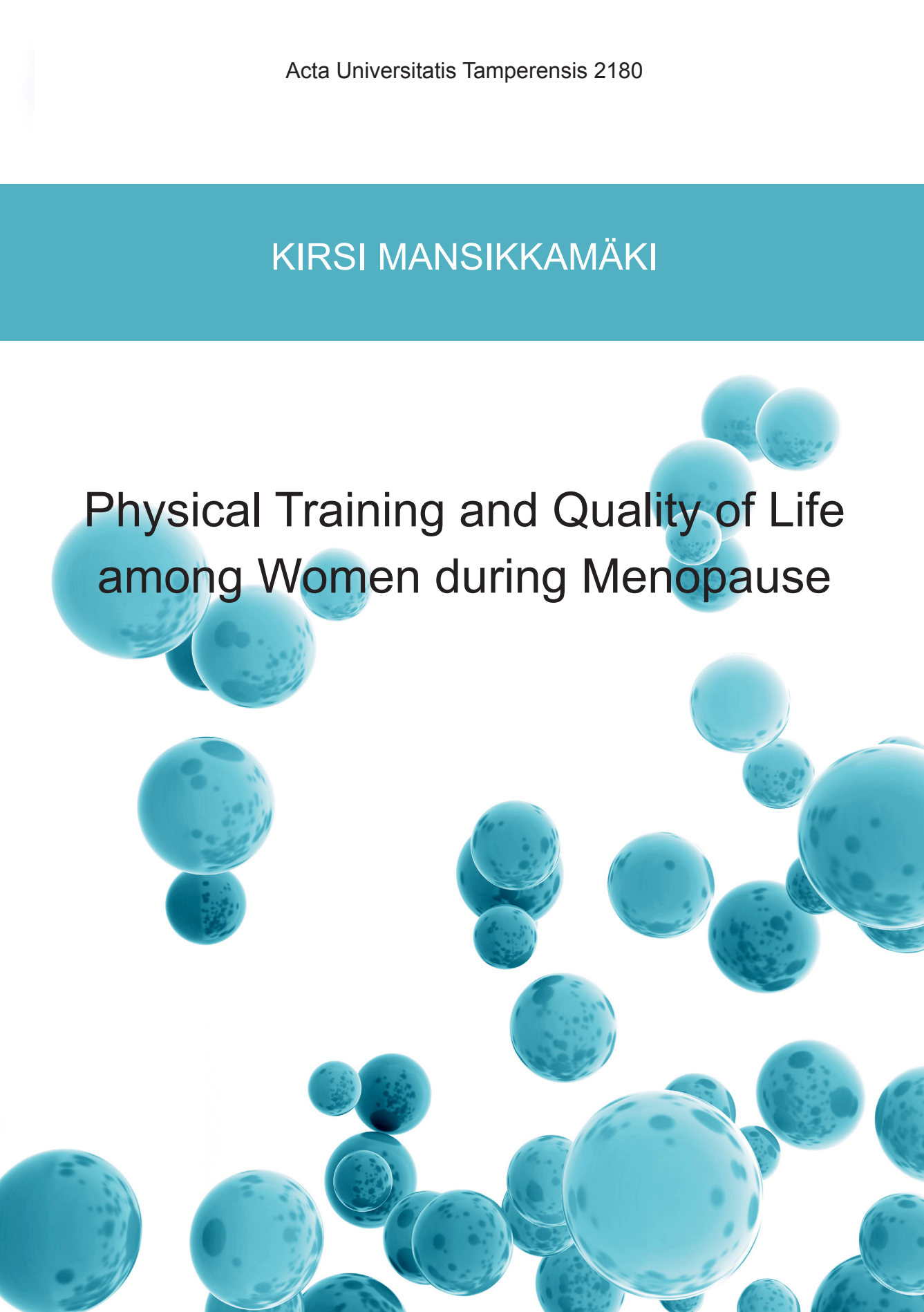# KIRSI MANSIKKAMÄKI

Physical Training and Quality of Life among Women during Menopause

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UNIVERSITY OF TAMPERE

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OF TAMPERE

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The originality of this thesis has been checked using the Turnitin OriginalityCheck service in accordance with the quality management system of the University of Tampere.

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To my family

Contents

LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following original publications:

I   Kirsi Mansikkamäki, Jani Raitanen, Nea Malila, Tytti Sarkeala, Satu Männistö, Jonna Fredman, Sirpa Heinävaara, Riitta Luoto. Physical activity and menopause-related quality of life – population-based cross-sectional study. Maturitas 2015;80(1):69-74.

II   Kirsi Mansikkamäki, Jani Raitanen, Clas-Håkan Nygård, Reetta Heinonen, Tomi Mikkola, Eija Tomás, Riitta Luoto. Sleep quality and aerobic training among menopausal women – a randomized controlled trial. Maturitas 2012;72(4):339-45.

III   Kirsi Mansikkamäki, Jani Raitanen, Clas-Håkan Nygård, Eija Tomás, Reetta Rutanen, Riitta Luoto. The long-term effect of physical activity on health-related quality of life among menopausal women: A four-year follow-up study of a randomised controlled trial. BMJ Open 2015. doi:10.1136/bmjopen-2015-008232.

IV   Kirsi Mansikkamäki, Clas-Håkan Nygård, Jani Raitanen, Katriina Kukkonen-Harjula, Eija Tomás, Reetta Rutanen, Riitta Luoto. Hot flushes among aging women: A 4-year follow-up study to a randomised controlled exercise trial. Maturitas 2016;88:84-89.

Permissions to append the articles to the doctoral dissertation was kindly granted by the publishers Elsevier and BMJ Open.

ABBREVIATIONS

BMI	body mass index
CI	confidence interval
CRF	cardiorespiratory fitness
CON	control group
DXA	dual X-ray absorptiometry
EX	exercise group
BMI	body mass index
FSH	follicle-stimulating hormone
FMP	final menstrual period
HEPA	health-enhancing physical activity
HFScore	hot flush score
HRF	health-related fitness
HRQL	health-related quality of life
HRR	heart rate reserve
HT	hormone therapy
LTPA	leisure-time physical activity
MENQOL	Menopause-Specific Quality of Life questionnaire
MET	metabolic equivalents
NAMS	The North American Menopausal Society
PA	physical activity
POR	proportional odds ratio
QoL	quality of life
RCT	randomised controlled trial
RPE	rating of perceived exertion
SD	standard deviation
SEM	standard error of mean
SF-36	The MOS (Medical Outcomes Study) 36-item Short Form survey questionnaire, developed by the RAND Corporation
STRAW	Stages of Reproductive aging Workshop
SWAN	Study of Women's Health Across the Nation
VO_2max	oxygen consumption ml/kg/min
VAS	visual analogue scale
VMS	vasomotor symptoms
WHQ	Women's Health questionnaire

ABSTRACT

The dissertation and its original publications are based on a survey from a national population-based breast cancer screening programme and a randomized controlled trial (RCT) with 4-year follow-up.

The purpose of the study was to examine the association between the leisure-time physical activity (LTPA) and quality of life (QoL), and to assess the effects of aerobic training on sleep quality, and on dimensions of quality of life and hot flushes.

The survey participants (n=2606) were a part of a cohort study that focuses on evaluating associations between breast cancer prevention, lifestyle and quality of life in relation to the population-based Finnish mammography screening programme. The survey was conducted from April to November in 2012. The study population was randomly drawn from the Finnish National Population Registry using the birth year as the only restricting factor. The participants were at the age of 49. Nearly one fourth of the participants (23%) had had no menstruation for 12 months and were thus postmenopausal. A third of the women (31%) had irregular menstruation, and were perimenopausal and 28% of the women were premenopausal with regular menstruation. The amount of leisure-time physical activity was elicited with a question to which the women responded with how much exercise they did in a typical week, during the previous 12 months and including any regular weekly physical activity for at least 10 min at a time, including commuting.

Participants for the training intervention were recruited via a newspaper advertisement in Pirkanmaa area, Finland, 176 women who fulfilled the inclusion criteria were randomly assigned to an exercise (EX) and a control (CON) group. The RCT and follow-up was conducted between March 2009 and June 2013 at the UKK Institute for Health Promotion Research, Tampere, Finland. All participants were symptomatic (had daily hot flushes), they were not current hormone therapy (HT) users, nor had they taken hormones in the past three months. The participants were not physically active (physical exercise less than twice a week), and 6-36 months since last menstruation. The unsupervised exercise programme consisted of aerobic training four times per week, with 50 min of exercise each time. The intensity of exercise was checked by ratings of perceived exertion (RPE) and the women were instructed to exercise at a level corresponding to 13-16 on a scale from 6-20, which corresponds to about 64-80% of maximal heart rate. EX was advised to include at least two sessions of walking or Nordic walking while the other two sessions could include other aerobic exercise. CON was advised to keep their physical activity habits unchanged. Adherence to the trial was supported by an option to participate

weekly in supervised aerobics session at the UKK Institute for Health Promotion Research twice a week.

All participants responded to questionnaires concerning menopause-specific quality of life (QoL) by Women's Health Questionnaire (WHQ) and health-related quality of life by using the SF-36 questionnaire (SF-36). In the RCT anthropometry, and cardiorespiratory fitness measurements were performed at baseline, after the 6-month intervention, and at 4-year follow-up. During the intervention women reported their training workouts, day-time and night-time hot flushes, other menopausal symptoms and sleep by making entries in a mobile-phone diary twice a day. At 4-year follow-up women were instructed to complete a one-week diary recording the number of hot flushes and their severity, type of physical exercise, duration and intensity, and sleep quality. In addition, women wore Hookie® accelerometers to record PA during one week.

In the survey participants advised that the recommended levels of LTPA were associated with better quality of life along four WHQ dimensions – anxiety/depressed mood, well-being, somatic symptoms and memory/concentration problems. In the RCT aerobic training for six months improved sleep quality and diminished hot flushes disturbing sleep hot flushes in women with menopausal symptoms. Long-term positive effects of aerobic training were found on the physical and mental dimensions of quality of life and hot flushes four years after beginning of the intervention.

This study demonstrated the importance of LTPA in menopausal women's lives. It moreover showed the positive short and long-term effects of aerobic training on menopausal symptoms, sleep and quality of life. Moderate intensity aerobic training, such as brisk walking, has many health benefits and it is safe and well-tolerated with minor adverse effects. For menopausal women physical exercise is a potential alternative to alleviate symptoms.

TIIVISTELMÄ

Vaihdevuodet ovat osa keski-ikäisten naisten elämää. Joka toisella suomalaisella naisella on vähintään yksi häiritsevä oire sekä vaihdevuosien aikana, että vaihdevuosien jälkeen. Yleisimpiä oireita ovat kuumat aallot, mielialan vaihtelut, ärtyneisyys, unihäiriöt sekä selkä- ja lihaskivut. Vaihdevuosien hormonihoito lievittää spesifejä vaihdevuosioireita, mutta muihin oireisiin ja elämänlaatuun vaikutukset saattavat olla ristiriiitaisia ja eivätkä lääkkeet sovi kaikille. Liikunnan merkitystä vaihdevuosioireiden hoitoon ja lievitykseen on tutkittu, mutta tulokset ovat olleet osin ristiriitaisia.

Väitöskirja ja sen osajulkaisut koostuvat kyselytutkimuksesta ja satunnaistetusta harjoittelututkimuksesta. Kyselytutkimuksessa tarkastellaan liikunnan vaikutusta vaihdevuosi-ikäisten naisten elämänlaatuun ja tutkimusaineisto kerättiin postikyselylomakkeella. Kyselytutkimus on osa Suomen Syöpärekisterin rintasyöpäseulontahanketta, jossa tutkitaan rintasyövän ennaltaehkäisyn, elämäntapojen ja elämänlaadun yhteyksiä. Kyselytutkimuksen osallistujat valittiin vuonna 2012 satunnaisesti väestötietojärjestelmästä syntymävuoden mukaan. Kyselytutkimukseen kutsuttiin 49-vuotiaita naisia vuosi ennen heidän ensimmäistä rintasyöpäseulontakutsuaan ja he vastasivat liikuntaa ja elämänlaatua koskevaan kyselyyn. Harjoittelututkimuksessa tarkastellaan liikuntaharjoittelun vaikutusta uneen ja unen laatuun sekä liikunnan pitkäaikaisvaikutuksia kuumiin aaltoihin ja elämänlaatuun. Satunnaistettu kontrolloitu liikuntaharjoittelututkimus ja seurantatutkimus toteutettiin UKK-instituutissa Tampereella vuosina 2009-2013. Satunnaistetun liikuntaharjoittelututkimuksen tavoitteena oli tutkia kuuden kuukauden aerobisen harjoittelun vaikutuksia uneen, elämänlaatuun ja vaihdevuosioireisiin.

