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YLIOPISTO**
UNIVERSITY
OF TURKU

**HORMONE REPLACEMENT
THERAPY AMONG FINNISH
MENOPAUSAL WOMEN
AROUND THE MILLENNIUM**
With Special Attention on the Psychosocial
Background

Jaana Jalava-Broman



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To my mother

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ABSTRACT

Women today can live up to half of their lives postmenopausal. That is why the treatment of climacteric symptoms has become increasingly important. Estrogen effectively alleviates climacteric symptoms and thus improves the quality of life. Until the beginning of 2000, the use of HT was rather common. International studies from the USA and England showed that HT increased the risk of breast cancer and cardiovascular diseases. These studies attracted considerable publicity and the use of HT decreased all over the world. The recommendations for the use of HT became stricter and alternative treatments were used more than previously.

The purpose of this study was to find out how and what kind of Finnish women between the ages of 52–56 years treated their climacteric symptoms in 2000, and how many of them had stopped the use of HT five years later and why they did so. Sociodemographic and personal characteristics, health behaviour, physical and psychological characteristics were examined associated with HT use.

Data was collected from HeSSup-cohort study. From this study two cohorts of women born in 1944–1948 (n=2702) and 1954–1958 (n=2771) were selected. The QoL-study- questionnaire was sent in 2000, 2005 and 2010 to these women.

The use of HT was predicted by symptoms associated with a deficiency of estrogen, being in a relationship, a weak SOC, consumption of alcohol, a BMI under 30, and use of psychopharmacas. The women started HT because of climacteric symptoms, to maintain health and prevent diseases.

In 2000, 47% of women used systemic HT, particularly those women who had more climacteric symptoms, normal weight, were educated and consumed alcohol. HT users seemed to be more stressed, more hostile, and had a weaker SOC than those who did not use HT. The publication of the recent HT research results and the fear of cancer were the reasons given by a third of women for discontinuing HT treatment during 2000 and 2005.

Medical professionals should take in account that many other factors affect how women experience climacteric symptoms and use HT; issues such as SOC and an individual's ways of coping with the climacteric years. The influence of circumstantial factors should be taken into account and possible disinformation should be corrected on the basis of evidence-based medicine.

KEY WORDS: Use of HT, menopause, personal factors

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JAANA JALAVA-BROMAN: Suomalaisen vaihdevuosi-ikäisten naisten hormonikorvaushoito vuosituhannen vaihteessa

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TIIVISTELMÄ

Nykyisin naiset elävät jopa puolet elämästään postmenopausissa. Täten vaihdevuosiin liittyvien oireiden hoitaminen on tullut entistäkin tärkeämmäksi. Estrogeeni helpottaa oireita tehokkaasti ja parantaa siten elämänlaatua. 2000-luvun alkuun asti HT:n käyttö oli varsin yleistä. Kansainväliset tutkimukset Amerikasta ja Englannista osoittivat HT:n lisäävän riskiä sairastua rintasyöpään ja verisuonitapahtumiin. Tutkimukset saivat paljon julkisuutta ja HT:n käyttö vaihdevuosi-ikäisillä naisilla väheni kaikkialla maailmassa. HT:n käyttösuosituksia tiukennettiin ja vaihtoehtoisia hoitomuotoja otettiin käyttöön.

Tämän tutkimuksen tarkoituksena oli selvittää, miten ja minkälaiset 52–56-vuotiaat suomalaiset naiset hoitivat vaihdevuosisoireitaan vuonna 2000 ja kuinka moni heistä oli viiden vuoden kuluttua lopettanut käytön ja mistä syystä. Sosiodemografisia tekijöitä, persoonallisuuspiirteitä, terveyskäyttäytymistä, fyysisiä sekä psyykkisiä ominaisuuksia tarkasteltiin suhteessa HT:n käyttöön.

Tutkimusaineisto muodostui HeSSup-kohorttitutkimuksesta, johon vastanneista naisista valikoitiin kaksi kohorttia: vuosina 1944–1948 (n=2702) ja 1954–1958 (n=2771) syntyneet naiset. QoL-elämänlaatuksely lähetettiin vuosina 2000, 2005 ja 2010.

HT:n käyttöä ennustivat estrogeenin puutteesta johtuvat vaihdevuosisoireet, parisuhde, heikko koherenssin tunne, alkoholin käyttö, alle 30:n painoindeksi ja psykofarmakoiden käyttö. Naiset aloittivat HT:n vaihdevuosisoireiden vuoksi, mutta myös ylläpitääkseen terveyttä ja estääkseen sairauksia.

Vuonna 2000 47 % naisista käytti HT:tä, erityisesti ne, joilla oli enemmän vaihdevuosisoireita, jotka olivat normaalipainoisia, koulutettuja ja käyttivät alkoholia. HT:n käyttäjät olivat stressaantuneempia, vihamielisempiä, sekä heikomman koherenssin tunteen omaavia kuin ne, jotka eivät käyttäneet HT:a. Viimeaikaiset HT:n käyttöön liittyvät tutkimustulokset ja syövän pelko olivat lopettamisen syynä kolmanneksella naisista, jotka lopettivat HT:n vuosien 2000–2005 välisenä aikana.

Vaihdevuosi-ikäisiä naisia hoitavien tulisikin huomioida, että vaihdevuosisoireiden kokemiseen ja HT:n käyttöön vaikuttavat vaihdevuosisoireiden lisäksi monet muut tekijät, kuten yksilön koherenssin tunne ja yksilölliset tavat selviytyä vaihdevuosista. Ympäristötekijöiden vaikutusta tulisikin tuoda esiin tutkimukseen perustuvien tietojen pohjalta ja oikaista mahdolliset väärinkäsitykset

AVAINSANAT: vaihdevuosien korvaushoito, vaihdevuodet, persoonallisuustekijät

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Abbreviations

AIC	Akaike information criterion
ATC	Anatomical Therapeutic Chemical
BDI	Beck Depression Inventory
BIC	Bayesian information criteria
BMI	Body mass index
CAM	Complementary and alternative medicine
CEE	Conjugated equine estrogens
CHD	Coronary heart disease
CNS	Central nervous system
DDD	Defined daily dose
HERS	Heart and Estrogen /Progestin Replacement Study
HeSSup	Health and Social Support Study
HRT	Hormone replacement therapy
HT	Hormone therapy
Kela	Social Insurance Institution of Finland
KI	Kupperman menopausal Index
LOT-R	Life Orientation Test-Revised
LPA	Latent profile analysis
MET	Metabolic Equivalent Task
MWS	Million Women Study
SD	Standard deviation
SERM	Selective estrogen receptor modulator
SNS	Sympathetic nervous system
SOC	Sense of coherence
QoL	Quality of Life
VMS	Vasomotor symptoms
VTE	Venous thromboembolism
WHI	Women's Health Initiative
WHQ	Women's Health Questionnaire

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

- I Jalava-Broman, J., Mäkinen, J., Ojanlatva, A., Jokinen, K., Sillanmäki, L., & Rautava, P. (2008). Treatment of climacteric symptoms in Finland prior to the controversial reports on hormone therapy. *Acta Obstetricia et Gynecologica Scandinavica*, 87(6), 682–686.
- II Jalava-Broman, J., Mäkinen, J., Ojanlatva, A., Jokinen, K., Sillanmäki, L., & Rautava, P. (2011). Change in the frequency of HRT use from 2000 to 2005 and reasons to discontinue; follow-up of a normal cohort in Finland. *Acta Obstetricia et Gynecologica Scandinavica*, 90(4), 351–357.
- III Jalava-Broman, J., Mäkinen, J., Sillanmäki, L., Vahtera, J., & Rautava, P. (2016). Characteristics associated with initiation of hormone replacement therapy among Finnish women: A register-linked study. *Maturitas*, 89, 73–78.
- IV Jalava-Broman, J., Junttila, N., Sillanmäki, L., Mäkinen, J., & Rautava, P. (2020). Psychological behavior patterns and coping with menopausal symptoms among users and non-users of hormone replacement therapy in Finnish cohorts of women aged 52–56 years. *Maturitas*, 133, 7–12.

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1 Introduction

Systemic hormone replacement therapy (HT) has been used to alleviate climacteric symptoms since the 1950s. Ethinyl estradiol was patented in 1937. The United States Food and Drug Administration approved diethylstilbestrol in 1941 and conjugated equine estrogens (CEE) in 1942 (Stefanick, 2005). The use of HT among postmenopausal women increased until the beginning of 2000, both in Finland and worldwide. HT was believed to offer an opportunity for “everlasting youth” for menopausal women, and decrease the risk of cardiovascular diseases, osteoporosis, and Alzheimer disease. In 1998 the Heart and Estrogen/Progestin Replacement Study (HERS) (Hulley et al., 1998) and its follow-up study in 2002 (Grady et al., 2002) showed that HT did not reduce cardiovascular events in women with coronary heart disease. The Women’s Health Initiative (WHI) study was published in July 2002 and its results changed the general conceptions of HT. The study actually showed that HT increased the risk of breast cancer and cardiovascular diseases (Rossouw et al., 2002). A year later the Million Women Study (MWS) in England strengthened the results of the WHI by showing that the risk of breast cancer increased among HT users (Million Women Study Collaborators, 2003).

Results from the WHI study showed that the use of HT was dangerous, and this information was quickly published worldwide by the press (Brown, 2012). This soon led to new recommendations which considered that HT should only be used for climacteric symptoms with a minimal dose and for as short a time as possible (The Finnish Medical Society Duodecim & Academy of Finland, 2004). After the huge publicity the WHI results received, women all over the world discontinued HT despite their climacteric symptoms (Burger et al., 2012).

In 2003, the final analysis of the WHI -estrogen plus progestin therapy results showed that the risk of coronary heart disease (CHD) might increase, especially during the first year after HT initiation, but the increase in CHD was not significant (Manson et al., 2003). If HT is started within 10 years of the onset of menopause, then there are no risk factors for women to cardiovascular diseases; in fact, HT seems to have protective effect on cardiovascular diseases. For those women who initiate HT after 10 years from the onset of menopause the risk for cardiovascular diseases increases (de Villiers et al., 2013). The risk for breast cancer increased 26%

(Rossouw et al., 2002) in the WHI-study among those women using a combined therapy, but was reduced by 18% (Stefanick et al., 2006) among those women using estrogen without progestin. However, since 2002, the positive results published by the WHI-studies about the use of HT have not received any publicity in the media in Finland, although it did receive attention for example in the USA and England; maybe only negative news sells? (Mikkola, 2007). In scientific papers the discussion is still going on.

After the WHI results, there has been growing interest in alternative treatments to HT. Due to the perceived health risks, confusion, and personal preferences associated with HT use, many women became afraid of using HT and resorted to complementary and alternative treatments (Nelson et al., 2006; Peng et al., 2014; Costanian et al., 2017). The period after the WHI results can be described as quite confusing regarding the use of HT.

Who should use HT and who can manage without hormones? Due to the effects of the decreasing estrogen level, the menopausal transition and future years can be associated with a significant decline in the quality of life (Pines et al., 2012). The capacity of postmenopausal woman to tolerate symptoms and stress is also individual. This capacity affects the experience of climacteric symptoms and, for example, how a woman copes when suddenly experiencing hot flashes. The combination of a woman's life situation, lifestyle, and former life events together with the lack of estrogen influence how women experience climacteric symptoms (Rutanen, 2003).

The purpose of this study was to investigate how Finnish women between the age of 52–56 years used systemic HT in 2000 before the WHI results were published, and how their use had changed by 2005. What were the reasons to commence or to discontinue the use of HT. Along with the climacteric symptoms an analysis was conducted on how sociodemographic factors, lifestyles, personal characteristics, the use of psychopharmacas, physiological and mental properties affected both the instigation and use of HT. In general, this thesis tries to determine what kind of features and experiences of menopausal women are involved when they choose a treatment for climacteric symptoms. This kind of information could also be helpful for the clinicians who treat postmenopausal women.

2 Review of the Literature

2.1 Menopause and climacterium

2.1.1 Definitions

Menopause is defined as a permanent cessation of menstrual periods caused by a decrease in ovarian estrogen biosynthesis. A 12-month period of amenorrhea is required to define the menopausal state (Burger, 1996; Harlow et al., 2012). Menopause occurs on average at 51 years of age (range: 40–60 years) both in Finland (Pakarinen et al., 2010; Turunen & Lyytinen 2014) and worldwide (Kok et al., 2005). Menopause for a woman under the age of 40 years is called premature ovarian insufficiency. Early menopause begins at the age of 40–45 years and natural menopause for women over 45 years. Menopause is a critical phenomenon in every woman's life and the complexity of menopause is associated with a deteriorating quality of life (QoL) (Blumel et al., 2000; Schneider & Birkhäuser, 2017).

Women usually experience climacteric-related symptoms a few years before menopause because of irregular menstrual periods and fluctuating levels of estrogen. This period is called premenopause (Harlow et al., 2012). Usually, menstrual periods first become shorter and after that the intervals between menstruations become longer until they totally cease. The menopause transition starts around 47 years and lasts for 5–8 years on average (Roberts & Hickey, 2016). However, for some women climacteric symptoms may persist for more than ten years (Avis et al., 2015; Freeman et al., 2011).

Postmenopause is the final period of the menopause and the rest of a woman's life (Harlow et al., 2012). The climacterium is defined as a long-lasting phenomenon when all the estrogen deficiency -related items can occur.

2.2 Climacteric symptoms

As the ovaries gradually stop working the estrogen levels decline and climacteric symptoms usually begin. The typical symptoms related to the lack of estrogen are vasomotor symptoms (hot flushes, night sweats, palpitations, irritability), sleep disturbances, mood changes, and vulvovaginal atrophy. Postmenopausal women

often report a variety of other symptoms including, sexual dysfunctioning, memory loss, fatigue, headaches, joint pains, weight gain and depression. These symptoms may also be related to aging. Associations between postmenopause and mood symptoms, cognitive disturbances, and somatic complaints are inconclusive (Woods & Mitchell, 2005). In a descriptive study of the Finnish female population, it was observed that during and after menopause women suffer from a variety of somatic and psychological symptoms. Half of them consider at least one of the symptoms as bothersome. The most common bothersome symptoms were the traditional menopausal symptoms, but also back pain, muscle pain and numbness were common (Moilanen et al., 2010).

2.2.1 Vasomotor symptoms

Vasomotor symptoms (VMS) are the most common postmenopausal symptoms also recognized as “hot flushes”. They are present in up to 80% of women of menopausal age (Stearns et al., 2002; Nelson, 2008)). In a cohort study by Jokinen et al. from 2003, only 5% of women aged 52–56 were asymptomatic (Jokinen et al., 2003).

The disturbance of the temperature-regulating mechanism in the hypothalamus due to the decline in estrogen concentration probably causes VMS, however, the precise mechanism behind VMS is still rather poorly understood (Archer et al., 2011).

VMS are sudden sensations of severe heat that usually start from the head or neck and then spread throughout the whole body, causing flushing, sweating, and palpitations (Freedman, 2014). These particular episodes usually last from one to five minutes and can reappear with varying frequency (Archer et al., 2011; Freedman, 2014). For some women, hot flushes may be everyday occurrences, while some women only have VMS occasionally and a minority of women are fortunate enough not to report any hot flushes. Usually, women have hot flushes for a few years, but about 15% of women have hot flushes for more than 15 years (Kronenberg, 1990). In an observational study, VMS frequently lasted for more than seven years during menopausal transition for more than half of the women (Avis et al., 2015). Thus far, it is not exactly known what triggers individual hot flushes or the explanation for why some women do or do not experience them (Kronenberg, 2010).

2.2.2 Urogenital symptoms

Estrogen loss is the major cause of vulvovaginal atrophy in climacteric women. Vaginal dryness, itching and vaginal irritation are the most prevalent urogenital symptoms. Atrophic skin can also cause dyspareunia and vaginal bleeding. Deficiency of estrogen causes urogenital complaints like urinary tract infections,

nocturia, stress urinary incontinence and frequency (Calleja-Agius & Brincat, 2015). The prevalence of past or current symptoms of atrophy was 45% among a sample of menopausal women and of these women about 50% were sexually active (Santoro & Komi, 2009). The prevalence of self-reported dryness of the vagina was 27% in the observational cohort of WHI (Pastore et al, 2004). Many symptoms of menopause diminish with age, but these local atrophic symptoms tend to increase and become worse during the following years (Tiitinen & Kero, 2020).

2.2.3 Sleep disturbances

During menopausal transition 40–60% of women suffer from subjective sleep disturbances especially awaking in the night-time resulting in sleep fragmentation (Polo-Kantola, 2011; Shaver & Woods, 2015). With age, sleep quality declines and the menopausal transition appears to cause at least part of this decline in women (Kravitz et al., 2003). The experience of vasomotor symptoms and their connection to insomnia (Shaver & Woods, 2015) and objectively measured weakening of sleep structure (de Zambotti et al. 2014, Joffe et al., 2013) has been observed in many studies. VMS can also be investigated objectively by measuring skin conductance in the sternal area. Measuring VMS this way seemed to also correlate with the worsening structure of sleep (de Zambotti et al., 2014, Joffe et al., 2013). In a cross-sectional study from Lampio et al., VMS seemed to be linked to sleep disturbances, especially difficulties to maintain sleep. Hot flushes were less harmful to sleep than night-time sweating. Night sweats affected the quality of sleep differently depending on the menopausal stage. For postmenopausal women, even occasional night sweats disturbed their sleep whereas premenopausal women experienced frequent night sweats as detrimental (Lampio et al., 2014). In a six-year follow-up study of the impact of VMS during menopausal transition on sleep architecture was unexceptionally weak (Lampio et al., 2017).

Acute or chronic pain, medication, sleep-disordered breathing, restless legs syndrome and several other diseases and conditions can also cause or make sleep problems worse for women in midlife (Polo-Kantola, 2011). At the same time as the menopausal transition women might experience other stress factors and challenges which can disturb sleep. The empty nest syndrome caused by children moving away from home and becoming independent, the growing need to take care of aging parents, the sickness of close relatives, one's own aging process as well as growing pressure at work can also be reasons for sleep difficulties (Lampio et al., 2018, Figure 1).

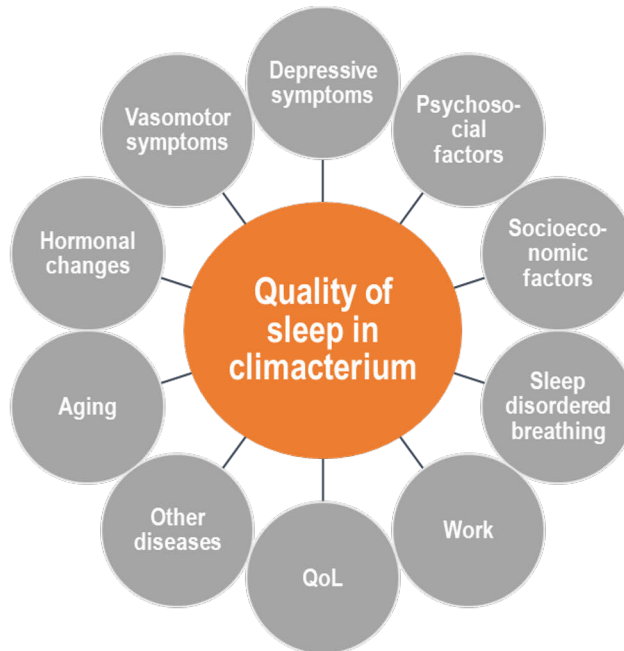


Figure 1. Multifactorial reasons behind insomnia in menopause, modified from the original figure of Lampio et al., 2018. Reproduced with permission of the copyright holders.

2.2.4 Depressive symptoms

During menopausal transition and in early postmenopause the risk for experiencing major depressive disorders is 2–4 times more likely compared to women who are premenopausal (Bromberg & Kravitz, 2011). Findings from a longitudinal-8-year cohort study in the USA showed that both a new onset of depression and depressive symptoms were more likely to occur in a woman in menopausal transition compared to women in premenopause (Freeman et al., 2006). In an Australian study, midlife women who were close to the menopause experienced increased symptoms of depression and postmenopausal women were more likely to experience symptoms of anxiety (Mulhall et al., 2018).

