Resistance Training and Physical Activity in Postmenopausal Women
Effects on Vasomotor Symptoms, Quality of Life and Microcirculation

Emilia Berin
Resistance Training and Physical Activity in Postmenopausal Women
Effects on Vasomotor Symptoms, Quality of Life and Microcirculation

Emilia Berin

Department of Biomedical and Clinical Sciences
Linköping University, Sweden
Linköping 2023
Resistance Training and Physical Activity in Postmenopausal Women: Effects on Vasomotor Symptoms, Quality of Life and Microcirculation

© Emilia Berin, 2023

This work is licensed under a Creative Commons Attribution 4.0 International License.
https://creativecommons.org/licenses/by/4.0

Cover illustration by Ebba Hammarlund

Printed in Sweden by LiU-Tryck, Linköping, Sweden, 2023

ISBN: 978-91-8075-098-1 (Print)
ISBN: 978-91-8075-099-8 (PDF)
https://doi.org/10.3384/9789180750998
ISSN: 0345-0082
ABSTRACT

Background
Menopause is a physiological event, but is associated with bothersome symptoms as well as physical changes that affect women’s health. About 75% of women experience vasomotor symptoms (hot flushes and night sweats) related to menopause that often reduce quality of life. The vasomotor symptoms may be attributed to dysfunctional temperature regulation centrally in the hypothalamus and peripherally in the skin’s circulation. The most effective treatment for vasomotor symptoms is menopausal hormone therapy, but not all women are able to, or want to, use it.

In addition to the impact on quality of life, studies have associated vasomotor symptoms and menopause with macrovascular endothelial dysfunction. Previous studies on the association of these factors with the skin’s microcirculatory function are small and few. Observational studies have associated physical activity and exercise with less vasomotor symptoms, but the evidence from intervention trials is of low quality and the results are ambiguous. Physical activity has established general health effects, and could potentially decrease vasomotor symptoms by effects on endogenous opioids centrally, and by more efficient thermoregulation peripherally.

The aim of this thesis was to investigate the effect of resistance training on vasomotor symptoms and health-related quality of life in postmenopausal women, and to explore the women’s experiences of the training to find barriers and facilitators. We also aimed to investigate whether the skin’s microcirculatory function differed between women regarding menopausal status, vasomotor symptoms, menopausal hormone therapy, and physical activity.

Material and methods
The first study was an open randomized controlled trial including 65 postmenopausal women with moderate to severe vasomotor symptoms and low physical activity levels. We randomized the women to 15 weeks of resistance training (intervention) or unchanged physical activity (control). The participants registered vasomotor symptoms daily in a diary, and answered health-related quality of life questionnaires at baseline and at 15 weeks. The first 15 women to finish the intervention were recruited to a qualitative study. The women’s experiences of the resistance training intervention were explored in individual interviews after the intervention period, and all were followed-up with telephone
interviews after one year. The third study was cross-sectional, including 1148 women from Linköping, 50-64 years old, who participated in the Swedish CArdioPulmonary bioImage Study (SCAPIS). These women answered a questionnaire about menopausal status, vasomotor symptoms and menopausal hormone therapy use, and wore accelerometers for seven days to assess physical activity. The skin’s microcirculation was assessed at rest and during post-occlusive reactive hyperemia.

**Results**

Moderate to severe vasomotor symptoms per 24 hours decreased significantly more in the group of women randomized to resistance training compared with the control group (mean difference -2.7, 95% CI -4.2 to -1.3). The resistance training group improved in domains of menopause-specific health-related quality of life compared with the control group but there was little impact on generic health-related quality of life. In the qualitative study we found that the vasomotor symptoms acted as a “trigger” for the women to become motivated to exercise. Their motivation then evolved from being driven by hopes of symptom relief into being driven by a wish for general well-being, which was still a driving force after one year. Microvascular function did not differ between postmenopausal and premenopausal women, or between women with or without vasomotor symptoms or menopausal hormone therapy. Women with higher levels of objectively measured and self-reported physical activity had a better reactivity of the skin’s microcirculation. The differences remained significant after adjusting for BMI, smoking, hypertension, diabetes, and education.

**Conclusions**

Resistance training could be effective for decreasing vasomotor symptoms and improving some aspects of health-related quality of life in motivated postmenopausal women. The vasomotor symptoms themselves spurred motivation to exercise, indicating they present an opportunity to increase physical activity. When a woman seeks medical advice for vasomotor symptoms, this could be a chance for health care professionals to help her initiate or increase exercise. Women who performed more physical activity and exercise had better skin microvascular function, but no association with VMS was found. Future studies are needed to investigate what type and dose of exercise is the most effective to reduce vasomotor symptoms and whether there is a way to predict for whom exercise will or will not be an effective intervention.
Populärvetenskaplig sammanfattning

Tre fjärdedelar av alla kvinnor rapporterar värmevallningar och svettningar i klimakteriet, och det är vanligt att dessa påverkar livskvaliteten negativt. Menopaus är den sista menstruationen och inträffar kring 52 års ålder i Sverige. Tiden därefter kallas postmenopaus. De hormonella förändringarna som sker i samband med menopaus, där framför allt lägre östrogennivåer tros spela roll, bidrar även till att öka risken för hjärt-kärlsjukdom hos kvinnor efter menopaus.

Mekanismerna som orsakar värmevallningar och svettningar är inte helt klarlagda, men anses vara en följd av de minskande östrogennivåerna. Kroppens ”termostat” i hjärnan blir satt ur spel och skickar plötsliga signaler till huden om att sänka kroppstemperaturen via svettning och ökat blodflöde till yttliga blodkärl. En sämre temperaturreglering som konsekvens av endoteldysfunktion lokalt i huden kan också spela in. Endoteldysfunktion, karakteriserat av nedsatt förmåga hos blodkärl att vidga sig som svar på olika stimuli, ses tidigt i utvecklingen av åderförkalkning och hjärt-kärlsjukdom. Tidigare studier har visat ett samband mellan värmevallningar och endoteldysfunktion i kroppens större blodkärl, men få studier har undersökt motsvarande för hudens mindre blodkärl.

Den mest effektiva behandlingen mot värmevallningar är hormonbehandling med östrogen, men det behövs behandlingsalternativ för de kvinnor som inte kan eller vill använda hormonbehandling. Enligt en kartläggning av Socialstyrelsen 2021 önskar över 80 % av kvinnor råd kring hur de själva kan lindra sina besvär. Tidigare studier har visat att kvinnor som är fysiskt aktiva eller tränar regelbundet rapporterar färre värmevallningar och svettningar, men det är inte säkerställt i behandlingsstudier. En teori är att fysisk aktivitet genom frisättning av kroppsegna morfinliknande ämnen skulle kunna stabilisera ”termostaten” och därmed minska värmevallningar. En annan mekanism skulle kunna vara en förbättrad temperaturregleringsförmåga i huden genom bättre endotelfunktion.

Syftet med denna avhandling var att undersöka effekten av styrketräning på värmevallningar och svettningar samt hälsorelaterad livskvalitet hos postmenopausala kvinnor, och att utforska kvinnornas erfarenheter av träningen för att identifiera hinder och möjligheter till träning. Syftet var också att undersöka huruvida funktionen i hudens mikrocirkulation skillde sig mellan kvinnor med olika menopausstatus, förekomst av värmevallningar, hormonbehandling och grad av fysisk aktivitet.
I den första studien lottades postmenopausala kvinnor med låg fysisk aktivitetsnivå till att genomgå ett styrketräningsprogram i 15 veckor, eller att leva som vanligt under samma tid (kontrollgrupp), och 58 kvinnor genomförde studien. Deltagarna registrerade dagligen värmevallningar i en dagbok och fyllde i två frågeformulär om hälsorelaterad livskvalitet vid studiens början och slut. Femton kvinnor från styrketräningsgruppen rekryterades sedan till en intervjujustudie med syfte att utforska deras erfarenheter av träningen. I den tredje studien användes data från 1148 kvinnor, 50-64 år gamla, från Linköping som deltagit i en nationell studie med syfte att studera hjärt-kärlsjukdomar (Swedish CArdioPulmonary bioImage Study, SCAPIS). Inom studien besvarade kvinnorna ett frågeformulär om menopaus, hormonbehandling och värmevallningar, och fysisk aktivitet registrerades med så kallade accelerometrar. Hudens mikrocirkulation undersöks med ett instrument som fästs på huden på underarmen och mäter syresättning och blodflöde.

Resultaten visade att värmevallningar och svettningar minskade med 44% i styrketräningsgruppen medan ingen förändring sågs i kontrollgruppen. Hos 45% av kvinnorna i styrketräningsgruppen sågs minst en halvering av antalet vallningar. I styrketräningsgruppen sågs en förbättring av några aspekter av livskvalitet relatert till menopaus, men endast liten förändring av allmän hälsorelaterad livskvalitet. Ur intervjujustudien fann vi att besvären med vallningar triggade igång motivation till träning hos kvinnorna, men att motivationen sedan utvecklades till att drivas av allmänt välbefinnande istället, oavsett om kvinnan upplevde effekt av träningen på besvären eller inte. Stöd av fysioterapeut var viktigt framför allt initialt. I den tredje studien fann vi att reaktiviteten i hudens mikrocirkulation var bättre hos kvinnor som utövade mer fysisk aktivitet, men vi fann inget samband mellan mikrocirkulationen och menopaustatus, hormonbehandling eller värmevallningar.

Sammanfattningsvis tyder resultaten på att styrketräning kan vara ett effektivt behandlingsalternativ för att minska besvärande värmevallningar och svettningar för kvinnor som är motiverade till träning. Besvären i sig kan trigga igång motivation till träning, och detta föreslås kunna användas i samtal om levnadsvanor när kvinnor söker vård för klimakteriebesvär. Fysiskt aktiva kvinnor hade också en bättre reaktivitet i hudens mikrocirkulation, men inget samband sågs mellan värmevallningar och mikrocirkulationen. Fler studier behövs för att undersöka om en viss typ av träning är mer effektiv än annan träning mot värmevallningar och svettningar. Resultaten från avhandlingen adderar viktig kunskap till de många kända hälsoeffekterna av fysisk aktivitet.
LIST OF SCIENTIFIC PAPERS

I. **Resistance training for hot flushes in postmenopausal women: A randomised controlled trial.**
   Published under CC-BY-NC-ND license

II. **Effects of resistance training on quality of life in postmenopausal women with vasomotor symptoms.**
    Published under CC-BY license

III. **Postmenopausal women’s experiences of a resistance training intervention against vasomotor symptoms: a qualitative study.**
     Published under CC-BY 4.0 license

IV. **Microvascular reactivity in mid-life women – Influence of menopause, hormone therapy, vasomotor symptoms and physical activity.**
    Berin E*, Henriksson M*, Hammar M, Jonasson H, Bergstrand S, Strömberg T, Ostgren, C J Spetz Holm AC. Manuscript
    *Equal contribution
ABBREVIATIONS

1RM – One repetition maximum
8RM – Eight repetitions maximum
CNS – Central nervous system
CVD – Cardiovascular disease
DRS – Diffuse Reflectance Spectroscopy
EPOS – Enhanced Perfusion and Oxygen Saturation
FMP – Final menstrual period
FSH – Follicle-stimulating hormone
GnRH – Gonadotropin-releasing hormone
LDF – Laser Doppler flowmetry
LH – Luteinizing hormone
MET – Metabolic equivalents
QoL – Quality of life
HRQoL – Health-related quality of life
KNDy – Kisspeptin/Neurokinin B/Dynorphin
LH – Luteinizing hormone
MHT – Menopausal hormone therapy
MVPA – Moderate-to vigorous physical activity
POA – Preoptic area of the hypothalamus
PORH – Post-occlusive Reactive Hyperemia
RCT – Randomized controlled trial
RM – Repetition maximum
SCAPIS – Swedish CArdioPulmonary bioImage Study
SF-36 – 36-item Short Form Health Survey
STRAW – Stages of Reproductive Aging Workshop
VMS – Vasomotor symptoms
WHO – World Health Organization
WHQ – Women’s Health Questionnaire
CONTENTS
ABSTRACT...............................................................................................................................ii
Populärvetenskaplig sammanfattning .......................................................................................iv
LIST OF SCIENTIFIC PAPERS ............................................................................................vi
ABBREVIATIONS ....................................................................................................................vii
BACKGROUND ......................................................................................................................1
Menopause .............................................................................................................................1
  Common symptoms .............................................................................................................2
  Physical changes and implications for health .....................................................................2
Vasomotor symptoms ..............................................................................................................3
  What are vasomotor symptoms? .........................................................................................3
  Temperature regulation and skin blood flow .....................................................................4
  Estrogen, skin blood flow and endothelial function ............................................................6
  Mechanisms of vasomotor symptoms .............................................................................7
  Treatment of vasomotor symptoms ..................................................................................9
Quality of life .........................................................................................................................10
Physical activity and exercise after menopause .................................................................11
  Definitions .......................................................................................................................11
  Effects of physical activity and exercise on vasomotor symptoms ................................11
  Summary ..........................................................................................................................13
HYPOTHESES .........................................................................................................................15
AIMS .........................................................................................................................................16
MATERIAL AND METHODS .................................................................................................17
ETHICAL CONSIDERATIONS ..............................................................................................32
RESULTS ................................................................................................................................35
DISCUSSION ..........................................................................................................................51
  METHODOLOGICAL CONSIDERATIONS ..................................................................57
CONCLUSIONS .......................................................................................................................65
CLINICAL IMPLICATIONS AND FUTURE PERSPECTIVES ...............................................66
ACKNOWLEDGMENTS ..........................................................................................................68
REFERENCES .........................................................................................................................71
APPENDIX .............................................................................................................................83

PAPERS I-IV
BACKGROUND

Menopause
Menopause is the permanent cessation of menstruation that occurs following a decline of ovarian follicular activity when the ovaries are no longer able to produce enough estrogen to stimulate endometrial growth. Menopause can also be induced by oophorectomy, or be caused by ovarian failure following radiation therapy or chemotherapy. All women who live long enough will experience menopause, and with the current life expectancy in Sweden, the average woman lives about 40% of her life after menopause, i.e., being postmenopausal.(1)

The stages of female reproductive aging are defined in the international consensus criteria from the Stages of Reproductive Aging Workshop (STRAW) +10.(2) The STRAW criteria divide the reproductive life span into three phases – the reproductive phase, the menopausal transition phase, and the postmenopausal phase with the final menstrual period (FMP) as a reference point. Natural menopause is diagnosed clinically one year after the FMP which occurs around 51 years of age, but there is a large individual variation.(2-4) A few years before menopause, the pituitary hormones follicle-stimulating hormone (FSH) and luteinizing hormone (LH) begin to increase as a result of decreased negative feedback from the ovaries.(5) This phase is classified as the menopausal transition and is characterized by increasing menstrual irregularity, varying hormone levels, and a high incidence of anovulation. The late stage of the menopausal transition lasts for one to three years before the FMP, and symptoms such as hot flushes often start to occur in this phase. Estrogen levels decrease rapidly at this stage.(2, 6) The early postmenopause stage lasts five to eight years and is characterized by high FSH levels, continued decline of estradiol levels and a peak in vasomotor symptoms (VMS).