Kyselytutkimukseen osallistuneista naisista melkein neljännes (23%) oli postmenopausaalisia (vuosi kuukautisten loppumisesta), 31% perimenopausaalisia (kuukautiset epäsäännölliset) ja 28%:lla naisista oli säännölliset kuukautiset eli he olivat premenopausaalisia. Tutkittavat vastasivat liikuntakysymykseen, jossa he arvioivat edeltävän vuoden ajalta viikoittaisen fyysisen aktiivisuuden määrän (ei työtä), joka oli kestänyt vähintään 10 minuuttia kerrallaan.

Harjoittelututkimuksesta kiinnostuneet naiset ilmoittautuivat lehti-ilmoituksen perusteella ja yhteensä 176 naista todettiin sopiviksi tutkimukseen. Tutkimukseen hyväksyttyjen tuli olla vähän liikkuvia, vaihdevuosioireisia, ja ilman hormonikorvaushoitoja. Ennen kuuden kuukauden harjoittelun alkua ja harjoittelun päätyttyä tutkittavat osallistuivat kehon koostumuksen ja aerobisen kunnon mittauksiin. Mittaukset tehtiin myös neljän vuoden seurantatutkimuksessa. Lisäksi he vastasivat kyselyyn elämänlaadusta ja raportoivat harjoittelun aikana puhelinpäiväkirjan

välityksellä aamuisin sekä iltaisin kuumien aaltojen määrän ja laadun, uneen liittyviin kysymyksiin (aamulla) sekä liikunnan toteutumisen harjoittelun aikana.

Kestävyysliikunnan harjoittelu kesti kuusi kuukautta ja liikuntaryhmään kuuluneet naiset ohjeistettiin liikkumaan neljä kertaa viikossa. Harjoittelun kesto oli 50 minuuttia kerrallaan, rasitustasolla 13-16 (hieman rasittavasta rasittavaan), joka vastaa 64-80% arvioidusta maksimaalisesta sykkeestä, asteikon vaihdellessa 6-20. Harjoittelu sisälsi vähintään kaksi kertaa kävelyä tai sauvakävelyä ja lisäksi muuta kestävyysliikuntaa. Tutkittavilla oli mahdollisuus osallistua ohjattuun liikuntatuntiin kaksi kertaa viikossa UKK-instituutissa. Verrokkiryhmän naiset ohjeistettiin pitämään liikuntatottumukset ennallaan. Molemmilla ryhmillä oli mahdollista osallistua 1-2 kertaa kuukaudessa järjestetyille luennoille, joissa aiheet liittyivät terveyteen ja hyvinvointiin.

Kyselytutkimuksen tulokset osoittivat että vaihdevuosi-ikäisillä naisilla, jotka liikkuivat väestön terveysliikuntasuosituksen mukaisesti oli vähemmän ahdistuneisuutta ja masentuneisuutta, somaattisia oireita, muisti- ja keskittymisongelmia. Lisäksi he kokivat elämänlaatunsa paremmaksi, kun heitä verrattiin naisiin, jotka eivät harrastaneet liikuntaa suosituksen mukaisesti. Kuuden kuukauden harjoittelututkimuksen jälkeen liikuntaryhmän vaihdevuosi-ikäisten naisten unen laatu oli parempi ja unta häiritsevien yöllisten kuumien aaltojen määrä oli vähäisempi verrattuna verrokeihin. Neljän vuoden seurannassa intervention alusta todettiin liikunnan pitkäaikaisvaikutuksena parempi sosiaalinen ja fyysinen toimintakyky (WHQ ja SF-36 -mittareilla mitattuna) sekä vähemmän kuumia aaltoja harjoitteluryhmän naisilla verrattuna verrokeihin.

Väitöskirjan tulokset osoittivat liikunnan tärkeyden ja merkityksen vaihdevuosi-ikäisten naisten elämässä. Vaikka tutkimusnäyttö liikunnan hyödyistä vaihdevuosioireiden hoidossa on edelleen osin ristiriitaista ja tutkimustieto vähäistä, liikunnan yleisistä terveyshyödyistä ollaan yhtä mieltä mieltä esim. valtimosairauksiin ja niiden vaaratekijöihin, osteoporoosiin, tiettyihin syöpiin ja mielenterveyteen liittyen. Liikunta tarjoaa naisille hyvän vaihtoehdon vaihdevuosioireiden lievittämiseen ja lisäksi liikunnan on todettu olevan yhteydessä parempaan elämänlaatuun ilman vakavia haittavaikutuksia.

1. INTRODUCTION

The word menopause comes from the Greek word men- (month) and pausis (cessation). Menopause is followed by loss of ovarian follicular function and determined as the end of the woman's fertile life. For women in midlife a number of signs and symptoms may appear, including vasomotor symptoms, mood changes, anxiety and sleep disturbances with the onset of menopause, which is a normal developmental process in women's life. This episode of menopause in the women's life is not an abrupt or sudden event, but takes place over several years (5-8 years). The time of menopause can be considered as a change in life and as an opportunity to reappraise health and health-related behaviour patterns and make changes in them (Kaufert et al. 1998; Elavsky 2009; Stojanovska et al. 2014).

Due to the rather long duration of the perimenopause, the impact of menopause on women's quality of life is noteworthy. Many symptoms, like hot flushes, night sweats, vaginal dryness, sleep disturbance and poor perceived health are associated with this process. (Utian 2005; McVeigh 2005). Furthermore, menopause is associated with a number of physical, psychological and social changes (Kumari et al. 2005). In addition, all these symptoms may lead to social impairment and work-related difficulties (Utian 2005).

Physical activity has been shown to be associated with a decrease in hot flushes (Ivarsson et al. 1998; Gold et al. 2000; Luoto et al. 2012). However, contradictory findings about the effect of moderate-intensity aerobic exercise on hot flushes or night sweats have been reported (Sternfeld et al. 2014; Daley et al. 2014; Daley et al. 2015). According to the results of certain randomized controlled trials exercise was not recommended by The North American Menopause Society (NAMS) position statement as a treatment for hot flushes or vasomotor symptoms (VMS) frequency (NAMS 2015). However, the results suggested possible small improvements in subjective sleep quality, insomnia, depressive symptoms and some from VMS. (Sternfeld et al. 2014; Daley et al. 2015).

Physical activity has been shown to enhance health-related quality of life among menopausal women (Bize et al. 2007; Elavsky 2009; Martin et al. 2009; Courneya et al. 2011). Higher PA activity levels have been associated with better or higher scores on various quality of life dimensions (Bize et al. 2007). There are many reasons why menopausal women should be encouraged to exercise regularly, namely to reduce the risk of cardiovascular disease and osteoporosis and to improve muscle strength to maintain functional capacity. Menopausal women may expect regular physical exercise to improve their overall health.

2.   REVIEW OF THE LITERATURE

2.1.   Health-related quality of life and menopause

2.1.1.   Menopause and aging

Menopause, permanent cessation of menstruation due to loss of ovarian follicular function, is a normal physiological event in middle-aged women's life and usually experienced between 40 and 58 years of age (Greendale et al. 1999; Soules et al. 2001; Zapantis and Santoro 2003). In Europe the median age of menopause ranges from 50.1 to 52.8 years (Palacios et al. 2010) and the mean age of menopause in Finland is 51 years (Luoto et al. 1991).

The Stages of Reproductive Aging Workshop (STRAW) was held in 2001 in order to develop a relevant and useful staging system for female reproductive aging and revise the nomenclature. The staging system was revised in 2012 and provides a more comprehensive basis for classification and assessment from the late reproductive stage to post-menopause (Harlow et al. 2012). Reproductive aging in a woman's life is a process and not an event. Chronological age is a poor indicator of this process, and the identification of the stage through which a woman is progressing the process of reproductive aging would be more appropriate. (Soules et al. 2001).

Menopausal transition, i.e. perimenopause, is a period of changing ovarian function. This is characterized by an increase in follicle-stimulating hormone (FSH) and wider variation in the length of menstrual cycle. (Soules et al. 2001; NIH 2005; Harlow et al. 2012). According to Harlow et al. (2012), perimenopause consists of early- and late stages; during the early stage ovulation begins to become dysregulated, with variations in cycle length of seven days or more, and late stage, during which ≥ 2 cycles are missed with an interval of amenorrhoea (≥ 60 days) (Greendale et al. 1999; Soules et al. 2001; Zapantis and Santoro 2003; Harlow et al. 2012). The perimenopause concludes with the final menstrual period (FMP) that can be recognized after 12 months of amenorrhoea (Soules et al. 2001; NIH 2005; Harlow et al. 2012). The beginning of post-menopause includes the time of FMP, although it cannot be recognized until after 12 months of amenorrhoea (Soules et al. 2001; NIH 2005; Harlow et al. 2012). During the post-menopause FSH continues to increase and estradiol continues to decrease until approximately two years after the FMP, after which the levels of each of these hormones stabilize (Figure 1) (Soules et al. 2001; Harlow et al. 2012). During the late stage of perimenopause and at the beginning of post-menopause vasomotor symptoms are likely to occur (Harlow et al. 2012).

Final menstrual period
FMP (0)

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

Figure 1. Definition and rationale for key revisions to the staging criteria. The Stages of Reproductive Aging Workshop (Harlow et al. 2012)

2.1.1.1. Prevalence and mechanism of menopausal symptoms

Menopause is a remarkable event in women's lives, as it means the end of fertile life and has a great physical, emotional and social impact (Daley et al. 2014). Despite variable and often complex definition and interpretation, the biological fact is that symptoms will occur as a result of the sudden drop in hormone levels in circulation. (Zöllner et al. 2005).

The menopausal transition period is typically characterized by a number of signs and symptoms, and the major three categories for menopausal symptoms can be divided into vasomotor, atrophic and psychological/sexual. (Philp 2003; Copeland et al. 2004; Freeman and Sherif 2007; Harlow et al. 2012; Schiff 2013). Hot flushes and night sweats are included in vasomotor symptoms, which may be accompanied by distress, fatigue and insomnia. Hot flushes are the most common symptoms among a high proportion of perimenopausal and early postmenopausal women. (Greendale et al. 1999; McVeigh 2005; Kumari et al. 2005; Thurston et al. 2011). Hot flushes and hot flashes are often used as synonymously (Thurston et al. 2011). Hot flushes are characterized by a sensation of warmth, frequent skin flushing of the face and chest and perspiration, as consequence a chill may follow when the body temperature drops (Greendale et al. 1999; Thurston et al. 2011). Hot flushes may be occasional or frequent and last from seconds to an hour causing sweating, and concurrently with palpitations and anxiety (Thurston et al. 2011). Urogenital atrophy, changes in and skin,

joint and muscle pain can be included in atrophic symptoms. These disorders have been reported to increase during menopause. The third category includes psychological/ sexual – symptoms, vaginal dryness, breast tenderness, dyspareunia and depressive mood. (Philp 2003; Copeland et al. 2004; Freeman and Sherif 2007). Menopausal women commonly report difficulties in daily activities with psychological symptoms (mood changes, depression, irritability, anxiety) and cognitive symptoms such as problems with memory or concentration. Additionally, sexual dysfunction, fatigue, headache, weight gain and joint pains may be associated with aging as well as with menopause itself (Woods et al. 2005; Stojanovska et al. 2014). Some women experience hot flushes as a minor irritation, whereas other women experience hot flushes the most bothersome symptom due to estrogen withdrawal causes during work, sleep, or daily activities. (Greendale et al. 1999; Thurston et al. 2011).

According to a review by Palacios et al. (2010) among women in the USA the prevalence of vasomotor symptoms ranged from 36% to 50%, and in the United Kingdom eight out of ten women experience perimenopausal symptoms. Symptoms typically last for about four years (Politi et al. 2008) and 25% of these may be severe enough to affect women's quality of life (Sarri et al. 2015). Sleep problems are likevise common among women during menopause, 16-42% of premenopausal, 39-47% of perimenopausal and 35-60% of postmenopausal women are bothered by poor sleep quality (NIH 2005).Various pains, such as headache, back pain and joint-ache were reported by 27% of women aged 45-64 in a Finnish population-based study, and 28% of women reported hot flushes and 38% tiredness (Hemminki et al. 1995). In Finland over one third (38%) of the premenopausal, half of the perimenopausal, and 54% of both postmenopausal and hysterectomized women reported any bothersome symptom in the nationally representative population-based Health 2000 study in women aged 45-64 years (Moilanen et al. 2010). Premenopausal women suffered from back pain less often than perimenopausal women (Moilanen et al. 2010).