In the review of Soares et al., the strongest predictor of depression and mood symptoms during the midlife years was a prior depressive episode. The risk of depression was also modulated by vasomotor symptoms, anxiety, and health-related issues (Soares, 2014).

2.3 Decisions of the treatment

Life expectancy during the recent decades has increased and every year more women reach the menopause. Nowadays, women are expected to spend more than a third or

even half of their lifetime in the postmenopausal stage in developed countries. In Finland, for example, the life expectancy of Finnish women was 84.6 years in 2020 (Statistics Finland, 22.10.2021). Thus, reducing the burden of menopause -related health conditions and improving their quality of life is increasingly important for women both in the present and for the future.

2.3.1 Indications

The only indications nowadays for prescribing systemic HT are hot flushes and sweating. HT is also recommended to those women who need treatment for osteoporosis and who cannot use osteoporosis medication but are able to use HT (Tiitinen, 2019). Rare indications for the use of systemic HT are ovarian atresia and premature insufficiency or iatrogenic oophorectomy. Additionally, local estrogen therapy (instead of systemic) is indicated for vaginal symptoms due to urogenital atrophy.

2.3.2 Contraindications

Systemic HT is contraindicated if women have had breast cancer, gynaecological cancer, uncertain uterine bleeding, venous thromboembolic disease, myocardial infarct, stroke, embolia or a tendency to thromboembolic complications. However, compared to peroral therapy, transdermal use of HT is not associated with any increased venous thromboembolic risk (Vinogradova et al, 2019). Difficult congestive heart failure, resistant blood pressure, certain liver diseases and systemic lupus erythematosus, when the antiphospholipids are positive, are also health situations in which the use of systemic HT is not recommended. Moreover, smoking increases the relative risk of HT on otherwise healthy women. In all these situations, HT can be considered if the women are young and the climacteric symptoms are very severe, but in these circumstances, it is also necessary that a gynaecologist estimates the balances between the risks and benefits of HT use. All the above-mentioned contraindications are not related to local estrogen use. Finally, the decision to start systemic HT use is dependent on the patient's choice (Tiitinen, 2019; Tuomikoski & Lyytinen, 2015).

2.3.3 Benefits

The positive effect of estrogen on VMS has been pointed out in numerous follow-up studies (Stearns et al., 2002). HT with estrogen alone or in combination with progestin is known to be the most effective treatment for vasomotor symptoms. The frequency of hot flushes diminishes over 70% and the effect of HT begins within

one or two weeks after a woman has started treatment with HT (Notelovitz et al., 2000; Grady et al., 2006).

The declining levels of estrogen during menopausal transition and the subsequent years can diminish the quality of life. HT has shown to improve the quality of life during postmenopause. In a study of Heikkinen et al., the quality of life of women was evaluated during the long-term use of HT and one year after discontinuing the treatment. Different factors affecting the quality of life such as health perception, sexual interest, daily functioning and enjoyment, anxiety and depressed moods improved with the use of HT, but became worse again during a follow-up of those not continuing HT (Heikkinen et al., 2006)

In a prospective study, 150 healthy women were interviewed about menopausal symptoms, general health, and health-related quality of life. Results revealed that HT alleviated hot flushes and at the same time improved health-related quality of life. On the other hand, HT had no benefit over a placebo for the quality of life of those women who had no hot flushes (Savolainen-Peltonen et al., 2014).

Throughout the menopausal transition the percentage of women experiencing vaginal dryness increases. About half of women between 50–60 years old suffer from vaginal atrophy and among women over 70 years the prevalence is already 70% (Tiitinen & Kero, 2020). Estrogen given systemically or especially locally is effective for vaginal atrophy (Palacios, 2009)

Postmenopausal depression is not indicated as a reason to recommend treatment with estrogen therapy. However, estrogen seems to have antidepressant effects particularly among those postmenopausal women who also suffer from VMS (Maki et al., 2018).

Vasomotor symptoms are also linked to sleep disturbances causing difficulty to maintain sleep. Hot flushes and sweating during the night-time seem to be especially detrimental to sleep (Lampio et al., 2014). HT should be considered in the management of postmenopausal sleep disturbances, particularly if vasomotor symptoms are present and there are no contraindications to the use of HT.

HT reduces the risk of fractures in women with or without osteoporosis and increases the density of bone minerality (Levin et al., 2018). In postmenopausal women HT in the form of either combined estrogen and progesterone or estrogen alone has been shown to be effective in reducing the number of fractures (Gartlehner et al., 2017).

HT decreases coronary heart disease (CHD) risk and overall mortality as a primary prevention when HT is started concurrent with or soon after menopause (Hodis & Mack, 2014). The placebo-controlled WHI trial however failed to confirm these results and furthermore showed that HT was harmful to vascular health (Roussow et al., 2002). Later, it has been shown that if HT is started within 10 years of the onset of the menopause, coronary risk is reduced (Roussow et al., 2007).

Mikkola et al. demonstrated that the risk of CHD death was reduced by between 18% to 54%, the risk of a stroke death by between 18% to 39% and the risk of all-causes of mortality by between 12% to 38% in HT users. Reduction was related to HT exposure time in CHD deaths and all-cause mortality but not in stroke deaths (Mikkola et al., 2015). The risk of a stroke or cardiac death was elevated after the first year of HT cessation. It was found especially harmful to discontinue the use of HT for women younger than 60 years old (Mikkola et al., 2015). Most of the common benefits and risks can be seen in Table I.

During menopausal transition the amount of adipose tissue often increases and is redistributed more centrally. Many women gain weight due to decreased energy expenditure with aging. When insulin secretion and sensitivity are impaired the risk of type 2 diabetes increases. For women with or without type 2 diabetes HT has a positive effect on glucose metabolism. HT could be suitable for postmenopausal women with type 2 diabetes with a low risk of cardiovascular disease. However, postmenopausal women with type 2 diabetes should primarily be guided into healthy ways of living and if needed commence diabetes medication (Slopien et al., 2018; Stuenkel, 2016).

There is evidence of a reduced risk of gastrointestinal cancer in HT users. Results from a prospective English study and from a meta-analysis of published data have shown that reduced risks for oesophageal, gastric, and colorectal cancers are associated with the use of HT (Green et al., 2012).

A certain number of women at menopause suffer from arthralgia. The lack of estrogen seems to be the reason for the pain in the joints but the pathogenesis behind this is multifactorial and not yet totally understood. The majority of studies manifest that HT slightly improves arthralgia in menopausal women. The prevalence of knee osteoarthritis was lower in participants with HT than in those without it (Jung et al, 2019). For those women who have arthralgia during menopause and at the same time significant vasomotor symptoms HT should be considered (Magliano, 2010).

2.3.4 Risks

According to Lyytinen et al., oral or transdermal estradiol use for 5 years or more caused 2–3 extra cases of breast cancer per 1,000 women when the follow-up time was 10 years. (Lyytinen et al., 2006). In the study by Lyytinen et al., combined therapy was also associated with an increased risk of breast cancer already after 3–5 years of use. There were 31% more breast cancer cases in those women who used a combined therapy compared to the average in women of the same age. The risk was lower for sequential rather than continuous use, but comparable for oral and transdermal use (Lyytinen et al., 2009). Therefore, the risk of breast cancer with estrogen-progesterone therapy is greater than with estrogen alone (Table 1).

A Danish nationwide, prospective cohort study from 2009 confirmed that women who used HT were at a higher risk of ovarian cancer than those women who did not use HT. The increased risk of ovarian cancer was not dependent on the dosage or duration of HT use, nor the means of administration or type of progestin. Two years after stopping HT, the risk of ovarian cancer disappeared (Morch et al., 2009).

According to a review study on the use of estrogen, tibolone or sequential combined HT use, there is an increased risk of endometrial cancer, even when the therapy is used for less than 5 years. Continuous combined therapy for more than 10 years did not increase the risk of endometrial cancer and might even lower the risk compared to those who have never used the therapy (Sjögren et al., 2016). However, oral and transdermal combined-therapy use are associated with comparable risk elevations for breast cancer (Lyytinen et al., 2009).

Findings from the WHI trial revealed that gallbladder diseases are associated with the use of oral estrogen with or without progestin (Cirillo et al., 2005). By using transdermal therapy instead of oral over a five-year period one cholecystectomy could be avoided in every 140 HT users (Liu et al., 2008).

There has been discussion about the decline in female hormones after the menopause causing memory disorders, however, the results of many large studies have been conflicting. In order to avoid memory disorders after the menopause it is most important to manage the risks for cardiac and heart diseases. The best preventive methods are proper healthy nutrition and regular exercise (Remes et al., 2015; Shao et al., 2012). However, the recent nationwide case-control study from Finnish postmenopausal women showed that the use of HT increased the risk of Alzheimer disease by 9–17%. The risk did not differ between users of combined or estrogen therapy. Practically, 9–18 more Alzheimer disease diagnosis per year appear in 10,000 women aged 70–80 years, especially if HT is used over 10 years. The age at initiation of systemic HT did not affect the risk of Alzheimer's disease. (Savolainen-Peltonen et al., 2019).

The risk of stroke increases during the use of HT. In the WHI study, the use of HT caused 9 extra strokes per 10,000 persons per year, but not in women under the age of 60 years. The risk of a stroke did not depend on the number of years after menopause or the presence of VMS (Rossouw et al., 2007). A case control study from Canada showed that the risk of a stroke was not elevated if the amount of transdermal estrogen with or without progestin was 50 ug or less (Renoux et al., 2010).

Venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism, is a major harmful effect of HT. The risk of VTE increases during the first year of oral estrogen treatment. Risk for past users seems to follow a similar risk as for those women who never used estrogen. VTE risk depends on the

route of administration. Transdermal estrogens alone or combined with micronized progesterone are at the moment the safest alternative for HT (Canonico, 2015).

Table 1. The effect of HT on women at the age of 50–59 years or those whose last menstruation was under 10 years ago, based on Tuomikoski & Lyytinen, 2015; Santen et al., 2010. Reproduced with permission of the copyright holders.

	Estrogen		Estrogen and progestin	
	Cases/1000 women who used HT for 5 years			
	Less	More	Less	More
Breast cancer	1–5			5–10
Angina pectoris	1–5			1–5
Bone fractures	5–10		1–5	
Type 2 diabetes	>10		>10	
Total mortality	5–10		5–10	
Deep venous thrombosis		1–5 ¹		5–10 ¹
Stroke		1–5 ²		0–1 ²
Colon cancer		0–1	1–5	
Ovarial cancer		0–1		
Gall bladder infection		>10		5–10

¹No increased risk when given transdermal with a dosage of 50 ug or ²under.

2.4 Treatment options

2.4.1 Systemic hormone therapy

Systemic hormone therapies either of estrogen combined with progestin or estrogen alone for women with a history of hysterectomy are the most effective treatments for the climacteric symptoms (Maclennan et al., 2004). In Finland, the estrogen used is either estradiolvalerate or estradiolhemihydrate, and both have an equal effect. Conjugated equine estrogen (CEE) is non-human, consisting of different estrogens, and is possibly more effective than synthetic estradiols. In venous and cardiac events CEE seems to be more thrombogenic than estradiol (Smith et al, 2014). In many countries CEE is used but is no longer prescribed in Finland.

The synthetic progesterones used in HT are medroksiprogesteroneacetate, noretistestosteroneacetate, and drospirerone. In addition, natural progesterone and

dydrogesterone can be used. Levonorgestrel is the progesterone used in hormonal intrauterine device. Different progesterones vary from each other a little as regards their benefit and side-effects profile, but in a healthy woman this does not have any clinical relevance.

Tibolone is a synthetic steroid having an estrogenic, progesterone-like and androgenic influence. The advantages and disadvantages are equal to other HT treatments. Testosterone itself, especially intramuscularly, was used up to the 1970s, but is no longer officially used. For women with hypoactive sexual desire disorder the current available research supports a moderate therapeutic benefit to testosterone. Data is still, however, insufficient to support the use of testosterone for treatment of any other symptom or disease prevention (Davis et al. 2019).

The oral hormones consist of estrogen, progestin, estrogen/progestin combinations and tibolone.

Selective estrogen receptor modulators (SERMs) block the estrogen receptor in some tissues (estrogen receptor antagonists) or stimulate the estrogen receptor in other tissues (estrogen receptor agonists). A tablet combining the SERM bazedoxifene and conjugated equine estrogen takes advantage of the antagonistic properties of the SERM while maintaining the benefits of estrogen therapy (Liu, 2017). In Finland, the use of SERM (Duavive[®]) is quite rare.

Transdermal hormones are comprised of an estrogen gel, an estrogen patch, an estrogen spray, and an estrogen/progestin patch. The bypass through the liver is avoided when HT is taken transdermally and the risk for thromboembolic complications diminishes.

2.4.2 Vaginal hormone therapy

Local estrogens can alleviate 80–90% of the symptoms of postmenopausal women suffering from dryness of vaginal mucosal membranes. In placebo-controlled studies estrogen has proven to be more efficient than non-hormonal treatments or a placebo (Lethaby et al., 2016). Local estrogen therapy can also diminish genital irritation, intermittent urinary tract infections, urge incontinence, and especially nocturia (Cody, et al., 2012). With aging, postmenopausal woman may often need local estrogen therapy in addition to systemic therapy (Mäkinen et al, 2001). Local estrogen therapy prevents effectively recurrent urinary tract infections in postmenopausal women and so diminishes the need for antibiotics (Raz & Stam, 1993).

In Finland, local vaginal preparations consist of estradiol or estriol and they are tested for safety and efficiency (Tiitinen & Kero, 2020). Estradiol is in the form of tablets or a ring. Estriol can be used in the form of a vagitory or cream.

2.4.3 Non-hormonal treatment

There are non-pharmacological and non-hormonal pharmacological treatments for use as alternatives for menopausal symptoms. For those women who especially wish to avoid HT or those for whom HT is contraindicated alternative treatments are needed. Non-hormonal pharmacological treatments to relieve VMS include serotonin and noradrenaline reuptake inhibitors, serotonin selective reuptake inhibitors, pregabalin, gabapentin, and clonidine (Hickey et al., 2017). Venlafaxine, for example, reduces both the frequency and severity of VMS compared to a placebo but is not as effective as estrogen (Joffe et al., 2014). For women with breast cancer venlafaxine is the drug of choice.

The North American Menopause Society guideline recommends cognitive behavioural therapy and hypnosis for the treatment of vasomotor symptoms (North American Menopause Society, 2015). A single-blind randomized controlled trial from Canada evaluated the effectiveness of cognitive behavioural therapy for menopausal symptoms. Self-reported vasomotor and depressive symptoms improved but also sleep difficulties, and sexual concerns diminished (Green et al., 2019).

In a population-based study of 45–64 year-old women, being overweight, a sedentary lifestyle and excessive alcohol use have been associated with troublesome VMS (Moilanen et al., 2010). Smoking has been related to worsening symptoms of VMS (Whiteman et al., 2003) but not in all studies (Moilanen et al., 2010). To some degree lifestyle changes like losing weight, quitting smoking and more physical activity can thus alleviate VMS. According to the meta-analysis of clinical trials composite and phytoestrogen supplements modestly reduced the frequency of hot flushes and vaginal dryness, but did not affect night sweats (Franco et al., 2016).

The Cochrane Database from 2014 summarized that exercise does not improve VMS (Daley et al., 2014). In a Finnish population-based study, women with a sedentary lifestyle reported more somatic symptoms than physically active women (Moilanen et al., 2010). In recently postmenopausal sedentary women, aerobic training for 6 months decreased night sweats, irritability, and mood swings (Moilanen et al., 2012).

2.5 Reports considering the use of hormone therapy

2.5.1 The Women's Health Initiative Study

The Women's Health Initiative Study (WHI-Study) (n=16608) was published in July 2002. The study aimed to assess the main health benefits and risks of the most

commonly used combined hormone preparation in the USA and how HT prevents chronic diseases. The first results showed that the risks exceeded the benefits, and the study was interrupted. The results however indicated that combined HT should not be initiated or continued as the primary prevention of CHD. A combined therapy also seemed to increase the risk of breast cancer (Roussow et al., 2002). The results have been analysed again and it seems that the timing of the treatment is relevant and should occur within 10 years of the onset of the menopause (Roussow et al., 2007). It has also been criticized that in the WHI study the women were older (mean age 63.3) and they had already many risk factors as regards heart-and vascular disease. In the WHI study from 2017 neither estrogen therapy for a median of 7.2 years or a combination HT for a median of 5.6 years was associated with a risk of all-cause, cardiovascular, or cancer mortality during the 18-year follow-up (Manson et al., 2017). The risk of breast cancer was greater for those who used combined HT, but not with estrogen therapy alone (Anderson et al., 2004). Local estrogen treatment used for about two years did not raise the risk of increased cardiovascular disease or mortality during the 6.4 years follow-up (Crandall et al., 2018).

2.5.2 The Million Women Study

The Million Women Study (n=1 084 110) was published in August 2003 in the United Kingdom a year after the WHI-results. The Million Women Study recruited women between 1996 and 2001 from those who were supposed to have mammography screening. Of these women half had used HT. This study was set up to investigate the effects of specific types of HT on incident and fatal breast cancer. The current use of HT was associated with an increased risk of incident and fatal breast cancer; the effect was substantially greater for estrogen-progestagen combinations than for other types of HT (Million Woman Study Collaborators, 2003). The current HT users also had an increased risk of ovarian cancer whereas past users of HT had no risk (Million Women Study Collaborators, 2007). The incidence of endometrial cancer was increased in users of estrogen-only therapy and tibolone compared to those who never used the treatment and also decreased in users of continuous combined HT (Million Women Study Collaborators, 2005).

2.6 Use of hormone therapy

2.6.1 Use of hormone therapy in Finland and other countries

HT was widely prescribed during the 1990s. In the USA, the use of HT was estimated to be up to 40% among postmenopausal women in 2001 (Hersh et al., 2004). In 2002 in 17 European countries the estimated use of HT varied from less than 5% to over

25% among 45–69 year-old women (Ameye et al., 2014, figure 2). In Finland, 28–44% of all postmenopausal women were using HT at the end of 1990 (Hirvonen, E., 1997; Martikainen, J., 1998). According to the register of medicine sales HT use was highest (G03CA, G03DC05 and G03F) in Finland in 1999 (DDD/1000) among women over 45 years old. In 2002, of the women aged between 50–59 years old, 38% received reimbursement for HT prescription expenses (Salmi et al., 2006, figure 3).