**Common symptoms**

Although a natural physiological event for most women, menopause is often associated with symptoms that may affect well-being and quality of life substantially. (7) The cardinal symptoms are hot flushes and night sweats, often referred to as VMS, which usually start about one year before the FMP and peak in the years following the FMP. (5, 8, 9) Other symptoms that mid-life women often report are sleep disturbances, mood changes, muscle and joint pain, depressive symptoms, anxiety, and cognitive symptoms. (7) Of these symptoms, only VMS and sleep disturbances secondary to VMS have been consistently linked to menopause in itself, while the others are probably more related to psychosocial factors, life events, and general aging. (10-12)

**Physical changes and implications for health**

The hormonal shift that occurs during the menopausal transition, where decreasing estrogen is the most notable, contributes to physical changes that affect women’s health. Because of a decreased production of sex hormone binding globulin, there is also more free testosterone that, together with the decreased estrogen, contributes to a more androgenic hormone profile. (13) As a result of this, body composition changes, and there is a redistribution of fat mass with an increase of visceral abdominal fat. (14) The visceral abdominal fat is
metabolically active and may contribute to increased risk of cardiovascular
disease (CVD) through low-grade inflammation, and increased insulin
resistance.(15) There is also an unfavorable change in blood lipids with
menopause, with higher total cholesterol, low-density lipoprotein (LDL-c) and
apolipoprotein B, and changed function of high-density lipoprotein (HDL-
c). (16, 17) Central obesity, dyslipidemia and insulin resistance are all
components of the metabolic syndrome, which predisposes for type-2 diabetes
mellitus and CVD. (15) Metabolic syndrome increases over the menopausal
transition, independent of chronological aging. (17) In addition to unfavorable
metabolic changes, bone loss is accelerated, which leads to increased risk of
osteoporosis and fractures. (18)

**Vasomotor symptoms**

**What are vasomotor symptoms?**

Vasomotor symptoms are the cardinal symptoms of the menopause transition
and a common reason for middle-aged women to seek medical advice related to
menopause. VMS will be experienced by 75-80% of all women and about one
third of these have such severe symptoms that they state a need for
treatment. (19-21) The median duration differs between studies from five to 10
years, with a longer duration if the symptoms start in the early transition, but the
VMS can also persist until old age. (8, 9, 22, 23) VMS are, in short,
inappropriate heat loss responses with sudden cutaneous vasodilation and
sweating, mainly in the upper body. (24) The VMS are experienced as a sudden
sensation of heat, often in the face, neck, chest and arms, accompanied by
flushing and a rise in heart rate, and sometimes followed by sweating and
shivering. VMS occur in the day and at night, often spontaneously, but
sometimes triggered by temperature changes. For research purposes VMS may
be categorized as mild, moderate, or severe as follows:

**Mild VMS:** sensation of heat without sweating,

**Moderate VMS:** sensation of heat with sweating but the woman is able to
continue her current activity,

**Severe VMS:** sensation of heat with sweating that leads to interruption of activity
(like loosening clothes, opening a window) or awakening during the night.

The VMS can be assessed objectively by measuring sternal skin conductance,
which shows a characteristic rapid rise at the onset of a hot flush. (25) The skin
conductance measurement can only determine whether there is a hot flush or
not, but cannot assess the severity of the hot flush or how bothered the woman is
by it. There is a high concordance between subjectively reported VMS and objectively recorded VMS in a laboratory environment, with an agreement rate of 86-95% reported in different studies. (25, 27)

Vasomotor symptoms are associated with poorer sleep quality, lower mood, depressive symptoms, irritability, difficulty concentrating and reduced quality of life. (7, 28, 29) A randomized controlled trial (RCT) of women with moderate and severe VMS showed a linear association between VMS frequency and self-rated sleep problems, and VMS frequency and menopause-specific quality of life. Treatment of bothersome VMS with estrogen improves health-related quality of life (HRQoL) and sleep. (30, 31)

**Temperature regulation and skin blood flow**

Vasomotor symptoms can be considered a result of a dysfunction in both the central and peripheral thermoregulation. Thermoregulation is controlled centrally by the hypothalamus, primarily in the preoptic area of the anterior hypothalamus (POA). The hypothalamus orchestrates reflex adjustments to changes in core and skin temperature to maintain a stable core temperature through warm- and cold-sensitive neurons. (32) When the core temperature increases, heat dissipation through cutaneous vasodilation and sweating will increase to keep the core temperature stable. Likewise, a decrease in core temperature will result in a reflex vasoconstriction of cutaneous blood vessels and eventually shivering. In response to internal and external stimuli, the thermoregulation keeps the core temperature within a narrow range by changes in heat dissipation and heat generation. This is called the thermoneutral zone, and it is normally maintained through small changes in the vasoconstrictor tone. (33)

The skin blood flow has a crucial role in temperature regulation and heat dissipation. Both sympathetic noradrenergic vasoconstrictor nerves and sympathetic cholinergic vasodilator nerves control the skin blood flow. The noradrenergic system is tonically active and controls temperature during normal activity by small adjustments in vasoconstriction, and thereby skin blood flow and heat dissipation. The vasodilator system is normally only activated during increases in core temperature outside the thermoneutral zone, by e.g. exercise or heating. Sweating, like active vasodilation, is mediated by sympathetic cholinergic nerves to increase heat dissipation. (33, 34)
Figure 2. Schematic description of the thermoregulation and feedback between the hypothalamus and skin. Increased skin temperature or internal temperature results in heat dissipation through vasodilation and sweating. Decreased skin temperature or internal temperature results in vasoconstriction and eventually in shivering. The thermoregulatory response in the skin is both a reflex response and signaled from the hypothalamus. The influence of internal temperature is greater than the influence of skin temperature; POA, Preoptic area, anterior hypothalamus. Adapted with permission from Charkoudian N. Skin blood flow in adult human thermoregulation: how it works, when it does not, and why. Mayo Clin Proc. 2003;78(5):603-12.

During exercise or exposure to heat, the small adjustments in the vasoconstrictor tone are not sufficient to decrease body temperature. Therefore, the increased core temperature triggers active cutaneous vasodilation and sweating, which increase until a steady temperature is reached. (35) Factors that can alter the threshold of active vasodilation and sweating are heat acclimation, exercise training, circadian rhythm, and reproductive hormone status. (33, 34) In women with VMS, the active vasodilation is triggered inappropriately, which is what causes the VMS. In addition to the central temperature regulation via the hypothalamus, the skin responds locally to heat and cold, such that local heating causes extensive nitric oxide-dependent vasodilation, even without intact sympathetic innervation. (33) Women with VMS may have a dysfunctional peripheral vascular response in the skin with enhanced reactivity to vasodilatory substances and lack of reflex vasoconstriction when exposed to cold. (36, 37)
Estrogen, skin blood flow and endothelial function

The thermoregulatory control of skin blood flow is altered by the decrease in sex hormone levels during the menopausal transition and postmenopause. Generally, estrogens promote skin vasodilation and lower core temperatures, while progesterone appears to promote higher core temperatures and less skin vasodilation. (34) Treatment with estrogen has been shown to decrease the resting core temperature by 0.5 degrees Celsius, caused by cutaneous vasodilation and thus a higher skin blood flow at any given core temperature. (33) This may reflect a better thermoregulatory function and less need for inappropriate heat loss responses such as VMS. (34) The effect on core temperature could also be due to less vasoconstriction. (38)

Apart from being crucial for temperature regulation, the function of the skin blood flow has been used as a proxy for cardiovascular health. (35) Dysfunction of the cutaneous microcirculation has been shown to precede macrovascular dysfunction and is associated with risk factors for CVD. (39, 40) A functional microcirculation is dependent on a healthy endothelium, the single layer of cells that line all blood vessels. The endothelium reacts to physical and chemical stimuli to regulate blood flow and blood pressure, e.g. by producing and releasing factors that lead to vasodilation. (41) Some of the most important endothelium-derived vasodilators are nitric oxide (NO) and endothelium-derived hyperpolarizing factors (EDHF), which are released as a response to shear stress. (41)

Vascular reactivity in the form of endothelial-dependent vasodilation is a key feature of endothelial function and can be assessed by examining the reflex dilation of blood vessels after complete occlusion (post-occlusive reactive hyperemia, PORH). (42) The skin’s microcirculation and microvascular reactivity can be assessed non-invasively by a method that combines diffuse reflectance spectroscopy (DRS) and laser Doppler flowmetry (LDF). The method is called Enhanced Perfusion and Oxygen Saturation (EPOS) and measures both the perfusion and oxygen saturation of the skin’s microcirculation. (43) Previous studies have found differences in the microcirculation assessed by EPOS between men and women. (44) The post-occlusive peak oxygen saturation has been associated with several important risk factors for CVD, such as age, diabetes, smoking, dyslipidemia, and hypertension. (40)

The effects of estrogen on the vasculature have implications for the risk of CVD for women, which accelerates after menopause. (17) Estrogen protects
endothelial function, and regulates blood pressure and vascular reactivity.(13, 45) Estrogen also augments endothelial-dependent vasodilation by stimulating both NO and EDHF release,(46) which could be an important mechanism in how estrogens may protect against CVD.(13, 47, 48) Low estrogen levels are associated with macrovascular endothelial dysfunction, which increases during the menopausal transition.(13) In addition, studies have found associations between the presence of VMS and macrovascular endothelial dysfunction as well as VMS and CVD.(18, 49, 50) Early onset VMS, frequent VMS, and severe VMS with night sweats have all been associated with CVD.(50, 51)

**Mechanisms of vasomotor symptoms**

The mechanisms that cause VMS are still incompletely understood, and several signaling pathways have been shown to be involved.(52, 53) As previously mentioned, women with VMS may have a dysfunctional vascular reactivity, and thus a peripheral dysfunction of temperature regulation contributing to the VMS. However, VMS can mainly be attributed to a central thermoregulatory dysfunction in the POA of the hypothalamus, with an instability in the thermoregulatory center in combination with a reduced thermoneutral zone.(52, 53) Even small increases in core temperature will then trigger a heat dissipation response with active vasodilation. The onset and occurrence of VMS are indirectly linked to the varying and declining estrogen levels at the time around the FMP, but not the absolute estrogen levels.(54) However, a more rapid decrease in estrogen levels, as after surgical menopause, leads to more severe VMS.

Luteinizing hormone pulses coincide with VMS, implying that neurons involved in stimulating LH release from the pituitary are also involved in the mechanisms of VMS.(55) LH release is controlled by hypothalamic gonadotropin-releasing hormone (GnRH), which in turn is controlled by kisspeptin/neurokinin B/dynorphin neurons (KNDy neurons) in the POA in the hypothalamus. Relatively recently, it has been shown that the KNDy neurons are also involved in thermoregulation and VMS, which could explain the simultaneous LH pulses.(53) Neurokinin B is upregulated in postmenopausal women due to decreased negative feedback from estrogen. Injection of neurokinin B in women triggers VMS, while blockage of the receptor for neurokinin B reduces VMS in symptomatic women.(56, 57)
Figure 3a. Proposed mechanisms of vasomotor symptoms: Estrogen normally stabilizes the thermoregulatory center in the hypothalamus via indirect pathways (e.g., KNDy neurons that project to the thermoregulatory center, and endogenous opioids such as β-endorphin). With decreasing levels of estrogen, there is decreased β-endorphin, and decreased negative feedback on KNDy neurons in the preoptic area of the hypothalamus. The KNDy neurons release Neurokinin B which binds to receptors in thermoregulatory neurons. Together with an increased sensitivity to core temperature changes, this triggers a heat dissipation response with active vasodilation of skin blood vessels and sweat gland activation. In addition, the decreased estrogen levels accelerate endothelial dysfunction, contributing to less effective peripheral temperature regulation. EDHF, Endothelium-derived hyperpolarizing factor; NO, Nitric oxide. Hypothalamus picture source: https://neuroscientificallychallenged.com/glossary/hypothalamus, published under Creative Commons license 4.0

Estrogen treatment acts to stabilize the thermoregulatory center in the POA and increases the sweating threshold.(58) Estrogen may act directly by binding to estrogen receptors in KNDy neurons,(53) but also indirectly through pathways that involve endogenous opioid signaling, for example by increased production of the opioid peptide β-endorphin in the central nervous system (CNS).(59) Studies have found that endogenous opioids are involved in the mechanisms of temperature regulation, and that estrogen mediates effects on temperature regulation through opioid signaling in the hypothalamus.(60, 61) The β-endorphin levels decrease after menopause, but the levels are restored by estrogen treatment.(62, 63) and could also be affected by physical exercise.(64-66) According to this theory, any treatment that increases β-endorphin or affects endogenous opioid activity in the POA would have the potential to reduce VMS.
Figure 3b. Proposed mechanisms of the effect of physical activity on vasomotor symptoms: Physical activity increases β-endorphin levels and affects endogenous opioid signaling, which stabilizes thermoregulation. In addition, physical activity could have positive effects on endothelial function and could thus improve temperature regulation peripherally. The question marks symbolize that physical exercise may exert effects via unknown mechanisms. EDHF, Endothelium-derived hyperpolarizing factor; NO, Nitric oxide. Hypothalamus picture source: https://neuroscientificallychallenged.com/glossary/hypothalamus, published under CC-BY 4.0 license.

Treatment of vasomotor symptoms

The most effective treatment for VMS is menopausal hormone therapy (MHT), which contains estrogen. In women with a detained uterus, estrogen should be combined with a progestogen to avoid endometrial hyperplasia and endometrial cancer. The treatment should be individualized to maximize benefits and minimize risks, which means that the lowest effective dose of estrogen to relieve VMS is recommended.(31) MHT decreases the frequency of VMS by about 75% and thereby also improves HRQoL and sleep.(67) Contraindications to MHT are unexplained vaginal bleeding, prior venous thromboembolism (VTE) or high risk of VTE (applies mostly to oral MHT), established CVD like prior myocardial infarction or stroke, serious liver or gall bladder disease, and a history of breast cancer or estrogen-sensitive cancer. MHT decreases the frequency of VMS by around 75% and thereby also improves HRQoL and sleep.(67) Generally, the benefits of MHT are considered to outweigh the risks in women initiating MHT within 10 years of menopause.(31)
Since MHT is not without risks, and since there are women who cannot use MHT due to the contraindications described above, there is a need for other treatment options for VMS that are safe and effective. Pharmacological alternatives are for instance selective serotonin reuptake inhibitors (SSRI), serotonin-norepinephrine reuptake inhibitors (SNRI) and gabapentin, which have been shown to reduce VMS. (68, 69) However, these medications are not as effective as MHT and side effects such as headache, nausea, dizziness, sexual dysfunction and perspiration are common reasons for discontinuation.