Prevalence of menopausal complaints is a culturally differing phenomenon. Regional patterns in prevalence of vasomotor symptoms and hot flushes are different in western countries and East Asian countries (Greendale et al. 1999; Freeman and Sherif 2007; Palacios et al. 2010). In East Asia postmenopausal women reported 22-63% prevalence of hot flushes whereas women from Latin America had a prevalence of 45-69% and from European countries women reported 55-74% prevalence of hot flushes (Freeman and Sherif 2007; Palacios et al. 2010).

The extent of reproductive hormone changes during the perimenopause are altered in obese women with lower estradiol levels before the FMP and the reverse after the FMP when compared to non-obese women. One possible explanation is the change in the primary source of circulating estradiol as the transition progresses. During the premenopause the source is the ovary, whereas in post-menopause the source is aromatization of androgens in the adipose tissue. This change in estradiol

source among postmenopausal obese women provides a reservoir of estrogen and higher circulating estradiol levels that women of normal weight do not have. (Wildman and Sowers, 2011; Randolph et al. 2011).

Obesity was initially hypothesized to be a protective factor against vasomotor symptoms according to an assumption that obese women have higher serum estradiol levels resulting from conversion of androgens to estrogens in the adipose tissue (Thurston and Hadine 2011; Wildman and Sowers 2011). However, several studies have found obesity to be a risk factor rather than a protective one. In addition, evidence suggests that obese women in the earlier stages of menopausal transition experience more vasomotor symptoms and more bothersome symptoms than women of normal weight (Wildman and Sowers 2011; Thurston et al. 2009). The positive association between BMI and VMS concurs with a thermoregulatory model of VMS, in which excessive adipose tissue acts as an insulator, inhibiting the heat dissipating function of VMS and thereby increasing the occurrence or severity of VMS (Thurston and Hadine 2011; Davis et al. 2012).

Cross-sectional studies have reported a greater amount of menopausal symptoms among women with higher BMI (Gold et al. 2000; Whiteman et al. 2003). In the Study of Women's Health Across the Nation (SWAN) in the United States higher rates of vasomotor symptoms were reported among overweight or obese perimenopausal women than among women with stable weight i.e. women who were neither gaining nor losing weight (Thurston et al. 2008) and also in the analyses over three years (Thurston et al. 2009). These findings are consistent with a thermoregulatory model of vasomotor symptoms in which body fat functions as an insulator, causing vasomotor symptoms rather more likely than a heat dissipation event (Thurston et al. 2009). No relationship between hot flushes and BMI was found in an Australian longitudinal study, the Melbourne Women's Midlife Health Project (Guthrie et al. 2005). In Finland obese (BMI >30 kg/m²) and overweight women (25kg/m² < BMI < 30 kg/m²) reported more psychological symptoms, and furthermore obese women reported more vasomotor symptoms than women of normal weight (Moilanen et al. 2010).

Weight gain of about 0.5 kg annually during menopause may be related to aging rather than to menopause itself (Wildman and Sowers 2011; Davis et al. 2012). The hormonal changes during the menopausal transition contribute to an increase in fat mass and a redistribution of fatty tissue, such as increased central abdominal fat and abdominal obesity (Davis et al. 2012). Weight reduction and decrease in abdominal circumference have been shown to alleviate menopausal symptoms among overweight and obese women (Davis et al. 2012). However, weight loss has been recommended with caution to be beneficial for alleviating vasomotor symptoms and it may not be optimal for women seeking immediate relief or for those with severe symptoms (NAMS 2015).

2.1.1.2. Sleep and sleep quality during menopause

Menopause may affect sleep and sleep quality among women, with the declining estrogen levels being the primary factor, likewise vasomotor symptoms, depression and anxiety. Sleep problems are common among menopausal women and during the menopause the prevalence of sleep problems increases substantially from 30% in premenopausal women to approximately 50% in peri- and postmenopausal women (Polo-Kantola 2011; Guidozzi 2013). Sleep problems are multifactorial since the decreasing levels of estradiol and increasing levels of follicle stimulating hormone (FSH) may disturb the secretion of melatonin and circadian hormones which regulate sleep (Guidozzi 2013). Sudden perspiration may disturb sleep in such a way that there is a need to change bed linen and clothing. Another problem is wakening up early in the morning and not being able to fall asleep again (Xu et al. 2014). Furthermore, psychosocial status and mental health problems, such as depression and anxiety, and mood symptoms have shown to contribute to sleep problems during menopause and beyond (Xu et al. 2014; Polo-Kantola 2011).

The available literature has not strictly determined whether the sleep problems during menopause are of menopausal origin, age-related or associated with symptoms that are coincidental with menopause (Guidozzi 2013). According to a systematic review (Xu et al. 2014) there is reasonable evidence for an increased risk of sleep disturbances among menopausal women. Sleep problems may follow from the impact of age itself, vasomotor symptoms, health behaviour (e.g. PA, alcohol and smoking), physical and psychological health. (Xu et al. 2014; Hachul et al. 2015). Furthermore, a change in the circadian rhythm, e.g. shift work or travel, may result in shortened sleep duration and early morning wakening among aging women (Polo-Kantola 2011; Guidozzi 2013; Xu et al. 2014).

Studies have consistently shown the associations with mood symptoms, depression or anxiety and sleep problems. Poor sleep, i.e. sleeping badly (Hollander et al. 2001) and poor subjective sleep quality (Freedman et al. 2007) have been found to be connected to high levels of both anxiety and depression among menopausal women. Furthermore, mental health problems have been shown to be a significant predisposing factor to various self-reported sleep problems (Vaari et al. 2008). According to a recent review, an association was found with both vasomotor and depressive symptoms and psychological factors, such as insomnia or anxiety (Worsley et al. 2014).

Subjective sleep quality has often been evaluated by a single question concerning sleep problems. More frequent sleep complaints, such as insomnia, were found after the menopause by posing a series of detailed questions to elicit the sleep characteristics among postmenopausal women. Higher insomnia scores were found in a the study where sleep quality was assessed more precisely with a more detailed questionnaire. Postmenopausal women reported more difficulties in getting back to sleep after

wakening in the middle of the night (Kalleinen et al. 2008; Lampio et al. 2014). The association between impaired quality of sleep and daytime sleepiness or impaired daytime performance has been found to be clinically relevant (Polo-Kantola 2011).

According to a sleep diary study, working postmenopausal women with FSH level above 30 IU/L slept more poorly than premenopausal women during the working week but at weekends women in both groups slept equally well, only sleep latency was longer in postmenopausal women (Lampio et al. 2013). They also found that both premenopausal and postmenopausal women had shorter total sleep duration on workdays than at weekends, which suggests that leisure days may offer an opportunity to recover. Furthermore, among postmenopausal workers an adequate number of leisure days is needed to ensure sufficient recovery and better work ability. (Lampio et al. 2013).

2.1.2. The concept of quality of life

Quality of life (QoL) can be considered as one's own perception of well-being and includes several areas of life in addition to health. QoL is often referred to as health-related quality of life (Utian 2007). The definition of health-related quality of life (HRQL) is defined as representing the patients' evaluation of the impact of a health condition and its treatment on daily life (Zöllner et al. 2005). During menopause the term quality of life is often related to menopausal symptoms such as hot flushes, night sweats and vaginal dryness or pain. It is comprehensible that these symptoms may have a negative influence on the QoL among menopausal women. However, it is important also to recognize other perspectives of QoL-related issues such as health status, life satisfaction, coping and psychological functioning (Utian 2007). The term quality of life should be defined by measurable domains. Furthermore, these QoL domains should include in addition to a symptom profile also physical, emotional, and social functioning or role limitations. (Zöllner et al. 2005; Utian 2007).

Global quality of life can be defined as a value-dependent overall evaluation of the different perspectives of what the subject means by quality of life (Hyland and Sodergren 1996). According to Leventhal and Colman (1997) symptoms affecting global quality of life can be interpreted by an individual as detracting from QoL, while another person may see them as a contributing positively to QoL. Global QoL refers to an overall well-being and self-satisfaction beyond the presence or absence of symptoms. In addition, global QoL indicates how women feel generally, and specifically, what their ability is to accomplish daily work with satisfaction, and how they maintain interpersonal relationships, sexuality and general well-being. (Utian et al. 2002; Utian 2007).

2.1.3. Assessments of quality of life

There are many validated methods for assessing quality of life. Here we summarize those scales presented, which are related specifically to menopause (WHQ, MENQOL), to health-related QOL (SF-36) or to global QOL (Ladder of life-scale) (Table 1).

The Women's Health Questionnaire (WHQ) was developed to measure symptom perceptions during menopausal transition and in postmenopausal women aged 45-65. The questionnaire assesses symptom experiences which are associated with the menopause, such as vasomotor symptoms and psychosocial factors, general health and aging, sleep, sexual and cognitive problems. The main application of the WHQ has been in evaluating the efficacy of medical and non-medical interventions for specific symptoms and health-related QoL. Additionally, the WHQ has been used extensively, ranging from the evaluation of hormone replacement treatments for menopause related problems to epidemiological studies with healthy women (Hunter 2003). The questionnaire has been validated for use in Finnish, and with a 2-week interval the test-retest reliability (Correlation factor between 0.69 and 0.96) has been evaluated (Table 1) (Zöllner et al. 2005).

The WHQ-questionnaire consists of 36 items assessing nine domains of physical and emotional health. Each item is rated on a four-point scale, the response options being Yes, definitely; Yes, sometimes; No, not much or No, not at all. A time frame of the past few days was selected to elicit symptom and mood states for that specific moment. The WHQ measures the following areas of health: Depressed mood (6 items), somatic symptoms (7 items), anxiety/fears (4 items), vasomotor symptoms (2 items), sleep problems (3 items), sexual behaviour (3 items), menstrual symptoms (4 items), memory/concentration (3 items) and attractiveness (2 items) (Hunter 2000; Hunter 2003). Items from all domains are spread across the questionnaire and symptoms are not listed in blocks to complete one domain and continue to the next (Hunter 2003; Zöllner et al. 2005).

The Menopause-Specific Quality of Life Questionnaire (MENQOL) is a quality of life questionnaire specific to the post-menopausal period measuring changes between menopausal women in their quality of life over time (Hilditch et al. 2008). As a result of development, the questionnaire is a 29-item menopause-specific health-related quality of life questionnaire that encompasses four subscales; physical, psychosocial, vasomotor, sexual and also questions on general QoL (Hilditch et al. 2008; Zöllner et al. 2005). Within each domain women are asked to indicate on a 7-point scale (from 0=not at all to 6=extremely) how severely the symptoms are bothering them (Table 1) (Zöllner et al. 2005).

The Medical Outcomes 36-item Short Form Health Survey (SF-36) is used to measure health-related quality of life. The SF-36 is a multi-purpose short form health survey with 36 questions to assess physical and mental quality of life. There

are eight scales that are hypothesized to form two distinct higher-ordered clusters, physical and mental health. The eight scales are: physical functioning, role limitations because of physical problems, bodily pain, general health, vitality, social functioning, mental health and role limitations because of the emotional problems (Table 2). Respondent reported scores are converted into scale scores ranging from 0 to 100, higher scores indicate better quality of life or better functioning on all scales. The SF-36 can also be scored as summary scales, a physical and a mental component summary scale (Martin et al. 2009; SF-36 Health Survey Update, http://www.sf-36. org/tools/SF36.shtml#LIT).

Ladder of Life Scale (Andrews and Withey 1976) is a global quality of life scale. The scale includes a picture of a ladder and at the bottom of the ladder is the worst life the subject might reasonably expect to have and at the top there is the best possible situation in the subjects life. Measurement of global QoL attempts to assess general feelings about life-as-a-whole using nonverbal scales. (Andrews and Withey 1976). The visual analogue scale (VAS), included in the Ladder of Life Scale, has been used to measure global QoL. On VAS respondents are asked to provide a subjective evaluation their own quality of life during the previous month. The VAS is used as a vertical scale of 15 cm such that 0 represents worst possible quality of life and 10 the best possible quality of life. (Heinonen et al. 2004). VAS has also been used in clinical studies (Hwang et al. 2002) and it has also been used to evaluate measures of health related QOL (Table 1) (Neudert et al. 2001).