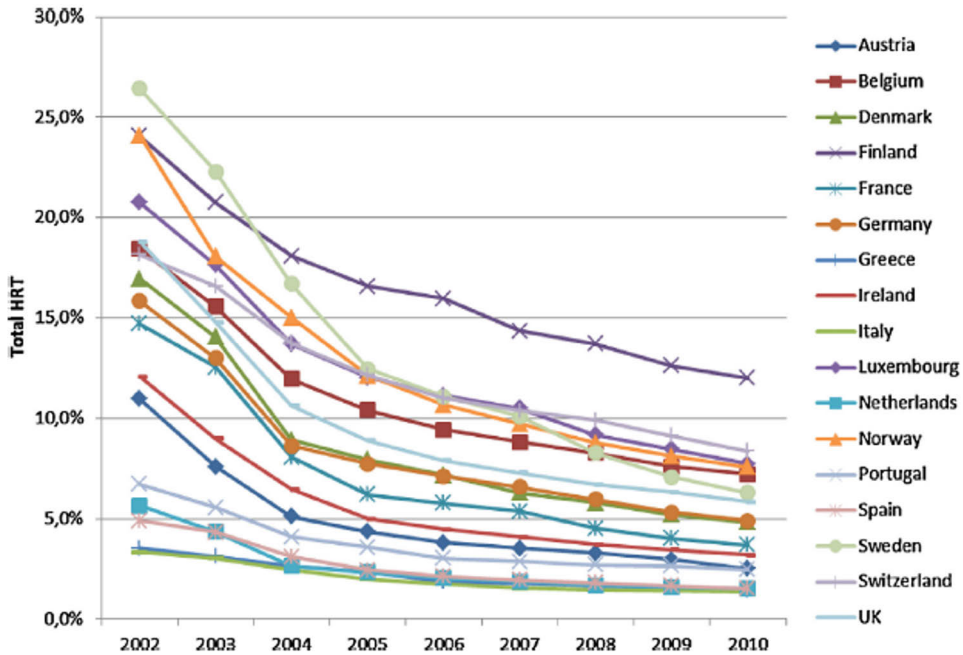


Figure 2. Changes in estimated proportion of women aged 45–69 years old, using HT, in 17 European countries based on Ameye et al., 2014. Reproduced with permission of the copyright holders

After publication of the WHI Study, the use of HT abruptly halved in the early 2000s but has been stable during the 2010s with about 5 million users in the USA and 1 million users in the UK (Beral et al., 2015). In 17 European countries, a profound decrease was seen, ranging from 50% to 77%, in the use of HT among women aged between 45–69 years. By the end of 2010, the HT uptake was lower than 10% in all these countries except Finland (Ameye et al., 2014). The use of HT in Finland was about 10% smaller between January and August 2003 compared to the same period one year earlier (Salmi et al., 2004). In 2005, HT use among Finnish 50–59 year-old women was 27% in Finland. The most frequent use was among 55–56 year-old women of whom 31% received reimbursement for prescription HT expenses (Salmi

et al., 2006, Figure 3). In 2012, the use of systemic HT was most prevalent (23%) among 56 year-old women (Holm et al., 2014). After the WHI results the sales of HT decreased in all Nordic countries, but the decrease was the lowest in Finland. The use of HT was most frequent among women of 50–59 years of age in Norway, Finland, and Sweden. In Finland, the estimated use of HT decreased from 43% in 2001 to 30% in 2005 (Hemminki, 2008).

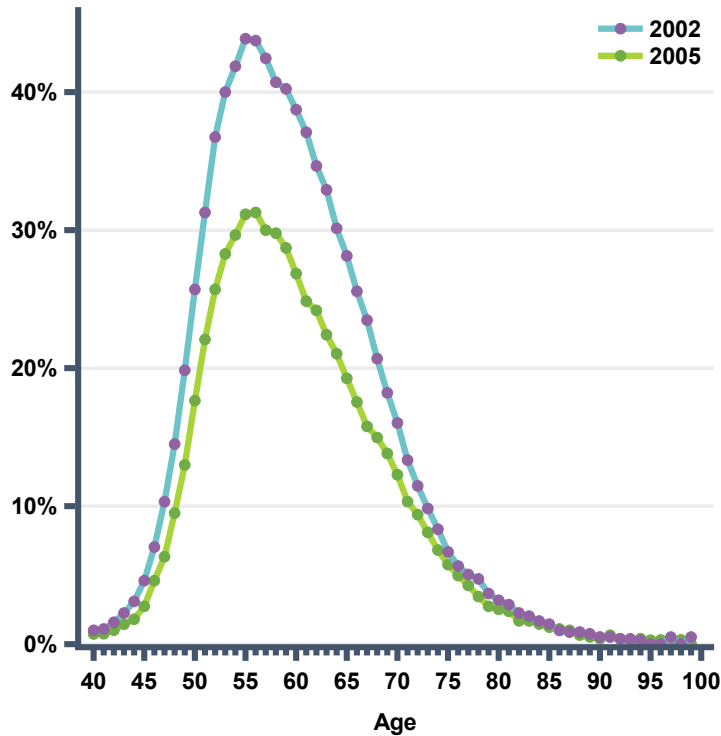


Figure 3. Women who have received reimbursement for HT prescription expenses and the % of these women from all the women of the same age in 2002 and 2005, modified from the original figure of Salmi et al., 2006. Reproduced with permission of the copyright holders.

2.6.2 Background factors

2.6.2.1 Sociodemographic factors

In previous studies, the users of HT have been found to be employed, have a partner, and better educated (Lucas & Barros, 2007; MacLennan et al., 2009). HT use was also more prevalent with a longer period of education, employment, and an individual's occupational status in a cross-sectional postal questionnaire survey from

1995 (Topo, 1995). However, the results from Sweden in 2000 showed that education and occupation did not affect the use of HT (Stadberg et al., 2000). Educational status did not affect HT use in a fairly recent Canadian study from 2017 (Costanian et al., 2018). In the same study, current employment was associated with a lower likelihood of HT.

Contradictory results between HT and the number of children exists. HT use has been more frequent among women without children (Manzoli et al., 2004) but in other studies it was not a determinant for the use of HT (Fistonic et al., 2004; Lucas & Barros, 2007).

2.6.2.2 Health behaviour

Structured exercise programmes have shown potential to reduce and alleviate vasomotor menopausal symptoms, but the evidence still remains insufficient (Daley et al., 2014). A cohort study showed that the effects of a 24-week trial of aerobic training still had positive effects after 4 years, especially for those women with the least amount of hot flushes (Mansikkamäki et al., 2016). In a recently published Swedish study a resistance-training lasting 15 weeks decreased the frequency of troublesome hot flushes among postmenopausal women (Berin et al., 2019). Regular sports practice was an independent determinant of HT use among Portuguese menopausal women (Lucas & Barros, 2007).

Obese and over-weight women tend to use less HT (Manzoli et al., 2004; Costanian et al., 2018), but in some studies there was no correlation between HT use and BMI (Pacello et al., 2018).

Regular smoking has been associated with a lower likelihood of current HT use (Ekström et al. 2003; Costanian et al., 2017) and use of HT was more frequent among those who had never smoked (Lucas & Barros, 2007). On the other hand, there are results showing no correlation between HT use and smoking (Manzoli et al., 2004; Pacello et al., 2018).

Alcohol consumption was a positive predictor of HT use in studies from Canada and USA (Costanian et al., 2017; Cauley et al., 1990) but not in the study from Portugal and Brazil (Lucas & Barros. 2007; Pacello et al., 2018).

Higher prevalence of HT use is associated with bilateral oophorectomy (Pacello et al., 2018; Costas et al., 2015; Stadberg et al., 2000). In a study from Portugal (women mean age 62.3) oophorectomy and HT use were more frequent among younger women but the age-specific prevalence of HT use was not significantly higher in any of the age groups (Lucas & Barros, 2007).

Women having a history of breast cancer have naturally lower prevalence of HT use, because systemic therapy is contraindicated after having breast cancer (Costanian et al., 2017). However, in one survey from Italy no difference was found

in HT use between women with and without a history of breast cancer. (Manzoli et al., 2004).

Women using antidepressive-medication, cardiovascular drugs or gastric acid-medication were found to be more frequently current users than those women who had never used HT (Ekström et al., 2003). Discontinuation of HT in menopausal women was associated with a 24% increased risk of starting antidepressants (Citarella et al., 2012).

In summary, Chapters 2.6.2.1 and 2.6.2.2 indicate that HT users are in general better educated, in a relationship, employed, consume alcohol, do not smoke, and are of normal weight.

2.6.2.3 Psychosocial factors, vasomotor symptoms and the use of hormone therapy

HT remains the most effective treatment for VMS. Those women who are younger than 60 years, have no contraindications and are within 10 years of the onset of the menopause benefit most from this treatment as regards troublesome VMS. Clinicians should try to find for each individual woman the most appropriate HT type, formulation, dose, and route. At regular intervals, the HT treatment should be checked, and the need estimated for further HT treatment – maximizing the benefits and minimizing the risks of use (North American Menopause Society, 2018).

HT treatment with estrogens alone or in combination with progestogens were associated with a small to moderate improvement in sexual functioning, particularly decreased pain in intercourse, when used for women with menopausal symptoms or in early postmenopause (within five years of amenorrhoea), but not in unselected postmenopausal women. In the Cochrane analysis, evidence regarding other HTs (synthetic steroids and SERM) was of low quality and their effect on sexual functioning was uncertain (Nastri et al., 2013). In many studies, HT has at least a minor positive effect on sexual functioning (Gambacciani et al., 2003; Veerus et al., 2012; Polisseni et al., 2013). In addition to hormones many other biological and psychosocial factors affect the libido (Kero et al., 2016). However, often local estrogen is enough for older women to alleviate urogenital symptoms like vaginal pain, urinary incontinence, pain in coitus and urinary tract infections (Mäkinen et al., 2001).

Little research has been done on the effectiveness of HT on stress. There are however studies on how stress influences vasomotor symptoms. In the presence of stress, estrogen may protect certain types of cognition. This kind of protection which estrogen offers under stressful situations can be beneficial to both the neural circuitry maintaining cognitive faculties and to cognition itself –also after acute stress situations (Herrera et al., 2017). A comparative study from Japan showed that

women who were vulnerable to stress had worsening climacteric symptoms during stress (Igarashi et al., 2000).

In a cross-sectional study, researchers showed that a poor working environment with interpersonal problems exacerbates menopausal symptoms (Hammam et al., 2012). Similar results from an online survey revealed that VMS were milder among women with good supervisor support (Bariola et al., 2016). In a cross-sectional study, researchers recently showed that lower stress correlated with minor menopausal symptoms (Sood et al., 2019). A nationwide cross-sectional study from Germany demonstrated an increasing severity of hot flushes with increasing stress perception and vice versa; hot flushes may also increase the experience of stress (Weidner et al., 2020).

Aaron Antonovsky (1923–1994) developed the theory of a sense of coherence (SOC). SOC is one of the psychosocial factors influencing mental health and appears to be effective for personal stress situations. A strong SOC is quite a stable characteristic. An individual with strong SOC has good resources to resist stressful situations and is able to maintain a sense of well-being (Antonovsky 1987). Caltabiano and Holzheimer had already reported in 1999 that a strong SOC is beneficial to health outcomes during menopause and that it has a positive effect on adaptation during menopause. Women with a strong SOC reported fewer menopausal symptoms (Caltabiano & Holzheimer, 1999). In a recent review study investigating resilience factors during menopausal transition, SOC was one of the resilience factors that had a positive effect on the experience of menopausal symptoms. In universal, higher resilience was associated with fewer and milder physical and psychological menopausal symptoms (Suss & Ehlert, 2020). In a Chinese study, the relationships were examined between menopausal symptoms, SOC, quality of life and coping strategies. The women who experienced more severe menopausal symptoms seemed to have a weaker SOC. They were also often prone to using more maladaptive coping styles which caused a poorer quality of life (Ngai, 2019).

Hostility has previously been shown to be associated with poor medical adherence (Christensen et al., 1997) and poor therapeutic alliance (Burns et al., 1999). A prospective cohort study from France did not find any association between hostility and HT use (Lemonage et al., 2012). On the contrary, chronically stressed postmenopausal women using HT reported lower levels of hostility compared to those who did not use HT (Steffen et al., 1999).

Optimism seems to have a positive effect on adaptation to menopausal symptoms (Caltabiano & Holzheimer, 1999; Elavsky & Mc Auley, 2009; Suss & Ehlert, 2020), while low optimism correlated with depressive symptoms (Bromberger et al., 2015). The purpose of the study from the USA was to discover personality dispositions which affect the reporting of vasomotor symptoms. Four traits were tested

(optimism, trait anxiety, pessimism, and neuroticism) and the results suggested that high trait anxiety and low optimism cause women to be more vulnerable to negative vasomotor and psychological symptoms (Elavsky & Mc Auley, 2009).

According to a review study from Finland, HT may alleviate depressive symptoms related to the menopause. Antidepressants should be combined with HT in severe depressive conditions among postmenopausal women (Toffol et al., 2015). In a consensus recommendation from 2018 it was stated that estrogen therapy is not recommended for the treatment of depression related to the menopause. However, there is evidence of the antidepressant effects of estrogens in women around menopause, especially among those simultaneously having vasomotor symptoms. Information about treatment with estrogen plus progestin is still inconclusive and sparse (Maki et al., 2018).

HT can alleviate sleeping problems related to vasomotor symptoms (Cintron et al., 2017). In a study from Kalleinen et al., it was shown that postmenopausal women's quality of sleep did not improve with estrogen-progesterone therapy (Kalleinen et al., 2008). It is still uncertain whether HT really makes the quality of sleep better by a direct influence on the central nervous system or whether the reason is a mediation of climacteric symptoms, especially by alleviating vasomotor symptoms (Lampio, et al., 2018).

2.6.2.4 Reasons to start hormone therapy

Former studies have shown that women start HT mainly because of the desire for VMS relief. Depression, irritability, mood changes, sleeping disturbances, joint pains, vaginal dryness, incontinence and urinary tract infections, problems with sexual life are the other reasons to start HT. Women have been motivated to start HT for prophylactic purpose like avoiding osteoporosis and cardiovascular diseases or improving health-especially before the studies published in the beginning of 2000 (Ettinger et al., 2003; Thunell et al., 2005; Øren, 2009; Crawford et al., 2018). The common reasons to start HT in a cohort study from the USA between the years 1996–2013 (both pre and post -WHI) were provider advice and menopausal symptom relief. Before the WHI results, the most commonly used reasons to start HT were prevention of heart disease and osteoporosis, but after the WHI results were published this was no longer the case (Crawford et al., 2018).

The opinion of physician affects women's decision to start HT (Levens & Williams, 2004). Different beliefs of physician about the safety of HT cause different prescribing practices and also advising strategies (Bush et al., 2006).

2.6.2.5 Reasons to discontinue hormone therapy

In a Swedish questionnaire study collected in 1992 and 1998 the most common reasons to discontinue HT were: no remaining symptoms, weight gain, fear of side-effects, fear of cancer, physician's recommendation, dislike of bleedings and breast tenderness (Thunell et al. 2005). In a questionnaire study from Norway made in summer 2005, the motives for permanent discontinuation were anxiety about the side effects, to see if the climacteric symptoms had ceased, experiencing side effects, and a recommendation by the doctor (Øren, 2009). In a Finnish questionnaire study from 2009 half of the respondents had experienced fears related to HT use. One third of the women using systemic HT had considered stopping using HT because of long-term use, fear of cancer and adverse reactions (Tiihonen et al., 2011). In a longitudinal, prospective cohort study between 1996–2013 the media reports and provider advice had more effect on women's decisions to discontinue HT post-WHI than pre-WHI. Contrary to current guidelines, a large decline has occurred in HT use in those subgroups for whom HT is mostly recommended i.e. those with more vasomotor symptoms and younger women. (Crawford et al., 2018, Salmi et al., 2004). For primary ovarian insufficiency patients HT is recommended until the normal age of menopause because of elevated risk for osteoporosis and cardiovascular diseases (Oksjoki & Jokimaa, 2015).

2.7 Recent recommendations for the use of hormone therapy and a summary of the factors affecting the use

The American Association of Clinical Endocrinologists and the American College of Endocrinology Position Statement updated the recommendations for the use of HT in 2017 (Cobin & Goodman, 2017). The updated recommendation takes into account the new clinical trials and new information regarding the benefits and risks of HT. The most effective treatment for vasomotor symptoms and other symptoms of the climacteric is HT. Benefits from the use of HT may exceed the risks for the majority of symptomatic postmenopausal women who are under the age of 60 or have less than 10 years since the onset of the menopause. Because of the greater absolute risks of a stroke, coronary heart disease, venous thromboembolism, and dementia the benefit-risk ratio is not as encouraging for women who initiate HT more than 10 or 20 years after the onset of the menopause or are 60 years or older. If HT is used for a longer period of time because of persistent VMS or bone loss, it should be approved in consultation with the women using the HT and controlled regularly. When HT is used transdermally the risk of thromboembolic complications is smaller because the metabolism of the liver is avoided. In a systematic review from 2015

even transdermal very low-dose estrogens seemed to alleviate and reduce hot flushes (Corbelli et al., 2015).

For troublesome urogenital symptoms, the use of low-dose vaginal estrogen therapy is recommended (The North American Menopause Society, 2018).

In summary, Figure 4 shows the factors which affect the use of HT among menopausal women.

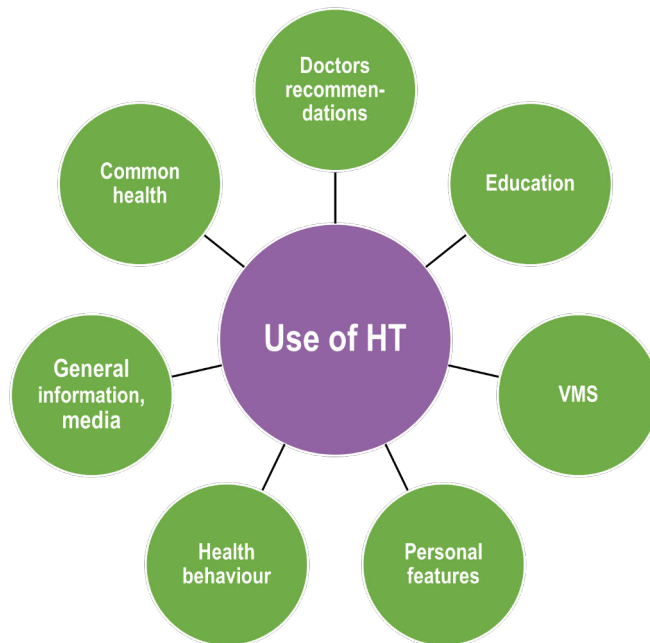


Figure 4. Factors affecting the use of hormone replacement therapy among postmenopausal women.

3 Aims of the studies

The purpose of the present study was to evaluate how Finnish women treated their climacteric symptoms in Finland before and after the controversial results at the beginning of the century and how the use changed after the publication of the results. Studies have been carried out to clarify personal characteristics associated with the initiation of HT and differences between psychological personality traits. The specific aims were:

1. To establish how 52–56 year-old Finnish women treated their climacteric symptoms in Finland in 2000, prior to the controversial reports by the WHI and MWS.
2. To examine why, in 2000, those women between the ages of 52–56 discontinued the use of HT during the following five years (2000–2005).
3. To investigate how personal traits, sociodemographic factors and health behaviours predicted the initiation of the HT among women born between 1954–1958.
4. To study the association between certain psychological behaviour patterns and use of HT among two cohorts of 52–56 year-old Finnish women in 2000 and 2010.

4 Materials and methods

4.1 Study designs

This dissertation consists of four publications based on follow-up questionnaires between 1998–2012. The use of HT of these two female cohorts (born in 1944–1948 and 1954–1958) and factors affecting the use as well as the reasons to begin or discontinue HT were evaluated in these cross-sectional studies. The information was obtained from the self-reported HeSSup -and QoL-questionnaires. The use of HT was obtained from the QoL-questionnaires in Studies I and II and from Social Insurance Institution of Finland (Kela)-registers in Studies III and IV.

Study I comprised all 52–56 year-old women of the cohort born in 1944–1948 who had participated the HeSSup-Study in 1998 and answered the QoL-questionnaire two years later in 2000. The 21 explanatory variables were derived from the HeSSup-questionnaire (1998) or the QoL-questionnaire (2000).

Study II was a follow-up cohort of the same women as in Study I during the following five years 2000–2005. The explanatory variables were derived from both the HeSSup-questionnaire (1998) and the QoL-questionnaire (2000, 2005).

Study III data were collected from the 40–44 year-old women in 1998 who had answered the HeSSup-questionnaire and then later QoL-questionnaire. The information explaining the use of HT was taken from those questionnaires closest to the time the woman started the use of HT. The information from the explanatory factors was used from the HeSSup questionnaire of 1998 and the QoL questionnaire of 2000 for those women who started HT in 1999–2003. For those women who started HT in 2004–2011, the explanatory factors were taken from HeSSup questionnaire of 2003 and the QoL questionnaire of 2005. The information on women who did not start HT at all was collected from the HeSSup questionnaire of 2003 and the QoL questionnaire of 2005. The severity of climacteric symptoms of both HT initiators and non-initiators were assessed from the response to the QoL questionnaires from the years 2000, 2005, 2010. The highest severity score from these responses was used in the analysis, irrespective of the year of the questionnaire.

