	1	2	3	4
10. Minulla on hyvä ruokahalu.	1	2	3	4
11. Olen levoton ja minun on vaikeaa pysyä paikoillani.	1	2	3	4
12. Olen ärtyisämpi kuin tavallisesti.	1	2	3	4
13. Olen huolissani vanhenemisesta.	1	2	3	4
14. Minulla on päänsärkyä.	1	2	3	4
15. Tunnen itseni tavallista väsyneemmäksi.	1	2	3	4
16. Minulla on huimausta.	1	2	3	4
17. Rintani ovat arat tai kireät.	1	2	3	4
18. Minulla on kipuja raajoissa tai selässä.	1	2	3	4
19. Minulla on kuumia aaltoja	1	2	3	4
20. Olen kömpelömpi kuin yleensä.	1	2	3	4
21. Tunnen itseni eloiseksi ja herkäksi.	1	2	3	4
22. Minulla on vatsakipuja tai -krampeja.	1	2	3	4
23. Minulla on pahoinvointia tai oksettava olo.	1	2	3	4
24. Olen menettänyt seksuaalisen mielenkiinnon.	1	2	3	4
25. Voin hyvin.	1	2	3	4
26. Minulla on runsaat kuukautiset.				
(Vastatkaa, jos teillä on vielä kuukautiset)	1	2	3	4
27. Kärsin yöhikoilusta.	1	2	3	4
28. Vatsani tuntuu turvonneelta.	1	2	3	4
29. Minulla on nukahtamisvaikeuksia.	1	2	3	4
30. Minulla on usein pistelyä käsissä ja jaloissa.	1	2	3	4
31. Olen tyytyväinen seksuaalielämäni.				
(Vastatkaa vain, jos sitä on)	1	2	3	4
32. Tunnen itseni fyysisesti viehättäväksi.	1	2	3	4
33. Minulla on keskittymisvaikeuksia.	1	2	3	4
34. Emättimen kuivuuden takia yhdyntä tuntuu epämiellyttävältä.				
(Vastatkaa vain, jos seksuaalielämää on)	1	2	3	4
35. Minun on käytävä tavallista useammin virtsalla.	1	2	3	4
36. Muistini on huono.	1	2	3	4

Appendix 3. The Revised 23-item Women's Health Questionnaire

Vasomotor symptoms (2 items)

(No missing answers allowed)

- 19. I have hot flushes
- 27. I suffer from night sweats

Sleeping problems (2 items)

(No missing answers allowed)

- 1. I wake early and then sleep badly for the rest of the night
- 29. I have difficulty in getting off to sleep

Anxiety/depressed mood (7 items)

(Two missing answers allowed)

- 2. I get very frightened or panic feelings for apparently no reason at all
- 3. I feel miserable and sad
- 4. I feel anxious when I go out of the house on my own
- 5. I have lost interest in things
- 6. I get palpitations or a sensation of "butterflies" in my stomach or chest
- 8. I feel life is not worth living
- 9. I feel tense or "wound up"

Well-being (4 items)

(One missing answer allowed)

- 7. I still enjoy the things I used to
- 10. I have a good appetite
- 25. I have feelings of well-being
- 32. I feel physically attractive

Cognitive difficulties (3 items)

(One missing answer allowed)

- 20. I am more clumsy than usual
 - 33. I have difficulty concentrating
 - 36. My memory is poor
- (One missing answer allowed)

Somatic symptoms (5 items)

- 14. I have headaches
- 15. I feel more tired than usual
- 16. I have dizzy spells
- 18. I suffer from backache or pain in my limbs
- 23. I feel sick or nauseous

Optional domains:

Sexual functioning (3 items)

(One missing answer allowed)

Instructions for answering:

If you are currently involved in a sexual relationship with a partner, please answer how you are feeling now, or how you have been feeling during the past month

- 24. I have lost interest in sexual activity
- 31. I am satisfied with my current sexual relationship (please omit if not sexually active)
- 34. As a result of vaginal dryness, sexual intercourse has become uncomfortable (please omit if not sexually active)

Menstrual symptoms (4 items)

(One missing answer allowed)

Instructions for answering:

If you are currently having menstrual periods (naturally or with Hormone Replacement Therapy), please indicate how you have been feeling when you had your last menstrual period

- 17. My breasts feel tender or uncomfortable
- 22. I have abdominal cramps or discomfort
- 26. I have heavy periods (please omit if no periods at all)
- 28. My stomach feels bloated

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