Table 1. Questionnaires on menopause-related quality of life and their assessment domains

Domains	WHQ	SF-36	MENQOL	Ladder of life / VAS
1	Depressed mood	Physical functioning	Vasomotor function	Global QoL scale
2	Somatic symptoms	Role function physical	Psychosocial function	–
3	Memory/concentration	Mental health	Physical function	–
4	Vasomotor symptoms	Role function emotional	Sexual function	–
5	Anxiety/fears	Social functioning	–	–
6	Sexual behavior	Bodily pain	–	–
7	Sleep problems	Vitality	–	–
8	Menstrual symptoms	General health	–	–
9	Attractiveness	–	–	–

QoL –questionnaires: WHQ (Hunter 200), SF-36 (Martin et al. 2009, SF-36 Health Survey Update, http://www.sf-36.org/tools/SF36.shtml#LIT), MENQOL (Hilditch et al. 2008, Zöllner et al. 2005), Ladder of life (Andrews and Withey 1976)

2.2. Physical activity and health-related quality of life among menopausal women

2.2.1. Health-enhancing physical activity and quality of life during menopause

The components of health-related fitness (HRF) are cardiorespiratory, morphological, musculoskeletal, motor and metabolic fitness (Caspersen et al. 1985; Bouchard and Shephard 1994). Health-enhancing physical activity (HEPA) can be defined as physical activity (PA) that will enhance health and thus improve HRF (Vuori et al. 1996). The principal message of HEPA is that PA should not only be vigorous, but also safe and feasible for the participant (Vuori et al. 1996).

It is known that physical activity is related to overall well-being and coping with daily tasks. The menopausal transition is a phase in a woman's life that may affect the physical and mental dimensions of QoL both at work and in leisure time in various ways. Women have reported about hot flushes, sleep problems, and mood swings and other menopause-related symptoms which have been disturbing during menopause (Freeman et al. 2007; Moilanen et al. 2010). In addition, alternative treatments are warranted among women during menopause as the risks of hormone therapy may

outweigh the benefits (Rossouw et al. 2002).

Figure 2 illustrates the connection between menopausal symptoms, health-enhancing PA and health-related physical fitness. Through increased physical activity it is possible to influence quality of life and managing daily tasks. From this basis the aims of the present study were formulated (Figure 2).
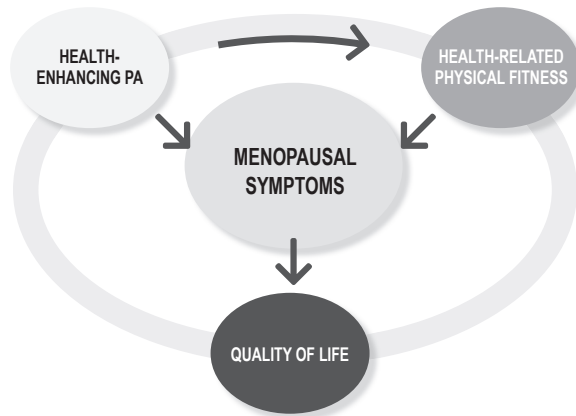

Figure 2. Connections between menopausal symptoms, HEPA, HRF and quality of life

2.2.2.   Physical activity and exercise during menopause

Physical activity (PA) is defined as any bodily movement produced by the skeletal muscles and resulting in elevated energy expenditure (Carpersen et al. 1985; Howley 2001). A commonly used categorization of physical activity identifies the activity occurring at work and during leisure. (Carpersen et al. 1985). Leisure-time physical activity (LTPA) is based on personal interests and needs concerning the activities in which one participates (Howley 2001). LTPA can be divided into light, moderate or heavy intensity, such as sports, keep-fit exercises, household tasks and other lifestyle activities. (Carpersen et al. 1985; Howley 2001.) The term exercise is not synonymous with physical activity but it is a subcategory of LTPA. Exercise can be defined as physical activity that is planned, structured, repetitive, and purposive in the sense of enhancing one or more components of physical fitness. Exercise may consist of different daily activities. (Carpensen et al. 1985; Howley 2001).

Regular physical activity has many health benefits, that may be relevant to menopausal women, such as reduction in the risk for diabetes, cardiovascular disease, cancer and depression (DHHS 2008). Walking is a feasible way to start for an inactive person and especially as incorporated into everyday life (Asikainen et al. 2004). Twenty-four weeks of a walking intervention at moderate intensity led to improvements in

VO$_2$max and body composition among sedentary, slightly overweight postmenopausal women (Asikainen et al. 2002b) and also when walking was performed in one or two daily sessions (Asikainen et al. 2002a). In addition to walking Nordic walking has been shown to improve health-enhancing physical fitness among non-obese inactive women aged from 50 to 60 (Kukkonen-Harjula et al. 2007). Asikainen et al. (2004) in their systematic review of randomised controlled trials of exercise for postmenopausal women found that health professionals are in a significant position to counsel their patients to improve health-related fitness by an exercise programme (Asikainen et al. 2004).

Physical activity is showed to be associated with a diminished amount of hot flushes (Ivarsson et al. 1998; Gold et al. 2000; Elavsky et al. 2012). The mechanism by which physical activity could have favorable effect on the frequency of vasomotor symptoms is through the release of β-endorphins, that occurs in response to a sustained bout of vigorous exercise (Sternfeld and Dugan 2011). β-endorphin is known to affect thermoregulation. In addition, exercise is known to increase hypothalamic β-endorphin production, and thereby exercise may stabilize the thermoregulatory centre and diminish the risk of hot flushes (Ivarsson et al. 1998; Hammar et al. 1990). On the other hand, physical activity may have dual roles, positively impacting on mood and body weight, which may improve vasomotor symptoms, and the acute rise in core temperature that occurs with exercise, might actually induce hot flushes, particularly if women have a narrowed thermoregulatory zone that lowers their threshold for sweating (Thurston et al. 2011; Sternfeld and Dugan 2011). Exercising women might be more familiar with sensation of heat and sweating and therefore they report sweating symptoms as less severe than sedentary women (Ivarsson et al. 1998).

The connection with weight and physical activity is an interesting issue when vasomotor symptoms are considered. The association between hot flushes and weight has been studied, and women with no or infrequent vasomotor symptoms had an average BMI 28 kg/m² while women with an average BMI 31 kg/m² had more frequent vasomotor symptoms (Gold et al. 2000; Thurston and Joffe 2011). Furthermore, the results of a 12-month moderate-to-vigorous exercise programme among menopausal women aged 42-68 years, showed significant improvements in body composition among the exercising group when compared to the control group (Aragao et al. 2014). A positive association with weight loss and menopausal symptoms was found in a study by de Azevedo Guimaraes AC et al. (2011), in which the influence of, at least moderate-intensity PA for 60 min/day for 12 weeks, was seen to affect the menopausal symptoms and the health-related QoL. The results showed that habitual PA was partially related to a decrease in the symptoms of menopause and/or to weight loss (de Azevedo Guimaraes AC et al. 2011).

2.2.3. Effects of training on menopausal symptoms and quality of life during menopause

A Cochrane review of exercise for vasomotor menopausal symptoms concluded that there was insufficient evidence to show whether exercise is an effective treatment for vasomotor menopausal symptoms. Five RCT's were included in the review, exercise was compared with no active treatment, exercise was compared with yoga, and exercise was compared with HT. In the comparison of exercise and no active treatment or exercise and yoga, no group differences were found in frequency or intensity of vasomotor symptoms. When exercise and HT were compared, the HT group reported significantly fewer hot flushes than the exercise group (Daley et al. 2014).

The effects of physical training on menopausal symptoms among menopausal women have been examined using various study designs. In a six month randomized controlled trial the objective was to investigate the effectiveness of exercise as treatment for vasomotor menopausal symptoms. The exercise training was incremental over time, during weeks 1-12 the goal was to achieve 30 minutes of moderate intensity exercise i.e. brisk walking, jogging, aerobics, swimming, cycling, at least three times per week. During the weeks 13-24 women were advised to concentrate their exercise onto 3-5 sessions per week. The exercise with DVD intervention included two exercise consultations, leaflets and a DVD, and in the exercise with social support intervention included exercise consultations and a support group. The control group was given a pedometer and an opportunity for exercise consultation after the study ended. Neither of the exercise groups resulted in significantly fewer hot flushes or night sweats per week at the 6-month and 12-month follow-ups when compared to women in the control group. The exercise-social group reported significantly lower scores on somatic symptoms, sleep problems and anxiety. Overall, this intervention had more effect on general symptoms of menopause than specifically on hot flushes or night sweats. However, PA was recommended as a good reason why women should be encouraged to take regular exercise, i.e. to reduce the risk of osteoporosis and cardiovascular disease and to improve muscle strength (Table 2) (Daley et al. 2015).

In a 12-week of individual, facility-based, moderate-intensity RCT study the participants in the exercise group could choose whether to exercise three times a week for 12 weeks on an elliptical trainer, on a treadmill or on a stationary bicycle. For the first month the target heart rate was 50-60% of the heart rate reserve (HRR) and for the next two months 60-70% of HRR. Duration of the session ranged from 40 to 60 minutes. The control group was instructed to keep their physical activity habits unchanged. At the end of the study they were offered a 1-month membership at a local fitness centre or a free yoga workshop, materials, and equipment. The

participants were inactive late peri- or postmenopausal women with 14 or more vasomotor symptoms per week according to daily diaries, and FSH higher than 20 IU/ml. In the trial it was shown that aerobic exercise training among inactive women did not alleviate frequent or bothersome vasomotor symptoms. However, it was concluded that exercise training improved fitness level and was safe, and that it may have improved sleep quality, symptoms of insomnia and depression (Table 2) (Sternfeld et al. 2014).

A yearlong randomized clinical trial evaluated the effects of moderate-intensity exercise on the occurrence and severity of menopause symptoms. Overweight postmenopausal women (n=173), not taking hormone therapy in the previous six months, were randomized to a moderate- intensity exercise group (45 minutes/5 days per week for 12 months, treadmill walking, walking, aerobics, bicycling) and to a control group (once-weekly 45 minutes of stretching for 12 months). Information on menopause symptoms and severity was elicited at baseline and at 3, 6, 9 and 12 months using a self-administered questionnaire. In this study exercise did not seem to substantially increase the risk of having menopause symptoms among overweight, postmenopausal women. The risk of severe symptoms, specifically hot flushes, was only increased in a very small number of participants. In addition, they found decreased risk of memory problems after three months of exercise (Table 2) (Aiello et al. 2004).

The relationship between exercise training and the improvement in menopause-related quality of life was examined in a randomized trial design in which the efficacy of yoga, exercise and usual activity was studied. Peri- and postmenopausal women were assigned randomly to yoga (n=107), exercise (n=106) and usual activity groups (n=142). The yoga intervention was provided with weekly 90-min classes and daily home practice when a participant was absent from class. Women in the exercise group had supervised aerobic training sessions at local fitness facilities three times per week, 40-60 min per session with the targeted training heart rate 50-60% of the heart rate reserve for the first month and 60-70% for the next two months. The usual activity group was asked not to change their physical activity habits during the study. As a result, the yoga intervention was found to have resulted in an improvement in menopause-related QoL scores after 12 weeks when compared to women in the usual activity group, while the exercise group seemed to benefit for only the physical domain of MENQOL scores (Table 2) (Reed et al. 2014).

A significant positive dose-response relationship was found between physical training and improvement in physical and mental QoL, measured by the SF-36. In this randomized controlled physical training trial postmenopausal women, aged between 45 and 75 years, were assigned to three exercise groups (50%, 100% and 150% of the recommended level of PA/NIH in 1996), involving 3 or 4 training sessions per week for six months, and a control group. All exercise sessions were

held under observation and supervision in an exercise laboratory using cycle ergometers and treadmills (Table 2) (Martin et al. 2009).

Table 2. Physical training studies concerning on menopausal symptoms and quality of life among women during menopause.