Study IV was based on two cohorts of Finnish women aged 52–56 years in 2000 (women born in 1944–1948) and 2010 (women born in 1954–1958) who had

responded to the HeSSup questionnaire including four psychological behaviour patterns. The explanatory factors were derived for women between 52–56 years old in 2000 from HeSSup (1998) and QoL (2000) and for the younger cohort from HeSSup (2011) and QoL (2010) questionnaires (Table 2).

Table 2. HeSSup and QoL questionnaires used in studies I–IV.

Questionnaire	Study I	Study II	Study III	Study IV
HeSSup 1998	X	X	X	X
HeSSup 2003			X	
HeSSup 2011				X
QoL 2000	X	X	X	X
QoL 2005		X	X	
QoL 2010			X	X

4.2 Data sources

4.2.1 Digital and Population Data Services Agency

The Digital and Population Data Services Agency (DVV; VRK abbreviations are used in Finnish) maintains the register of the Finnish population. The DVV provides basic information such as names, personal identity codes, family relationships, addresses, native language, and parental citizenship. The DVV established a random population sample for HeSSup study in 1998 to represent the Finnish working-age population, stratified by age into four groups aged 20–24, 30–34, 40–44 and 50–54 years. In the present studies women were from age groups 40–44 (Study III, IV) and 50–54 (Study I, II, IV) years.

4.2.2 Prescription Register in Finland

In Finland, systemic HT is available on prescription only. The nation-wide Prescription Register is managed by the Social Insurance Institution of Finland (Kela). The register was founded in 1994, and it includes data on the dispensing date, birth date, gender, and residential area. For each drug, the dispensing date and the Anatomical Therapeutic Chemical (ATC) classification code are recorded. The following codes are used for HT preparations estrogens (ATC G03C), progesterones (ATC G03D), progesterones and estrogens in combination (ATC G03F). Other

ATC-codes used are for antidepressants (ATC N06A, ATC N06C), tranquilizers (ATC N05B) and hypnotics (ATC N05C).

In Study I and II the use of medication was obtained directly from the QoL-questionnaire whereas information concerning medication in Studies III and IV came from the registers of Social Insurance Institution of Finland (Kela). The data on medication was available for the years 1994–2011. The data from the questionnaires matched the data from the Kela register well. The self-reported use of systemic HT among women born between 1944–1948 was 47% in 2000, and from Kela's register 49%.

4.3 Subjects

The subjects in the studies were chosen from the nationwide randomized “Health and Social Support (HeSSup) study” which started in 1998. The HeSSup study is a longitudinal, prospective follow-up study on the psychosocial health of the Finnish working-age population. The Finnish Population Register established a random population sample in even-sized age groups 20–24, 30–34, 40–44, and 50–54 years of age.

The HeSSup study is based on a comprehensive questionnaire of 110 questions, mostly well-validated from international measures consisting psychosocial, behavioural, and medical questions. The baseline survey was established in 1998 when the questionnaires were sent to these four age groups. The initial response rate for women in 1998 was 47.7% after one reminder. The response rate for women born in 1944–1948 was 45.3% and for women born in 1954–1958 it was 45.5% (Korkeila et al, 2001). The following HeSSup-questionnaires were sent in 2003 and 2011–2012 to those who had answered the questionnaire in 1998 (Figure 5).

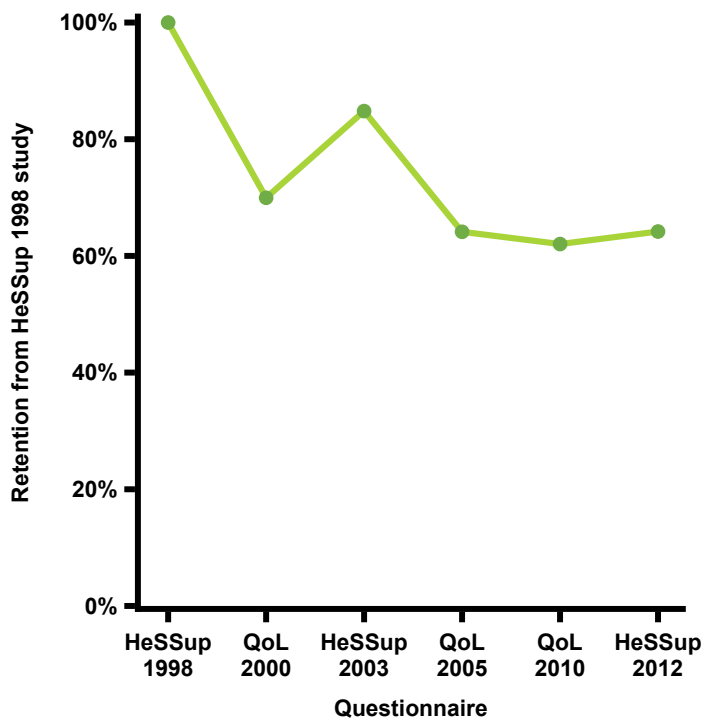


Figure 5. The retention rate in the HeSSup and QoL-follow-up questionnaires used in the studies. QoL-questionnaires were sent each time to those women born in 1944–1948 and 1954–1958 who had answered the HeSSup-questionnaire in 1998.

All 52–56 and 42–46 year-old women in 2000 (corresponding to birth cohorts born in 1944–1948 and 1954–1958) who had answered the HeSSup questionnaire in 1998 received the “Quality of Life Among Middle-Aged Women Study” (the QoL Study) questionnaire two years later. This questionnaire included 29 questions focusing on climacteric symptoms, sexual activity, gynaecological background and the use of HT or other treatments for climacteric symptoms. It also contained questions related to starting or stopping the use of HT. The follow-up QoL-questionnaires were sent in 2005 and 2010 to the same population as in 2000.

4.4 Outcome variables

In Study I the outcome of interest was the use of HT among 52–56 year-old women in 2000 as explained by the 12 physical and 9 background and social variables before the WHI results.

In Study II the interest focused on the same group of women as in Study I, but the interest was on the outcome of how many of the women used HT in 2005 and how many had discontinued HT use between 2000–2005 and why this had occurred.

Study III focused on the initiation of HT and to possible explanatory factors predicting the use of HT among 42–46 year old women in 2000.

Study IV focused on the relationship between psychological behaviour patterns (hostility, stress, optimism, and SOC) in two cohorts of 52–56 year-old women and how the experience of menopausal symptoms is related to the use of HT.

4.5 Explanatory factors

Explanatory factors were used to identify differences in sociodemographic factors, health behaviour, physiological and mental symptoms, personality, and sexual functioning among women between the HT users and the non-HT users. Information on the explanatory factors in all these four studies were collected from the women who answered the HeSSup-and QoL-questionnaires.

4.5.1 Sociodemographic factors

Living alone or with a partner and the number of children (none /one or more) were included, as well as basic (< 9 years, 9 years, >9 years) and professional education (none, vocational, college, university). The employment status was regarded as employed or unemployed. The alternatives given for the question on the reasons for starting HT were: severe climacteric symptoms to maintain health and prevent diseases, family history or other reasons. Women were also asked if they had received sufficient information about the positive and negative effects of HT from a physician before starting HT. HT use in complete years was calculated.

4.5.2 Personality and sexual satisfaction

Sense of coherence (SOC) was measured using Antonovsky's 13-item scale (Antonovsky, 1993) which was one part of HeSSup-questionnaire. This questionnaire covers three components of SOC: comprehensibility, manageability, and meaningfulness of life. Each item was scored from 1 to 7, and the total score varied from 13 to 91, where low scores represented a weaker SOC. In a prospective study from part of HeSSup-population the 13-item SOC measure seemed to have relatively high structural validity and high stability. SOC also seemed to become more stable following maturation (Feldt et al., 2007).

Hostility was measured with three questions “do you get angry easily” (scale 1–7/ easily-not easily) and “how easily do you become irritated” (score 1–7/very easily-

not easily) and “how often do you quarrel” (score 1–7/very often-very seldom or never). The total hostility varied from 3–21, a low score indicating a high degree of hostility (Koskenvuo et al., 1988).

The Reeder Stress Inventory was used to measure general perceptions of stressfulness in daily life (Metcalf et al., 2003). The questionnaire consists of four statements (1) “I am, in general, usually tense and nervous.”; (2) “There is great amount of nervous strain connected with my daily activities.”; (3) “At the end of the day, I am mentally and physically completely exhausted”; and (4) “My daily activities are extremely trying and stressful.” For each statement a score from 1–5 could be given and the total score varied from 4–20. Thus, a high score indicated a high degree of stressfulness.

The Life Orientation Test -Revised (LOT-R) was used to measure optimism with a 6-item version. Each item was scored from 1 to 5. The total score varied from 6–30, a high score indicating a high degree of optimism (Scheier et al., 1994).

Sexual satisfaction was examined with the question “Are you satisfied with your sex life?”, responses were measured on a scale of 1–7 and categorized as ‘very satisfied’ (values 1–2), ‘quite satisfied’ (values 3–5) and ‘not satisfied’ (values 6–7) (Ojanlatva et al., 2005).

Self-rated health questions with precoded answers strongly predict future health problems and mortality (Heistaro et al., 2001). The perceived health status was determined by the question “How is your health: good, rather good, moderate, rather bad or bad?” and the answers were divided into two categories good/rather good and moderate/rather bad/bad.

4.5.3 Health behaviour

Body mass index (BMI) was measured to identify women who were underweight or normal ($BMI < 25.0 \text{ kg/m}^2$), overweight ($25 \leq BMI < 30 \text{ kg/m}^2$), or obese ($BMI \geq 30 \text{ kg/m}^2$). Leisure time physical activity was measured with the Metabolic Equivalent Task (MET) (Ainsworth et al, 1993). Index and the respondents were classified as follows: In Study III physical activity per week was divided into $MET < 14$, $14 \leq MET < 30$, $MET \geq 30$, and in Study IV per day $MET < 2$ or $MET \geq 2$ MET. In Study II weekly exercise was divided into two categories: women who exercised at least 2–3 times weekly for at least 30 minutes each time and those who did less exercise.

Alcohol consumption was divided into two classes: never/none/mild (weekly consumption $\leq 22\text{g}$) or moderate/heavy users (weekly consumption $> 22\text{g}$). Smoking was classified either to three categories (never/previous/current) in Study III or two classes (no and previous/ regular smoking) in Studies I and IV.

4.5.4 Measurement of physiological and mental symptoms

Experience of climacteric symptoms were modified from earlier studies (Kupperman et al., 1953; Stadberg et al., 2000) and included twelve symptoms such as sweating, hot flushes, vaginal dryness and tenderness, recurrent urinary infections, urinary incontinence, sleeping problems, depression, irritability, dizziness, palpitation, dyspareunia and lack of sexual desire. The intensity of symptom was selected using a 10-item categorization, which were then divided into four categories: no symptoms (value 1), mild symptoms (values 2–4), moderate symptoms (values 5–7) and severe symptoms (values 8–10). For statistical purposes sweating, hot flushes, sleeping problems and vaginal dryness and tenderness, the four symptoms that have most often been associated with estrogen deficiency (Oldenhave et al., 1993), formed a sum score of 2–40. The symptoms were divided into none (values 2–4), mild (values 5–16), moderate (values 17–28) and severe (29–40) symptoms. Those who had responded to at least two of these four symptoms were included to statistical analysis.

Symptoms of sympathetic nervous system hyperactivity was measured on an 8-item scale (Vahtera et al., 2007). Sympathetic symptoms like irregular heartbeat, palpitation without exercise, sweating without exercise, flushing, tremor of voice, tremor of hands, muscle twisting and chest pain upon anger and emotion were included. The frequency of symptoms was regarded as daily, almost daily, weekly, or less often than weekly or never. When the mean score on these eight statements had been calculated, the women were classified as having a low, middle, or high level of sympathetic hyperactivity.

The Beck Depression Inventory (BDI) consisting of 21 questions was used to measure depressive symptoms. The sum score responses were classified and dichotomized to 1–18 (no depressive symptoms) and more than 18 (depressive symptoms) (Beck et al., 1988).

Sleep disturbances were measured by self-reported sleep and was determined by the answer to the question: “How well do you sleep in general” with replies on a 5-point response scale. The quality of sleep was dichotomized to undisturbed (well/rather well) and disturbed (rather poor/poor). If the woman had answered “Cannot say” it was coded as a missing response (Vahtera et al., 2007).

4.6 Statistical methods

In Study I, the associations between HT use and the 21 explanatory factors were analysed first with binary response logistic regression, where HT use was the binary response variable. The multiple logistic regression analysis consisted of all the significant factors ($p < 0.05$) from the single predictor logistic analyses. Only significant factors were included in the final model, which was carried out using the

backward variable selection method. All tests were two tailed and p-values < 0.05 were considered to indicate statistical significance (Jalava-Broman et al., 2008).

In Study II, the associations between discontinuation of HT between 2000–2005 and the explanatory factors were analysed with a single and multiple logistic regression analyses (Jalava-Broman et al., 2011).

In Study III, the association between starting HT and the explanatory factors were analysed in three stages. All significant associations or those close to it ($p < 0.1$) were then analysed in a multipredictor model with similar or associated variables in same groups. Those variables that still had a significant ($p < 0.1$) association were then analysed in the final logistic regression model, where $p < 0.05$ was considered to be of statistical significance. Women who started HT between 1.1.1999–31.12.2011 were included. Women who started HT before 1999 were excluded. The medication data for the years 1994–2011 was sampled from the national Prescription Register. For a woman to be classified as having started HT, the criterion was that a minimum of one HT prescription had been dispensed from a pharmacy (Jalava-Broman et al., 2016).

In Study IV, a latent profile analysis (LPA) was used in order to identify women with similar patterns of stress, hostility, optimism and SOC. The LPA's purpose was to identify unobserved subpopulations (latent classes) within the data (Muthén, 2008; Vermunt & Magidson, 2002; Wang & Bodner, 2007). To compare the identified latent classes an Akaike information criterion (AIC) and a Bayesian information criterion (BIC), and an Entropy value were used. Based on the estimates, a three-class solution was created including 1) high in stress and hostility, low in optimism and SOC 2) moderate in stress, optimism, SOC and hostility 3) low in stress and hostility, high in optimism and SOC (Jalava-Broman et al., 2020).

4.7 Drop-out analysis

The respondents with a high level of education replied more often to the HeSSup questionnaire in 1998 than those with less education. Those who responded after a reminder smoked and used more psychopharmaceutic drugs than those who responded without a reminder. This suggests similar features for late-respondents and non-respondents. On the other hand, smokers consented to participate to the study more often than non-smokers. The detailed and careful non-respondent analysis can be seen in another paper (Korkeila et al., 2001).

In the drop-out analysis of the QoL Study in 2000, basic and professional education, use of psychopharmaceutic drugs and employment status were examined (Jokinen et al., 2003). In this study, the women with a high level of basic and professional education responded more often than the rest.

In Study II a drop-out analysis was made of those women born in 1944–1948 who answered in 2000. Basic education, professional education, age, working status, and the use of HT did not differ between those who did or did not respond to the “Quality of Life” -questionnaire in 2005.

4.8 Ethical considerations

The Ethics Committee of Turku University Hospital considered that a statement of approval was not required. Although ethical approval is not needed for studies of this kind, the participants were requested to sign a document containing information about the study. This consent will be needed if subsequent studies are made with the same data set and information linked to specific registers. The ethical committee of the Social Insurance Institution of Finland accepted the application before allowing access to the information on the pharmaceuticals. Strengthening the reporting of observational studies in epidemiology (STROBE) guidelines were followed in the research and reporting in Study IV.

5 Results

5.1 Treatment of climacteric symptoms in 2000 (Study I)

This questionnaire study was made in 2000 before the WHI and MWS were published. At that time, two thirds (66%) of women born between 1944–1948 used some form of treatment for their menopausal symptoms and 46.7% of these women used systemic HT. Of those women who used hormonal therapy 58.7% used it orally. One third (32.2 %) favoured transdermal use (Table 3). Some women (9.1%) used systemic hormones both orally and transdermally. Overall, 34% of women did not use anything for their climacteric symptoms.

Table 3. Percentages of methods (%) used to alleviate climacteric symptoms among 52–56-year-old Finnish women (n=1270) in 2000, based on Jalava-Broman et al., 2008.

Method	% (n=1270)
Hormonal therapy	70.7 % (898)
Oral	58.7 % (527)
Transdermal	32.2 % (289)
Oral and transdermal	9.1 % (82)
Vaginal therapy (alone)	3.9 % (50)
Alternative treatment	25.4 % (322)
Vitamins, trace elements, natural products, diet, sports, etc.	83.8 % (270)
Sleeping pills, antidepressants, tranquilizers	8.4 % (27)
Combined	7.8 % (25)

Among HT users 50.9 % used only estrogen, 46.9% used cyclic or a combination therapy of estrogen and progestin, 1.2% used tibolone and 1 % used testosterone. Of the systemic HT users 3.5% also had a levonorgestrel intrauterine device. A minor part of the systemic HT users (4.9%) also used a local estrogen.

Use of systemic HT was linked to the severity of climacteric symptoms. Of the women with mild symptoms 37% used systemic HT, those with moderate symptoms 60% and those with severe symptoms 67%. At the beginning of 2000 however, 27% of those who used systemic HT used it without any climacteric symptoms while 33% of those women having severe symptoms did not use any HT.

Local vaginal estrogen was used as the only therapy in 3.9% among those using some form of treatment (50/1270) and 4.9% (44/898) of women used it together with systemic HT. Of all the women in the cohort 4.9% (94/1921) used a local estrogen treatment.

Alternative treatments like vitamins, trace elements, natural products, diet, sports, sleeping pills, antidepressants and tranquilizers were used by 25.4% of those women using some form of treatment.

The use of HT was associated with the severity of the climacteric symptoms, oophorectomy, level of education (the more professional education the more HT use), a higher alcohol consumption, low BMI and no history of breast cancer (Table 4).

Table 4. Factors explaining the use of HT among 52–56 year-old Finnish women in 2000 (in a multivariate logistic regression analysis), based on Jalava-Broman et al., 2008.

Explanatory variable	Odds ratio	95 % Confidence Interval	P-Value
Climacteric symptoms			<0.001
None	1.0		
Mild	1.54	0.92–2.56	
Moderate	4.76	2.83–8.00	
Severe	7.00	3.90–12.55	
Professional education			<0.001
None	1.0		
Vocational	1.17	0.87–1.58	
College	1.71	1.26–2.31	
University	2.00	1.39–2.88	
Alcohol intake			<0.001
Never/none/mild	1.0		
Moderate/heavy	1.53	1.23–1.89	
BMI			<0.001
>29.9	1.0		
25-29.9	1.60	1.14–2.23	
<25	2.20	1.59–3.04	
Oophorectomy			<0.001
No	1.0		
Yes	3.80	2.60–5.56	
Breast cancer			<0.001
Yes	1.0		
No	5.10	2.48–10.53	

5.2 Change in the frequency of HT use from 2000 to 2005 and the reasons for discontinuing (Study II)

In 2000, of the women in the 52–56 year-old Finnish cohort 47% (898/1921 women) were using systemic HT and five years later this figure had decreased to 35.9% (719/2001 women). In 2005, the most frequent HT use of 26.1% was among those women aged 59 years and was least used among 61 year-old women 17.6%. Local estrogen was used at the same time by 15.7% of woman using systemic HT. Altogether 17.5% (351 women of 2001) of the cohort used local estrogen. Other treatments but not systemic HT was used by 59.5% of the women. A minor section of the women, only 4.6%, did not use any treatment for their climacteric symptoms.

Of those women who responded in 2005, a total of 23.5% (471/2001 women) had also used HT 5 years earlier. They had used it for a median of 10 years and had started it at a median age of 50.4 years. Those women who discontinued HT had started the use at the same median age and had used it for 7.5 years.