**Quality of life**

The term Quality of Life (QoL) is multi-faceted and there is no general consensus about its definition. Like “health”, it encompasses several aspects of well-being and function. The World Health Organization (WHO) defines health as “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity” and thus includes physical, mental and social aspects in the definition. Regarding QoL, the WHO defines it as “an individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns”. The term HRQoL is often used in a medical research context to assess how a condition affects functioning within physical, emotional and social domains, role performance within these domains, and pain. (70) It represents a person’s own evaluation of the impact of a health condition on daily life. HRQoL can be used to assess the physical, social, and emotional aspects of living with a condition and is thought to represent the views of the affected individuals themselves. (71)

Quality of life instruments can be generic or disease-specific. The advantages of generic HRQoL questionnaires are their wide applicability in different conditions and different populations, and the fact that they cover many dimensions of importance to HRQoL. A drawback is that they are often less sensitive to change than disease-specific instruments. (70) Possible reasons include that the instrument may include items of little relevance to a particular patient group, that some areas are relatively static or not targeted by a health care intervention, or that there may be a floor or ceiling effect. (70) Disease-specific HRQoL instruments are usually used to understand how symptoms impact daily life and to describe the symptom burden, but also to evaluate treatment effects in trials. Both generic and disease-specific instruments are valuable to achieve a more complete picture of how a treatment affects patients. (72) The disease-specific instruments are more likely to be responsive to change but make comparisons between different conditions difficult.
Physical activity and exercise after menopause

Definitions

Physical activity is defined as any bodily movement that increases energy expenditure to above resting level. Sedentary behavior is defined as waking activities that do not increase energy expenditure substantially more than resting levels, such as lying down or sitting. Exercise is planned, structured physical activity with the goal of preserving or improving physical fitness. (73) The absolute intensity of physical activity describes the absolute demands of the activity and is not related to individual capacity. Absolute intensity can be expressed in metabolic equivalents (MET). (74) One MET is defined as the energy expenditure while sitting at rest and is approximately equal to consumption of 3.5 ml O₂ per kg bodyweight and minute, while vigorous physical activity can be defined as ≥6.0 MET. MET minutes (i.e., MET x minutes spent doing the activity) can be used to express energy expenditure over a period of time. (75) An objective method to measure physical activity that uses absolute intensity is with accelerometers. Accelerometers are sensors, usually worn on the hip or wrist, that register acceleration in one or three axes. After data processing, results are often generated in MET or minutes spent in different intensities of physical activity. (76)

The relative intensity of physical activities depends on individual capacity. For resistance training, the relative intensity can be expressed as the eight repetition maximum (8RM) or the percentage of one repetition maximum (1RM), for example. 8RM is the maximum resistance at which an individual can perform an exercise for exactly eight repetitions with a correct technique and approximately corresponds to 79% of 1RM. (74) Muscle strength can be assessed by finding an individual’s 8RM through testing. (77, 78) The test result can also be used to prescribe the intensity of resistance training in a standardized individually adjusted manner. (79) The dose of resistance training consists of intensity, number of repetitions, number of sets and frequency of training. The American College of Sports Medicine recommends that novices train with loads that correspond to 8-12 RM to gain both strength and hypertrophy and that the loads are increased by 2-10% when the individual can perform more repetitions than the desired 8-12. (80)

Effects of physical activity and exercise on vasomotor symptoms

In 1990, in Linköping, Sweden, it was first reported that postmenopausal women who exercised regularly were about half as likely to report moderate and severe VMS compared with a control group of women of the same age. (81) Since then,
several observational studies have found that regular physical activity and exercise are associated with less VMS among peri- and postmenopausal women and one study found a shorter duration of symptoms.(9, 82-87) In addition, a higher BMI is also associated with VMS.(28, 86, 88-91) However, other studies did not find an association between VMS and physical activity or exercise.(92-94) Theoretically, exercise of longer duration and/or vigorous intensity affects the production of β-endorphin and other endogenous opioids that could potentially reduce VMS.(95) Another mechanism by which exercise could reduce VMS is through improved thermoregulation peripherally by enhanced vascular function and thereby more efficient heat loss through small changes in skin blood flow.(96) The results from intervention trials that examined the effect of exercise on VMS as a primary outcome are ambiguous and in general show little or no effect.(97) The interventions mostly consisted of exercise types such as walking, Nordic walking, jogging and aerobics of low to moderate intensity, or any aerobic exercise type of the participants’ choice with poor control of the dose and of compliance.(98-102) Previous trials have struggled with low compliance in the intervention group, had low control of the exercise dose, used low-moderate intensity exercise, or mixed different exercise modalities and intensities. All these factors might together explain the lack of a significant effect on VMS in these studies. Thus, the quality of evidence is insufficient to determine whether or not exercise might be an effective intervention against VMS.(97) The WHO recommends that all adults perform muscle-strengthening activities two times per week to increase bone mass and muscle mass.(103) Even though this is especially important for women after menopause to counteract osteopenia and sarcopenia, according to data from Scotland and Finland, approximately only one out of six middle-aged women meet the recommendations regarding strength training.(104, 105) In comparison, at least two thirds of Swedish women aged 45-64 years reported adhering to recommendations regarding aerobic physical activity (≥150-300 minutes/week moderate intensity or ≥75-150 minutes/week vigorous intensity).(106) This indicates that it may be more difficult to start resistance training than aerobic exercise and that fewer women have experience of resistance training. Adherence to an exercise intervention is necessary to achieve health effects but can be challenging, especially for novices to training. As mentioned before, exercise intervention trials against VMS in postmenopausal women have been affected by attrition or low compliance to the
intervention. It is therefore of interest to investigate factors that could affect adherence to an exercise intervention.

**Summary**

In summary, for many women menopause is associated with bothersome VMS that reduce quality of life. In addition, the hormonal changes after menopause result in adverse physical and metabolic changes that accelerate the risk of CVD. Studies have associated menopause, low estrogen levels and VMS with macrovascular endothelial dysfunction and CVD, but previous studies on the cutaneous microcirculation are small and few. If endothelial dysfunction could be detected at an early stage, it would give the opportunity for preventive measures. We hypothesized that cutaneous microcirculation would differ between women depending on menopausal status, MHT treatment, and the presence of VMS.

Some observational studies have associated physical activity and exercise with less VMS, but the evidence from intervention trials is of low quality and results are ambiguous. From what is known about the mechanisms that cause VMS, physical activity with activation of large muscle groups could potentially decrease VMS through effects on endogenous opioids centrally, and by a more efficient thermoregulation peripherally. Our hypothesis was that resistance training would be an effective intervention to decrease VMS in postmenopausal women, and would have a positive effect on HRQoL.

When this thesis was planned, no studies had assessed resistance training with change in VMS as the primary outcome. Our research group has previously experienced a high dropout rate when conducting an exercise trial on women with VMS. For this reason, a qualitative study was planned to explore the experiences of a resistance training intervention and specifically the barriers and facilitators related to starting and adhering to the training.
HYPOTHESES

- Moderate to severe vasomotor symptoms will decrease more in a group of postmenopausal women with low physical activity randomized to a resistance training intervention compared with a control group of postmenopausal women with unchanged low physical activity.

- Menopause-specific and generic health-related quality of life will improve more in a group of postmenopausal women with low physical activity randomized to a resistance training intervention compared with a control group of postmenopausal women with unchanged low physical activity.

- Cutaneous microcirculatory function differs between women grouped according to menopausal status, menopausal hormone therapy, vasomotor symptoms and physical activity.
AIMS

General aim
The general aim of this thesis was to investigate the effect of exercise on vasomotor symptoms and quality of life in postmenopausal women and explore differences in cutaneous microcirculation in middle-aged women.

Specific aims

- To determine the effect of a structured resistance training intervention on the number of daily moderate to severe vasomotor symptoms in postmenopausal women with low physical activity, compared with a control group of postmenopausal women with unchanged low physical activity.

- To determine the effect of a structured resistance training intervention on menopause-specific and generic health-related quality of life in postmenopausal women with low physical activity, compared with a control group of postmenopausal women with unchanged low physical activity.

- To explore the individual experiences of participation in a resistance training intervention in postmenopausal women with low physical activity, and to find barriers and facilitators for the training.

- To investigate if cutaneous microcirculatory function, including microcirculatory reactivity, differs between women grouped according to menopausal status, menopausal hormone therapy, vasomotor symptoms and self-reported or objectively measured physical activity.
MATERIAL AND METHODS

Table 1. Description of the studies included in this thesis.

<table>
<thead>
<tr>
<th>STUDY</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAPER</td>
<td>I-II</td>
<td>III</td>
<td>IV</td>
</tr>
<tr>
<td>Study type</td>
<td>Intervention study</td>
<td>Qualitative</td>
<td>Observational</td>
</tr>
<tr>
<td>Design</td>
<td>Open randomized controlled trial</td>
<td>Interview study</td>
<td>Cross-sectional</td>
</tr>
<tr>
<td>Study population</td>
<td>65 postmenopausal women with at least four moderate-severe VMS/24 hours</td>
<td>15 postmenopausal women who participated in resistance training intervention in Study 1</td>
<td>1148 women aged 50-64 years, randomly invited to the SCAPIS study from the general population in Linköping municipality</td>
</tr>
<tr>
<td>Data source</td>
<td>VMS diaries WHQ SF-36 IPAQ (last 7 days) Physical activity diaries</td>
<td>Semi-structured individual interviews</td>
<td>SCAPIS database, SCAPIS Survey on Women’s Health, Microcirculatory data from SCAPIS Micro</td>
</tr>
<tr>
<td>Intervention/Exposure</td>
<td>15 weeks of resistance training</td>
<td>Participants grouped according to: menopausal status, menopausal hormone therapy, VMS, physical activity</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>Unchanged low physical activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome</td>
<td>Change in: VMS, HRQoL domains, MET minutes</td>
<td></td>
<td>Skin microvascular function</td>
</tr>
<tr>
<td>Analytic methods</td>
<td>Descriptive statistics, ANCOVA, Mixed-model ANOVA, Mann-Whitney U, Wilcoxon signed rank, Pearson and Spearman correlation</td>
<td>Thematic analysis</td>
<td>Descriptive statistics, Student’s t-test, Chi-square test, Mann-Whitney U ANOVA Linear regression ANCOVA</td>
</tr>
</tbody>
</table>

ANOVA, Analysis of Variance; ANCOVA, Analysis of covariance; IPAQ, International Physical activity Questionnaire; MET, Metabolic equivalents; SCAPIS – Swedish CArdioPulmonary bioImaging Study; SF-36, 36-item Short Form Health Survey; WHQ, Women’s Health Questionnaire
Study designs and populations

Study 1

This study was an open RCT with 65 participants randomized in a 1:1 allocation to a 15-week resistance training intervention or a control group with unchanged physical activity. Participants were postmenopausal women, ≥45 years old, who reported a mean of at least four moderate and/or severe VMS per 24 hours or 28 moderate and/or severe VMS per week during a two-week screening period. To be included, the women had to be healthy and report low physical activity at baseline (maximum 75 minutes of vigorous physical activity per week) based on a screening interview.

Recruitment

Participants were recruited through advertisements twice per year. After telephone screening, possibly eligible participants were sent information about the study and invited to a screening visit where written informed consent was collected. The eligibility criteria were checked, and a two-week VMS and physical activity diary was distributed. After the two-week screening period, the women attended the clinic again for a randomization visit. An evaluation of eligibility was conducted based on the number of moderate to severe VMS registered in the diary, and those eligible were included and randomized. Included women filled out baseline questionnaires about HRQoL and physical activity. At the end of the 15-week study period, all attended a third visit to fill out the questionnaires and repeat the baseline measurements.

Randomization

The randomization sequence was created by an independent statistician and was concealed in opaque, sealed and sequentially numbered envelopes that were stored in a locked location and handled by a research nurse. Participants were block randomized in a 1:1 allocation. When a new participant was included, the investigator opened the envelope in the presence of the participant to reveal the group allocation.

Intervention

The intervention was a 15-week resistance training program with six exercises performed in seated resistance machines and two body weight exercises. The exercises were: chest press, leg press, seated row, leg curl, latissimus dorsi pull-down, leg extension, crunches, and back raises. The exercises were performed with 8-12 repetitions in two sets with two minutes of rest between sets. Loads
were set to 8-12 RM after individual testing by a physiotherapist who was part of the study team. Body weight exercises were performed until exhaustion in two sets (approximately 20 repetitions/set). The training was preceded by 7-10 minutes of warm-up and finished with dynamic and static stretching. The loads were lower in the first three weeks (15-20 repetitions at 15-20 RM) to decrease the risk of injury and to avoid dropout due to an excessively rapid increase in exercise.

One training session per week with the physiotherapist was mandatory to follow progress, increase loads and control for adverse events. Every participant had an individual introductory session with the physiotherapist to find appropriate settings on the machines and to become familiar with the exercises. The participants were instructed to aim for three resistance training sessions per week. Attendance was logged via the electronic card system at the gym, and the participants registered exercises and loads in a personal training logbook at the gym. Compliance was defined as completion of a mean of at least two sessions/week.

**Control group**

The participants in the control group were asked to maintain the same amount and type of physical activity as they had upon inclusion. They were not allowed to start another treatment for VMS during the study. After 15 weeks, they received a four-month membership card at the same gym where the intervention took place, and everyone was offered an introduction to resistance training and the same program that the intervention group followed.

**Study 2**

This study was a qualitative study and was developed as an add-on to study 1. The aim was to explore the experiences of the resistance training intervention and specifically barriers and facilitators related to starting and adhering to the training. Fifteen participants from the intervention group in Study 1 were consecutively invited to individual interviews following completion of the 15-week resistance training program, irrespective of compliance.

**Study 3**

Study 3 was a cross-sectional study based on data from the female Linköping cohort of the Swedish CArdioPulmonary bioImage Study (SCAPIS). SCAPIS is
a multi-center population-based cohort study of individuals 50-64 years old, with the overall goal to predict and prevent CVD by collection of a large amount of epidemiological, clinical and laboratory data. Data for this study were extracted from the SCAPIS database and microcirculatory data retrieved from a microcirculatory add-on study in Linköping. The female participants in Linköping were asked to complete an additional questionnaire about women’s health, called Survey on Women’s Health (SWH, Appendix). (107) Figure 5 describes the selection of participants for the study. All female participants of the Linköping SCAPIS cohort who answered the SWH and had valid data from the microcirculatory assessment were assessed for inclusion in this study. We excluded women classified as perimenopausal and those with uncertain menopausal status. This resulted in a study population of 1148 women.
Figure 5. Selection of the study population of Study 3. ACE, Angiotensin-Converting Enzyme; ARB, Angiotensin II Receptor Blocker, SCAPIS, Swedish CArdioPulmonary bioImaging Study; SWH, Survey of Women’s Health.
Outcomes and variables

Vasomotor symptoms (Paper I)

The women in the RCT registered VMS daily in a diary during the 15-week study period. Each diary covered four weeks and they sent the diary to the research nurse after completion of each four-week period. In the diary they registered the number of mild, moderate, and severe VMS separately. They received written instructions on how to classify VMS into mild, moderate or severe. The moderate and severe VMS were added for the primary outcome and a mean for baseline and each week was calculated.

Health-related quality of life (Paper II)

WHQ

The Women’s Health Questionnaire (WHQ), used in the RCT, was designed to assess middle-aged women’s perceptions of emotional and physical symptoms (108, 109) and evaluate HRQoL in women during the menopausal transition and postmenopausal years. It has been validated in several languages, including Swedish (110) and is sensitive to change in intervention trials of treatments for VMS. (98, 111) The WHQ has 36 items that are answered on a four-point scale. The instrument generates scores from 0 to 1 in nine domains of importance to menopause-specific HRQoL, where a higher score indicates worse HRQoL.

Table 2. The domains and corresponding items of the WHQ.

<table>
<thead>
<tr>
<th>Domains</th>
<th>Items</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressed mood</td>
<td>Loss of interest, Lack of enjoyment, Miserable and sad, Reduced well-being, Irritability, Loss of appetite, Life not worth living</td>
</tr>
<tr>
<td>Somatic symptoms</td>
<td>Headaches, Tiredness, Dizzy spells, Joint pain, Nausea, Pins and needles in hands/feet, Frequent urination</td>
</tr>
<tr>
<td>Memory/concentration</td>
<td>Clumsiness, Difficulty concentrating, Poor memory</td>
</tr>
<tr>
<td>Vasomotor symptoms</td>
<td>Hot flushes, bothersome night sweats</td>
</tr>
<tr>
<td>Anxiety/fears</td>
<td>Panicky feelings, Anxious, Tension, Palpitations/”butterflies“</td>
</tr>
<tr>
<td>Sexual behaviour</td>
<td>Loss of interest, Dissatisfaction, Uncomfortable due to vaginal dryness</td>
</tr>
<tr>
<td>Sleep Problems</td>
<td>Early awakenings, Restlessness, Insomnia,</td>
</tr>
<tr>
<td>Menstrual symptoms</td>
<td>Breast tenderness, Abdominal discomfort, Heavy periods, Bloatedness</td>
</tr>
<tr>
<td>Attractiveness</td>
<td>Not lively, Feeling unattractive</td>
</tr>
</tbody>
</table>

WHQ, Women’s Health Questionnaire
**SF-36**

The 36-item Short Form Health Survey is a broadly used instrument to measure generic HRQoL and was used in the RCT to assess generic HRQoL. It consists of 36 questions generating scores on eight scales related to HRQoL: Physical functioning, Physical role functioning RP, Bodily pain BP, General health perception, Vitality, Social functioning, Emotional role functioning, and Mental health. For each scale, a score from 0 to 100 is calculated, where a higher score indicates better HRQoL. A difference of 5 points has been suggested to be a clinically meaningful change. Two summary scores are also calculated; a physical (PCS) and a mental (MCS). (112) The Swedish translation of SF-36 has been found to be valid and reliable in a Swedish setting. (113)

**Physical activity (Paper I and IV)**

Physical activity in the RCT was assessed using the last seven-days version of IPAQ. It contains nine questions regarding the amount of time spent on vigorous-intensity activity, moderate-intensity activity, walking and sitting during the last seven days which lets the user calculate MET minutes. IPAQ has been validated in several languages to assess physical activity level, including Swedish. (114, 115) The participating women also documented minutes spent on physical activity in the VMS diary.