	METHODS	INTERVENTION	OUTCOMES	RESULTS
Daley et al. 2015 Peri- and postmeno-pausal women, n=261, aged 48-57 years	RCT; 2 exercise groups and control group	Two exercise groups: Exercise-DVD inter-vention (two exercise consultations plus leaflets & DVD) and Exercise-social support intervention (Exercise consultations and support groups) and Control group	Frequency of hot flushes/night sweats at 6-month and 12-month follow-up	Neither of the exercise groups resulted in significantly fewer hot flushes / night sweats at the 6 -and 12 –month follow-ups.
Sternfeld et al. 2014 Late perimenopausal or postmenopausal, n=355, aged 40-62 years	RCT; exercise and control group	12 weeks; three times/ week exercise on an elliptical trainer, a tread-mill or stationary bicy-cle. First month 50-60% of the heart rate reserve (HRR), next two months 60-70% of HRR	Vasomotor and other menopausal symptoms	12 weeks of modera-te-intensity aerobic exercise did not alleviate vasomotor symptoms. Small improvements in sleep quality, insomnia and depression were found
Aiello et al. 2004 Postmenopausal, n=173, aged 50-75 years	RCT; exercise (tread-mill walking, walking, aerobics, bicycling) vs. control (stretching)	12 months, in the exercise group modera-te-intensity exercise and stretching in control group	The occurence and severity of menopause symptoms	A significant increase in hot flash severity, the numbers affected were small. A decreased risk of memory problems in exercisers vs. controls
Reed et al. 2014 Peri- and postmeno-pausal, N=355, aged 40-62 years	RCT; yoga, exercise and control groups, additionally assigned randomly to a doub-le-blind comparison of omega-3 or placebo	12 weeks; weekly 90 min. yoga classes with daily at-home practice, facility-based aerobic exercise training 3 times/week and ome-ga-3 supplement, 3 times/day	Menopausal quality of life questionnaire (MENQOL), total and four domain scores of vasomotor symptoms (VMS), psychosocial, physical and sexual functioning	12 –week yoga interve-ntion slightly improved menopause-related QoL, exercise and omega-3 supplement had no effect on these measures. Slight benefit for VMS and sexual functioning was found from yoga, and only for the physical domain from the exercise intervention
Martin et al. 2009 Postmenopausal women, n=430, aged 45-75 years	RCT; 2 groups, exercise vs. control	Three exercise groups (50%, 100% and 150% of recommended level of PA/NIH 1996) 3 or 4 training sessions /week for 6 months	Change in quality of life, measured by SF-36	Dose dependent improved physical and mental QoL, except bodily pain

Over the course of throughout the menopause PA and exercise participation have been shown to have positive effects on menopause-related symptoms and health outcomes such as depression, sleep patterns, cognitive functioning, weight maintenance and cardiovascular disease (Daley 2008; Eriksen et al. 2004; Stojanovska et al. 2014; Grindler et al. 2015). In addition, exercise may represent an encouraging and inexpensive alternative to hormone therapy with a few known side effects. (Daley et al. 2014; Stojanovska et al. 2014; Martin et al. 2009). According to The Royal College of Obstetricians and Gynaecologists in the United Kingdom physically active women tend to suffer less from menopausal symptoms and they have been recommended regular aerobic exercise such as swimming and running (RCOG 2006), walking has also been shown to have favourable effects on health among menopausal women (Asikainen et al. 2002). Stojanovska et al. (2014) concluded that although exercise has not been proven to alleviate menopausal symptoms, women who are physically active during the menopausal transition have better overall QoL and they are less stressed.

Contradictory results have been reported regarding the association between exercise and lower level of severe vasomotor symptoms (Daley et al. 2014; Stojanovska et al. 2014). Severe vasomotor symptoms were more common among menopausal women reporting lower levels of regular exercise in a study on a multiracial population of women (Gold 2000). According to Stadberg et al. (2000) a low level of vasomotor symptoms was correlated with regular exercise and leisure time activities. Similar results were reported in a 13-year follow-up study, where shorter symptom duration was related to exercise participation (Col 2009).

Hormone therapy has previously been the mainstay of treatment for vasomotor symptoms, but also other alternatives are needed because of personal preferences or medical contraindications such as cancers dependent on hormones (NAMS 2015). According to the position statement on non-hormonal management of menopause-associated vasomotor symptoms of The North American Menopause Society, exercise, yoga and paced respiration are not recommended for relief of vasomotor symptoms, although there are several health benefits associated with these. Nor are herbal therapies, cooling techniques or avoidance of triggers was recommended, instead of these, cognitive-behavioural therapy is claimed to be effective in alleviating symptoms. Also, non-hormonal pharmacologic therapies such as off-label use of antidepressants, gabapentin or clonidine was recommended in the statement. (NAMS 2015).

3. PURPOSE OF THE STUDY

The aim was to study the relationships between physical activity, health-related quality of life and menopausal symptoms of women in a cross-sectional population-based cohort study and in a randomized controlled training trial with follow-up.

The specific research questions were:

1.   What kinds of relationships are found between physical activity, perceived aerobic fitness and quality of life among Finnish women aged 49 years? (Study I)

2.   What are the effects of aerobic training on sleep quality among menopausal women with daily hot flushes? (Study II)

3.   What are the long-term consequences of a physical exercise intervention on quality of life and hot flushes? (Studies III, IV)

4. MATERIAL AND METHODS

4.1. Study design

This doctoral thesis and the related original publications are based on a cohort study from a population-based breast cancer screening programme, the RCT study (ISRCTN54690027) and the follow-up. In Study I the cohort study was used to to investigate the association between engagement in the recommended level of physical activity and quality of life among middle-aged women. The RCT aimed to investigate whether exercise training improves sleep quality or reduces the number of night time hot flushes among menopausal women with vasomotor symptoms, Study II. The follow-up study explored the long-term effects of exercise training on health-related quality of life, Study III, and hot flushes, Study IV, four years after the beginning of the trial (Figure 3).

Study I Finnish Cancer Registry cohort study n= 2606	Study II Randomized trial of aerobic training n= 176	Studies III and IV 3.5-year follow-up study after the RCT n=95
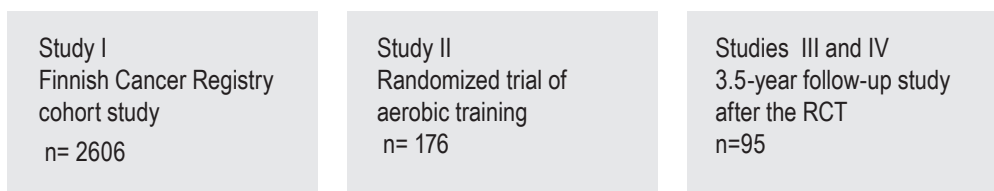
Figure 3. Scheme of the subjects in Studies I, II, III and IV

4.2. Participant recruitment

4.2.1. Participants for the cohort study and recruitment for the RCT and for the follow-up

The participants for the Study I were randomly drawn from the Finnish Population Register Centre in 2012. The existing data was collated with the Finnish Cancer Registry, Helsinki and the UKK Institute for Health Promotion Research, Tampere. The participants were sent a postal questionnaire along with an informed consent form, one year before their first invitation to mammography screening. A random sample of 5,000 women aged 49 was obtained. After two reminders altogether 52% of the study population (n=2606) returned completed questionnaires and

written informed consent forms (Figure 4).

Participants in the survey responded to questions about menopausal status and nearly a fourth of the participants (23%) had had no menstruation for 12 months and thus were postmenopausal, 31% of women were perimenopausal with irregular menstruation. A third of the respondents (28%) were premenopausal with regular menstruation and 18% of participants were on hormone therapy.

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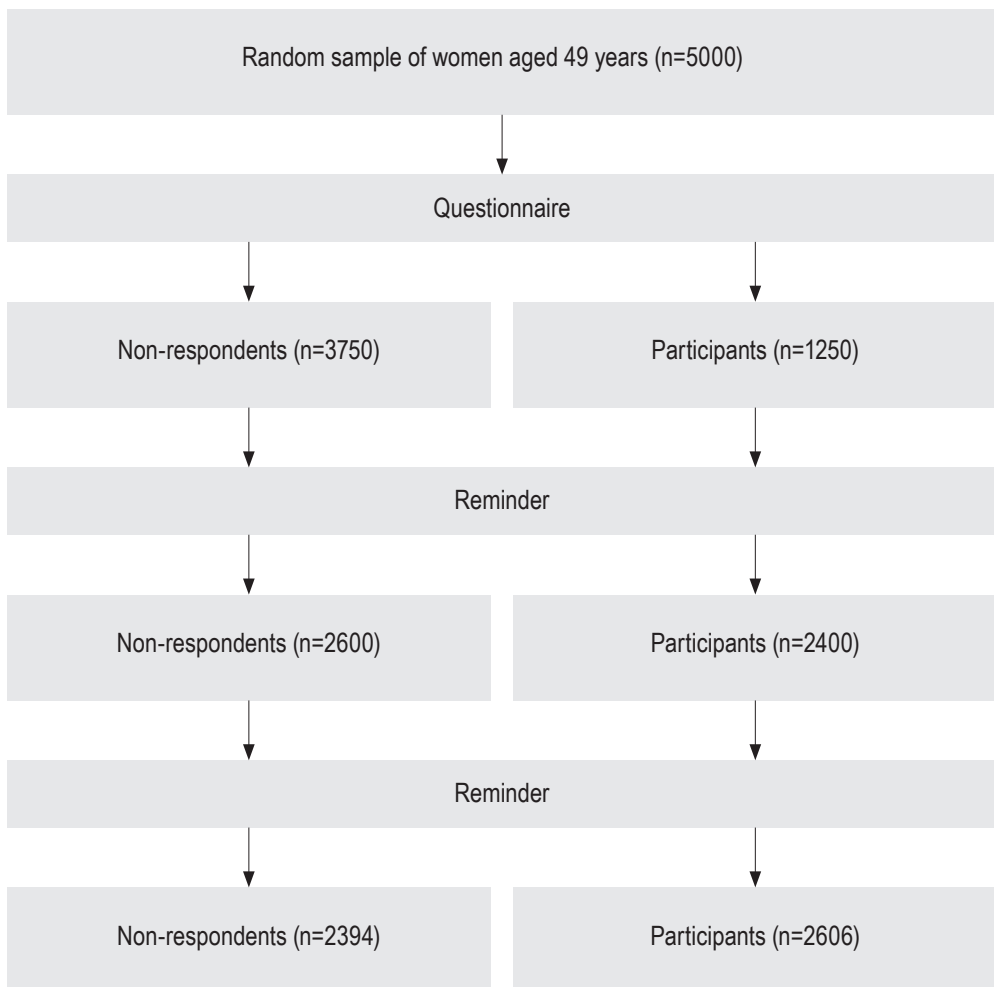
Figure 4. Data collection in Study I.

Participants for the RCT (Study II) were recruited through advertisements in the local newspaper in the southern Finnish region of Pirkanmaa area in early 2009. Women who were interested in participating were screened for eligibility through a telephone interview conducted by research nurses.

According to the inclusion criteria participants had to be menopause symptomatic i.e. daily hot flushes, and 6-36 months since last menstruation. Other inclusion criteria were 40-63 years of age, no current use of hormone therapy (HT) or use in the past three months, and physically inactive, exercising less than twice a week for at least 30 minutes each time. Women were excluded if they took regular exercise more than twice a week, or if their body mass index (BMI) was over 35 kg/m², if they had coronary heart disease or orthopaedic or other diseases preventing them from taking exercise. A further reason for exclusion was medication influencing heart rate (β-blockers, sympathomimetics) since these would have biased aerobic fitness testing results based on heart rate. If women were eligible according to the telephone interview, they received more information about the study by post. In total 351 women were interested in participating in the study, 176 women were included and 175 were excluded since they did not meet the inclusion criteria (Figure 5).

For the first follow-up study 2.5 years after the beginning of the intervention, the participants received a postal questionnaire eliciting among other things work ability (Rutanen et al. 2014) and quality of life according to the WHQ questionnaire with nine domains of physical and emotional experiences (Hunter 2000). The follow-up questionnaire was sent to all randomized participants, N=176 and 102 of these responded.