The main reason to start HT were severe climacteric symptoms for both those who used HT in 2000 and 2005 (65.2%) and for those who used HT in 2000 but no longer in 2005 (69.5%). “To maintain health and prevent diseases” was the reason to start for 39.7% of users and 45.5% for those who had stopped using HT between 2000–2005. There were no significant differences between those who continued HT and those who discontinued HT (Table 5).

Table 5. Reasons to start HT among the cohort of women born 1944–1948 who continued or stopped HT in 2005*, based on Jalava-Broman et al., 2011.

Reasons to start HT	HT users in 2000 who continued in 2005 (%, n=423)	HT users in 2000 who have stopped HT use in 2005 (%, n=187)
Climacteric symptoms	65.2	69.5
To maintain health and prevent diseases	39.7	45.5
Family history of illness	15.6	13.9
Other reasons	22.7	20.9

*It was possible to choose more than one reason.

The desire not to use HT was the most common reason (69%) to stop HT use. The other main reasons to stop using HT were the side effects of HT (42%), anxiety due to the recent research reports (38%) and a fear of cancer (36%). Breast cancer, physicians' recommendations and absence of climacteric symptoms were the other reasons (28%) to stop HT use (Table 6).

Discontinuation of using HT was predicted by older age ($p < 0.01$), maintaining the health as the reason to start HT ($p < 0.05$), and a shorter HT use 7.5 years versus 10 years ($p < 0.001$).

Table 6. Reasons to discontinue HT in 2005 among the cohort born in 1944–1948 ($n=188$)*, based on Jalava-Broman et al., 2011.

Reasons to discontinue HT	Overall distribution (n)	Percentage
Desire not to use HT	129	68.6
Side-effects of HT	79	42.0
Tenderness of breast	29	
Excess weight	29	
Hypertension	14	
Bleeding	13	
Mood fluctuations	11	
Headache	11	
Lack of sexual desire	9	
Depression	5	
Eczema	4	
Nausea	0	
Anxiety to recent reports	71	37.8
Fear of cancer	67	35.6
Other reasons	53	28.1
Cost	14	7.4
Poor effect	7	3.7
Difficult method of administration	2	1.1

*It was possible to choose more than one reason.

5.3 Characteristics associated with initiation of HT (Study III)

To discover which women's characteristics predict the initiation of HT in a cohort of Finnish women between the ages of 42–46 in 2000, single- and multi-predictor analyses were performed. Moderate and severe climacteric symptoms were the strongest predictors for starting HT. A BMI of less than 30 kg/m², a weaker SOC, a higher level of symptoms in the sympathetic nervous system, use of psychopharmaceuticals, high or moderate alcohol consumption, and living with a partner were also predictors for starting HT (Table 7).

SOC and climacteric symptoms were analysed further as predictors of HT initiation. Using climacteric symptoms as the covariate, the association between SOC and HT initiation still remained statistically significant ($p=0.002$) and did not interact significantly with the symptom score (2-way model, interaction $p=0.433$). In conclusion, climacteric symptoms do not modify the association between SOC and the initiation of HT. Regardless of the severity of climacteric symptoms SOC seemed to be associated with initiation of HT.

Table 7. Associations between explanatory variables and starting HT (summary of multi-predictor logistic regression analyses), based on Jalava-Broman et al., 2016.

Explanatory variables	Final model OR (95 % CI)	p
Living alone		<0.001
No (1163)	1.67 (1.26–2.21)	
Yes (334)	1 (ref.)	
SOC		0.012
SOC 0–25% (313)	1.62 (1.13–2.32)	
SOC 25–75% (792)	1.46 (1.10–1.90)	
SOC 75–100% (392)	1 (ref.)	
BMI		<0.001
Obese (207)	1 (ref.)	
Overweight (462)	1.75 (1.20–2.55)	
Underweight/normal (820)	2.45 (1.71–3.50)	
Alcohol consumption		0.026
Moderate/heavy (931)	1.32 (1.03–1.67)	
Abstinent/mild (569)	1 (ref.)	
Symptoms of SNS		<0.001
Lowest tertile (544)	1 (ref.)	
Middle tertile (565)	1.86 (1.40–2.47)	
Highest tertile (385)	1.34 (0.98–1.84)	
Climacteric symptoms		<0.001
None (70)	1 (ref.)	
Mild (655)	0.92 (0.53–1.61)	
Moderate (600)	2.44 (1.38–4.30)	
Severe (223)	4.68 (2.48–8.83)	
Use of psychopharmaceuticals		0.008
No (1427)	1 (ref.)	
Yes (140)	1.80 (1.17–2.77)	

5.4 Psychological behaviour patterns and coping with menopausal symptoms in 2000 and 2010 (Study IV)

Women born between 1944–1948 at the age of 52–56 years ($n=1601$) seemed to have more stress and a weaker SOC than women at the same age born 10 years later. In 2000, of the women aged 52–56 years, 61.5% used HT and in 2010 38.5% used HT. HT users reported a lower SOC and more stress and hostility than nonusers (Table 8).

Table 8. Means, standard deviations and the significance of differences in stress, hostility, optimism and SOC between age group and between HT users and non-users, based on Jalava-Broman et al., 2020.

	Born 1944–1948 ($n=1601$)	Born 1954–1958 ($n=1794$)	Difference between age groups		Systemic HT non- users ($n=2111$)	Systemic HT users ($n=1284$)	Difference between non-users and users
	Mean (SD)	Mean (SD)	p		Mean (SD)	Mean (SD)	p
Stress	9.23 (3.11)	8.88 (3.05)	0.003		8.81 (3.06)	9.42 (3.15)	0.001
Hostility	8.36 (3.89)	8.09 (3.74)	0.065		8.02 (3.71)	8.52 (3.95)	0.001
Optimism	22.78 (3.72)	22.75 (4.17)	0.848		22.79 (3.98)	22.74 (3.93)	0.750
SOC	66.39 (11.31)	68.24 (11.15)	0.001		67.82 (11.23)	66.58 (11.28)	0.005

In this study three different psychosocial profile classes were formed which differed with respect to hostility, self-evaluated stress, SOC, and optimism. Class 1 (23.8%) consisted of women with more stress and hostility and less optimism and SOC. In class 2 (52.2%) the women were moderate as regards stress, hostility, optimism, and SOC and in class 3 (24.0%) the women had low stress and hostility and high optimism and SOC (Figure 6).

The use of HT was higher in class 1 (43%) than in class 3 (35%). Vasomotor symptoms were also higher in class 1 (mean=20.0, SD=0.36) than in class 3 (mean=15.3, SD=0.34).

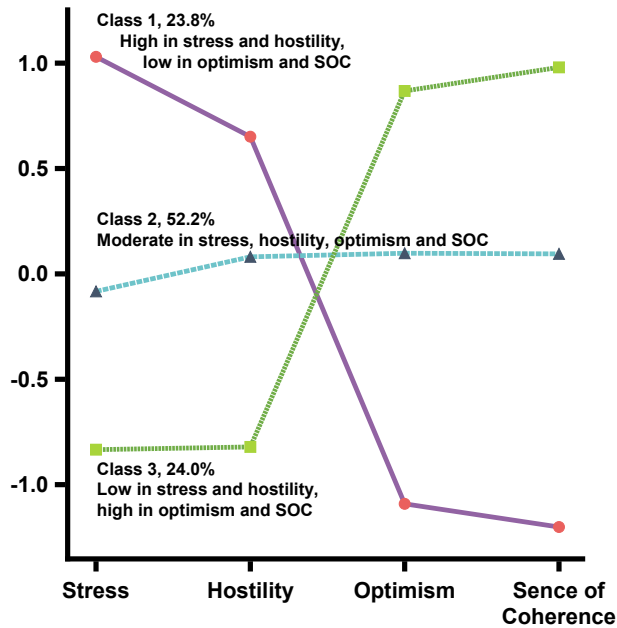


Figure 6. Standard mean values (vertical axis) of Latent Profile Analysis classes consisted of stress, hostility, optimism, and SOC.

The tested background variables differed between class 1 and class 3. More women in class 3 were in a relationship (78% vs 72%), more were professionally educated (65% vs 50%), and were more often still in work life (84% vs 66%). They also consumed less alcohol (48% vs 41%), were more physically active (81% vs 65%), had better self-estimated health (87% vs 40%), and less depressive symptoms (0% vs 33%).

6 Discussion

6.1 Summary of the results

The use of HT in Finland was quite common among Finnish middle-aged women at the beginning of 2000. From the cohort of 52–56 year-old women almost half of the women used systemic HT in 2000. One quarter of the users were symptomless whereas one third of non-users had severe climacteric symptoms. Severity of climacteric symptoms, higher level of education, alcohol consumption and lower BMI were positively associated with HT use.

The initiation of systemic HT was predicted by living with a partner, a BMI of less than 30, heavy or moderate alcohol consumption, symptoms of hyperreactivity of the sympathetic nervous system, moderate or severe climacteric symptoms and use of psychopharmaceuticals. The new finding, however, was that a low sense of coherence (SOC) was a reason for some women to start HT compared to those having good SOC.

The use of HT decreased from 2000 to 2005 among the same cohort of 52–56 year-old women in 2000 from almost a half to about third by 2005. At the same time use of local estrogen treatment increased and so did the use of alternative medications.

Climacteric symptoms were the main reason to start HT for both those women who continued and discontinued HT. To maintain health and prevent diseases were the reasons to start HT for almost half of the women who stopped using HT between 2000–2005. The main reasons for discontinuing HT between 2000–2005 were a desire to stay without HT mostly due to its side effects, the reaction to recent controversial findings in “HT publications” and fear of cancer. Those women who discontinued the use of HT were older and had used HT for a shorter time than those who continued. Maintenance of health as the reason to start HT use predicted also quitting.

The proportion of HT users among 52–56 year-old women born in 1944–1948 was higher compared to women at the same age born ten years later. These women had a poorer SOC and were more stressed than women of the same age one decade later. Generally HT- users reported more stress and hostility and a poorer SOC than the non-users. In those women exhibiting more stress and hostility and less optimism

and a poorer SOC the menopausal symptoms were also more prevalent. These kinds of personal characteristics related to the use of HT have not been the subject of many publications previously.

6.2 General discussion

6.2.1 The use of HT

At the beginning of the 2000s, almost half of the women between the ages of 52–56 years in this studied cohort used systemic HT. After the WHI and the MWS the use of systemic HT decreased all over the world (Beral et al., 2015). During 2000–2009 in the USA the use of oral HT declined from 19% to 5% (Steinkellner et al., 2012). In 2002, the use of HT in 17 European countries among women aged between 45–69 years varied ranging from less than 5% to more than 25% (Figure 2). A significant decrease in HT use occurred in all these countries after the WHI was published. In 2010, the use of HT was under 10% in all these other countries, although not in Finland (Amey et al., 2014, Figure 6). The use of HT in 2003 was at its highest, 41% among 56 year-old Finnish women but then declined to 23% in 2012. Total (local and systemic) use remained common among women aged 55–59 years, but the number of systemic HT users decreased from 40% to 22% while the use of vaginal estrogen increased from 11% to 23% between the years 2003–2012 (Holm et al., 2014). An equal trend was also seen in the USA, where users favoured vaginal estrogen more than before (Steinkellner et al., 2012). In this study, the use of local estrogen was found to be 4.9% in the cohort of 52–56 year-old women in 2000 and increased to 17.5% for the same women five years later. HT use was still rather high 35.9% among 57–61 year-old women in 2005 and was most prevalent among 59 year-old women.

6.2.2 Vasomotor symptoms, symptoms of sympathetic nervous system and the use of hormone therapy

VMS was the strongest predictor of the initiation of HT and explained the use of HT. VMS was also the main reason to start HT among the 52–56 year-old women. The main reason to start HT should be VSM (Tiitinen, 2019) and this was the most common reason to start HT in the present study too.

Symptoms of sympathetic nervous system (SNS) hyperactivity also predicted the use of HT. SNS symptoms like palpitation, flushing and sweating are quite similar to vasomotor symptoms. The etiopathology behind vasomotor symptoms is not yet clear. Decline in estrogen levels and an overactivity of the SNS are related to VMS. Low endogenous estrogen and an elevated activity in the SNS are partly responsible

for narrowing the thermoneutral zone in the thermoregulatory center in the brain. These changes in temperature regulation then cause minor increases in the core body temperature triggering vasomotor symptoms in symptomatic women (Freedman, 2014). In a review by Wyss and Carlson estrogen was reported as appearing to reduce SNS activity and thereby having antihypertensive effects (Wyss & Carlson, 2003).

6.2.3 The effect of sociodemographic and health behaviour to the use of hormone therapy

A higher level of education explained the use of HT in the present study and similar association has been reported in earlier studies (Lucas & Barros, 2007; MacLennan et al., 2009; Manzoli et al., 2004). Women with more education may have a higher level of knowledge and awareness about HT and more ability to obtain information about the menopause than less educated women (Domn et al., 2000, Donati et al., 2009). However, in this study among the women born between 1954–1958, a higher level of education did not predict the use of HT. There is a ten-year difference between the birth cohorts which has meant an increase in the level of education, so that 48% of women born in 1944–1948 had a basic education of under 9 years compared to 27% for those women who were born in 1954–1958 (Jokinen et al., 2003). This was perhaps one of the reasons why the level of education no longer predicted the use of HT among women born 10 years later. In a study from Brazil between 2012–2013, the educational level did not affect the use of HT, but women who obtained information about the menopause from healthcare workers and who had extensive knowledge about menopause were associated with a higher prevalence of HT use (Pacello et al., 2018).

Living with a partner predicted the start of HT among women born in 1954–1958 but did not explain the use of HT among women born in 1944–1948 in the present study. An Australian population-based study from 2008 showed that HT use was significantly more common in women in partnerships (Mac Lennan et al., 2009). A study from Lithuania showed that HT is beneficial to lubrication, satisfaction, desire, and lower pain and in that way improves sexual life (Jonusiene et al., 2013). In a randomized clinical trial of HT in early postmenopausal women, treatment with transdermal estradiol therapy contributed modest benefits to sexual functioning in early menopausal women (Taylor et al., 2017).

Earlier studies have shown that VMS are more frequent among alcohol drinkers than non-drinkers (Parazzini et al., 2005; Katainen et al., 2014), but there are also contradictory results showing that alcohol intake was significantly associated with decreased hot flushes (Gallicchio et al., 2015). In a study from Finland, middle-aged women who consumed more than 16 portions of alcohol weekly, had more vasomotor symptoms than women who consumed fewer than 10 portions of alcohol

weekly (1 portion=12 g pure alcohol) (Moilanen et al., 2010). In this study, moderate or heavy alcohol consumption predicted initiation and explained the use of HT. The association between alcohol intake and HT has also been noted previously (Cauley et al., 1990; Costanian et al., 2018). It may also be so that women first used alcohol to relieve their climacteric symptoms, but later started HT.

Below normal or normal body weight has been reported as being a determinant of HT use (Du et al., 2005; Costanian et al., 2018) and this was also confirmed by the present study. Normal or underweight predicted HT initiation and explained the use of HT. The connection between body weight and the occurrence of hot flushes in menopausal transition is not clear. In a recently published study, the risk of increased VMS was associated with a higher BMI around menopause, but was reduced in postmenopause (Anderson, 2020). VMS are related to overactivity of SNS and this excess sympathetic activity may in turn be associated with a metabolic syndrome (Tuomikoski & Savolainen-Peltonen, 2017). However, BMI or its changes were not related to hot flushes in a 5-year cohort study from Maryland (Gallicchio et al., 2014). In a French cohort study during a 10-year follow up period the risk of the onset of menopausal symptoms was lower in underweight, overweight, and obese postmenopausal women (Sabia et al., 2008).

Alternative therapies have become more popular for symptom relief among menopause-aged women. Of the women in 2000 at the age of 52–56 years one out of five used some therapy but not systemic HT for their climacteric symptoms. Compared to these same women 5 years later the use of alternative therapies had increased to three out of five. In a systematic review based on nine surveys published between 2000 and 2012 half of the menopausal women reported using complementary and alternative medication (Posadzki et al., 2013).

Use of psychopharmaceuticals predicted use of HT in women born between 1954–1958 in the present study. After the WHI results the number of HT prescriptions decreased and the number of serotonergic antidepressants increased (Mc Intyre et al., 2005). In addition, the women who had stopped HT had an increased risk of starting treatment with antidepressants (Vegter et al., 2009; Citarella et al., 2012). In the present study the women perhaps first tried to alleviate their symptoms with antidepressants, but with worsening climacteric symptoms started later to use HT.

6.2.4 HT use and personality and character traits

The publication of the first set of results from the WHI changed the hormonal landscape and confused women about HT use. HT was no longer the drug of choice for primary or secondary prevention of diseases. Individual factors like woman's characteristics, attitudes, values, beliefs, and preferences as well as external factors

including information, health care, opinions of physician and facts started to affect the decision for the treatment and management of menopausal symptoms (Levens & Williams 2004; Bush et al., 2006; Carpenter et al., 2011)

Character traits and personality has become a popular target in research because these factors may affect the severity of climacteric symptoms and perceived quality of life during the menopausal transition. Women's capacity to tolerate hot flushes seems to vary quite considerably. Flushes that are hardly noticed by some women may for other women be intolerable (Freeman et al., 2005). However, studies of HT use and different psychosocial factors related to use are sparse. HT is used for vasomotor symptoms and the stronger the symptoms are the more HT is usually used. Different character traits affect the experience of climacteric symptoms either making them worse or milder. The influence of vasomotor symptoms may indirectly affect the use of HT.

A weak SOC predicted HT use in the present study. HT users also reported more stress and hostility and a poorer SOC compared to non-users. SOC has not previously been reported as being related to the initiation of HT to the best of the authors knowledge.

In a Chinese study from 2019, women with severe menopausal symptoms had a weaker SOC and they experienced a poorer health-related quality of life. In contrast, women with a higher level of SOC, had a better health-related quality of life and they were less prone to menopausal symptoms (Ngai, 2019). Women with a strong SOC reported more days without stressful events and less stressful events than those with a weak SOC in a study among women having breast cancer (Sarenmalm et al., 2013). In accordance with the nature of SOC, women with a strong SOC and better stress control manage stressful situations like climacteric symptoms better without HT than those women with a weaker SOC. Former studies have shown that higher resilience and mindfulness are associated with milder menopausal symptoms (Zhao et al., 2018; Sood et al., 2019). It might be that high resilience is associated with a strong SOC and positive coping strategies. Estrogen did not alter stress-coping in women with moderate to severe VMS, but relieved the VMS (Nedstrand et al., 1998). This indicates that stress-coping is associated with the SOC and is not changed by the HT, and this was also the situation in the present study (results in the study IV).

Menopausal symptoms were more prevalent in the group of women exhibiting more hostility and stress and less optimism and a poorer SOC. One may surmise that those HT users in this group had experienced the menopause differently and were more likely to be using HT at the time of the survey than their counterparts who did not exhibit these psychological behaviour patterns. Optimism and strong SOC has previously been shown to positively affect the experience of climacteric symptoms in menopausal and postmenopausal women (Caltabiano & Holzheimer, 1999). In

this study, women with a high SOC, optimism, low hostility and low stress seemed to manage climacteric symptoms more often without HT.

In this modern world women can live almost half of their lives in the postmenopausal stage and working life is becoming increasingly demanding and hectic. For some women, menopausal symptoms, especially vasomotor symptoms, can be quite severe and decrease their quality of life. It is important to know how to give women the exactly correct and individual treatment for their menopausal symptoms. In addition to climacteric symptoms, clinicians should take note of the woman's own attitudes, health situation, personal characteristics, and surrounding circumstances of her daily life. There are other options available for those with vasomotor symptoms who prefer not to use HT or who have contraindications for HT.