In Study 3, the participants wore accelerometers (wGT3X-BT, ActiGraph LCC, Pensacola, FL, USA) for seven days to collect data on physical activity and sedentary time. Data on self-reported physical activity and exercise, and accelerometer-recorded daily sedentary time, low-intensity physical activity, moderate-intensity physical activity and vigorous-intensity physical activity were extracted from the SCAPIS database.

**Menopause, VMS and MHT (Paper IV)**

The data derived from the SWH were menstrual status, FMP, previous gynecological surgery, current and previous VMS, and current or previous use of MHT, including type of administration. The women were classified as postmenopausal if they reported no menstruation for one year, and as premenopausal if they were still menstruating. We dichotomized current VMS into daily/not daily VMS and MHT use into current/not current MHT.
Cutaneous microcirculatory function (Paper IV)

In Study 3, skin microcirculation was assessed at rest and during PORH using a multimodal optical instrument (PeriFlux 6000 EPOS, Perimed AB). A fiber-optic probe attached to the skin registered the DRS and LDF data and a model-based algorithm was used to produce the microcirculatory data. The method has been tested and validated previously.\(^{(43, 44)}\) The protocol was 20 minutes long and consisted of a five-minute baseline assessment, five-minute arterial occlusion, and a 10-minute post-occlusive reperfusion phase (Figure 6).

![Figure 6. Illustration of the microcirculatory measurement method. A blood pressure cuff was placed on the right upper arm and quickly inflated to 250 mmHg to achieve complete arterial occlusion and then released to achieve a reactive hyperemia. The illustrated diagram shows oxygen saturation during the occlusion protocol, where the maximum vasodilation during peak oxygen saturation is marked. Reprinted from Jonasson H, Bergstrand S, Fredriksson I, Larsson M, Ostgren CJ, Stromberg T. Post-ischemic skin peak oxygen saturation is associated with cardiovascular risk factors: a Swedish cohort study. Microvasc Res. 2022;140:104284 with permission from Elsevier.](image)

The microcirculatory variables collected and included in this study were:

- Baseline values of oxygen saturation, red blood cell tissue fraction and perfusion
- Post-occlusive peak values of oxygen saturation, red blood cell tissue fraction and perfusion
Baseline values were defined for each participant as the median over the first three minutes of the five-minutes baseline phase, while peak values were defined as the highest value reached during the reperfusion phase.

Further variables collected in Study 3
The core protocol in SCAPIS included three visits during a two-week period for questionnaire fulfillment, examinations, and blood sampling.(107)
The following variables were retrieved from the SCAPIS database:
Demographic variables
- Age, marital status, education, employment, country of birth

Anthropometry and CVD risk factors
- Body weight, height, waist circumference, waist/hip ratio
- Total cholesterol, HDL-c, LDL-c, triglycerides, plasma glucose, HbA1c
- Hypertension, dyslipidemia (self-reported diagnosed by physician, and currently using antihypertensive or lipid-lowering medication, respectively)
- Diabetes, defined by self-report or fasting p-glucose ≥7.0 mmol/l or HbA1c ≥48 mmol/mol

Group comparisons in Study 3
We compared the microcirculatory variables between the following groups:
- Premenopausal vs. Postmenopausal
- Postmenopausal, current MHT vs. Postmenopausal, not current MHT
- Postmenopausal, not current MHT
  - Daily VMS vs. Not daily VMS

Next, we considered only the outcome “peak oxygen saturation” and compared it in adjusted analyses between the same groups described above. This variable of microvascular reactivity was chosen since it has previously been shown to be associated with CVD risk factors and to be different between men and women.(40, 116)

In the analyses of physical activity, the study population was split into tertiles based on the accelerometer-recorded weekly moderate to vigorous physical activity (MVPA) and sedentary time, respectively. Only sedentary time longer
than 20 minutes at a time was included. Peak oxygen saturation was compared between the tertiles.

**Semi-structured interviews (Paper III)**

The interviews in the qualitative study were individual and scheduled after the woman had accepted participation. To achieve a neutral environment, the setting for the interviews was distant from the clinic where the visits in the RCT took place, in a different building in the university hospital area.

The interviews were semi-structured, with the use of an interview guide (Appendix) with questions to assist the interviewer and ensure that relevant topics were covered during the interview. Informal small talk preceded the interview to establish some rapport between the interviewer and respondent. The interviewer could add questions, use probes, ask for clarification, and ask follow-up questions to achieve richer descriptions from the respondent and follow the respondent during the interview. All interviews were audio-recorded and transcribed verbatim. Background information about the woman’s social situation, history and duration of menopausal symptoms was collected after the interview.

A short telephone interview was conducted after one year with the purpose to follow up on physical activity and adherence to resistance training. The interview followed an interview guide containing questions about current symptoms, and exercise- and resistance training habits.
STATISTICS AND DATA ANALYSIS

Sample size and power
A sample size calculation was performed for Study 1 based on pilot results from the first 16 participants included in the RCT. With an alpha level of 0.05 and an assumed dropout rate of 20%, we needed 40 participants in total to detect a difference of 50% with 80% power. A decrease of VMS by 50% has previously been shown to be a desired decrease in VMS for women and was considered clinically significant. (117) To increase the power to find effects on secondary outcomes we aimed to include at least 60 women in total.

Post-hoc power analyses was performed for HRQoL outcomes, based on the 57 participants included in the analyses of HRQoL. With a two-sided alpha value of 0.05 and observed baseline standard deviations of 0.2-0.3, the analyses showed 45-80% power to detect a difference of 0.15 in WHQ domains between groups. For SF-36 domains, the analyses showed 10-45% power to detect a difference of 5 with a two-sided alpha value of 0.05 and observed baseline standard deviations of 7-34.

Statistical methods
All analyses were performed using IBM SPSS Statistics, v 24-28 (IBM, New York, USA).

Descriptive statistics
The data were plotted in scatter plots and histograms and visually inspected to assess the distribution. For continuous variables that were approximately normally distributed, the central tendency and dispersion were presented using means and standard deviations. The central tendency of skewed variables was presented using the median and interquartile range. Categorical variables were presented using absolute number and percentages.

Missing data
In the RCT, baseline variables between participants with missing vs. complete diary data were compared using the Mann-Whitney U test to investigate differences. Missing data from VMS diaries was handled in two ways. If a participant had completed at least 13 of the intended 15 weeks registration, the mean of the last seven registered days was carried forward and used as the post-intervention (week 15) value. If fewer weeks were registered, mean imputation was used. Missing data were not imputed in the remaining analyses.
Inferences

Vasomotor symptoms (Paper I)

All participants who provided more than only baseline data were included in the intention-to-treat analysis. Analysis of covariance (ANCOVA) was used to compare the post-intervention mean VMS frequency between the intervention and control groups with the baseline mean VMS frequency as covariate. The adjusted mean difference was presented with a 95% confidence interval. We also performed a mixed-model repeated measures ANOVA to assess the change over time in mean VMS frequency with three-week interval. To visualize the change in both groups separately, absolute and percentage change of mean VMS frequency and mean VMS score were calculated and compared between the intervention and control groups using Student’s t-test. Chi² test was used to compare the proportion of participants in each group that reported at least a 50% decrease in VMS.

Pearson correlation analysis was used to evaluate the correlation between mean completed resistance training sessions/week and the change in VMS frequency, as well as the correlation between change in VMS frequency and change in MET minutes/week in the intervention group. In this thesis, the same correlation analyses was performed using Spearman’s rank correlation.

HRQoL (Paper II)

For HRQoL data, the change from baseline to post-intervention was calculated for each HRQoL domain. ANCOVA was used to compare the post-intervention scores between groups with adjustment for the baseline score. Since some of the HRQoL domains had a skewed distribution, we also compared the change scores between the groups using the non-parametric Mann-Whitney U test. To assess within-group change from baseline to post-intervention we used the Wilcoxon signed rank test for each group separately. We assessed correlations between change in HRQoL domain scores and change in VMS frequency and VMS score with Pearson correlation and Spearman’s rank correlation. We also compared the HRQoL change scores between the participants in the intervention group defined as compliant vs. non-compliant with the intervention.

Microcirculatory function (Paper IV)

To test for differences in background variables between groups, Student’s T-test was used for continuous variables, and Chi² for categorical variables. Microcirculatory outcome data were compared between premenopausal and postmenopausal women using Student’s t-test in unadjusted analyses and
ANCOVA in adjusted analyses. Student’s t-test was used to compare microcirculatory outcomes between MHT users and non-users and women with daily VMS vs. not daily VMS. In the analyses of VMS, MHT users were excluded.

We then focused on post-occlusive peak oxygen saturation. Simple linear regressions were used to investigate associations between post-occlusive peak oxygen saturation and each background variable in premenopausal and postmenopausal women. The variables that displayed a significant association and were different between the compared groups were used as covariates in general linear models that compared peak oxygen saturation between the following groups: postmenopausal vs. premenopausal; postmenopausal with daily VMS vs. postmenopausal without daily VMS. The analyses were checked to not violate assumptions of normality or homoscedasticity by inspection of a normal probability plot of the standardized residuals and plotting standardized residuals and predicted values in a scatterplot. A correlation matrix was constructed to check for correlations between independent variables, ensuring there was no problem with multicollinearity.

The study population was split into tertiles based on accelerometer-recorded MVPA and sedentary time. Post-occlusive peak oxygen saturation was compared between the tertiles in general linear models that were further adjusted for age, BMI, hypertension, smoking and university degree. Post-hoc were performed to detect differences between the individual groups, and the significance level was adjusted with Bonferroni correction in the post-hoc tests. The same procedure was performed to compare peak oxygen saturation between the groups of self-reported exercise and physical activity.

**Qualitative data analysis (Paper III)**

Data analysis in the qualitative study was performed using thematic analysis according to Braun & Clarke. We adopted a constructionist approach during the analysis and searched for both explicit and latent meaning and themes. Table 3 gives a description of the analytical phases.
Table 3. The table shows the phases of thematic analysis that the researchers implemented.

<table>
<thead>
<tr>
<th>Phase</th>
<th>Description</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Data familiarization</td>
<td>Transcripts from interviews were read several times and initial notes and thoughts were written down</td>
<td>“Positive experience, no obstacles” (notes Participant 6)</td>
</tr>
<tr>
<td>2. Generation of initial codes</td>
<td>Coding was performed separately by two researchers (EB, CB), and data extracts collated within each code. Codes were then compared and discussed between the two researchers</td>
<td>&quot;I have a craving for it (the resistance training) now, because I think it’s such fun, so I still exercise at least three times per week&quot; Initial code: Developed craving for resistance training</td>
</tr>
<tr>
<td>3. Generation of initial themes</td>
<td>Codes were collated into initial themes and subthemes independently by two researchers (EB, CB), a thematic map was constructed for each interview</td>
<td>Initial code: “Developed craving for resistance training” Initial theme: Lifestyle change – exercise addictive</td>
</tr>
<tr>
<td>4. Initial themes reviewed</td>
<td>The initial themes were reviewed by reading all data extracts belonging to each initial theme and the initial themes reworked to generate a preliminary thematic map of the whole data set. The themes were further reviewed by re-reading the whole data set and ensuring an accurate representation of the raw data in the themes.</td>
<td>See Figure 4a and 4b for example of the preliminary thematic map, and reworked thematic map</td>
</tr>
<tr>
<td>5. Refining and defining themes</td>
<td>The themes were refined in an analytic process of discussing the meaning and definition of each theme, and checking the final themes against the raw data set.</td>
<td>See Figure 13 for final thematic map</td>
</tr>
<tr>
<td>6. Report writing</td>
<td>The themes were presented in a report with definitions of each theme, along with data extracts that represent the themes</td>
<td></td>
</tr>
</tbody>
</table>

During the analysis the researchers went back and forth through the phases as the analysis evolved. EB – Emilia Berin. CB – Carina Berterö.
Figure 4a and 4b show the evolvement of the thematic maps during the analysis.
ETHICAL CONSIDERATIONS

All studies included in this thesis were approved by the Regional Ethical Review Boards in Linköping or Umeå, or the Swedish Ethical Review Authority, respectively (Study 1 and 2 Dnr 2013/285-31, study 3 Dnr 2010-228-31M, 2015-246/32, 2018/156-31, 2018/478-31, 2020-03101 and 2021-07061-02).

The studies were conducted in line with the Declaration of Helsinki and Study 1 was conducted according to applicable standards of Good Clinical Practice. In studies 1, 2 and 3, all participants received oral and written information about the study and were able to ask questions about the study before deciding if they wanted to participate. All participants gave both oral and written informed consent to participate. The information was given by a physician during the first visit before the data collection and the physician collected informed consent. The women were assured that their participation was voluntary, and that their decision on whether or not to participate would not affect the future care for them as patients. Study 2 was an attachment to the RCT about resistance training, and it was therefore especially important that the participants were informed that the decision about whether or not to take part in the qualitative study would not affect the future follow-up in the RCT. In all studies that require informed consent it is important that the participants have the right to withdraw at any time without giving further explanation to the researchers, which we informed the participants thoroughly about upon inclusion.

Recruitment for Study 1 was primarily achieved through advertisements in the local newspaper and social media, and interested women contacted the research group. This means that the risk of any participant feeling pressured to enter the study was low. Since the intervention consisted of exercise, which could be expected to have several positive effects on health, one might argue that participants randomized to the control group missed potential benefits. However, the control participants were not asked to refrain from exercise and physical activity, only to maintain the same low level they were already doing for 15 weeks. This means no additional harm was inflicted upon the participants in the control group to put them at risk of adverse health effects. In addition, they received a gym membership for four months after completion of the study period, so they also had the possibility to start exercise during the follow-up. All were thoroughly informed about the randomization procedure before the collection of informed consent and inclusion in the study.
Qualitative studies may pose different challenges or ethical problems than quantitative studies, depending on the method of data collection. In Study 2 we used recorded interviews to collect data, with the hope and aim that the participants would share their personal experiences and thoughts. The risk of evoking negative or unexpected feelings in the informant is always present when conducting interviews and must be taken into consideration. In this case, the risk was considered low since the focus of the interviews was not of a deeply personal or sensitive nature. However, the interviewer still has to take care to debrief with the informant, and acknowledge any negative feelings during and after the interview since people have different limits to their integrity and personal space. On the other hand, qualitative interviews have the possibility to make the informant feel validated and listened to in a non-stressed setting, which may be rewarding for the individual.

Study 3 was a cross-sectional study of the Linköping cohort of SCAPIS, a population-based cohort study of approximately 30,000 women and men randomized from the general population. The overall aim of SCAPIS was to gather detailed information on multiple clinical and epidemiological factors to improve the detection, prevention and treatment of CVD, as well as to investigate disease mechanisms. Six university hospitals collaborated in the study, and individuals from the municipality of each participating university hospital were randomly selected and invited. The initial contact was made by sending out an information brochure asking the individual to contact the study center. If contact was not initiated, three telephone calls were made to try to reach the recipient, and finally a letter was sent.