The second follow-up was four years after the beginning of the trial (Studies III and IV). Ninety-five out 176 women participated. The women were invited to attend assessments which included the UKK Walk Test, weight and waist circumference measurements and the SF-36 Health Survey questionnaire. Twelve of the participants declined to take the UKK Walk Test, however, they participated in other measurements and completed the questionnaire (Figure 5).
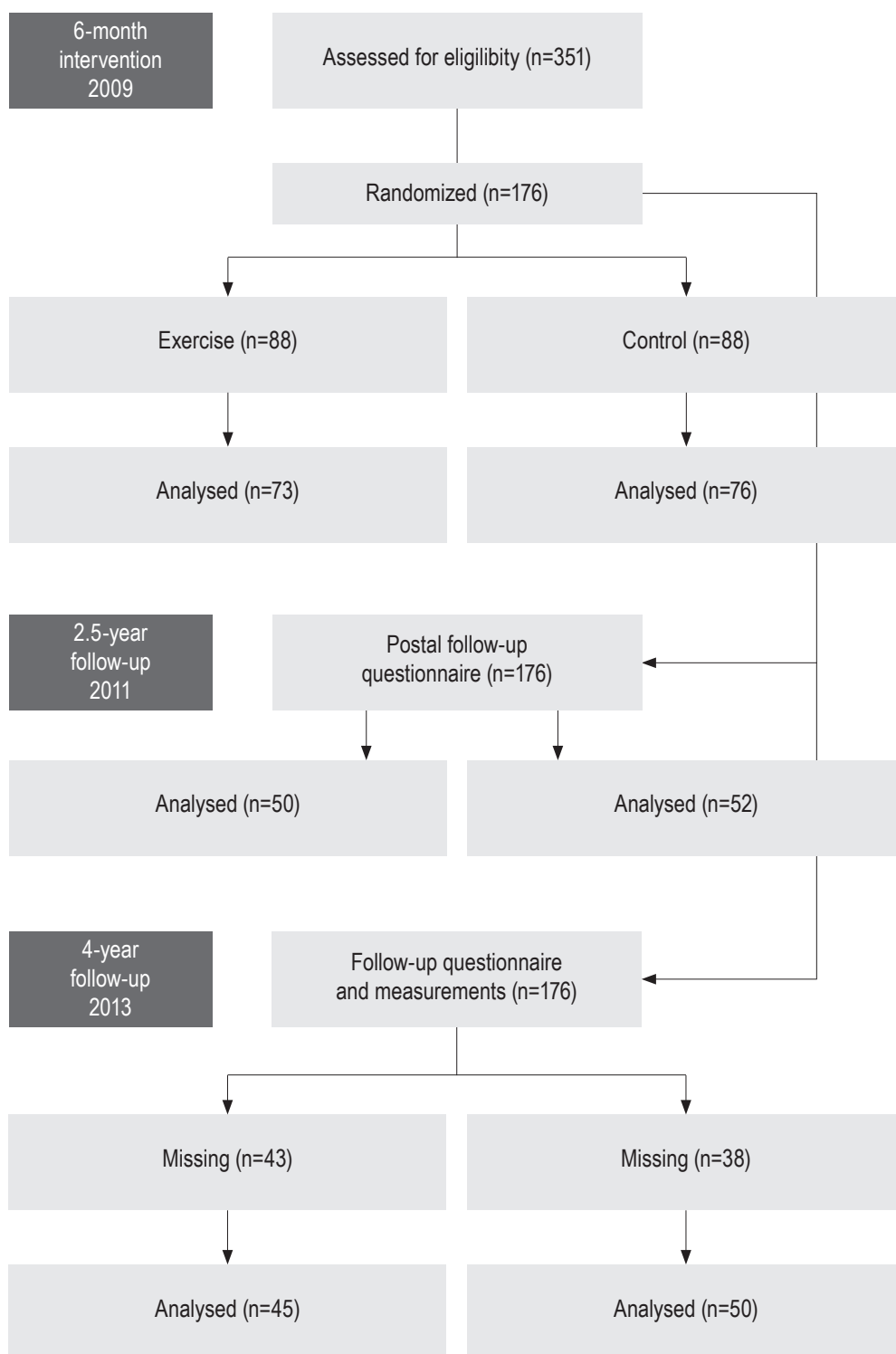
Figure 5. Flow-chart of Studies II-IV.

4.3.Exercise intervention

In the RCT eligible women (n=176) were assigned to an exercise group (EX) and a control group (CON) by computer randomization. Research nurses provided participants with sealed envelopes containing information on the assigned group to participants. The intervention lasted for six months and 149 women continued until the end of the intervention.

The aerobic exercise training programme was unsupervised and included 50 minutes of training four times per week in the 6-month training intervention (Study II). The intensity of training was ensured by using the ratings of perceived exertion (RPE) (Borg 1970) and women in the exercise group were instructed to exercise at a level which corresponded to 13-16 on a scale from 6 to 20; this level corresponds to about 60%-84% of maximal heart rate (Howley 2001). The instruction was given in small groups and participants were advised to keep their eating habits unchanged. The training programme was planned to include at least two sessions of walking or Nordic walking, and the other two sessions could include jogging, cycling, swimming, skiing, aerobics or other gymnastic exercise. The intervention mainly consisted of walking, because earlier trials have shown favourable results on health among menopausal and post-menopausal women (Kukkonen-Harjula et al. 2007). In addition, women had an option to participate in instructed aerobics or step aerobics sessions twice a week. The control group participants were advised to keep their exercise and eating habits unchanged.

The women in the exercise group wore Suunto® heart rate monitor belts (Suunto®; memory belt, Suunto, Vantaa, Finland) during training sessions. Every second week the women received feedback from a training supervisor concerning the training sessions. Data collected from the heart rate belts were transferred to a computer and analysed with the software program, Firstbeat Technologies HEALTH (Firstbeat Health®, Finland). Participants were also instructed to report their training workouts by mobile phone. Both the phone-based exercise training diary and the heart rate monitor belt formed as a basis for the frequency and intensity of exercise taken in training sessions. The mobile phone application was commercial, Symbian-based, and was downloaded onto the participants' own mobile phones. Phones was offered to participants if their own mobile phones did not have the necessary features. All participants were introduced and trained to use the program installed on their mobile phones. The research project covered all the costs of the use of the mobile phone diary. All data from the mobile phone diaries were automatically transferred via Internet into digital format to a server of the service provider.

In addition, both the exercise and the control groups attended lectures once or twice a month during the 6-month intervention. The themes of the lectures included

physical activity and general health. The principal investigator of the study was the lecturer and each meetings lasted about 60-75 minutes.

4.4.   Study outcomes and data collection

The primary outcomes of this thesis were quality of life measured with the Women's Health Questionnaire and hot flushes reported by phone-based and paper-based diaries among women going through the menopause. Secondary outcomes to be reported in the thesis are health-related quality of measured with the SF-36, and sleep disturbing hot flushes and sleep quality.

All measurements were done in the cohort study, at baseline in the RCT, then 6-months (the end-point of the intervention), 2.5 years and 4 years after the beginning of the intervention.

4.4.1.   Baseline questionnaire, anthropometry and body composition

All study participants (Studies I-IV) completed a questionnaire which elicited information on age, education, employment, smoking and PA. The options for level of education were primary, secondary (i.e. completed secondary school or vocational school), and higher (i.e. bachelor's or master's degree) education. The occupation and type of work was elicited with the question; what was your most recent position at work? The variable was classified into two classes. The lower class, blue-collar, were included farmers, employees with vocational education and employees with only basic compulsory education. The upper class, white-collar, included entrepreneurs, women in managerial positions, and upper and lower public officials. In addition, the employment status was elicited, namely whether the participants were employed, unemployed, studying or retired. Smoking habits and the amount of physical activity was included in the questionnaire (Study I).

The survey participants were instructed to measure their waist circumference at the navel height. BMI was calculated from self-reported height and weight. In the RCT and 4-year follow-up (Studies II and IV) height and weight were measured in light clothing and without shoes. BMI was calculated as the ratio of weight to height squared. In addition, in the RCT body composition was assessed by dual X-ray absorptiometry (DXA) to quantify fat and lean mass.

4.4.2. Physical activity

Physical activity was elicited (Study I) with the question "How much do you exercise in a typical week?" (Borodulin et al. 2016). The women were asked to consider the previous 12 months and include any regular physical exercise taken weekly for at least 10 min at a time, with frequency expressed in days per week, total hours and minutes per week. The question included five sub-categories: 1) slow-paced and easy aerobic exercise, and 2) moderately fast aerobic exercise, and 3) strenuous aerobic exercise, 4) strength training, and 5) balance training. It was not possible to differentiate different types of aerobic exercise. The question had five response options from "no regular exercise" up to "strenuous aerobic exercise" (heavy sweating and/or accelerated breathing, as in jogging or running). In addition, the women reported the amount of strength training and balance training they had performed in a typical week during the last 12 months.

In Study I, total amount of PA was graded into one of two categories according to the UKK Institute's physical - activity recommendations for health and fitness (Fogelholm et al. 2005, DHHS 2008). Women were classified as active when they met the criterion of the recommended level of PA by being active on several days a week with, in total, at least 2 h 30 min of moderate-intensity physical activity or 1 h 15 min of vigorous activity. In addition, they had muscle-strengthening and balance training at least twice a week, whereas women reporting with less physical activity were considered inactive.

In the RCT cardiorespiratory (aerobic) fitness (CRF) was measured by the UKK Walk Test before and after training and in the 4-year follow-up study. The UKK Walk Test is a reliable method for 20 to 65-year-old adults who have no illnesses or disabilities that limit brisk walking and, in addition, who are not on medication affecting heart rate (Oja et al. 1991). Heart rate was monitored during the walk test and registered immediately at the end of the test (M61, Polar Electro, Oulu, Finland). Maximal oxygen consumption was estimated by a formula on a gender-specific model including walking time, heart rate at the end of the test, age and BMI (Oja et al. 1991). The UKK Walk Test was done twice at baseline before training, once for habituation and the latter test was used in the analyses.

At 4-year follow-up study the amount of physical activity was evaluated objectively with the Hookie® accelerometer (Traxmeet Ltd, Espoo, Finland). The accelerometer was attached to a flexible belt and participants were instructed to wear the belt around their waists for seven consecutive days during waking hours, except in the shower and when otherwise in water. The accelerometers collected and stored tri-axial data in raw mode in actual g-units. The data was analysed in six seconds' epoch length. PA was categorized into three intensity categories according to the metabolic equivalents

(MET): light, moderate and vigorous. Light PA was defined as activity corresponding 1.5–2.9 MET, moderate activity as 3.0–5.9 MET and vigorous activity more than 6 MET (Matthews et al. 2012).

4.4.3. Quality of life

The shorter version of the WHQ questionnaire was used in the survey (Study I). It consists of seven domains of quality of life: anxiety/depressed mood, well-being issues, somatic symptoms, memory/concentration problems, vasomotor symptoms and sleep problems (Hunter 2003; Girod et al. 2006). Global quality of life assessment was done with the VAS (visual analogue scale) using respondents' subjective evaluations of their own quality of life during the last month, 0 meaning the worst possible and 10 the best possible QoL (Hwang et al. 2002). Self-perceived health was elicited with two questions (Study I) using a five-point scale with the options "very good", "good", "average", "poor" and "very poor" and a three-point scale with the options in respondents' estimation "better than", "worse than" or "similar to" that of women of the same age (Zöllner et al. 2005).

The RCT (Study II) used the longer version of the WHQ questionnaire with nine domains of physical and emotional experiences (Hunter 2000). In the WHQ questionnaire participants noted self-reported symptoms on a four-point scale describing frequency: "Yes, definitely"; "yes, sometimes"; "No, not much"; "No, not at all" (Hunter 2003). The test-retest reliability of the WHQ questionnaire has been evaluated at two-week intervals. Correlations were above 0.75, ranging from 0.96 to 0.78. Additionally, the questionnaire has been validated in the Finnish language. (Hunter 2003, Zöllner et al. 2005).

The SF-36 Health Survey Questionnaire was used as an instrument to measure health-related quality of life in the 4-year follow-up study (Study III). The questionnaire has been validated in Finland (Aalto et al. 1995) and is known to be reliable for measuring QoL. The SF-36 questionnaire consists of eight domains of quality of life: physical functioning, physical role limitations, bodily pain, general health, vitality, social functioning, emotional role limitations and mental health. The scores for each of the eight domains range from 0 (maximal impairment) to 100 (no impairment, best possible quality of life).

4.4.4. Menopausal symptoms

In the RCT the participating women kept a 2-week diary concerning day-time and night-time hot flushes before beginning the exercise training. A hot flush was defined

as a sensation of warmth, with or without concomitant sweating. The aim of the diary was to obtain an estimate of the overall number of hot flushes before the intervention. In addition, before the trial the concentration of plasma follicle-stimulating hormone (FSH) was analysed to verify menopausal status, FSH had to be >30 IU/L. Both day-time and night-time frequency of hot flushes was reported during the intervention.

During the intervention (RCT) participants responded twice a day to a mobile phone questionnaire about menopausal symptoms. The phone was used to collect information on day-time and night-time hot flushes (Study II). Participants answered pre-specified questions on hot flushes, sleep and other symptoms. In the morning the women answered five questions on hot flushes (yes/no), one question on night sweating (yes/no), and two questions on sleep quality (yes/no). The mobile phone questionnaire appears in the Appendix I.

In the evening the women answered the same questions as in the morning (sleep was not included), with additional questions (yes/no) about experiencing headache, mood swings, dysphoria, depression, vaginal dryness and urinary and other symptoms. Since mobile-phone data collection has not been used earlier, the symptom diary method was evaluated with the System Usability Scale, SUS (Brooke 1996) immediately after the intervention. Most of the participants responded to the questionnaire (response rate 72.7%) and the score on the usability questionnaire was 75.4 (range 0-100). According to the usability questionnaire, this is a feasible and usable tool for data collection in an exercise training study (Heinonen et al. 2012).

In Study IV a one-week diary was completed the extent of daytime and night-time hot flushes and their severity (mild, moderate, severe). Data on the hot flushes and their severity was available from 56 women (n=56) at three time-points, baseline and 2.5 years and 4 years. The analyses in Study IV were based on data from these three time-points. Based on a hot flush diary HFScore was defined as frequency of 24-h hot flushes multiplied by average severity (Sloan et al. 2001). The multiple of mild hot flushes was one, that of moderate hot flushes two, that of severe hot flushes three, and the total sum was defined as HFScore. HFScore was divided into three classes and the rationale for that was based on the finding that 30% of the participants in our study had HFScore <13 points, 40% of women had a score <22 points and 50% <35 points when all three-time point measurements (baseline, 2.5- and 4-year) where taken into account.