6.2.5 The reasons to start and stop hormone therapy use

Menopausal symptoms, in this study, proved to be the most common reason to start HT for both those who continued (65.2%) and discontinued (69.5%) HT, which supports the results from previous studies (Øren, 2009; Thunell et al., 2005). Maintenance of health and prevention of diseases was the reason to start HT for almost half of the women born in 1944-1948. In a Norwegian study about one quarter of the women reported the initiation of HT for prophylactic reasons (Øren, 2009). In the present study, there were also women without symptoms who used HT in 2000, but there were also women with severe symptoms who did not use HT. Before the WHI the reported reasons to start could have been prevention of disease, increased feeling of well-being, and staying young as mentioned in literature (Collins & Landgren, 1997; Thunell et al., 2005).

In this study, those women who had used HT for a brief period were more likely to discontinue use compared to those who had been using it for longer. In Spain, in a study between 1998–2007, the findings were similar for users who had been on HT for a long time (average 8 years), but the results also showed that HT was started less often than before (Barbaglia et al., 2009).

The side-effects of the treatment, a fear of cancer and the physician's recommendation were the reasons to discontinue HT in Finland in 1995 (Vihtamäki et al., 1999). According to a Finnish questionnaire study in 2003 one third of the HT users had experienced fears concerning HT use and more than half of the HT users felt that the media had influenced their attitudes (Tiihonen et al., 2007). According to a Norwegian study fear of the side-effects of HT was the reason for discontinuing treatment (Øren, 2009). In a questionnaire survey in Finland half of the HT users were worried and had fears related to HT use. The most common fear was breast cancer (Tiihonen et al., 2011). Anxiety due to the recent research reports was one of

the reasons in this study for over one third (37.8%) of women discontinuing HT during 2000–2005. The present study confirms that the reasons to discontinue altered in the beginning of 2000. However, as before, the side-effects were still a significant reason to stop HT (42%). The impact of the media and the fear of cancer seems to have had a stronger influence on HT discontinuation in the 20th century than previously.

6.3 Methodological considerations, strengths and limitations of the study

The main strength of this study is that the Health and Social Support Study (HeSSup) is a longitudinal, prospective cohort study with a rather large sample size. HeSSup is a representative sample of the Finnish population in the age groups: 20–24, 30–34, 40–44, and 50–54 years at baseline 1998. The response rate after one reminder was relatively low, 40% in 1998, but no major physical health-related selection has been detected in a non-response analysis (Korkeila et al., 2001). Obviously, the rather low baseline response rate to the HeSSup questionnaire must be regarded as a limitation of the study, but it was shown to be sufficiently representative of the target population (Korkeila et al., 2001).

After the first survey, the response rates to the following HeSSup-surveys (2003 and 2011) were better, 81% in 2003 and 70% in 2011. These two HeSSup-surveys were sent to those respondents who answered the HeSSup questionnaire in 1998.

The response rate after one reminder from the QoL studies was rather good, 70% in 2000, 76% in 2005 and 72% in 2010. The QoL questionnaires were mailed each time to the same original group of women and the drop-out analyses did not disclose any severe bias.

The study describes Finnish menopausal middle-aged women quite well. The instruments used in this study are well-known and reliable. There has been a large set of comprehensive questionnaires in HeSSup with well-validated, widely used questions assessing social background, personal resources, personality, health behaviours and medical matters (medications, depressive symptoms, chronic diseases). Antonovsky's SOC model, Beck's depression scale and the Reeder Stress Inventory, for example, are well recognized, internationally used, and validated measures to estimate an individual's sense of coherence, depression, and general perception of stressfulness in daily life.

The Kupperman menopausal index (KI) was used to measure climacteric-related symptoms in the QoL-questionnaire. Of the 11 items used in the Kupperman menopausal index, only vasomotor symptoms (hot flushes and sweating) are hallmarks of estrogen insufficiency (Alder, 1998). That is why the original KI was modified in this study with symptoms referring to a lack of estrogen namely vaginal

dryness and tenderness and sleeping problems. Currently, for example the Women's Health Questionnaire (WHQ) could have been used instead of KI. This questionnaire evaluates various physical and emotional symptoms and sensations related to the climacteric (Hunter, 2001). The WHQ has proved to be a valid instrument for measuring climacteric-related symptoms in Finnish middle-aged women. The psychometric properties of the revised WHQ are as good as in the original WHQ and it has been warmly recommended for use in postal surveys (Katainen et al., 2017).

Both the HeSSup – and QoL -questionnaire were instigated before I started my research, so there was no possibility to alter or modulate the questions. The QoL-questionnaire consisted of some open questions which were challenging to deal with.

In Studies I and II the information from the use of systemic and local HT were obtained from the QoL-questionnaire, in order to know the number of years of HT use. The register information from Kela was possible from 1994 onwards, and it was used in Studies III and IV. The information from Kela concerning the HT users matched well with information received from the QoL-questionnaires.

The first QoL questionnaire was mailed before the results of the WHI, which fortunately made it possible to compare the time before and after the WHI. The LPA method in the present study facilitated the examination of the use of HT in a multifaceted fashion and the personal behaviour patterns associated with the users were analysed in detail.

The response rate was lower among less educated women in the HeSSup study and also women with a higher level of basic and professional education responded more often to the QoL study. This was taken into account by using education as a controlling factor when applicable. In this kind of study, those who are highly educated usually answer more frequently than those who are less educated (van den Akker et al., 1998). It is also challenging to formulate questions about intimate areas so that everybody understands them in the same way.

7 Conclusions

This thesis describes how Finnish women used HT for their menopausal symptoms in Finland in the early 2000s and how sociodemographic factors, health behaviours, physiological, psychological and mental symptoms are associated with the initiation, use, and discontinuation of HT. After the WHI and MWS results were published, the recommendations for the use of HT changed; therefore, it was also possible to evaluate HT use in the time before and after the WHI “collapse”.

1. In 2000, almost half of the Finnish women aged between 52–56 years used systemic HT to alleviate their climacteric symptoms. One quarter of the women using HT used it without experiencing any symptoms while one third of women with severe symptoms did not use HT.
2. The use of HT in Finland in 2005 was still rather common compared to many other countries despite the controversial results from the WHI and MWS. Anxiety caused by the research reports was the reason given by a third of those women who stopped HT use between 2000 and 2005. These results together with a desire to avoid using HT, a fear of cancer and the side-effects of HT played an important role.
3. Climacteric symptoms, a BMI under 30, living with a partner, heavy or moderate alcohol use and the use of psychopharmacas, were all predictors of the use of HT at the beginning of the 2000s among women born between 1954–1958. A poor SOC and symptoms of SNS were also predictors of the initiation of HT.
4. In the present study differences in psychological behaviour patterns influenced the perception of menopausal symptoms and the use of HT. HT use was higher among those with more hostility and stress and less optimism and lower SOC. The postmenopausal symptoms were also more prevalent in this group of women.

8 Clinical implications

Whether systemic HT treatment should be initiated depends on several factors and, in addition, to the severity of the symptoms. Health behaviours, life situation, and the psychological symptoms should also be considered. While interviewing a patient suffering from climacteric symptoms, the clinician should consider the personal and working life status as well as the psychological properties of the patient when considering a suitable individual treatment.

In this study in the early 2000s, there were some women who used HT while being asymptomatic, and some women who did not have HT despite severe menopausal symptoms. In the future, it would be interesting to discover whether those symptomatic women who did not use HT had a better SOC and a better ability to tolerate stress.

Childhood events, for example, an early childhood in the 1940s, during the 2nd world war and immediately after, have been shown to have an impact on life in general and proven to have influenced how climacteric symptoms are tolerated (Carson & Thurston, 2019; Thurston et al., 2008). The HeSSup questionnaire on childhood experiences could be used in order to judge the connection between climacteric symptoms and the use of HT treatment in future studies.

There was considerable publicity about the possible side effects and fear of cancer as a result of HT due to the WHI reports. Such publicity scared many women, who did not then want to be treated with HT and would rather tolerate the symptoms. In the future, it is important that physicians take into account not only objective but also subjective factors. Correct information about HT-treatment should be given, whilst listening to the patient, who should make the final decision of whether to accept the treatment or not.

In contrast to many European countries and the United States, the use of HT has not decreased that dramatically in Finland. However, it would be interesting to know how Finnish 52–56 year-old women use systemic HT in the 2020s. In Study IV according to Kela-registers the use of HT among 52–56 year-old women in 2000 was 49% and among 52–56 year-old women in 2010 it was 28%. It was not possible to obtain the most recent information about this in the present Kela registers.

It is important to educate general practitioners about HT-treatment, its advantages, risks, and contraindications. Proper education enables the usage of the correct treatment. It would be important for general practitioners taking care of menopausal women to have the possibility of low level consultations with gynaecologists. As a result of the published WHI and MWS studies, the usage of alternative non-hormonal treatments has increased. This was also shown to be the case according to this study. Clinicians should familiarize themselves with the usage and management of alternate treatments. Aerobic training in a randomized controlled trial among slightly overweight, symptomatic, sedentary women improved the quality of life and especially decreased night-time hot flushes (Luoto et al., 2012). Sedentary lifestyle, excessive alcohol consumption (Moilanen et al., 2010) and smoking (Whiteman et al, 2003) worsen vasomotor symptoms. Lifestyle changes made in a healthier direction such as stopping smoking, regular exercise, keeping weight under control and reducing the consumption of alcohol decreases VMS and alleviates sleeping problems. Alternative treatments should become a real alternative for women with contraindications to HT and for those women who do not want to use HT. In order to relieve climacteric symptoms cognitive psychotherapy, antidepressants, acupuncture and improved resilience may also be used.

A structured and formulated document to support clinicians when mapping climacteric symptoms should be created. This document should include questions related to climacteric symptoms such as the quality of life, mood changes and the patient's sense of coherence. A mobile application is available in the United States for clinicians to estimate impairments due to the menopause (Manson et al., 2015). The usage of optimal individual treatment is naturally important for the woman herself but also benefits family members, the work community and society in general.

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References

- Ainsworth, B. E., Haskell, W. L., Leon, A. S., Jacobs, D. R., Montoye, H. J., Sallis, J. F., et al. (1993). Compendium of physical activities: classification of energy costs of human physical activities. *Medicine & Science in Sports & Exercise*, 25(1), 71–80.
- Alder, E. (1998). The Blatt-Kupperman menopausal index: a critique. *Maturitas*, 29(1), 19–24.
- Anderson, G. L., Limacher, M., Assaf, A. R., Bassford, T., Beresford, S. A. A., Black, H., et al. (2004). Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: The Women’s Health Initiative randomized controlled trial. *JAMA*, 291(14), 1701–1712.
- Anderson, D. J., Chung, H.-F., Seib, C. A., Dobson, A. J., Kuh, D., Brunner, E. J., et al. (2020). Obesity, smoking, and risk of vasomotor symptoms: a pooled analysis of eight cohort studies. *American Journal of Obstetrics & Gynecology*, 222 (5), 478.e1–17. <https://doi.org/10.1016/j.ajog.2019.10.103>
- Ameye, L., Antoine, C., Paesmans, M., Azambuja, E., & Rozenberg, S. (2014). Menopausal hormone therapy use in 17 European countries during the last decade. *Maturitas*, 79(3), 287–291.
- Antonovsky, A. (1987). *Unraveling the mystery of health. How people manage stress and stay well.* San Francisco: Jossey-Bass Publishers.
- Antonovsky, A. (1993). The structure and properties of the sense of coherence scale. *Social Science & Medicine*, 36(6), 725–733.
- Archer, D. F., Sturdee, D. W., Baber, R., deVilliers, T. J., Pines, A., Freedman, R. R., et al. (2011). Menopausal hot flashes and night sweats: where are we now? *Climacteric*, 14(5), 515–528.
- Avis, N. E., Crawford, S. L., Greendale, G., Bromberger, J. T., Everson-Rose, S. A., Gold, E. B., et al. (2015). Duration of menopausal vasomotor symptoms over the menopause transition. *JAMA Internal Medicine*, 175(4), 531–539.
- Barbaglia, G., Macia, F., Comas, M., Sala, M., Vernet, M., Casamitjana, M., et al. (2009). Trends in hormone therapy use before and after publication of the Women’s Health Initiative trial: 10 years of follow-up. *Menopause*, 16(5), 1061–1064.
- Bariola, E., Jack, G., Pitts, M., Riach, K., & Sarrel, P. (2017). Employment conditions and work-related stressors are associated with menopausal symptom reporting among perimenopausal and postmenopausal women. *Menopause*, 24(3), 247–251.
- Beck, A. T., Steer, A. R., & Garbin, M. G. (1988). Psychometric properties of the Beck Depression Inventory; twenty-five years evaluation. *Clinical Psychology Review*, 8(1), 77–100.
- Beral, V., Gaitskell, K., Hermon, C., Moser, K., Reeves, G., & Peto, R. (2015). Menopausal hormone use and ovarian cancer risk: individual participant meta-analysis of 52 epidemiological studies. *Lancet*, 385, 1835–1842.
- Berin, E., Hammar, M., Lindblom, H., Lindh-Åstrand, L., Ruber, M., & Spetz Holm, A.-C. (2019). Resistance training for hot flashes in postmenopausal women: a randomised controlled trial. *Maturitas*, 126:55–60.
- Blumel, J. E., Castelo-Branco, C., Binfa, L., Gramegna, G., Tacla, X., Aracena, B., et al. (2000). Quality of life after the menopause: a population study. *Maturitas*, 34(1), 17–23.

- Bromberger, J. T., & Kravitz, H. M. (2011). Mood and menopause: findings from the Study of Women's Health Across the Nation (SWAN) over 10 years. *Obstetrics and Gynecology Clinics of North America*, 38(3), 609–625.
- Bromberger, J. T., Schott, L., Kravitz, H. M., & Joffe, H. (2015). Risk factors for major depression during midlife among a community sample of women with and without prior major depression: are they the same or different? *Psychological Medicine*, 45, 1653–1664.
- Brown, S. (2012). Shock, terror and controversy: how the media reacted to the Women's Health Initiative. *Climacteric*, 15(3), 275–280.
- Burger, H. G. (1996). The endocrinology of the menopause. *Maturitas*, 23(2), 129–136.
- Burger, H. G., Mac Lennan, A. H., Huang, K.-E., & Castello-Branco, C. (2012). Evidence-based assessment of the impact of the WHI on women's health. *Climacteric*, 15(3), 281–287.
- Burns, J. W., Higdon, L. J., Mullen, J. T., Lansky, D., & Wei, J. M. (1999). Relationships among patient hostility, anger expression, depression, and the working alliance in a work hardening program. *Annals of Behavioral Medicine*, 21(1), 77–82.
- Bush, T. M., Bonomi, A. E., Nekhlyudov, L., Ludman, E. J., Reed, S. D., Connelly, M. T., et al. (2006). How Women's Health Initiative (WHI) influenced physicians' practice and attitudes. *Society of General Internal Medicine*, 22, 1311–1316.
- Canonica, M. (2015). Hormone therapy and risk of venous thromboembolism among postmenopausal women. *Maturitas*, 82(3), 303–306.
- Calleja-Agius, J., & Brincat, M. P. (2015). The urogenital system and the menopause. *Climacteric*, 18(suppl 1), 18–22.
- Caltabiano, M. L., & Holzheimer, M. (1999). Dispositional factors, coping and adaptation during menopause. *Climacteric*, 2(1), 21–28.
- Carson, M. Y., & Thurston, R. C. (2019). Childhood abuse and vasomotor symptoms among midlife women. *Menopause*, 26(10), 1093–1099.
- Carpenter, J. S., Byrne, M. M., & Studts, J. L. (2010). Factors related to menopausal symptom management decisions. *Maturitas*, 70(1), 10–15.
- Cauley, J. A., Cummings, S. R., Black, D. M., Mascioli, S. R., & Seeley, D. G. (1990). Prevalence and determinants of estrogen replacement therapy in elderly women. *American Journal of Obstetrics and Gynecology*, 163(5), 1438–1444.
- Christensen, A. J., Wiebe, J. S., & Lawton, W. J. (1997). Cynical hostility, powerful others control expectancies, and patient adherence in hemodialysis. *Psychosomatic Medicine*, 59(3), 307–312.
- Cintron, D., Lipford, M., Larrea-Mantilla, L., Spencer-Bonilla, G., Lloyd, R., Gionfriddo, M. R., et al. (2017). Efficacy of menopausal hormone therapy on sleep quality: systematic review and meta-analysis. *Endocrine*, 55(3), 702–711.
- Cirillo, D. J., Wallace, R. B., Rodabough, R. J., Greenland, P., LaCroix, A. Z., Limacher, M. C., et al. (2005). Effects of estrogen therapy on gallbladder disease. *JAMA*, 293(3), 330–339.
- Citarella, A., Andersen, M., Sundström, A., Bardage, C., Hultman, C. M., & Kieler, H. (2012). Initiating therapy with antidepressants after discontinuation of hormone therapy. *Menopause*, 20(2), 146–151.
- Cobin, R. H., & Goodman, N. F. (2017). American association of clinical endocrinologists and American college of endocrinology position statement on menopause-2017 update. (2017). *Endocrine Practice*, 23(7), 869–880.
- Cody, J. D., Jacobs, M. L., Richardson, K., Moehrer, B., & Hextall, A. (2012). Oestrogen therapy for urinary incontinence in postmenopausal women. *Cochrane Database Systematic Reviews*, 10, CD001405.
- Collins, A., & Landgren, B.-M. (1997). Psychosocial factors associated with the use of hormonal replacement therapy in a longitudinal follow-up study of Swedish women. *Maturitas*, 28(1), 1–9.
- Corbelli, J., Shaikh, N., Wessel, C., & Hess, R. (2015). Low-dose transdermal estradiol for vasomotor symptoms: a systematic review. *Menopause*, 22(1), 114–121.