Since the aim was to gather information from a representative sample of the general population, no exclusion criteria were applied, except inability to understand written and spoken Swedish for informed consent. However, this may have contributed to under-representation of persons with lower socioeconomic status and those with poorer knowledge of the Swedish language. Several attempts were made to contact those who did not respond, but fewer women born outside of Sweden than expected were included in the Linköping cohort (6.5% born outside Sweden in Study 3, compared to 14-18% in the population 50-64 years in Linköping between year 2013-2018 when recruitment for the SCAPIS study was active)(119)

With extensive testing as in the SCAPIS study, there will be pathological findings that need further evaluation and possibly treatment. Naturally, this can be positive for the individuals that participate, but findings may also cause
worry, and lead to a series of extra examinations to determine if a finding is clinically significant which both encumbers the individual and puts a strain on the health care system. There was also a risk of finding abnormal lab results or clinical findings in Study 1. In that case, the woman was either referred to her general health practitioner for further evaluation or further assessed by one of the physicians in the study group if she needed further gynecological assessment.

The microcirculatory testing in Study 3 could cause discomfort for the participants during the five-minute occlusive phase when a blood pressure cuff was inflated to occlude blood flow. To minimize this, the participants received information about the procedure in advance and were assured that it was safe. Only two participants asked for the testing to be interrupted, indicating a high feasibility of the procedure.
RESULTS

Effects of resistance training on VMS and HRQoL (Paper I-II)

In total, 312 women were screened, and 65 included and randomized in the RCT. Fifty-eight women were included in the intention-to-treat analyses of VMS after the exclusion of participants who withdrew from the study without providing any outcome data and the exclusion of one participant who was wrongly included because of too few VMS at baseline. The mean age was 55.2 years (±5.5), and median time since menopause 2.9 years (IQR 5.3). The participants in the resistance training group completed a mean of 2.2 training sessions per week, and 62% were defined as compliant, i.e., they had completed at least two sessions per week.

Table 4. Baseline characteristics of included participants.

<table>
<thead>
<tr>
<th></th>
<th>Intervention group n=29</th>
<th>Control group n=29</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at inclusion, years</td>
<td>55.2 (5.5)</td>
<td>55.4 (5.0)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>76.3 (12.0)</td>
<td>72.3 (11.5)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.2 (4.1)</td>
<td>26.7 (3.6)</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>92.2 (12.5)</td>
<td>88.8 (12.9)</td>
</tr>
<tr>
<td>Smoker</td>
<td>1 (3.4)</td>
<td>1 (3.4)</td>
</tr>
<tr>
<td>Physical activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total physical activity, min/wk</td>
<td>115 (118.75)</td>
<td>160 (152.5)</td>
</tr>
<tr>
<td>Low-intensity, min/wk</td>
<td>82.5 (107.5)</td>
<td>120 (130.25)</td>
</tr>
<tr>
<td>Moderate-vigorous intensity, min/wk</td>
<td>15 (35.0)</td>
<td>0 (48.8)</td>
</tr>
<tr>
<td>MET minutes</td>
<td>429 (573)</td>
<td>596 (490)</td>
</tr>
<tr>
<td>VMS/24 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>3.2 (1.5)</td>
<td>2.9 (1.7)</td>
</tr>
<tr>
<td>Severe</td>
<td>4.3 (3.4)</td>
<td>3.8 (2.6)</td>
</tr>
<tr>
<td>Moderate + Severe</td>
<td>7.5 (4.0)</td>
<td>6.6 (2.2)</td>
</tr>
<tr>
<td>VMS score</td>
<td>20.5 (11.6)</td>
<td>17.9 (6.4)</td>
</tr>
</tbody>
</table>

Baseline characteristics of included participants. There were no significant differences between the groups in any of the variables. VMS score = the sum of mean VMS multiplied by severity (mild x 1, moderate x 2, severe x 3). Physical activity data derived from the VMS screening diary and IPAQ. MET – Metabolic equivalents; IPAQ, International Physical Activity Questionnaire; VMS, Vasomotor symptoms.
**Vasomotor symptoms**

The frequency of moderate and severe VMS in the resistance training group decreased significantly compared with the control group (mean difference -2.7, 95% CI -4.2 to -1.3, (Figure 7)). The percentage decrease was 43.6% in the resistance training group, (95% CI 56.0 – 31.3) vs. no change in the control group. The mean VMS score decreased significantly more in the resistance training group (-8.8, 95% CI -12.2 – -5.3) compared with the control group (0.1, 95% CI -2.5 – 2.7) (p<0.001 for difference between groups).

**Figure 7.** The mean sum of moderate and severe VMS at baseline and week 15 (end of intervention) in postmenopausal women randomized to a resistance training intervention or unchanged low physical activity. Error bars represent 95% CI. P<0.001 for difference in change between groups. Intervention N=29, Control N=29. VMS, Vasomotor symptoms.
Figure 8. Mean VMS score at baseline and week 15 (end of intervention) in postmenopausal women randomized to a resistance training intervention or unchanged low physical activity. Error bars represent 95% CI. VMS score=the sum of mean VMS multiplied by severity (mild x 1, moderate x 2, severe x 3). Intervention N=29, Control N=29. VMS, Vasomotor symptoms.

Figure 9. Moderate VMS and severe VMS in postmenopausal women randomized to a resistance training intervention or unchanged low physical activity. The intervention group decreased significantly in moderate VMS (p<0.001) and severe VMS (p<0.001). The changes in the control group were not significant (p=0.07 for moderate VMS and p=0.3 for severe VMS). Error bars represent 95% CI. Intervention N=29, Control N=29. Week 15 = end of intervention. VMS, Vasomotor symptoms.

The severe VMS decreased slightly more than the moderate VMS, but both decreased significantly in the resistance training group. Approximately 45% in the resistance training group (13/29) reported a decrease of moderate to severe VMS of at least 50% but only 1/29 (3.4%) in the control group (p for difference
between groups <0.001). There was no significant difference in change of VMS frequency between compliant and non-compliant participants.

![Figure 10](image.png)

**Figure 10.** Mean moderate and severe VMS/24 hours in postmenopausal women randomized to a resistance training intervention or unchanged low physical activity. The figure shows the change over time during the trial. Error bars represent 95% CI Intervention N=29, Control N=29. VMS, Vasomotor symptoms.

When the frequency of VMS was plotted in a line chart to show the change over time, the VMS in the resistance training group showed a decreasing trend during the whole trial, while the VMS in the control group remained unchanged. The repeated measures ANOVA showed a significant group x time interaction effect (p<0.001). The post-hoc tests revealed that VMS decreased significantly in the resistance training group already between week 0 and week 3. Since the vigorous resistance training started after 3 weeks, we also compared the change in VMS from week 3 to week 15 between the groups and found that the group x time interaction was still significant (p=0.007).

There were no significant differences in baseline anthropometric variables or VMS frequency between the women who reported at least 50% decrease in moderate to severe VMS, and those who did not. Neither were there any differences in the change in MET minutes, physical activity and exercise registered in the diary, or change in weight, BMI or waist circumference between the women who reported at least 50% decrease in moderate to severe VMS and those who did not.
Health-related quality of life

There were 57 participants with HRQoL outcome data in the RCT. At 15 weeks the group who performed resistance training reported greater mean improvements from baseline than the control group in three domains in the WHQ. These were the Vasomotor symptoms domain, the Sleep problems domain and the Menstrual symptoms domain.

Figure 11. WHQ scores at baseline and week 15 (end of intervention) in postmenopausal women randomized to a resistance training intervention or unchanged low physical activity. Error bars represent 95% CI. Only domains with statistically significant changes are shown. Higher scores indicate worse HRQoL. Intervention N=28, Control N=29. WHQ - Women’s Health Questionnaire.
Assessing the change within groups, the scores of the Vasomotor symptoms domain (p=0.007), Sleep problems domain (p=0.003), Menstrual symptoms domain (p=0.005) and Anxiety domain (p=0.046) decreased significantly from baseline to week 15 in the resistance training group. The control group did not change significantly in any WHQ domain.

We found significant correlations between the change in VMS frequency and change in the Vasomotor symptoms domain of the WHQ (Spearman correlation $\rho=0.64$, p<0.001) and change in VMS frequency and the Anxiety domain (Spearman’s $\rho=0.51$, p=0.007) in the resistance training group.

At end of intervention, the resistance training group displayed an increase in the General Health domain score of SF-36 that was significantly different from the control group (p=0.045, Mann-Whitney U), although the within group change in the resistance training group did not reach statistical significance in the non-parametric analysis (median change 5.0, IQR 10, p=0.07). There were no significant differences in change between the groups in the other domains, including the composite physical and mental scores. Within groups, the women who were randomized to resistance training improved in the Vitality domain (median change 5.0, IQR 20, p=0.003).

**Figure 12.** SF-36 General Health and Vitality scores at baseline and week 15 (end of intervention) in postmenopausal women randomized to a resistance training intervention or unchanged low physical activity. Bars represent 95% CI. Intervention N=28, Control N=29.
Postmenopausal women’s experiences of resistance training (Paper III)
There were 29 women who completed the resistance training intervention in Study 1, and 15 were included in the qualitative study. We considered that the data collected until this point was rich and meaningful with a varied sample within the group of women. (120, 121) The mean duration of the interviews was 19 minutes and the follow-up telephone interviews 6.5 minutes. The participants were 49 – 68 years old and they had experienced VMS for 1 to 18 years (Table 5).

Table 5. Characteristics of participating women in the qualitative study. N=15.

<table>
<thead>
<tr>
<th>Age, years, categorical</th>
<th>N=15</th>
</tr>
</thead>
<tbody>
<tr>
<td>49-50</td>
<td>3</td>
</tr>
<tr>
<td>51-55</td>
<td>5</td>
</tr>
<tr>
<td>56-60</td>
<td>2</td>
</tr>
<tr>
<td>61-65</td>
<td>4</td>
</tr>
<tr>
<td>65-68</td>
<td>1</td>
</tr>
<tr>
<td>Time since menopause, years</td>
<td>Median (range)</td>
</tr>
<tr>
<td></td>
<td>4.1 (1.1 – 16.25)</td>
</tr>
<tr>
<td>Duration of vasomotor symptoms, years</td>
<td>Median (range)</td>
</tr>
<tr>
<td></td>
<td>4.5 (1 - 18)</td>
</tr>
</tbody>
</table>

Social status

| Married or living with partner, N | 13 |
| Single, living alone, N | 2 |
| Living with children, N | 6 |
| Single parent, N | 2 |

Employment status

| Employed, N | 13 |
| Retired, N | 2 |

Compliance with resistance training intervention (At least 2 sessions/week)

| Compliant | 9 |
| Not compliant | 6 |

The themes that were constructed in the analysis were the trigger “Hopes of symptom relief”, the process “An evolving motivation as a driving force for change” and “Finding new triggers” (Figure 13).
Figure 13. The three themes that were constructed as a result of the analysis. The map shows the themes as a process.

The VMS had a large impact on the daily lives of the women by interfering with work and activities, limiting choices of clothes, and causing social awkwardness. Many had night sweats that affected their sleep quality. Some also described being emotionally sensitive, or in a low mood. The symptoms triggered them to want to make a change, and the hope of improving symptoms, and receive support to make a change triggered them to apply for the trial in Study 1.

**An evolving motivation as a driving force for change**

The participant’s motivation was in itself a process that evolved during the course of the intervention. It was affected by different inputs that changed during the trial. Initially, the participants felt accountable to the researchers, and to themselves because they had signed up for the trial.

> I think I managed seven minutes on one of these cross-trainers, and just felt that no, this is, if I get a chance like this, get an opportunity like this. To get rid of my symptoms, but at the same time increase my fitness, I must give it all I have. I can’t join this half-heartedly; it must be whole-heartedly. (Participant 11)

Accountability was also felt toward the study’s physiotherapist who would notice if there were missed training sessions in the participant’s log book, and this motivated them to go to the gym on days when they did not feel like it. At this stage, expectations from close ones and colleagues created pressure to keep up with the regular training.

> I have talked a lot about this, with others, shared, so there are many who... well, then I couldn’t disappoint, I couldn’t stop since I had talked about this with so many and told everyone that this, this has helped me. No, I have never thought about quitting (Participant 10)

The participants had to adjust their life schedule and priorities. This was accomplished by adjusting their schedule at work, giving up other activities and
making the whole family adapt to new routines. Interestingly, the participants did not consider this a problem. Most felt that there had been no problems adhering to the exercise. Their motivation made it natural for them to do the necessary adjustments. However, factors such as having a large distance to work, stay-at-home children or low control over their work schedule can all be interpreted as barriers.

There was a need for both practical and emotional support, and the physiotherapist was especially important for this. The participants felt encouraged to continue, rather than stop at a comfortable level of exhaustion when they became tired during the training. They received feedback on technique and performance, which gave the participants a sense of security. As they felt more and more competent, they needed less of a “push” from the physiotherapist. To meet the physiotherapist also made them feel important and validated.

*Otherwise, I wouldn’t have dared to join this resistance training program, because I felt a bit like, curious but not eager enough to like, go in there by myself and put myself there. But now I’ve got it going, and now I think it is fun actually. (...) She has shown me how all the machines work and what exercises I should do and how I should perform the exercises. So, she kind of started something that I now have with me (...) I dare to try new things now because she has shown me. (Participant 7)*

The women noticed physical effects of the resistance training some weeks into the intervention. They felt stronger, more energetic, and experienced less muscle and joint pain. Physically demanding activities became easier. These changes were rewarding and sparked motivation to exercise to maintain the physical effects.

*To feel good, yes at my age, and feel that the body can manage what it’s supposed to. That I’m not stiff, no pain or illness or, of course that can happen but it’s a way to keep my health and all. Yes, and it is nice to feel like, I manage to walk the stairs, I can lift that thing, it’s good for both body and mind. (Participant 12)*

The women felt increasingly proud to exercise, and they started to reshape their identity and consider themselves to be “someone who exercises”. To exercise generated feelings of happiness or well-being, and some started to crave and long for exercise. Although the motivational trigger from the beginning was the hope of relieving menopausal symptoms, that was no longer what drove their motivation.
Finding new triggers
After one year, almost all the women exercised regularly and about half did resistance training. They had changed their lifestyle from how it had been at the study start with new habits of regular exercise. To establish a routine was found to be important to continue. With the routine, it was not as important if the exercise was not fun every time, they just did it without thinking. Life events that disrupted routines, such as illness or moving further away from training facilities were barriers to keep up the training. At this time, the motivation was no longer linked to the menopausal symptoms; instead, the women had found their own motivation.

Cutaneous microcirculation (Paper IV)
In the study of microcirculation, the postmenopausal women were older, less often employed and more often born in Sweden compared to the premenopausal women. Postmenopausal women were more often smokers, had a higher prevalence of dyslipidemia and hypertension, and a higher waist-hip-ratio but there was no difference in BMI, waist circumference or diabetes prevalence. Premenopausal women reported more exercise and had higher accelerometer-assessed vigorous physical activity. Within the group of postmenopausal women, there were 853 women with valid VMS data and no current use of MHT. Women with daily VMS were younger (mean age 57.2 vs. 59.2, p<0.001) and had fewer years since FMP (mean 6.1 vs 8.3) than women without daily VMS.
Table 6. Background characteristics of participants.