4.5.   Ethical considerations and funding

The survey, a population-based breast-cancer screening programme, from the Finnish Population Register Centre was granted ethical approval from the ethics

committee of the Hospital District of Helsinki and Uusimaa. The original randomized controlled trial was registered with the number: ISRCTN54690027 (http://www.controlled-trials.com). The trial and the 4-year follow-up study were granted ethical approval by the Pirkanmaa Hospital District Ethics Committee.

4.6.   Statistical analyses

Characteristics of the participants in Studies I, II, III and IV were outlined by means, standard errors of means (SEMs), frequencies and proportions. In Study I the association between WHQ domains or three life-quality variables (dependent variable) and physical activity (independent variable) was analysed by ordered logistic regression models. Models were adjusted for BMI and education. Ordered logistic regression is used when the dependent variable is ordered and the cell count is adequate. Because of the sparseness of our data it was not possible to use the original scale, thus the WHQ variables were categorized into 5-9 categories and the quality of life variables into 4-6 categories. The categorization was based on the frequency distributions for the above-mentioned variables. The assumption of proportional odds (i.e. that the regression coefficients are constant across the various levels of the dependent variable) was also tested for all models using the test of parallel lines. In ordered logistic regression the results are expressed as proportional odds ratios (PORs) and 95% confidence intervals (CIs). Each POR may be interpreted as the effect of the variable on the odds of a higher-category outcome for WHQ and life-quality variables, higher being better.

In Study II differences between groups were tested with Student's t-test for continuous variables when they were normally distributed. Chi-square test was used for dichotomized variables. In the mobile phone questionnaire data, correlation was expected between repeated responses recorded by the same individual. For that reason, multilevel logistic and ordinal regression models were constructed to analyse the effects of aerobic training on sleep quality and menopause symptoms. The multi-level regression model allows for a difference between the groups at baseline, linear changes in responses over time and the difference in the rate of improvement between groups. Interaction between group and time can be viewed as the intervention effect. The number of mobile phone responses varied for each respondent, and therefore the average numbers of responses by respondents were calculated and

used in the descriptive analysis of the data. Thus not only respondents who answered every time, but also respondents with missing responses contributed to the data. Data was not complete for all respondents, but applying maximum likelihood estimation for incomplete data allows all information to be used.

In the follow-up Study III multilevel mixed-effects logistic regression models were constructed to account for the within-subject correlation between four time points i.e. baseline, 6 months, 2.5 and 4 years after the beginning of the trial. The odds model was used for the analysis of the association between the outcomes both on the physical dimensions and on the psychological dimensions over time and those belonging to the exercise vs. the control group. The distributions of SF-36 variables were skewed or discrete, thus multilevel linear regression models could not be used. In addition, because the conditions necessary for the use of multilevel ordinal logistic regression models were not met, these models could not be used, either. The multilevel logistic regression model for dichotomous outcome allows for a difference between groups at baseline, and linear changes in the log odds of outcome over time with slopes in the control group and in the exercise group. Therefore the difference in the rate of improvement (on the log odds scale) between the groups can be viewed as changing over time between groups (Rabe-Hesketh et al. 2008). In addition, second- and third-order functions of time were included in the model to test whether a model with a non-linear effect improved the fit. In Study IV differences between the groups were assessed using t-test for normally distributed continuous variables and Mann-Whitney-test with non-normally distributed variables, and with categorical variables Chi-square-test was used. A multilevel mixed-effects logistic regression model was used for the analysis of the HFScore over time and between groups. This model was constructed for within-participant correlation between three time points, baseline, 2.5 and 4 years from the beginning of the trial. The multilevel logistic regression model for dichotomous outcome was identical with the Study III analysis. The estimates of the parameter were presented as odds ratios (ORs) with 95% confidence intervals (CIs). HFScore were divided into three variables, HFScore <13, <22 and <35 points. These variables were not classified according to subjective experiences of bothersome hot flushes; only the total HFScore points were taken into account. HT and sleep quality were used as covariates in the model.

5.   RESULTS

5.1.   Participants' characteristics

In the dissertation as a whole participants' ages ranged from 49 to 58 years. The survey respondents were 49 years of age and participants in the RCT were at baseline at the mean age of 54 years and in the 4-year follow-up study on average 58 years of age. Regarding educational background, nearly one third of the women (28%) in the survey had higher education, half of the women (52%) were white-collar workers and most of the respondents were employed (84%). A quarter of the women (26%) who participated in the RCT and in the follow-up study had university degrees. During the RCT the participants were mostly employed (85% EX vs. 78% CON) and at 4-year follow-up employed or part-time workers (71% EX vs. 78% CON).

In the survey, according to self-reported weight and height results, half of the women had BMI <25 kg/m² and waist circumference less than 88 cm. Participants in the RCT were slightly overweight with mean a BMI of 26 kg/m² in the exercise group and 27 kg/m² in the control group. At the beginning of the trial no significant differences between the groups were found in baseline characteristics. At 4-year follow-up, among women who had measured HFScore (n=56), the situation concerning mean BMI was unchanged with BMI 26 kg/m² in EX and BMI 27 kg/m² in CON and the mean values in waist circumference varied from 86 cm in EX to 90 cm in CON (Table 3). A small proportion of women (17%) in the exercise group and (12%) in the control group were smokers or occasional smokers at the beginning of the RCT.

As to use of medicines, no differences between groups were observed in use of medications against hypercholesterolaemia or hypertension at 4-year follow-up. The use of headache medicines and other analgesics, sedatives and hypnotics and antidepressants had decreased in both the exercise group (from n=43 to n=14) and in the control group (from n=33 to n=14). Use of vitamins and mineral preparations had decreased in the exercise group (n=43 to n=31) and in the control group (n=42 to n=17) from baseline to 4-year follow-up respectively. The current users of hormone therapy were 14 women (31%) in the exercise group and eight (16%) in the control group.

Table 3. Participants' characteristics in the cohort study, RCT and the 4-year follow-up study (means, SD and percentages).

	Survey	RCT, baseline		4-year follow-up	
	(n=2606)	EX (n=83)	CON(n=86)	EX (n=28)	EX (n=28)
Age, (y)	49	54.2 (3.7)	53.9 (3.8)	58 (0.7)	57.8(0.7)
BMI, (kg/m^2)		26 (3.8)	27 (4.5)	26 (0.7)	27 (1.0)
N(%) < 25	1265 (49)				
N(%) 25-29.9	784 (31)				
N(%) ≥ 30	523 (20)				
Waist circumference cm		86 (2.6)	88 (2.7)	86 (2.5)	90 (2.9)
N(%) < 88 cm	1209 (50)				
N(%) ≥ 88 cm	1211 (50)				
Education, (%)					
higher	27.9	25.9	24.7	25.9	24.7
secondary	37.8				
basic compulsory	34.3				
Employed, (%)	84	85	78	71	78
Use of medicine in the past 7 days					
Hypercholesterolaemia or hypertension, N (%)	-	16 (21)	12 (15)	10 (22)	11 (22)
Headache medicines and other analgesics, N (%)	-	43 (55)	33 (41)	14 (31)	14 (28)
Vitamins and mineral preparations, N (%)	-	43 (55)	42 (52)	31 (69)	17 (34)
Hormone therapy, N (%)	18 (0.7)	2 (2.6)	1 (2.8)	14 (31)	8 (16)

5.2.   Physical activity in the cohort-study and in the follow-up study

Half of the respondents (51%) in the survey met the recommendation in the physical activity guidelines (Fogelholm et al. 2005, DHHS 2008) on aerobic training, muscle-strength and balance training, thus they were defined as physically active. The proportion of women who fulfilled the recommendation for both types of PA was 14%, and that for only one type was 37%.

The UKK 2-km Walk Test was also taken at 4-year follow-up. No differences between groups were found in walking time (16.6 min EX vs. 17.2 min CON) or estimated VO_2max ml/kg/min (32.1 EX vs. 30.6 CON) at 4-year follow-up (Table 4). Additionally, when comparing the between-group differences in changes from 6-month exercise intervention to 4-year follow-up (n=56), estimated VO_2max had decreased more on EX group. However, the difference was not statistically significant (p=0.13).

The amount of physical activity was measured at follow-up with the Hookie® accelerometer. The participants were instructed to wear the belt with the accelerometer for seven consecutive days and during waking hours, except when in the shower of otherwise in water. One-week measurement revealed no differences between exercise and control group in proportions (%) of lying down/sitting (58.2 EX vs. 56.8 CON), standing/light exercise (32.7 EX vs. 34.2 CON) or brisk/strenuous exercise (9.1 EX vs. 9.0 CON) (Table 4).

Table 4. Walking time, VO$_2$max and amount of physical activity measured by accelerometer of participants with Hot Flush Score at three time-points at 4 -year follow-up in the exercise (n=28) and control group (n=28) (mean and SEM or frequency and percentage).

	Exercise (EX)	Control (CON)	p
N	28	28	
Walking time (min)	16.6 (0.23)	17.2 (0.3)	0.10[2]
VO$_2$Max (ml/kg/min), estimated*	32.1 (1.0)	30.6 (1.2)	0.33[1]
Physical activity (accelerometer)			
Lying down and sitting (%)**	58.2 (1.6)	56.8 (1.6)	0.55[1]
Standing and light exercise (%)**	32.7 (1.6)	34.2 (1.4)	0.48[1]
Brisk and strenuous exercise (%)**	9.1 (0.5)	9.0 (0.9)	0.47[2]

*Oxygen consumption ml/kg/min
** proportion (% of time) of one-week measurement

[1] T-test
[2] Mann-Whitney test

5.3.   Effects of physical activity on quality of life (Studies I and III)

Table 5 shows the association between quality of life (WHQ) domains and the recommended level of PA. Women in the survey who did not meet the recommendation in the PA guidelines (inactive) in the non-adjusted models had greater probability for WHQ-variables anxiety/depressed mood (POR 1.44; 95% CI 1.26–1.65), poorer well-being (POR 1.96; 95% CI 1.71–2.25), somatic symptoms (POR 1.61; 95% CI 1.40–1.85), memory/concentration problems (POR 1.48; 95% CI 1.29–1.70), and vasomotor symptoms (POR 1.19; 95% CI 1.03–1.36) than the physically active women. For example, the odds for the combination of categories representing higher levels of vasomotor symptoms were 1.19 times higher for the active than for the inactive women when other variables (education and BMI) were held constant in the model. The associations remained significant in the adjusted model on all dimensions except vasomotor symptoms, sleep problems and sexual behavior (Table 5).

Table 5: Proportional odds ratios (PORs) with 95% confidence intervals (CIs) and p-values for seven aspects of WHQ (The Women's Health Questionnaire) as a function of physical activity. Each POR may be interpreted as the effect of the variable on the odds of a higher-category (i.e. better) outcome for the WHQ variables.

Component of QoL	Unadjusted model, active vs. inactive			Adjusted for education and BMI, active vs. inactive		
	N	POR (95% CI)	p	N	POR (95% CI)	p
Anxiety / depressed mood	2,588	1.44 (1.26–1.65)	<0.001	2,547	1.31 (1.14–1.51)	<0.001
Well-being	2,584	1.96 (1.71–2.25)	<0.001	2,543	1.64 (1.42–1.89)	<0.001
Somatic symptoms	2,584	1.61 (1.40–1.85)	<0.001	2,544	1.39 (1.21–1.61)	<0.001
Memory/ concentration	2,586	1.48 (1.29–1.70)	<0.001	2,544	1.29 (1.12–1.49)	<0.001
Vasomotor symptoms	2,568	1.19 (1.03–1.36)	0.015	2,527	1.12 (0.97–1.29)	0.13
Sleep problems	2,573	1.11 (0.97–1.28)	0.13	2,533	1.04 (0.90–1.20)	0.58
Sexual behaviour	2,130	1.13 (0.98–1.32)	0.099	2,095	1.10 (0.94–1.29)	0.22

Women with the recommended level of physical activity had better self-perceived health (POR 3.22; 95% CI 2.76–3.74), relative health (POR 3.42; 95% CI 2.91–4.02), and global quality of life (POR 1.91; 95% CI 1.65–2.20) than other women of their age (Table 6).

Table 6: Proportional odds ratios (PORs) with 95% confidence intervals (CIs) and p-values for self- perceived health, relative health and global quality of life as a function of physical activity. Each POR may be interpreted as the effect of the variable on the odds of the subject showing a higher category for the output related to quality of life variables, with higher categories being better.