- Costanian, C., Christensen, R. A. G., Edgell, H., Ardern, C. I., & Tamim, H. (2017). Factors associated with complementary and alternative medicine use among women at midlife. *Climacteric*, 20(5), 421–426.
- Costanian, C., Edgell H., Ardern C. I., & Tamim, H. (2018). Hormone therapy use in the Canadian Longitudinal Study on Aging: a cross-sectional analysis. *Menopause*, 25(1), 46–53.
- Costas, L., Sequera, V. -G., Quesada P., Altzibar, J. M., Lope, V., Perez-Gomez, B. et al. (2015). Hormonal contraception and postmenopausal hormone therapy in Spain: time trends and patterns of use. *Menopause*, 22(10), 1138–1146.
- Crandall, C. J., Hovey, K. M., Andrews, C. A., Chlebowski, R. T., Stefanick, M. L., Lane, D. et al. (2018). Breast cancer, endometrial cancer, and cardiovascular events in participants who used vaginal estrogen in the Women’s Health Initiative Observational Study. *Menopause*, 25(1), 11–20.
- Crawford, S. L., Crandall C. J., Derby, C. A., El Khoudary, S. R., Waetjen, L. E., Fischer, M., et al. (2018). Menopausal hormone therapy trends before versus after 2002: impact of the Women’s Health Initiative Study results. *Menopause*, 26(6), 588–597.
- Daley, A., Stokes-Lambard, H., Thomas, A., & MacArthur, C. (2014). Exercise for vasomotor menopausal symptoms. *Cochrane Database Systematic Reviews*, 11, CD006108.
- Davis, S., R., Baber, R., Panay, N., Bitzer, J., Perez, S. C., Islam, R. M., et al. (2019). Global consensus position statement on the use of testosterone therapy for women. *Climacteric*, 22(5), 429–434.
- deVilliers, T. J., Pines, A., Panay, N., Gambacciani, M., Archer, D. F., Baber, R. J., et al. (2013). Updated 2013 International Menopause Society recommendations on menopausal hormone therapy and preventive strategies for midlife health. *Climacteric*, 16(3), 316–337.
- de Zambotti, M., Colrain, I. M., Javitz, H. S., & Baker, F. C. (2014). Magnitude of the impact of hot flashes on sleep in perimenopausal women. *Fertility and Sterility*, 102(6), 1708–1715.
- Dommm, J. A., Parker E. E., Reed, G. W., German, D. C., & Eisenberg, E. (2000). Factors affecting access to menopause information. *Menopause*, 7(1), 62–67.
- Donati, S., Cotichini, R., Mosconi, P., Satolli, R., Colombo, C., Liberati, A., et al. (2009). Knowledge, attitude and practice among Italian women. *Maturitas*, 63(3), 246–252.
- Du, Y., Melchert, H. -U., & Schäfer-Korting, M. (2005). Hormone replacement therapy in Germany: Determinants and possible health-related outcomes. Results of National Health Surveys from 1984 to 1999. *Maturitas*, 52(3-4), 223–234.
- Ekström, H., Esseveld, J., & Hovellius, B. (2003). Associations between attitudes towards hormone therapy and current use of it in middle-aged women. *Maturitas*, 46(1), 45–57.
- Elavsky, S., & Mc Auley, E. (2009). Personality, menopausal symptoms, and physical activity outcomes in middle-aged women. *Personality and Individual Differences*, 46(2), 123–128.
- Ettinger, B., Grady, D., Tosteson, A.N., Pressman, A., & Macer, J. L. (2003). Effect of the Women’s Health Initiative on women’s decisions to discontinue postmenopausal hormone therapy. *Obstetrics & Gynecology*, 102(6), 1225–1232.
- Feldt, T., Lintula, H., Suominen, S., Koskenvuo, M., Vahtera, J., & Kivimäki, M. (2007). Structural validity and temporal stability of the 13-item sense of coherence scale: prospective evidence from the population-based HeSSup study. *Quality of Life Research*, 16, 483–493.
- Finnish Medical Society Duodecim & Academy of Finland. (2004). *Vaihdevuosien hormonihoito. Konsensuslausuma*. 1–21. (In Finnish).
- Fistonc, I., Srecko C., Fistonc, M., & Skegro, I. (2004). Menopause in Croatia, Socio-demographic characteristics, women’s attitudes and source of information, compliance with HRT. *Maturitas*, 47(2), 91–98.
- Franco, O. H., Chowdhury, R., Troup, J., Voortman, T., Kunutsor, S., Kavousi, M., et al. (2016). Use of plant-based therapies and menopausal symptoms. A systematic review and meta-analysis. *JAMA*, 315(23), 2554–2563.
- Freedman, R. R. (2014). Menopausal hot flashes: mechanisms, endocrinology, treatment. *Journal of Steroid Biochemistry & Molecular Biology*, 142, 115–120.

- Freeman, E. W., Sammel, M. D., Lin, H., Gracia, C. R., Kapoor, S., & Ferdousi, T. (2005). The role of anxiety and hormonal changes in menopausal hot flashes. *Menopause*, 12(3), 258–266.
- Freeman, E. W., Sammel, M. D., Lin, H., & Nelson D. B. (2006). Association of hormones and menopausal status with depressed mood in women with no history of depression. *Archives of General Psychiatry*, 63(4), 375–382.
- Freeman, E. W., Sammel, M. D., Lin, H., Liu, Z., & Gracia, C. R. (2011). Duration of hot flashes and associated risk factors. *Obstetrics & Gynecology*, 117(5), 1095–1104.
- Gallicchio, L., Miller, S. R., Kiefer, J., Greene, T., Zacur, H. A., & Flaws J. A. (2014). Change in body mass index, weight, and hot flashes: a longitudinal analysis from midlife women's health study. (2014). *Journal of Women's Health*, 23(3), 231–237. doi: 10.1089/jwh.2013.4526
- Gallicchio, L., Miller, S. R., Kiefer, J., Greene, T., Zacur, H. A., & Flaws J. A. (2015). Risk factors for hot flashes among women undergoing the menopausal transition: baseline results from the Midlife Women's Health Study. *Menopause*, 22(10), 1098–1107.
- Gambacciani, M., Ciaponi M., Cappagli, B., Monteleone, P., Benussi, C., Bevilacqua, G., et al. (2003). Effects of low-dose, continuous combined estradiol and noretisterone actate on menopausal quality of life in early postmenopausal women. *Maturitas*, 44(2), 157–163.
- Gartlehner, G., Patel, S. V., Feltner, C., Weber R. P., Long, R., Mullican, K, et al. (2017). Hormone therapy for the primary prevention of chronic conditions in postmenopausal women. Evidence report and systemic review for the US preventive services task force. *JAMA*, 318(22), 2234–2249.
- Grady, D., Herrington, D., Bittner, V., Blumenthal, R., Davidson, M., Hlatky, M., et al. (2002). Cardiovascular disease outcomes during 6.8 years of hormone therapy: : Heart and Estrogen/progestin Replacement Study follow-up (HERS II). *JAMA*, 288(1), 49–57.
- Grady, D. (2006). Management of Menopausal symptoms. *The New England Journal of Medicine*, 355, 2338–2347.
- Green, J., Czanner, G., Reeves, G., Watson, J., Wise, L., Roddam, A., et al. (2012). Menopausal hormone therapy and risk of gastrointestinal cancer: nested case-control study within a prospective cohort, and meta-analysis. *International Journal of Cancer*, 130(10), 2387–2396.
- Green, S. M., Donegan, E., Frey, B. N., Fedorkow, D. M., Key, B. L., Streiner, D. L., et al. (2019). Cognitive behavior therapy for menopausal symptoms (CBT-Meno): a randomized controlled trial. *Menopause*, 26(9), 972–980.
- Hammam, R. A. M., Abbas, R. A., & Hunter M. S. (2012). Menopause and work-The experience of middle-aged female teaching stuff in an Egyptian governmental faculty of medicine. *Maturitas*, 71(3), 294–300.
- Harlow, S. D., Gass, M., Hall, J. E., Lobo, R., Maki, P., Rebar, R. W., et al. (2012). Executive summary of stages of reproductive aging workshop+10: addressing the unfinished agenda of staging reproductive aging. *Menopause*, 19(4), 387–395.
- Heikkinen, J., Vaheri, R., & Timonen, U. (2006). A 10-year follow-up of postmenopausal women on long-term continuous combined replacement therapy: Update of safety and quality-of-life findings. *Journal of the British Menopause Society*, 12(3), 115–125.
- Heistaro, S., Jousilahti, P., Lahelma, E., Vartiainen, E., & Puska, P. (2001). Self-rated health and mortality: a long-term prospective study in eastern Finland. *Journal of Epidemiology and Community Health*, 55(4), 227–232.
- Hemminki, E. (2008). Vaihdevuosisien hormonikorvauslääkkeiden myynti Suomessa on Pohjoismaiden suurin. *Suomen Lääkärilehti*, 63(11), 1072–1073. (In Finnish).
- Herrera, A. Y., Hodis, H. N., Mack, W. J., & Mather, M. (2017). Estradiol therapy after menopause mitigates effects of stress on cortisol and working memory. *Journal of Clinical Endocrinology & Metabolism*, 102(12), 4457–4466.
- Hersh, A. L., Stefanick, M. L., & Stafford, R. S. (2004). National use of postmenopausal hormone therapy. Annual trends and response to recent evidence. *JAMA*, 291(1), 47–53.
- Hickey, M., Szabo, R. A., & Hunter, M. S. (2017). Non-hormonal treatments for menopausal symptoms. *BMJ*, Nov 23;359:j5101. doi: 10.1136/bmj.j5101

- Hirvonen, E. (1997). Vaihdevuosien hormonikorvaushoito Suomessa. Suomen Lääkärilehti, 52(14), 1669–1672. (In Finnish).
- Hodis, H. N., & Mack, W.J. (2014). Hormone replacement therapy and the association with coronary heart disease and overall mortality: clinical application of the timing hypothesis. *Journal of Steroid Biochemistry & Molecular Biology*, 142, 68–75.
- Holm, E., Aaltonen, K., Heikkinen, A-M., & Tiihonen, M. (2014). From systemic hormone therapy to vaginal estrogen-A nationwide register study in Finland, 2003-2012. *Maturitas*, 78(4), 293–297.
- Hulley, S., Grady, D., Bush T., Furberg, C., Herrington D, RiggsB., et al. (1998). Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA*, 280(7), 605–613.
- Hunter, M. (2000). The Women’s Health Questionnaire (WHQ). The development, standardization and application of a measure of mid-aged women’s emotional and physical health. (2001). *Quality of Life Research*, 9, 733-738.
- Igarashi, M., Saito, H., Morioka, Y., Oiji, A., Nadaoka, T., & Kashiwakura, M. (2000). Stress vulnerability, climacteric symptoms: life events, coping, behavior, and severity of symptoms. *Gynecologica and Obstetric Investigation*, 49(3), 170–178.
- Jalava-Broman, J., Mäkinen, J., Ojanlatva, A., Jokinen, K., Sillanmäki, L., & Rautava, P. (2008). Treatment of climacteric symptoms in Finland prior to the controversial reports on hormone therapy. *Acta Obstetricia et Gynecologica Scandinavica*, 87(6), 682–686.
- Jalava-Broman, J., Mäkinen, J., Ojanlatva, A., Jokinen, K., Sillanmäki, L., & Rautava, P. (2011). Change in the frequency of HRT use from 2000 to 2005 and reasons to discontinue; follow-up of a normal cohort in Finland. *Acta Obstetricia et Gynecologica Scandinavica*, 90(4), 351–357.
- Jalava-Broman, J., Mäkinen, J., Sillanmäki, L., Vahtera, J., & Rautava P. (2016). Characteristics associated with initiation of hormone replacement therapy among Finnish women: A register-linked study. *Maturitas*, 89, 73–78.
- Jalava-Broman, J., Junttila, N., Sillanmäki, L., Mäkinen, J., & Rautava P. (2020). Psychological behavior patterns and coping with menopausal symptoms among users and non-users of hormone replacement therapy in Finnish cohorts of women aged 52–56 years. *Maturitas*, 133, 7–12.
- Joffe, H., White, D. P., Crawford, S. L., McCurnin, K. E., Economou, N., Connors, S., et al. (2013). Adverse effects of induced hot flashes on objectively recorded and subjectively reported sleep: results of a gonadotropin-releasing hormone agonist experimental protocol. *Menopause*, 20(9), 905–914.
- Joffe, H., Guthrie, K. A., LaCroix, A. Z., Reed, S. D., Ensrud, K. E., Manson, J. E., et al. (2014). Low-dose estradiol and the serotonin-norepinephrine reuptake inhibitor venlafaxine for vasomotor symptoms. A randomized clinical trial. *JAMA Internal Medicine*, 174(7), 1058–1066.
- Jokinen, K., Rautava, P., Mäkinen, J., Ojanlatva, A., Sundell, J., & Helenius, H. (2003). Experience of climacteric symptoms among 42-46 and 52-56-year-old women. *Maturitas*, 46(3), 199–205.
- Jonusiene, G., Zilaitiene, B., Adomaitiene, V., Aniliene, R., & Bancroft, J. (2013). Sexual function, mood and menopause symptoms in Lithuanian postmenopausal women. *Climacteric*, 16(1), 185–193.
- Jung, J. H., Bang, C. H., Song, G. G., Kim, C., Kim, J-H., & Choi, S.J. (2019). Knee osteoarthritis and menopausal hormone therapy in postmenopausal women: a nationwide cross-sectional study. *Menopause*, 26(6), 598–602.
- Kalleinen, N., Polo, O., Himanen, S. -L., Joutsen, A., & Polo-Kantola, P. (2008). The effect of estrogen plus progestin treatment on sleep: a randomized, placebo-controlled, double-blind trial in premenopausal and late postmenopausal women. *Climacteric*, 11(3), 233–243.
- Katainen, R. E., Siirtola, T. J., Engblom, J. R., Erkkola, R. U., & Polo-Kantola, P. (2014). A population-based survey of quality of life in middle-aged Finnish women. *Menopause*, 22(4), 402–413.
- Katainen, R. E., Engblom, J. R., Vahlberg, T. J., & Polo-Kantola, P. (2017). Psychometric properties of the Finnish version of the Women’s Health Questionnaire. *Menopause*, 24(8), 923–931.

- Kero, K., Väisälä, L., & Brusila, P. (2016). Voiko naisen seksuaalista haluttomuutta hoitaa lääkkeillä? *Duodecim*, 132, 1307–1309. (In Finnish).
- Kok, H. S., van Asselt, K. M., van der Schouw, Y. T., Peeters, P. H. M., & Wijmenga, C. (2005). Genetic studies to identify genes underlying menopausal age. *Human Reproduction Update*, 11(5), 483–493.
- Koskenvuo, M., Kaprio, J., Rose, R. J., Kesäniemi, A., Sarna, S., Heikkilä, K., et al. (1988). Hostility as a risk factor for mortality and ischemic heart disease in men. *Psychosomatic Medicine*, 50(4), 330–340.
- Korkeila, K., Suominen, S., Ahvenainen, J., Ojanlatva, A., Rautava, P., Helenius, H., et al. (2001). Non-response and related factors in nationwide health survey. *European Journal of Epidemiology*, 17(11), 991–999.
- Kravitz, H. M., Ganz, P. A., Bromberger, J., Powell, L. H., Sutton-Tyrrell, K., & Meyer, P.M. (2003). Sleep difficulty in women at midlife: a community survey of sleep and the menopausal transition. *Menopause*, 10(1), 19–28.
- Kronenberg, F. (1990). Hot flashes: epidemiology and physiology. *Annals of New York Academy of Sciences*, 592, 52–86.
- Kronenberg, F. (2010). Menopausal hot flashes: A review of physiology and biosociocultural perspective on methods of assessment. *The Journal of Nutrition*, 140, 1380S–1385S.
- Kupperman, H. S., Blatt, M. H., Wiesbader, H., & Filler, W. (1953). Comparative clinical evaluation of estrogenic preparations by the menopausal and amenorrheal indices. *Endocrinology*, 13(6), 688–703.
- Lampio, L., Polo-Kantola, P., Polo, O., Kauko, T., Aittokallio, J., & Saaresranta, T. (2014). Sleep in midlife women: effects of menopause, vasomotor symptoms, and depressive symptoms. *Menopause*, 21(11), 1217–1224.
- Lampio, L., Polo-Kantola, P., Himanen, S. -L., Kurki, S., Huupponen, E., Engblom, J. et al. (2017). Sleep during menopausal transition: A 6-year follow-up. *Sleep*, 40(7), doi: 10.1093/sleep/zsx090.
- Lampio, L., Saaresranta, T., & Polo, P. (2018). Unettomuusoireet vaihdevuosisien aikana. *Duodecim*, 134(6), 555–562. (In Finnish).
- Lemonage, C., Consoli, S. M., Panjo, H., Nabi, H., Goldberg, M., Zins, M., et al. (2012). Personality and hormone therapy use among postmenopausal women in GASEL cohort study. *Fertility and Sterility*, 98(4), 929–936.
- Lethaby, A., Ayeleke, R. O., & Roberts H. (2016). Local oestrogen for vaginal atrophy in postmenopausal women. *Cochrane Database of Systematic Reviews*, 8, CD001500.
- Levens, E., & Williams, R. S. (2004). Current opinions and understandings of menopausal women about hormone replacement therapy(HRT)-The University of Florida Experience, *American Journal of Obstetrics and Gynecology*, 191, 641–647.
- Levin, V. A., Jiang, X., & Kagan, R. (2018). Estrogen therapy for osteoporosis in the modern era. *Osteoporosis International*, 29(5), 1049–1055.
- Liu, B., Beral, V., Balkwill, A., Green, J., Sweetland, S., & Reeves, G. (2008). Gallbladder disease and use of transdermal versus oral hormone replacement therapy in postmenopausal women: prospective cohort study. *BMJ*, 10;337:a386. doi: 10.1136/bmj.a386.
- Liu, J. H. (2017). Is there a SERM in your menopause toolkit? *Menopause*, 24(3), 320–321.
- Lucas, R., & Barros, H. (2007). Life prevalence and determinants of hormone replacement therapy in women living in Porto, Portugal. (2007). *Maturitas*, 57(3), 226–232.
- Luoto, R., Moilanen, J., Heinonen, R., Mikkola, T., Raitanen, J., Tomas, E., et al. (2012) Effect of aerobic training on hot flushes and quality of life-a randomized controlled trial. *Annals of Medicine*, 44, 616–626.
- Lyytinen, H., Pukkala, E., & Ylikorkala, O. (2006). Breast cancer risk in postmenopausal women using estrogen-only therapy. *Obstetrics and Gynecology*, 108(6), 1354–1360.
- Lyytinen, H., Pukkala, E., & Ylikorkala, O. (2009). Breast cancer risk in postmenopausal women using estradiol-progestogen therapy. *Obstetrics & Gynecology*, 113(1), 65–73.

- MacLennan, A. H., Broadbent, J. L., Lester, S., & Moore, V. (2004). Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flushes. *Cochrane Database of Systematic Reviews*, 4, CD002978.
- MacLennan, A. H., Gill, T. K., Broadbent, J. L., & Taylor, A. W. (2009). Continuing decline in hormone therapy use: population trends over 17 years. *Climacteric*, 12(2), 122–130.
- Magliano, M. (2010). Menopausal arthralgia: fact and fiction. *Maturitas*, 67(1), 29–33.
- Maki, P. M., Kornstein, S. G., Joffe, H., Bromberger, J. T., Freeman, E. W., Athappilly, G., et al. (2018). Guidelines for the evaluation and treatment of perimenopausal depression: summary and recommendations. *Menopause*, 25(10), 1069–1085.
- Mansikkamäki, K., Nygård, C. -H., Raitanen, J., Kukkonen-Harjula, K., Tomas, E., Rutanen R., et al. (2016). Hot flushes among aging women. A 4-year follow-up study to a randomised controlled exercise study. *Maturitas*, 88, 84–89.
- Manson, J. E., Hsia, J., Johnson, K. C., Rossouw, J. E., Assaf, A. R., Lasser, N. L., et al. (2003). Estrogen plus progestin and the risk of coronary heart disease. *The New England Journal of Medicine*, 349(6), 523–534.
- Manson, J. E., Ames, J. M., Shapiro, M., Gass, M. L. S., Shifren, J. L., Stuenkel, C.A., et al. (2015). Algorithm and mobile app for menopausal symptom management and hormonal/nonhormonal therapy decision making: a clinical decision-support tool from The North American Menopause Society. *Menopause*, 22(3), 247–253.
- Manson, J. E., Aragaki, A. K., Rossouw, J. E., Anderson, G. L., Prentice, R. L., LaCroix, A. Z., et al. (2017). Menopausal hormone therapy and long-term all-cause and cause-specific mortality. The Women’s Health Initiative randomized trials. *JAMA*, 318(10), 927–938.
- Manzoli, L., Di Giovanni, P., Del Duca, L., De Aloysio, D., Festi, D., Capodicasa, S., et al. (2004). Use of hormone replacement therapy in Italian women aged 50-70 years. *Maturitas*, 49(3), 241–251.
- Martikainen, J. (1998). Vaihdevuosien hormonihoido Suomessa [Climacteric hormone therapy in Finland n 1997]. *Kapseli*, 28, 34–36. (In Finnish).
- Mc Intyre, R. S., Konarski, J. Z., Grigoriadis, S., Fan, N. C., Mancini, D. A., Fulto, K. A., et al. (2005). Hormone replacement therapy and antidepressant prescription patterns: a reciprocal relationship. *Canadian Medical Association Journal*, 172(1), 57–59.
- Metcalf, A., Smith, G., Wadsworth, E., Sterne, J. A. C., Heslop, P., Macleod, J., et al. (2003). A contemporary validation of the Reeder stress inventory. *British Journal of Health Psychology*, 8(1), 83–94.
- Mikkola, T. (2007). Vaihdevuosien hormonihoido-miksi hyvät uutiset eivät ylitä uutiskynnystä? *Suomen Lääkärilehti*, 123, 2049–2050. (In Finnish).
- Mikkola, T. S., Tuomikoski, P., Lyytinen, H., Korhonen, P., Hoti, F., Vattulainen, P., et al. (2015). Estradiol-based postmenopausal hormone therapy and risk of cardiovascular and all-cause mortality. *Menopause*, 22(9), 976–983.
- Mikkola, T. S., Tuomikoski, P., Lyytinen, H., Korhonen, P., Hoti, F., Vattulainen, P., et al. (2015). Increased cardiovascular mortality risk in women discontinuing postmenopausal hormone therapy. *The Journal of Clinical Endocrinology & Metabolism*, 100(12), 4588–4594.
- Million Women Study Collaborators. (2003). Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet*, 362, 419–427.
- Million Women Study Collaborators. (2005). Endometrial cancer and hormone replacement therapy in the Million Women Study. *Lancet*, 365, 154–1551.
- Million Women Study Collaborators. (2007). Ovarian cancer and hormone replacement therapy in the Million Women Study. *Lancet*, 369, 1703–1710.
- Moilanen, J., Aalto, A. -M., Hemminki, E., Aro, A. R., Raitanen, J., & Luoto, R. (2010). Prevalence of menopause symptoms and their association with lifestyle among Finnish middle-aged women. *Maturitas*, 67(4), 368–374.