<table>
<thead>
<tr>
<th>Participant characteristics</th>
<th>Premenopausal N=157</th>
<th>Postmenopausal N=991</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>52.7 ± 2.3</td>
<td>58.9 ± 3.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Years since menopause</td>
<td>8 ± 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>N (94.1)</td>
<td>N (81.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Born in Sweden</td>
<td>138 (89.0)</td>
<td>926 (94.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>Current smoker</td>
<td>9 (6.0)</td>
<td>112 (11.5)</td>
<td>0.04</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15 (9.7)</td>
<td>159 (16.3)</td>
<td>0.04</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>3 (1.9)</td>
<td>63 (6.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8 (5.1)</td>
<td>63 (6.5)</td>
<td>0.73</td>
</tr>
<tr>
<td>BMI</td>
<td>26.5 ± 4.5</td>
<td>26.4 ± 4.7</td>
<td>0.88</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>86 ± 12</td>
<td>88 ± 12</td>
<td>0.10</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.84 ± 0.06</td>
<td>0.86 ± 0.07</td>
<td>0.02</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>5.2 ± 0.9</td>
<td>5.8 ± 1.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HDL-c</td>
<td>1.8 ± 0.4</td>
<td>1.9 ± 0.5</td>
<td>0.08</td>
</tr>
<tr>
<td>LDL-c</td>
<td>3.0 ± 0.9</td>
<td>3.4 ± 1.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1.0 ± 0.5</td>
<td>1.1 ± 0.7</td>
<td>0.01</td>
</tr>
<tr>
<td>Current MHT</td>
<td>87 (8.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration current MHT, years (N=87)</td>
<td>4.2 (1.7-6.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical activity</td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
<td></td>
</tr>
<tr>
<td>Weekly MVPA, min</td>
<td>357 (217)</td>
<td>343 (245)</td>
<td>0.5</td>
</tr>
<tr>
<td>Weekly VPA, min</td>
<td>0 (49)</td>
<td>0 (21)</td>
<td>0.02</td>
</tr>
<tr>
<td>Weekly prolonged sedentary, min</td>
<td>1076 (523)</td>
<td>1047 (515)</td>
<td>0.39</td>
</tr>
<tr>
<td>Exercise last 3 months, self-reported</td>
<td>N (%)</td>
<td>N (%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Never or occasionally</td>
<td>59 (38.3)</td>
<td>469 (48.3)</td>
<td></td>
</tr>
<tr>
<td>≥ 1 time per week</td>
<td>95 (61.7)</td>
<td>502 (51.7)</td>
<td></td>
</tr>
</tbody>
</table>

Differences in background characteristics assessed by Student’s t-test (continuous variables) or Chi² test (categorical variables). Physical activity assessed by Mann-Whitney U test. BMI, body mass index; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; MHT, menopausal hormone therapy; MVPA, moderate to vigorous physical activity; VPA, vigorous physical activity.
We found no differences in any of the variables of skin microcirculatory perfusion or oxygen saturation between pre- and postmenopausal women in the crude and age-adjusted analyses. There were no differences in microcirculatory outcomes between the women with or without daily VMS in the crude or age-adjusted analyses.

Neither were there any statistically significant differences in microcirculatory outcomes between current users of MHT vs. non-users or never-users. The results were similar for all comparisons of microcirculatory variables when excluding women with hypertension, dyslipidemia, diabetes, and current smokers.

**Post-ischemic peak oxygen saturation**

In the simple linear regressions including both pre- and postmenopausal women, age, BMI, waist circumference, waist/hip ratio, triglyceride levels, sedentary minutes, and smoking, presence of diabetes, hypertension and dyslipidemia were negatively associated with post-ischemic peak oxygen saturation. HDL-c levels and vigorous and moderate physical activity were positively associated with peak oxygen saturation, as well as having a partner, employment and having a university degree.
Table 8. Associations between peak oxygen saturation and clinical and laboratory variables in pre- and postmenopausal women.

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>Standardized Beta</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.16</td>
<td>-0.12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.14</td>
<td>-0.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist</td>
<td>-0.08</td>
<td>-0.16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist hip ratio</td>
<td>-11.74</td>
<td>-0.14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>-0.07</td>
<td>-0.01</td>
<td>0.672</td>
</tr>
<tr>
<td>HDL-c</td>
<td>1.09</td>
<td>0.09</td>
<td>0.002</td>
</tr>
<tr>
<td>LDL-c</td>
<td>-0.08</td>
<td>-0.01</td>
<td>0.544</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-1.50</td>
<td>-0.16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VPA Weekly</td>
<td>0.014</td>
<td>0.13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MVPA Weekly</td>
<td>0.003</td>
<td>0.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sedentary Weekly</td>
<td>-0.001</td>
<td>-0.06</td>
<td>0.04</td>
</tr>
<tr>
<td>Diabetes</td>
<td>-2.83</td>
<td>-0.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoker</td>
<td>-4.05</td>
<td>-0.21</td>
<td>0.034</td>
</tr>
<tr>
<td>Hypertension</td>
<td>-1.87</td>
<td>-0.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>-3.56</td>
<td>-0.14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>University degree</td>
<td>1.13</td>
<td>0.10</td>
<td>0.001</td>
</tr>
<tr>
<td>Employed</td>
<td>1.72</td>
<td>0.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Partner</td>
<td>1.66</td>
<td>0.10</td>
<td>0.002</td>
</tr>
<tr>
<td>Daily VMS</td>
<td>0.72</td>
<td>0.05</td>
<td>0.13</td>
</tr>
<tr>
<td>Current MHT</td>
<td>0.02</td>
<td>0.001</td>
<td>0.98</td>
</tr>
<tr>
<td>Premenopausal</td>
<td>0.27</td>
<td>0.016</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Simple linear regression of associations between peak oxygen saturation and clinical and laboratory variables in pre- and postmenopausal women. BMI, Body mass index; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; MHT, menopausal hormone therapy; MVPA, moderate to vigorous physical activity; VPA, vigorous physical activity.

Several of the variables that were significantly associated with peak oxygen saturation were different between pre- and postmenopausal women, and postmenopausal women with daily VMS vs. not daily VMS. In linear models that adjusted for Age, Employment, Current smoking, Hypertension, Dyslipidemia, Waist/hip ratio, Triglycerides and Vigorous physical activity, postmenopausal women had a significantly higher peak oxygen saturation than premenopausal women (adjusted means 88.0 vs. 89.2, p=0.031). There was no difference in peak oxygen saturation between postmenopausal women with daily VMS vs not daily VMS in the crude or adjusted analyses (p=0.5 in unadjusted analysis).
Post-ischemic peak oxygen saturation and physical activity

The age-adjusted analysis showed significant differences in peak oxygen saturation between the tertiles of MVPA ($p < 0.001$). Post-hoc analyses revealed significant differences between the first and second ($p=0.003$), and first and third tertiles ($p<0.001$), i.e., those with a higher MVPA had higher peak oxygen saturation (Figure 14).

![Graph showing post-ischemic peak oxygen saturation in tertiles of moderate to vigorous physical activity](image)

**Figure 14.** Comparison of post-ischemic peak oxygen saturation between tertiles of accelerometer-recorded moderate to vigorous physical activity, ANCOVA. Mean peak oxygen saturation tertile 1: 87.8 % (95% CI 87.2 - 88.4), tertile 2: 89.2 % (95% CI 88.6 - 89.8), tertile 3: 89.8 % (95% CI 89.2 - 90.4). Post-hoc analyses revealed significant differences between the first and second ($p=0.003$), and first and third tertiles ($p<0.001$). Analysis adjusted for age and post hoc analysis adjusted by Bonferroni correction. The lower graph is zoomed. ANCOVA, Analysis of covariance.
For sedentary behavior, the third tertile which had the highest amount of sedentary time had lower peak oxygen saturation, compared with the second tertile (p=0.013). Stratified analyses showed a significant difference between the second and third tertiles of sedentary behavior only in premenopausal women, but not in postmenopausal women.

Figure 15. Comparison of post-ischemic peak oxygen saturation between tertiles of accelerometer-recorded sedentary behavior stratified by menopausal status. Mean peak oxygen saturation tertile 1: 89.3 % (95% CI 88.4 – 90.2), tertile 2: 89.8 % (95% CI 89.0 – 90.7), tertile 3: 88.1 % (95% CI 87.2 – 88.9). Significant difference between the second and third tertiles in premenopausal women (p=0.016). P-value adjusted by Bonferroni correction. The lower graph is zoomed.
For self-reported exercise, those who reported exercise ≥1 time per week had a higher peak oxygen saturation than those who reported exercise < 1 time per week, (89.8% ± 5.8 vs 88.2% ± 5.9, p<0.001 adjusted for age).

**Figure 16.** Post-ischemic peak oxygen saturation by categories of self-reported exercise. In the statistical analysis, the variable was dichotomized into never/occasionally and ≥1 time per week. The lower graph is zoomed.
DISCUSSION

Exercise and vasomotor symptoms

We found that moderate and severe VMS decreased significantly in postmenopausal women after 15 weeks of resistance training compared with a control group with unchanged low physical activity. About half of the participants in the intervention group reported a clinically significant decrease of more than 50%. The magnitude of the decrease of VMS was similar to the effect that has been found for non-hormonal pharmacological therapies like SSRI/SNRIs but lower than the decrease expected from MHT, which is on average 75%. (67, 69) In the separate analyses of moderate and severe VMS, the severe VMS decreased more than the moderate VMS. According to the definition used in our study, severe VMS includes night sweats, which were not reported separately. A previous study from Finland that used Nordic walking as an intervention against VMS showed a slight decrease in the proportion of women with nightly VMS. (98) It is especially relevant if exercise has an effect on severe VMS and nightly awakenings, since these often have a larger impact on quality of life than mild VMS.

This was the first study to assess resistance training as an intervention to reduce VMS, whereas there have been previous studies of aerobic exercise that have mostly found no or modest effects. (97-99) According to our hypothesis, the exercise has to be performed at a sufficient intensity to have an effect on VMS, which could explain why light and moderate-intensity exercise was not effective in previous studies with these interventions. In support of this in an animal model, a recent study of rats that had undergone bilateral ovariectomy to induce menopause, found that eight weeks of vigorous aerobic exercise prevented “VMS” in the rats to the same extent as rats who received estrogen therapy, compared with control rats with no treatment. The “VMS” is actually increased skin tail temperature, which is the established animal model to study VMS. (53, 122) In our intervention study, the resistance training was performed with loads as recommended to increase both strength and hypertrophy, and the participants were regularly supervised to ensure they trained at the intended level. We found in the qualitative study that the regular presence of the physiotherapist (one session per week) was important, especially during the first weeks, for the women to dare to perform the exercises with the prescribed loads and thus reach the intended intensity.
Another point to consider that perhaps could explain the difference in outcomes between our study and previous studies, is different physiological responses to resistance training and aerobic exercise. Although both exercise modalities can be designed to activate large muscle groups, there might be differences in the afferent signaling from the skeletal muscle nerve fibers as a response to the different demands during exercise, and thus different responses in the CNS. (65) It is not known whether resistance training affects the endogenous opioids differently than aerobic exercise, but both vigorous aerobic exercise and resistance training have been shown to increase β-endorphin levels in the blood. (123, 124)

Another mechanism that could be involved is improved temperature regulation in the skin. In the study on cutaneous microcirculation, we found that postmenopausal women with higher levels of physical activity had a better microcirculatory reactivity in the skin. Although the method does not measure how effective the temperature regulation is, it assesses the vasodilatory function of the skin, which is central for thermoregulation. However, since we did not find differences in any microcirculatory variables between women with and without VMS, there is no support for this hypothesis in our data. It would have been interesting to also assess the skin’s microcirculation in the resistance training intervention study, to investigate if there is an association between reduced VMS and improved microvascular function.

**Exercise and HRQoL**

In the RCT of resistance training, the women in the resistance training group improved more in the domains of menopause-specific HRQoL concerning sleep, VMS and “Menstrual symptoms” compared with the control group. Regarding generic HRQoL the resistance training group improved in the Vitality and General Health perception domains of SF-36, but the rest of the SF-36 domains did not change.

In WHQ, the greatest change in the intervention group was seen in the Vasomotor domain (-0.26 points on the scale from 0-1). This was expected since the VMS frequency assessed through the VMS diary decreased significantly in the same group. The change exceeded the threshold that is usually considered clinically significant (0.1-0.2) and indicates less bother from VMS which is an important aspect when evaluating the treatment effect. (109) The Vasomotor domain of the WHQ can be considered an additional tool to evaluate the effect of the intervention on VMS, and this change strengthens the conclusion that the intervention was effective. The improvements in the Sleep problems domain
also reached the level of clinical significance (mean change 0.17). Nightly VMS are known to be associated with sleep problems, so the improvement in the Sleep domain could be a result of less disturbance by nightly VMS. (125) We did not ask the women to register nightly VMS specifically, but the fact that severe VMS decreased indicates an effect on nightly VMS, since these would be classified as severe according to the definition used in the study. However, there was no significant correlation between change in the WHQ Sleep domain and change in VMS frequency in the intervention group. This could be due to too low power in the analysis, or that the exercise had an independent effect on the Sleep domain. Moderate aerobic exercise has been shown to improve sleep quality, but there is insufficient evidence regarding resistance training. (126, 127) Considering the probable mechanisms of the effect of exercise on sleep, which includes increased sleep demand because of physical exertion, and improved temperature regulation, it is plausible that resistance training can also improve sleep problems independent of improvement in VMS. (127)

The domain Menstrual symptoms is constructed of items that concern several somatic symptoms – abdominal cramps, breast tenderness and feeling bloated – all symptoms that postmenopausal women can experience even though they do not have menstrual bleeding. We therefore chose to include the menstrual symptoms domain in the assessment, and our interpretation of the result was that resistance training improved some aspects of somatic symptoms. Regarding generic HRQoL, the change scores within groups were positive for all domains in the resistance training group, but only Vitality reached statistical significance in the within-group analyses (median change 5.0, IQR 20 p=0.005). The within-group increase in General Health in the resistance training group did not reach statistical significance (p=0.072), although the median change was 5.0 and the difference in change between groups was statistically significant. The Vitality and General Health domains reflect both physical and mental well-being, and are two of the most important domains for quality of life and health satisfaction. (128)

In most of the domains of both WHQ and SF-36, there was no statistically significant change from baseline to post-intervention. This could at least in part be explained by a combination of low power in the analyses, and by the rather “good” scores in most domains at baseline. All WHQ domains, except for the Vasomotor domain, were better than norms for women of the same age. The SF-36 domains were in line with, or higher than, Swedish norms. (129) Consequently, there was not much room for improvement since the scores were
already quite high. Previous studies that assessed the effect of aerobic exercise on HRQoL in women with VMS reported that low to moderate aerobic exercise improved the domains Somatic symptoms, Sleep problems and Depressed mood of WHQ, as well as physical domains of generic HRQoL. A recent meta-analysis found non-significant improvements in physical and mental domains of generic HRQoL from aerobic exercise interventions in postmenopausal women with VMS. The findings from the qualitative study (Paper III) gave a more nuanced understanding of the participants’ experiences of the resistance training. They described increased well-being, feeling stronger, feeling more confident and more physically capable, which did not come through in the HRQoL instruments. Our findings support the hypothesis that resistance training can improve some aspects of menopause-specific and generic HRQoL in otherwise healthy postmenopausal women with VMS. Since we have found no previous trials that have investigated the effect of resistance training on HRQoL in women with VMS, our findings contribute important new knowledge.