- Moilanen, J. M., Mikkola, T. S., Raitanen, J. A., Heinonen, R. H., Tomas, E. I., Nygård, C-H., et al. (2012). Effect of aerobic training on menopausal symptoms-a randomized controlled trial. *Menopause*, 19(6), 691–696.
- Morch, L. S., Lokkegaard, E., Andreasen, A. H., Kruger-Kjaer, S., & Lidegaard, O. (2009). Hormone therapy and ovarian cancer. *JAMA*, 302(3), 298–305.
- Mulhall, S., Andel, R., & Anstey, K. J. (2018). Variation in symptoms of depression and anxiety in midlife women by menopausal status. *Maturitas*, 108, 7–12.
- Muthén, B. (2008). Latent variable hybrids: overview of old and new models, in: G.R. Hancock, K.M. Samuelson (Eds.), *Advances in Latent variable Mixture Models*, Information Age Publishing, Charlotte, NC, 1–24.
- Mäkinen, J., Meltomaa, S., Neirama, O., Klemi, P., Miettunen, T., Kenraali, J., et al. (2001). Estrogeenia tarvitaa myös paikallishoitona emättimeen. *Suomen Lääkärilehti*, 56(18), 2015–2018. (In Finnish).
- Nastri, C. O., Lara, L. A., Ferriani, R. A., Rosa-e-Silva, A. E., Figueiredo, J., & Martins, W. E. (2013). Hormone therapy for sexual function in perimenopausal and postmenopausal women. *Cochrane Database Systematic Reviews*, 6, CD009672.
- Nedstrand, E., Wijma, K., Lindgren, M., & Hammar, M. (1998). The relationship between stress-coping and vasomotor symptoms in postmenopausal women. *Maturitas*, 31, 29–34.
- Nelson, H. D., Vesco, K. K., Haney, E., Fu, R., Nedrow, A., Miller, J., et al. (2006). Nonhormonal therapies for menopausal hot flashes. Systemic review and meta-analysis. *JAMA*, 295(17), 2057–2071.
- Nelson, H. D. (2008). Menopause. *Lancet*, 371, 760–770.
- Ngai, F. W. (2019). Relationships between menopausal symptoms, sense of coherence, coping strategies, and quality of life. *Menopause*, 26(7), 758–764.
- North American Menopause Society. (2015). Nonhormonal management of menopause-associated vasomotor symptoms: 2015 position statement of The North American Menopause Society. *Menopause*, 22(11), 1155–1174.
- North American Menopause Society. (2018). The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause*, 25(11), 1362–1387.
- Notelovitz, M., Cassel, D., Hille, D., Furst, K. W., Dain, M. -P., VandePol, C., et al. (2000). Efficacy of continuous sequential transdermal estradiol and norethindrone acetate in relieving vasomotor symptoms associated with menopause. *The American Journal of Obstetrics and Gynecology*, 182(1), 7–12.
- Ojanlatva, A., Rautava, P., Helenius, H., Korkeila, K., Sundell, J., Kivimäki, M., et al. (2005). Associations of sexual support and sex life-the HeSSup-study. *Patient Education and Counseling*, 58, 71–81.
- Oksjoki, S., & Jokimaa, V. (2015). Premature ovarian insufficiency-a threat for a woman's health. *Duodecim*, 131(2), 136–142. (In Finnish).
- Oldenhave, A., Jaszmann, L. J., Haspels, A. A., & Everaerd, W. T. (1993). Impact of climacteric on well-being. *The American Journal of Obstetrics and Gynecology*, 168(3), 772–780.
- Øren A. (2009). Motives for initiation, temporary discontinuation, and permanent discontinuation of hormone replacement therapy use among Norwegian women. *Maturitas*, 64(1), 33–37.
- Pacello, P., Baccaro, L. F., Pedro, A. O., & Costa-Paiva, L. (2018). Prevalence of hormone therapy, factors associated with its use, and knowledge about menopause: a population-based household survey. *Menopause*, 25(6), 683–690.
- Pakarinen, M., Raitanen, J., Kaaja, R., & Luoto, R. (2010). Secular trend in the menopausal age in Finland 1997-2007 and correlation with socioeconomic, reproductive and lifestyle factors. *Maturitas*, 66(4), 417–422.
- Palacios, S. (2009). Managing urogenital atrophy. *Maturitas*, 63(4), 315–318.

- Parazzini, F., Di Donato, P., Giulini, N.A., Bacchi Modena, A., Cicchetti, G., Comitini, G., et al. (2005). Factors associated with climacteric symptoms in women around menopause attending menopause clinics in Italy. *Maturitas*, 52(3-4), 81–89.
- Pastore, L. M., Carter, R. A., Hulka, B. S., & Wells, E. (2004). Self-reported urogenital symptoms in postmenopausal women: Women’s Health Initiative. *Maturitas*, 49(4), 292–303.
- Peng, W., Adams, J., Sibbritt, D. W., & Frawley, J. E. (2014). Critical review of complementary and alternative medicine use in menopause: focus on prevalence, motivation, decision-making, and communication. *Menopause*, 21(5), 536–548.
- Pines, A., Sturdee, D. W., & MacLennan, A. H. (2012). Quality of life and the role of menopausal hormone therapy. *Climacteric*, 15(3), 213–216.
- Polisseni, A. F., Andrade, A. T., Ribeiro, L. C., Castro, I. Q., Brandao, M., Polisseni, F., et al. (2013). Effects of a continuous-combined regimen of low-dose hormone therapy (oestradiol and norethindro acetate) and tibolone on the quality of life in symptomatic postmenopausal women: A double-blind, randomised study. *Maturitas*, 74(2), 172–178.
- Polo-Kantola, P. (2011). Sleep problems in midlife and beyond. *Maturitas*, 68(3), 224–232.
- Posadzki, P., Lee, M. S., Moon, T.W., Choi, T.Y., Park, T.Y., & Ernst, E. (2013). Prevalence of complementary and alternative medicine (CAM) use by menopausal women: A systematic review of surveys. *Maturitas*, 75(1), 34–43.
- Raz, R. & Stamm, E., E. (1993). A controlled trial of intravaginal estriol in postmenopausal women with recurrent urinary tract infections. *The New England Journal of Medicine*, 329(11), 753–756.
- Remes, A., Tanila, H., & Hallikainen, M. (2015). Meneekö muisti menopaussin myötä-voiko ikääntyvä nainen suojautua muistitaudeilta? *Duodecim*, 131(16), 1499–1505. (In Finnish).
- Renoux, C., Dell’ Aniello, S., Garbe, E., & Suissa, S. (2010). Transdermal and oral hormone replacement therapy and the risk of stroke: a nested case-control study. *BMJ*, Jun 3;340:c2519. doi: 10.1136/bmj.c2519.
- Roberts, H., & Hickey, M. (2016). Managing the menopause: An update. *Maturitas*, 86, 53–58.
- Rossouw, J., E., Anderson, G. L., Prentice, R. L., LaCroix, A. Z., Kooperberg, C., Hutchinson, F., et al. (2002). Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women’s Health Initiative randomized controlled trial. *JAMA*, 288(3), 321–333.
- Rossouw, J. E., Prentice, R. L., Manson, J., E., Wu, L., Barad, D., Barnabei, V. M., et al. (2007). Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA*, 297(13), 1465–1477.
- Rutanen, E-R. (2003). Estrogeenista elämänlaatua. *Duodecim*, 119(22): 2217–2223. (In Finnish).
- Sabia, S., Fournier, A., Mesrine, S., Boutron-Ruault, M.-C., & Clavel-Chapelon, F. (2008). Risk factors for onset of menopausal symptoms. Results from a large cohort. *Maturitas*, 60(2), 108–121.
- Salmi, T., Paldan, M., & Klaukka T. (2004). Vaihevuosihormonien käyttö on vähentynyt maan kaikissa osissa. *Suomen lääkirilehti*, 59(10), 1042–1045. (In Finnish)
- Salmi, T., Paldan, M., Virta, L., & Klaukka, T. (2006). Vaihevuosihormonien käyttö on vähentynyt edelleen. *Suomen Lääkirilehti*, 61(48), 5064–5066. (In Finnish).
- Santen, R. J., Allred, D. C., Ardoin, S.P., Archer, D. F., Boyd, N., Braunstein, G. D., et al. (2010). Postmenopausal hormone therapy: An Endocrine Society Scientific Statement. *The Journal of Clinical Endocrinology & Metabolism*, 95(Suppl 1), S1–S66.
- Santoro, N., & Komi, J. (2009). Prevalence and impact of vaginal symptoms among postmenopausal women. *The Journal of Sexual Medicine*, 6(8), 2133–2142.
- Sarenmalm, E. K., Browall, M., Persson, L.-O., Fall-Dickson, J., & Gaston-Johansson, F. (2013). Relationship of sense of coherence to stressful events, coping strategies, health status, and quality of life in women with breast cancer. *PsychoOncology*, 22(1), 20–27.
- Savolainen-Peltonen, H., Hautamäki, H., Tuomikoski, P., Ylikorkala, O., & Mikkola, T. S. (2014). Health-related quality of life in women with or without hot flashes: a randomized placebo-controlled trial with hormone therapy. *Menopause*, 21(7), 732–739.

- Savolainen-Peltonen, H., Rahkola-Soisalo, P., Hoti, F., Vattulainen, P., Gissler, M., Ylikorkala, O., et al. (2019). Use of postmenopausal hormone therapy and risk of Alzheimer's disease in Finland: nationwide case-control study. *BMJ*, 364, 1665. doi: 10.1136/bmj.1665.
- Scheier, M. F., Carver, C. S., & Bridges, M. W. (1994). Distinguishing optimism from neuroticism (and trait anxiety, self-mastery, and self-esteem): a reevaluation of the life orientation. *Journal of Personality and Social Psychology*, 67(6), 1063–1078.
- Schneider, H. P. G., & Birkhäuser, M. (2017). Quality of life in climacteric women. *Climacteric*, 20(3), 187–194.
- Shao, H., Breitner, J. C. S., Whitmer, R. A., Wang, J., Hayden, K., Wengreen, H., et al. (2012). Hormone therapy and Alzheimer disease dementia. *Neurology*, 79(18), 1846–1852.
- Shaver, J. L., & Woods, N. F. (2015). Sleep and menopause: a narrative review. *Menopause*, 22(8), 899–915.
- Sjögren, L. L., Morch, L. S., & Lokkegaard, E. (2016). Hormone replacement therapy and the risk of endometrial cancer: a systemic review. *Maturitas*, 91, 25–35.
- Slopien, R., Wender-Ozegowska, E., Rogowicz-Frontczak, A., Meczekalski, B., Zozulinska-Ziolkiewicz, D., Jaremek, J. D., et al. (2018). Menopause and diabetes: EMAS clinical guide. *Maturitas*, 117, 6–10.
- Smith, N. L., Blondon, M., Wiggins, K. L., Harrington, L. B., van Hyleckama Vlieg, A., Floyd, J. S., et al. (2014). Lower risk of cardiovascular events in postmenopausal women taking oral estradiol compared with oral conjugated equine estrogens. *JAMA Internal Medicine*, 174(1):25–31.
- Soares, C. N. (2014). Mood disorders in midlife women: understanding the critical window and its clinical implications. *Menopause*, 21(2), 198–206.
- Sood, R., Kuhle, C. L., Kapoor, E., Thielen, J. M., Frohmader, K. S., Mara, K. C., et al. (2019). Association of mindfulness and stress with menopausal symptoms in midlife women. *Climacteric*, 22 (4), 377–382.
- Stadberg, E., Mattsson, L. -Å., & Milsom, I. (2000). Factors associated with climacteric symptoms and the use of hormone replacement therapy. *Acta Obstetrica et Gynecologica Scandinavica*, 79(4), 286–292.
- Stearns, V., Ullmer, L., Lo'pez, J. F., Smith, Y., Isaacs, C., & Hayes, D. F. (2002). Hot flushes. *Lancet*, 360, 1851–1861.
- Stefanik, M. L. (2005). Estrogens and progestins: background and history, trends in use, and guidelines and regimens approved by the US Food and Drug Administration. *The American Journal of Medicine*, 118(12B), 64S–73S.
- Stefanick, M. L., Anderson, G. L., Margolis, K. L., Hendrix, S. L., Rodabough, R. J., Paskett, E. D., et al. (2006). Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. *JAMA*, 295(14), 1647–1657.
- Steffen, A. M., Thompson, L. W., Gallagher-Thompson, D., & Koin, D. (1999). Physical and psychosocial correlates of hormone replacement therapy with chronically stressed postmenopausal women. *Journal of Aging and Health*, 11(1), 3–26.
- Steinkellner, A. R., Denison, S. E., Eldridge, S. L., Lenzi, L. L., Chen, W., & Bowlin, S. J. (2012). A decade of postmenopausal hormone therapy prescribing in the United States: long-term effects of the Women's Health Initiative. *Menopause*, 19(6), 616–621.
- Stuenkel, C. A. (2016). Menopause, hormone therapy and diabetes. *Climacteric*, 20(1), 11–21.
- Süss, H., & Ehlert, U. (2020). Psychological resilience during the perimenopause. *Maturitas*, 131, 48–56.
- Taylor, H. S., Tal, A., Pal, L., Li, F., Black, D. M., & Brinton, E. A. (2017). Effects of oral vs transdermal estrogen therapy on sexual function in early postmenopause. Ancillary study of the Kronos Early Estrogen Prevention Study (KEEPS), *JAMA Internal Medicine*, 177(10), 1471–1479.

- Thunell, L., Stadberg, E., Milsom, I., & Mattsson, L. -Å. (2005). Changes in attitudes, knowledge and hormone replacement therapy use: a comparative study in two random samples 6-year interval. *Acta Obstetrica et Gynecologica Scandinavica*, 84(4), 395–401.
- Thurston, R. C., Bromberger, J., Chang, Y., Goldbacher, E., Brown, C., Cyranowski, J. M., et al. (2008). Childhood abuse or neglect is associated with increased vasomotor symptom reporting among midlife women. *Menopause*, 15(1), 16–22.
- Tiihonen, M. J., Heikkinen, A.-M., & Ahonen, R. S. (2007). Do Finnish women using hormone replacement therapy need more information about risks. *Pharmacy World and Science*, 29(6), 635–640.
- Tiihonen, M., Saarela, M., Saarinen, S., Ahonen, R., & Heikkinen, A. -M. (2011). Menopausal hormone therapy- Benefits, adverse reactions, concerns and information sources in 2009. *Maturitas*, 70(1), 69–73.
- Tiitinen, A. *Vaihdevuosisoireet ja hormonikorvaushoito*. (2019). Lääkärin käsikirja. (In Finnish).
- Tiitinen, A., & Kero, K. (2020). Paikallisestrogeenit ja rintasyöpä. *Suomen Lääkärilehti*, 75(3), 117–121. (In Finnish).
- Toffol, E., Heikinheimo, O., & Partonen, T. (2015). Hormone therapy and mood in perimenopausal and postmenopausal women: a narrative review. *Menopause*, 22(5), 564–578.
- Topo, P., Køster, A., Holte, A., Collins, A., Langgren, B.-M., Hemminki, E., et al. (1995). Trends in the use of climacteric and postclimacteric hormones in Nordic countries. *Maturitas*, 22(2), 89–95.
- Tuomikoski, P., & Lyytinen, H. (2015). Näin hoidan vaihdevuosisoireita. *Duodecim*, 131(16), 1515–1521. (In Finnish).
- Tuomikoski, P., & Savolainen-Peltonen, H. (2017). Vasomotor symptoms and metabolic syndrome. *Maturitas*, 97, 61–65.
- Turunen, H., & Lyytinen, H. (2014). Perimenopausi ja hormonihoito. *Suomen Lääkärilehti*, 69(19), 1395–1401. (In Finnish).
- Vahtera, J., Kivimäki, M., Hublin, C., Korkeila, K., Suominen, S., Paunio, T., et al. (2007). Liability to anxiety and severe life events as predictors of new-onset sleep disturbances. *Sleep*, 30(11), 1537–1546.
- van den Akker, M., Buntinx, F., Metsemakers, J. F., & Knottnerus, J. A. (1998). Morbidity in responders and non-responders in a register-based population survey. *Family Practice*, 15(3), 261–263.
- Veerus, P., Hovi, S.-L., Sevon, T., Hunter, M., & Hemminki, E. (2012). The effect of hormone therapy on women’s quality of life in the first year of the Estonian Postmenopausal Hormone Therapy trial. *BMC Research Notes*, 5, 176. doi: 10.1186/1756-0500-5-176.
- Vegter, S., Kölling, P., Töben, M., Visser, S. T., & de Jong-van den Berg, L. T. (2009). Replacing hormone therapy- is the decline in prescribing sustained, and are nonhormonal drugs substituted? *Menopause*, 16(2), 329–335.
- Vermunt, K.J. K., & Magidson, J. (2002). Latent class cluster analysis, in: J. Hagenaars, A. McCutcheon (Eds.), *Applied Latent Class Analysis*, Cambridge, 89–106.
- Vihtämäki, T., Savilahti, R., & Tuimala, R. (1999). Why do postmenopausal women discontinue hormone replacement therapy? *Maturitas*, 33(2), 99–105.
- Vinogradova, Y., Coupland, C., & Hippisley-Cox, J. (2019). Use of hormone therapy and risk of venous thromboembolism: nested case-control studies using the QResearch and CRPD databases. *BMJ*, 364:k4810/doi:10.1136/bmj.k4810.
- Wang, M., & Bodner, T. E. (2007). Growth mixture modeling: identifying and predicting unobserved subpopulations with longitudinal data. *Organ. Res. Methods*, 10, 635–656.
- Weidner, K., Bittner, A., Beutel, M., Goeckenjan, M., Brähler, E., & Garthus-Niegel, S. (2020). The role of stress and self-efficacy in somatic and psychological symptoms during climacteric period- Is there a specific association? *Maturitas*, 136, 1–6.

- Whiteman, M. K., Staropoli, C. A., Langenberg, P. W., McCarter, R. J., Kjerulff, K. H., & Flaws, J.A. (2003). Smoking, body mass, and hot flashes in midlife women. *The American College of Obstetricians and Gynecologists*, 101(2), 264–272.
- Woods, N. F., & Mitchell, E. S. (2005). Symptoms during the perimenopause; prevalence, severity, trajectory, and significance in women's lives. *The American Journal of Medicine*, 118(12B), 14S–24S.
- Wyss, J. M., & Carlson, S. H. (2003). Effects of hormone replacement therapy on the sympathetic nervous system and blood pressure. *Current Hypertension Reports*, 5(3), 241–246.
- Zhao, D., Liu, C., Feng, X., Hou, F., Xu, X., & Li, P. (2018). Menopausal symptoms in different substages of perimenopause and their relationships with social support and resilience, *Menopause*, 26(3), 233–239.



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