An evolving motivation to exercise

In the qualitative analysis we found an evolving motivation to exercise that progressed from accountability through need for support to exercise to feel good. This change in motivating factors has been described by others. Similar to our findings, Viljoen et al., found that a wish to improve health problems together with the need for a structured exercise program acted as major motivators for the initial contact and early phase of an exercise trial, while adherence during the trial was influenced by social factors and obligation toward the researcher. This obligation is a form of introjected regulation, and has previously been described as important for early adoption of a physical activity program. Also in line with previous findings, practical and emotional support from professionals and significant others was important to facilitate exercise. The physiotherapist had an important role. Although the intention of the original intervention was not primarily to affect exercise habits but to treat VMS, all women reported they had increased their physical activity at the one-year follow-up interview and about half of participants performed resistance training regularly one year after the intervention had ended. The increased physical activity can thus be recognized as a bonus effect of participation. At the beginning, the women’s main concern was a desire for improvement of problematic VMS and they were willing to try exercise as a potential treatment. The motivation made them do the necessary
adaptations in their lives to incorporate the training without recognizing the adaptations as barriers. Hence, they entered the trial with a high motivation to exercise, which is not always the case in a real-world clinical context. These factors probably contributed to the effect of the intervention via a better adherence and positive expectations among the participants.

Still, it was interesting to find that the wish to reduce VMS was no longer as important for the women at the end of the trial to motivate them to do exercise. It could have been expected that the decrease in VMS would act as a motivation to continue the training. Instead, we found that the motivation to exercise evolved in all women regardless of their experience of treatment effect. It seemed that the motivation had evolved from being mainly external with a wish to relieve symptoms, to more internal with the aim of achieving general well-being. What came through as valuable was the increased self-confidence regarding resistance training and exercise. This probably contributed to the fact that all participants reported increased physical activity after one year, regardless of the effects on VMS.

**Menopause, VMS and microcirculatory function**

We found no differences in microcirculatory function in women with respect to MHT use or presence of VMS. We hypothesized that postmenopausal women would have a lower microcirculatory reactivity and specifically lower post-ischemic peak oxygen saturation than premenopausal women, but we could not confirm our hypothesis. A previous study of both women and men found that women had higher post-ischemic peak oxygen saturation than men, which indicated that the difference could be related to differences in estrogen status. (116) Few studies have investigated the role of menopause and MHT on microcirculatory function, and the results are mixed, with no strong evidence of an independent association of menopause with microcirculatory function. (135-138) Two studies found better microvascular reactivity in postmenopausal current users of MHT compared with non-users (136, 137), while another found no effect of six months of treatment with MHT on microcirculatory function. (138) The previous studies have been small, with 40-70 participants, so our study of about 1000 women included from the general population contributes significantly to previous data.

As expected, we found that post-ischemic peak oxygen saturation was negatively associated with increasing age, increasing BMI, the presence of smoking, dyslipidemia and hypertension, which are all established risk factors for CVD and endothelial dysfunction. Having a university degree, living with a
partner and being employed were positively associated with post-ischemic peak oxygen saturation. These variables indicate a higher socioeconomic status, which in itself is associated with better cardiovascular health. After adjustment for covariates, postmenopausal women had a slightly higher post-ischemic peak oxygen saturation than premenopausal. We have no biological explanation for this, but it is plausible that it is a result of bias from over-adjusting in the analysis and should be interpreted with caution.

We hypothesized that women with daily VMS would have a lower post-ischemic peak oxygen saturation than women without daily VMS, but found no differences between these groups. Other researchers have found that women with VMS have lower vascular reactivity assessed by FMD, and thus impaired endothelial function compared to women without daily VMS. The women in those studies were younger than in our study, which could explain the difference in results. Maybe VMS is a marker of vascular dysfunction only in younger women, where traditional CVD risk factors are not as common as in older women. The presence of VMS in itself may also not be an important enough risk marker to become significant compared to other risk factors that probably have a greater impact, such as diabetes and smoking. Two previous studies that assessed microvascular reactivity in postmenopausal women with VMS were found, and these both showed increased microvascular reactivity in postmenopausal women with frequent VMS compared to women without VMS. Different methods to assess microvascular reactivity could account for the discrepancy in results with our study, since we assessed only endothelial-dependent vasodilation, whereas the previous studies assessed both endothelial-dependent and endothelial-independent vasodilation. If women with VMS have an enhanced sensitivity to vasodilatory stimuli in the skin’s microcirculation that is not dependent on endothelial function, this would explain why the post-ischemic peak oxygen saturation did not differ between women with and without daily VMS in our study.

Physical activity and microcirculatory function

We found that women in the lowest tertile of objectively measured MVPA had lower peak oxygen saturation than women in the other two tertiles. Similar results was found when analyzing self-reported exercise. Our results contrast with an earlier study of 1298 individuals (of which 601 were women) that found an association between total physical activity and skin microvascular reactivity in persons with type-2 diabetes but not in persons without diabetes. A possible explanation of the difference in findings is that it takes higher
intensities of physical activity for beneficial effects on microvascular function. We found a higher microcirculatory reactivity with higher amounts of MVPA, but not low-intensity physical activity (data not shown). In support of this, Tew and colleagues reported that six months of aerobic exercise that progressed from moderate to vigorous intensity enhanced microvascular reactivity in postmenopausal women.(143) A meta-analysis of seven small studies also showed improved microvascular reactivity after moderate-vigorous exercise interventions, but most participants were male.(144) This indicates that physical activity has the possibility to counteract some of the decline in skin microvascular function seen with aging and disease.

METHODOLOGICAL CONSIDERATIONS

Study 1
Study 1 was an open RCT that could not be blinded due to the nature of the intervention. To increase the quality of the trial, it was planned according to applicable principles of Good Clinical Practice. Randomization and allocation concealment is essential to reduce the risk of selection bias in the assignment of a treatment. A successful randomization balances known and unknown factors that may affect the outcome. In the RCT, the randomization sequence was created by an independent statistician not involved in the study procedures, and the randomization sequence was concealed from the investigators in opaque envelopes.

The trial was non-blinded, and the primary outcome was based on a patient-reported outcome, namely self-reporting of VMS in a diary. This means that there is a risk of both performance and detection bias if the intervention group expected a treatment effect and thereby registered fewer VMS. It is known that placebo effects are common in treatment studies of VMS, as with a wide range of medical conditions. The placebo response has been found to be 20-30% in previous trials using VMS diaries to evaluate effect, with about 25% of participants in the placebo group reporting >50% decrease in VMS. Another pooled analysis found that 33% in placebo groups improved at end of treatment.(145, 146) In our study, the VMS decreased by 44% in the intervention group, with 45% reporting a >50% decrease, which indicates that the effect was due to more than positive expectations. We found that VMS in the intervention group decreased during the whole study period. At the follow-up after six months, the VMS had continued to decrease, although non-significantly
compared to end-of-intervention, and remained significantly different between groups. A placebo effect would probably be most pronounced during the first weeks and have a lesser impact on the number of VMS registered at the end of the study, or at follow-up.

Even so, the absence of a placebo or sham intervention was a limitation of the study, since non-specific/placebo effects may have affected the outcome. It was not considered appropriate to assign the control group to another type of exercise since we wanted the control group to remain untreated and not to increase their physical activity. Even though our hypothesis was that a low-intensity type of exercise would not affect VMS, the aim was to compare resistance training to no treatment, since it was the first study, to our knowledge, that tested resistance training as an intervention for VMS. An alternative could have been a more frequent regular contact with participants in the control group, to mimic the weekly contact with the physiotherapist in the intervention group.

A drawback with attention-control groups might be that it can be considered less ethical because it requires extra time and effort for participants in the control group with no expected benefit.

The method of using personal diaries to report VMS has been used in many previous treatment studies on VMS, in combination with questionnaires or symptom scores, and has been shown to be sensitive to change with few missing data.(67, 97, 145, 147) Ideally, participants, those who deliver the intervention, and outcome assessors should all be blinded to decrease the risk of bias in outcome assessment. When that is not possible, it is preferable to use an objective measurement of the primary outcome to reduce detection bias. An alternative in our study could have been to assess VMS by measuring skin conductance with monitors worn by the women. In an ambulatory setting, there tends to be underreporting of VMS with subjective recording compared to objective recording, so that more VMS are registered when assessed objectively. However, there does not seem to be a problem in the other direction, so the VMS actually reported can be assumed to be valid.(148) Unfortunately, the technique and equipment to record VMS by skin conductance monitors is expensive and when the study was planned it was uncertain if it would have been possible from a financial perspective to invest in the equipment. Also, a recent publication at that time concluded that none of the available devices for ambulatory recording of VMS met the requirements of both validity and patient acceptability.(27)
Important benefits of self-reporting VMS through diaries is the possibility to retrieve data on both VMS severity and frequency, which is not possible with objective recording. Since change in VMS severity is also an important outcome measure, some kind of subjective method of assessment will still be necessary. It is the woman’s own experience of her VMS, and the bother caused by them, that is the reason for seeking medical advice and treatment. Therefore, the main outcome of interest should be the woman’s own assessment of her symptoms, because she is the one who can judge when the symptoms affect her quality of life.

To assess HRQoL, we chose to use WHQ as a disease-specific instrument and SF-36 as a generic HRQoL instrument. Both instruments have been validated in a Swedish setting.\(^{110, 113}\) When planning the sample size of the study, it was calculated based on the primary outcome change in VMS. The power to detect clinically significant changes in WHQ was >80\% for four out of eight domains, but for SF-36 it was 45\% at best. The study was thus limited by low power to detect effects in several HRQoL domains, and we would have needed a larger sample size to decrease the risk of type II error.

A strength of the study was the resistance training intervention, which was standardized based on individual strength tests to ensure everyone exercised at the same relative intensity. The same physiotherapist performed the tests and followed the participants during the trial. Loads were increased progressively to make sure that the participants exercised at the same intensity during the whole time. The 8RM strength test has been validated against the gold standard to measure muscle strength, isokinetic dynamometry, and has been found to be valid and reliable.\(^{77, 78}\) It is the preferred test in novices to reduce the risk of injury that may occur with a maximum strength test.\(^{74}\)

**Study 2**

In Study 2, a qualitative method was used for data collection, and thematic analysis to analyze the data. The approach was inductive, i.e., we did not set out to test a hypothesis but wanted to learn from the participants’ perspectives and experiences. The data were collected through semi-structured interviews which give the interviewer guidance during the interview, and aid the focus of the questions. They still allow for new questions to emerge and for the interviewer to adapt the questions according to the situation.\(^{149}\) The qualitative interview is an interaction between the interviewer and respondent, and it is important to establish rapport between the two. The interviewer should aim for empathic neutrality, i.e. being open and responsive without judging the respondent and not
leading her in a certain direction based on the interviewers own preconceptions. (149, 150) In this study, the interviewer was not involved in the resistance training intervention. This could have the advantage that the respondent dared to be more honest about negative experiences of the intervention. It is also possible that an interviewer with experience of the intervention would have asked different questions and revealed other nuances of the respondents’ experiences. Our intention during recruitment was to capture different experiences of the intervention and therefore to recruit participants in the intervention group with consecutive sampling, regardless of compliance or treatment effect. We therefore also planned to interview women who dropped out, but of the four women who did, three withdrew because of reasons unrelated to the trial (the fourth for an unknown reason) and none of them received the intervention.

The interviews could be considered short, or the sample size of 15 small, but it is the study aim and data richness that guide data collection and sample size in qualitative studies. In reflexive thematic analysis there is no minimum sample size that is regarded as sufficient. (121) A recommended method is to consider the information power of the data, i.e., the richer and more relevant the collected data are in relation to the aim of the study, the fewer participants are needed. (120) In this study, almost the entire data sets were considered relevant and coded, meaning the data was rich in relation to the aim. The interviewer had long experience of qualitative research, including conducting interviews, which probably resulted in interviews focused on the aim, and thus shorter interviews. We stopped data collection when the interviewer considered that the interviews generated similar data without obvious new topics, and it therefore seemed reasonable to stop inclusion. (120, 151) Still, we might have missed alternative meanings and experiences by not interviewing all participants.

Thematic analysis was chosen as the analytic method, since it provides an accessible and structured method to analyze data that also involves interpretation in construction of the themes, and is not only descriptive. With thematic analysis, a goal is to identify the shared meaning, or story, the data tell. The researchers entered this study with different preconceptions and experiences, which will have affected the analysis, especially with regard to the interpretation of data in the construction of the themes. By repeatedly checking and validating the themes in relation to the data and to each other, and re-reading the whole data set during the process of analysis, the risk of over-interpretation of the data was reduced. An optional analytic method could have been to use content
analysis, which is descriptive and gives less room for interpretation. However, thematic analysis provided a better method to consider both the semantic and latent meaning in the interviews.

We coded the data set and created candidate thematic maps independently. This analyst triangulation was performed to reduce the risk of selective perception and increase credibility.(152) Further strategies we used to increase the quality of the study were to establish an audit trail of the data, e.g. by saving the transcripts, initial codes, different ideas for arranging them into potential themes and the evolving thematic maps for reference to make it possible to track the analytic process. Notes documenting discussions during the research process were kept.(153)

With a qualitative method we cannot generalize the findings to other contexts which must be kept in mind when interpreting the results. However, with a thorough description of the context of the study, the transferability of the study is increased so that the reader can determine if and how to apply the findings in his/her context.

Study 3

Study 3 was a cross-sectional study, so it is not possible to study causality or risk, but rather prevalence and associations. We did not find differences in microvascular reactivity between pre- and postmenopausal women, between current users/not current users of MHT or women with/without daily VMS. We classified the women as premenopausal/postmenopausal and current users/not current users of MHT based on questionnaire data, which lends an insecurity to the classifications. Although the questions on MHT concerned indication and route of administration, there is still a risk of misclassification if a woman interpreted the questions in another way than intended. In this case, the risk of a systemic error was considered low, and should therefore not have lead to misclassification bias. The proportion of postmenopausal women classified as current users of MHT was 9%, which is comparable to national data on dispensed drugs.(154)

When asking participants about previous symptoms or exposures in observational studies, those with more severe symptoms or a worse outcome may be more inclined to recall and report them, which can introduce bias in the analyses. We chose to primarily consider current use of MHT, and current experience of VMS, since we considered these variables more trustworthy and less prone to recall bias than previous use/ever use, and previous VMS. We
hypothesized that the biological effects of MHT on vascular function would be evident in current users. It is possible that previous use of MHT, classified as “not current” use in the analyses, could have attenuated possible differences between users/non-users, since initiation of MHT close to menopause possibly has protective effects on the endothelium. We performed sensitivity analyses excluding those who reported previous use of MHT, which did not affect the results.

According to previous studies that have investigated the association between VMS and endothelial dysfunction as well as microvascular function, early onset VMS, more frequent VMS and more severe VMS have all been associated with endothelial dysfunction and/or CVD risk. Since we dichotomized VMS into daily/not daily, the groups may not have been distinct enough to find a difference. It is also possible that the group with no daily VMS had severe and/or frequent VMS in the past, which could have evened out the differences between the two groups when analysing current VMS. We performed additional analyses that were restricted to women who had never used MHT with daily severe VMS, and women who reported never having had VMS, but found no differences in microvascular reactivity.

The use of accelerometers to assess physical activity is an objective method that provides a more valid assessment than self-reported data. However, a hip-worn accelerometer will underestimate physical activity from cycling so there is a possibility that all physical activity was not captured. In addition, accelerometers are unsuitable to assess resistance training, and unfortunately there were no questions regarding resistance training in the questionnaires. Thus, we could not analyze whether skin microcirculatory function was associated with resistance training, so this remains to be investigated in a different study.

The method to assess microvascular function, called EPOS, is based on DRS and LDF which by themselves are established methods to evaluate the skin’s microcirculation, as well as to use PORH to assess microvascular reactivity. One advantage with EPOS is that the assessment of the microcirculation is performed using a single probe for both perfusion and oxygen saturation, and that the output is given in absolute units, which has previously not been possible. The method has been validated and found to have moderate to good reproducibility regarding oxygen saturation, but lower for the perfusion variables. A limitation of the assessment is the small sampling area of the skin, which increases the variability between measurements. This especially regards perfusion and is caused by the variation in the microvascular anatomy of
the skin, so there is a possibility that small differences in skin perfusion were not detected in this study. Another limitation is that variable post-ischemic peak oxygen saturation has not yet been validated against clinical endpoints, such as cardiovascular events. Consequently, it is not known whether a statistically significant difference in post-ischemic peak oxygenation is clinically significant. The provocation with PORH assesses endothelial-dependent vasodilation, but the hyperemic reaction depends mostly on EDHF rather than NO.(42) Although estrogen has been found to be involved in both pathways, the NO pathway is by far the most established. For our comparisons, it might have been better to use a heat provocation of the skin instead, which is mostly dependent on NO release.(156)

A strength with the study was the population-based recruitment, which increases the study’s generalizability. However, there is a risk that the participants who accepted the invitation to the study were healthier than the general population and of a higher socioeconomic status, since a prerequisite to be included was to be able to communicate in Swedish. Of those invited, just over 50% chose to participate. This is an expected participation rate, but means that non-response bias could have affected the results, and that we studied a sample that was healthier than the general population.(157)
CONCLUSIONS

- In postmenopausal women, moderate to severe vasomotor symptoms decreased significantly after 15 weeks of resistance training compared with a control group with unchanged physical activity. Almost half of postmenopausal women reported a clinically significant decrease in VMS of ≥50% after 15 weeks of resistance training.
- Resistance training for 15 weeks in postmenopausal women with vasomotor symptoms improved domains of health-related quality of life related to vasomotor symptoms, sleep, certain somatic symptoms and vitality.
- Vasomotor symptoms acted as a motivational trigger to initiate exercise in low-active postmenopausal women. Accountability and continuous professional and emotional support were factors that fueled motivation after initiation. The motivation changed over time from being driven by hopes of symptom relief to being driven by general well-being from exercise.
- There was no difference in microcirculatory function between pre- and postmenopausal women, postmenopausal women who currently used or did not use menopausal hormone therapy, and postmenopausal women with or without daily vasomotor symptoms.
- A higher amount of both self-reported and objectively assessed physical activity was positively associated with cutaneous microcirculatory reactivity measured as post-ischemic peak oxygen saturation.
CLINICAL IMPLICATIONS AND FUTURE PERSPECTIVES

We found that resistance training for 15 weeks was an effective intervention to reduce self-reported VMS in postmenopausal women and to improve some aspects of menopause-specific HRQoL. Women who seek advice for menopausal symptoms should receive evidence-based recommendations, and these should take account of the woman’s individual preferences. Many women with VMS seek guidance on what they can do themselves to improve their symptoms. Our findings support that resistance training can be an option for women with bothersome VMS who are motivated to try it. For health care professionals and physicians who counsel women about VMS, our findings add important options to the “tool box” of different treatments and interventions to discuss with women who are bothered by VMS but are either unwilling or unable to use MHT.

Our findings concern resistance training, but it remains to be studied whether vigorous-intensity aerobic exercise can improve VMS. Future studies should compare resistance training with aerobic exercise to determine if one type of exercise is more effective than the other, and these studies could include different exercise doses. Another question to answer is “For whom is exercise effective in reducing VMS?”. Perhaps women with more sleep disturbances, or symptoms of depression or anxiety with VMS, experience a better effect of exercise because of a simultaneous effect on those symptoms as well? The effect of exercise on self-reported VMS vs. objectively measured VMS also warrants further investigation since self-reported VMS may be more responsive to placebo effects.

The possible effect of resistance training on VMS adds to other health benefits of resistance training and physical activity after menopause, e.g. to improve or preserve cardiovascular health, muscle strength and function. An important finding was that the VMS themselves acted as a motivational trigger for the women to become more physically active. Given the adverse change in cardiovascular risk factors that follows menopause, this implies that the consultation situation when a woman seeks medical advice for menopausal symptoms is a good opportunity to give advice about the health effects of physical activity.

Middle-aged women who engaged in regular exercise had better microvascular reactivity of the skin than those who did not, and the same was true for the women who performed the most moderate to vigorous physical activity. A lower
Cutaneous microvascular reactivity in the form of peak oxygen saturation has previously been found to be associated with CVD risk factors, but it was a novel finding that a higher peak oxygen saturation was positively associated with physical activity. Although our study was cross-sectional, it supports the hypothesis that exercise and physical activity are beneficial for the cutaneous microvascular function. Contrary to our hypothesis, the microvascular function was similar in middle-aged women of the same age independent of menopausal status, hormone therapy or VMS. As expected, traditional risk factors for CVD were associated with lower microvascular function. The results need to be followed-up in a longitudinal study to determine whether cutaneous microvascular function can predict clinical CVD events in women. It would be interesting to assess the skin’s microvascular function in younger women with early menopause and/or early onset VMS to explore whether the VMS are associated with endothelial dysfunction before traditional risk factors become more prevalent.

We found that resistance training performed in two sets with eight exercises, and loads corresponding to 8-12 RM, with loads of 15-20 RM in the first three weeks, was a safe intervention for the postmenopausal women in our study. The training was performed using machines instead of with free weights to reduce the risk of injury and to make the program easier for novices. Still, the instruction and regular support from the study physiotherapist were important for the women to “dare” to perform the exercise at the beginning and to increase the loads during the intervention. If resistance training is to be used in a real-world clinical setting, we suggest there is regular contact with a physiotherapist or professional instructor, at least initially.
ACKNOWLEDGMENTS

I am grateful to each and everyone around me that in different ways supported me to able to finish this. Especially, I would like to thank:

Associate professor Anna-Clara Spetz Holm, my main supervisor. For your never-ending encouragement, dedication, and for always taking the time to discuss things, big or small. You have supported me when I have found it difficult to find time for this in between the clinical work, and you are a role model when it comes to caring for those around you!

Professor emeritus, Mats Hammar, my co-supervisor. Your warm enthusiasm is truly inspiring, and is what drew me into research in the first place. Thank you! You have a way of lifting others up and making them grow that is truly special, and I am happy and grateful that I get to experience it.

Lotta Lindh-Åstrand, PhD, my co-supervisor. For being such a great constructive “bollplank”, for your bright, structured mind and immense knowledge about clinical trials. I have valued your support and critical thinking.

Professor Carina Berterö. With your warm and firm wisdom and huge knowledge about research, you have introduced me to the field of qualitative methods. Thank you for your patience and guidance during these first steps, I have really enjoyed it.

Hanna Lindblom, PhD. You are clever, kind and productive and you inspire me! Thank you for fruitful discussions and for your work with constructing and managing the resistance training in “Styrka-studien”.

The women who participated in the studies!

Moa Henriksson, for your thorough work, interesting discussions and a great cooperation in Paper IV. Sigrid Nilsson, for your thorough work, interesting discussions and lovely congress company.

Associate professor Karin Leander, for a nice cooperation and constructive input.

SCAPIS Mikro and SCAPIS. Professor Tomas Strömberg, associate professor Sara Bergstrand, Professor Carl-Johan Östgren and especially Hanna Jonasson, PhD, for a nice cooperation and valuable input.

Research nurses Åsa Rydmark Kersley and Linda Shosholli, for your work with the resistance training trial and keeping track of everything.

Associate professor Mats Fredriksson and Lars Valter for statistical advice and enjoyable fika company when I borrowed a place to work at Forum Östergötland.

Professor Preben Kjölhede and Professor Jan Brynhildsen. Thank you for your time and thorough work reviewing and giving wise and constructive input to my “kappa” to enable me to improve it.

Dr Nina Lindell, Dr Emelie Wolgast, Dr Agota Malmborg, Dr Louise Möller. Thank you for skillfully reviewing my manuscripts and providing valuable comments.
Associate professor **Kajsa Johansson** and Dr **Gabriella Falk**, for your time and input during my half-time seminar to help me improve this project.

Associate professor **Elizabeth Nedstrand**, Dr **Anna Karlsson**, Dr **Sofia Pihl**, for giving me the time to work on this thesis.

My colleagues at Kvinnokliniken, Linköping. For making it so fun and inspiring to go to work!

**Micaela Sundell**, without you, this would not have happened! Thank you for being my first teammate in research in medical school. You are a great friend and I have appreciated going through this journey parallel with you. I look forward to cooperating in the future!

**My friends!** Thank you for your support, encouragement and all the happy moments that will hopefully be even more plentiful when this thesis is finished.

**Alva, Johanna, Ingo** (and **Malte**)!, for friendship, Spielplatz-fika, and lovingly cheering me on. And for all the Laugengebäck!

My family, **mamma, pappa, Helge, mormor, morfar, Tuss** for love and support and encouragement throughout these years.

My parents-in-law **Ylva** and **Sten**, and the big Hammarlund family. You are wonderful.

**Ebba Hammarlund**, for brilliantly illustrating the cover of this book.

My sister, **Isa**. Thank you for your company, for cooking and baking, and for all the hours you carried and comforted Ester these three months.

**Ester**, I am so happy you came into this world. You fill my heart with love and help me realize what really matters.

Finally, **Olof**, thank you for always supporting and never doubting. For patience, kindness and perspective. I love being in a team with you!
REFERENCES


APPENDIX

Appendix 1
Interview guide used in Study 2 with the main questions and examples of follow-up questions.

<table>
<thead>
<tr>
<th>Main question</th>
<th>Example follow-up questions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First interview</strong></td>
<td></td>
</tr>
<tr>
<td>Please, tell me about the climacteric symptoms you experienced</td>
<td><strong>Tell me more about...</strong></td>
</tr>
<tr>
<td>What made you join this project?</td>
<td><strong>How was it for you? What did you think about...?</strong></td>
</tr>
<tr>
<td>Please tell me about the resistance training</td>
<td><strong>How will you continue now?</strong></td>
</tr>
<tr>
<td>Is there anything in the project that has made you change your lifestyle/habits?</td>
<td></td>
</tr>
<tr>
<td>How?</td>
<td></td>
</tr>
<tr>
<td>Is there anything that has been an obstacle for you?</td>
<td></td>
</tr>
<tr>
<td><strong>Telephone follow-up interview</strong></td>
<td></td>
</tr>
<tr>
<td>Could you please tell me about your climacteric symptoms at this time?</td>
<td><strong>What kind?/To what extent?/How often? Do you perform resistance training?</strong></td>
</tr>
<tr>
<td>Do you perform any exercise?</td>
<td><strong>Have you encountered any obstacles?</strong></td>
</tr>
<tr>
<td>Is there anything in the project that has made you change your lifestyle/habits?</td>
<td></td>
</tr>
</tbody>
</table>
Extra frågor till kvinnor i SCAPIS

1. Har din mens upphört eller delvis upphört? (oavsett orsak)
□ Ja, upphört (ingen mens senaste året). Vid vilken ålder hade du din sista mens (ange ungefärligt om du inte minns säkert)? Vid ___års ålder.
□ Ja, delvis upphört (mens gjort uppehåll minst 3 månader i sträck senaste året).

2. Om din mens upphört på grund av gynekologisk operation, vid vilken ålder skedde operationen? Vid ___års ålder.

3. Om din mens upphört på grund av hormonbehandling eller hormonella preventivmedel, vid vilken ålder skedde detta? Vid ___års ålder.

4. Om din mens upphört eller delvis upphört på grund av klimakteriet, var/är klimakteriet förknippat med klimakterierelaterade besvär?
Värmevallningar och/eller nattliga svettningar:
□ Ja, besvär i hög grad. Om ja, hur länge varade dina besvär? Mellan ___och___års ålder eller pågår fortfarande sedan ___års ålder.
□ Ja, besvär i ganska hög grad. Om ja, hur länge varade dina besvär? Mellan ___och___års ålder eller pågår fortfarande sedan ___års ålder.
□ Ja, besvär i mindre grad. Om ja, hur länge varade dina besvär? Mellan ___och___års ålder eller pågår fortfarande sedan ___års ålder.
□ Nej, inga besvär.
Andra typer av klimakterierelaterade besvär (flera alternativ möjliga om olika typer av besvär):
□ Ja, besvär i hög grad. Om ja, vilken/vilka typer av besvär? __________________________
Hur länge varade dina besvär? Mellan ___och___års ålder eller pågår fortfarande sedan ___års ålder.
□ Ja, besvär i ganska hög grad. Om ja, vilken/vilka typer av besvär? ________________________
Hur länge varade dina besvär? Mellan ___och___års ålder eller pågår fortfarande sedan ___års ålder.
□ Ja, besvär i mindre grad. Om ja, vilken/vilka typer av besvär? ___________________________
Hur länge varade dina besvär? Mellan ___och___års ålder eller pågår fortfarande sedan ___års ålder.
□ Nej, inga besvär.

5. Har du under de senaste 2 veckorna haft klimakterieskvällar i form av värmevallningar och/eller svettningar?
□ Ja, flera gånger/dag
□ Ja, enstaka gånger/dag
□ Ja, ett par gånger/vecka
□ Ja, enstaka besvär
□ Nej, inga besvär

FORTSÄTTNING PÅ NÄSTA SIDA!
6. Använder/använde du någon receptbelagd östrogeninnehållande behandling för klimakteriebesvär i form av värmevallningar och/eller nattliga svettningar?

Tabletter:
- Ja, använder nu. Vid vilken ålder började behandlingen? Vid ___ års ålder.
- Nej, har aldrig använt.

Plåster eller gel:
- Ja, använder nu. Vid vilken ålder började behandlingen? Vid ___ års ålder.
- Nej, har aldrig använt.

7. Använder/använde du någon receptbelagd östrogeninnehållande behandling för klimakteriebesvär i form av torra slemhinnor?

Tabletter:
- Ja, använder nu. Vid vilken ålder började behandlingen? Vid ___ års ålder.
- Nej, har aldrig använt.

Plåster eller gel:
- Ja, använder nu. Vid vilken ålder började behandlingen? Vid ___ års ålder.
- Nej, har aldrig använt.

Vagitorier (slidpiller), vaginal kräm/gel eller vaginalinlägg:
- Ja, använder nu. Vid vilken ålder började behandlingen? Vid ___ års ålder.
- Nej, har aldrig använt.

8. Använder/använde du något naturläkemedel, till exempel s.k. fytoöstrogen som behandling för klimakteriebesvär?

- Ja, använder nu. Vid vilken ålder började behandlingen? Vid ___ års ålder.
- Nej, har aldrig använt.

9. Har du någon gång under livet använt hormonella preventivmedel? (flera alternativ möjliga)

- Ja, p-pillar. Ungefär under hur lång period sammanlagt? Totalt ___ år.
- Ja, minipiller. Ungefär under hur lång period sammanlagt? Totalt ___ år.
- Ja, annan typ av hormonellt preventivmedel (p-pläster, p-ring, p-stav, p-spruta, hormonspiral eller kopparspiral). Ungefär under hur lång period sammanlagt? Totalt ___ år.
- Nej, har inte använt.

10. Har du någon period i livet haft besvär med premenstruella spänningar (PMS) såsom nedstämdhet, humörsvängningar, lätt att gråta, bröstspänningar, svullnadskänsla i kroppen?

- Ja, besvär i hög grad.
- Ja, besvär i ganska hög grad.
- Ja, besvär i mindre grad.
- Nej, inga besvär.

Hur länge varade dina PMS-besvär? Mellan ___ och ___ års ålder eller pågår fortfarande sedan ___ års ålder.

Tack för din medverkan!

SCAPIS/Kompletterande enkät/Klimakteriet/Linköping/FINAL/2015-09-28
Papers

The papers associated with this thesis have been removed for copyright reasons. For more details about these see:

https://doi.org/10.3384/9789180750998
Resistance Training and Physical Activity in Postmenopausal Women
Effects on Vasomotor Symptoms, Quality of Life and Microcirculation

Emilia Berin