Quality of life variables	Unadjusted model, ref. inactive			Adjusted for education and BMI, ref. inactive		
	N	POR (95% CI)	p	N	POR (95% CI)	p
Self-perceived health*	2,583	3.22 (2.76–3.74)	<0.001	2,550	2.56 (2.19–3.00)	<0.001
Relative health**	2,577	3.42 (2.91–4.02)	<0.001	2,544	2.60 (2.19–3.07)	<0.001
Global quality of life (VAS)***	2,546	1.91 (1.65–2.20)	<0.001	2,514	1.63 (1.40–1.89)	<0.001

* Four categories were used for the variable: 1 = very poor / poor, 2 = average, 3 = good, 4 = very good.
** 1 = worse than, 2 = similar to, 3 = better than women of the same age.
*** Because of the small number of observations, 6 categories of the original 10 were used for the variable categories: 1 = 1–4, 2 = 5–6, 3 = 7, 4 = 8, 5 = 9, 6 = 10.

At 4-year follow-up in the analyses of QoL results from baseline, the end of the intervention, 2.5-year and 4-year follow-up questionnaires were included. The results show that women in the exercise group had a greater likelihood of improvement on the various QoL dimensions from baseline to the end of 4-year follow-up. Overall, women in the exercise group sustained their improved QoL more often than did women in the control group. Figures 6 and 7 present the proportions observed for the physical and mental dimensions of QoL.
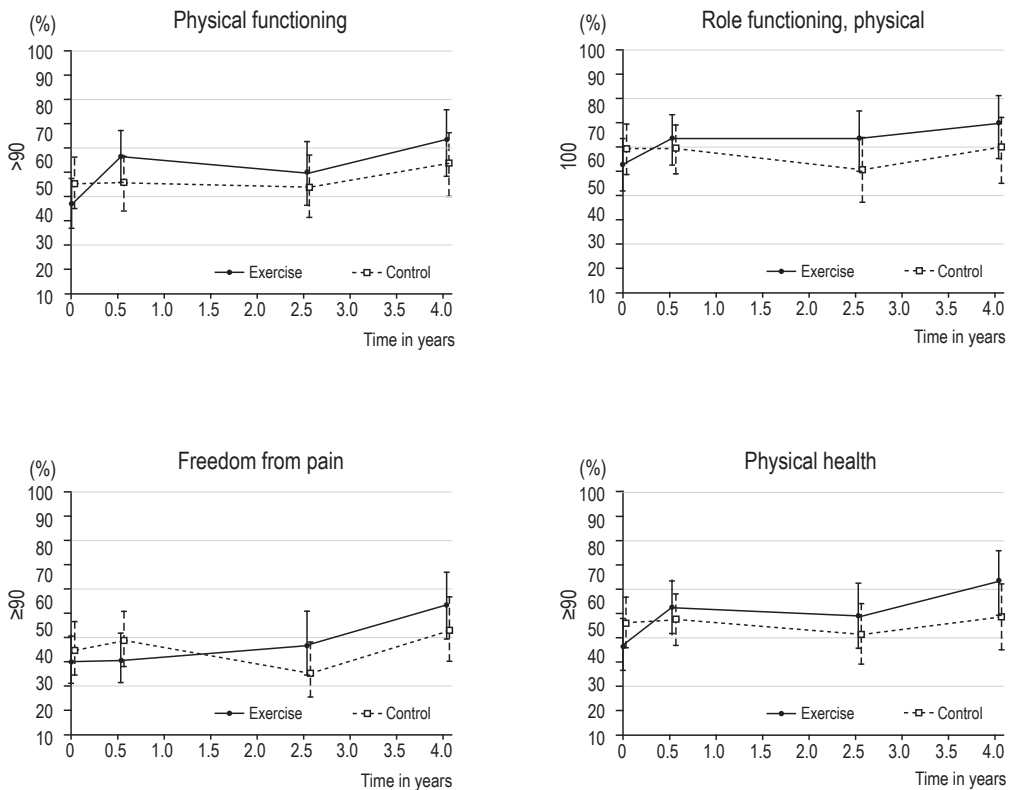
Figure 6. Proportions for the 4 physical dimensions of QoL over time in the exercise and control groups with 95%CI. The outcomes of QoL dimensions were classified into two categories according to medians. The proportions of women scoring higher than or equal to the median are shown. Higher score (>90%) of QoL refers to a more favourable state of health measured with the SF-36 Health Survey Questionnaire.
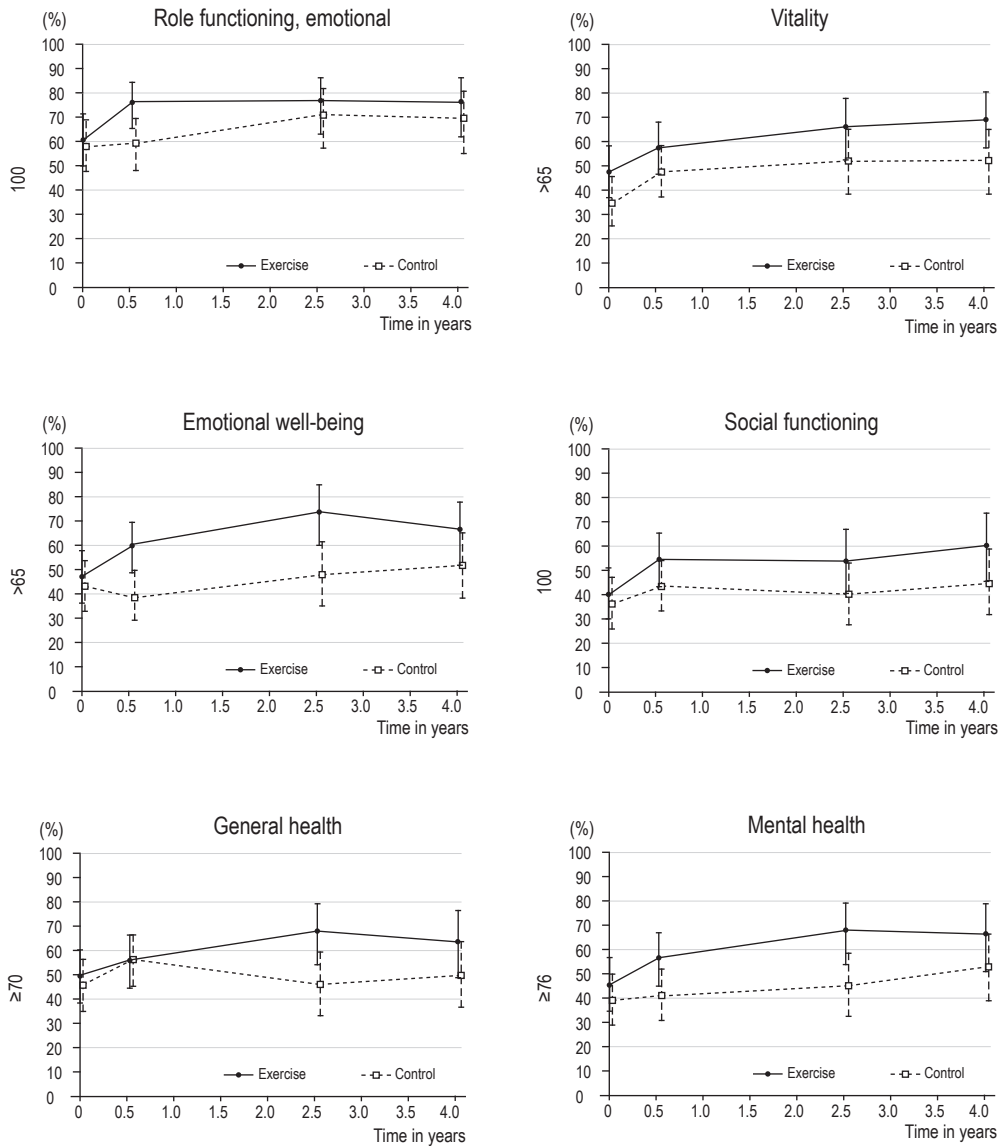
Figure 7. Proportions for the 6 mental dimensions of QoL over time in the exercise and control groups with 95% CI. The outcomes of QoL dimensions were classified into two categories according to medians. The proportions of women scoring higher than or equal to the median are shown. Higher scores indicate a more favourable state of health.

46

In the follow-up measurements at 4-year follow-up, (Study III), women in the exercise group showed an improvement in physical functioning (OR 1.41; 95% CI 1.00–1.99) when compared to the control group. However, no significant differences were observed in the other QoL variables (Table 7). Changes in the mental dimensions of QoL did not reach statistical significance (Table 8).

Table 7: Multilevel mixed-effects logistic regression, odds ratios (ORs) and 95% confidence intervals of physical dimensions of QoL. Women in the exercise group compared to women in the control group at baseline, and 6 months, 2.5 years and 4 years after the beginning of the study as a whole.

	Physical functioning	Role functioning, physical	Freedom from pain	Physical health
N	159	159	159	159
Group baseline	0.52 (0.17–1.61)	0.84 (0.33–2.12)	0.58 (0.22–1.54)	0.72 (0.28–1.81)
Time	1.03 (0.10–11.1)	0.93 (0.75–1.17)	1.07 (0.85–1.34)	0.97 (0.77–1.22)
Group × time	44.7 (1.45–1374)*	1.21 (0.88–1.67)	1.25 (0.90–1.73)	1.33 (0.96–1.84)
$Time^2$	0.86 (0.19–3.82)			
Group × $time^2$	0.11 (0.01–0.91)*			
$Time^3$	1.04 (0.82–1.32)			
Group × $time^3$	1.41 (1.00–1.99)*			

* $p < 0.05$

Table 8: Multilevel mixed-effects logistic regression, odds ratios (ORs) and 95% confidence intervals of the mental dimensions of QoL. Women in the exercise group compared to women in the control group at baseline, and 6 months, 2.5 years and 4 years after the beginning of the study as a whole.

	Role functioning, emotional	Vitality	Emotional well-being	Social functioning	General health	Mental health
N	159	159	159	159	159	159
Group baseline	1.74 (0.72–4.18)	1.93 (0.82–4.57)	2.50 (0.86–7.28)	1.46 (0.60–3.55)	1.04 (0.33–3.25)	1.98 (0.77–5.13)
Time	1.25 (1.00–1.57)*	1.28 (1.03–1.58)*	1.31 (1.03–1.67)*	1.10 (0.89–1.36)	0.98 (0.78–1.24)	1.29 (1.03–1.63)*
Group × time	0.93 (0.67–1.29)	0.97 (0.71–1.33)	1.02 (0.72–1.44)	1.05 (0.77–1.43)	1.14 (0.81–1.62)	0.97 (0.70–1.35)

* $p < 0.05$

5.4. Effects of physical activity on hot flushes, sleep and sleep quality (Studies II and IV)

In the RCT hot flushes interrupting sleep and sleep quality were reported by the mobile phone questionnaire during the intervention. In the mobile phone questionnaire the numbers of responses reporting hot flushes varied from 3.2 to 6.1 per woman (n=149) weekly and the numbers of responses on quality of sleep from 3.2 to 6.2 respectively. The frequency of responses remained at a similar level from week 2 to week 21. At baseline there were neither between-group differences in reporting poor sleep quality (p=0.62) nor in hot flushes related to sleep (p=0.17). Figure 8a shows how after approximately 10 weeks from baseline the women in the exercise group reported fewer hot flushes disturbing sleep than did the women in the control group.

In the exercise group the odds for sleep improvement were 2% per week while in the control group there was a decrease of 0.5% per week during the trial. The differences in improvement in sleep between the groups began to emerge after six weeks (Figure 8b).
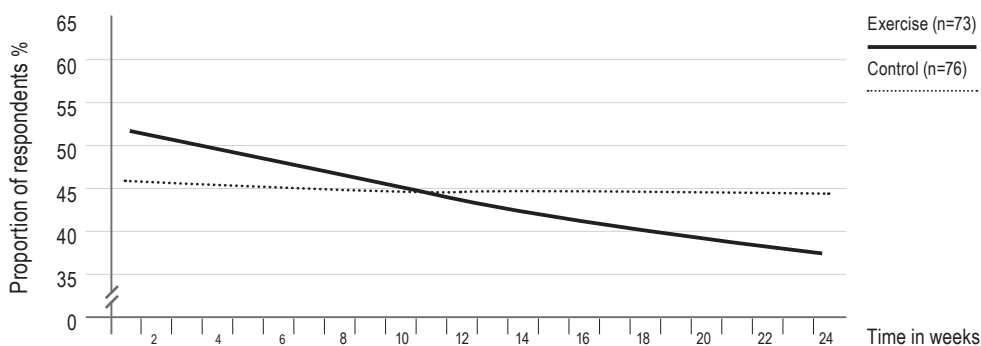
Figure 8a. Estimated proportion of responses with fewer hot flushes disturbing sleep. A multilevel logistic regression model was constructed to analyse the effects of aerobic training on menopause symptoms.
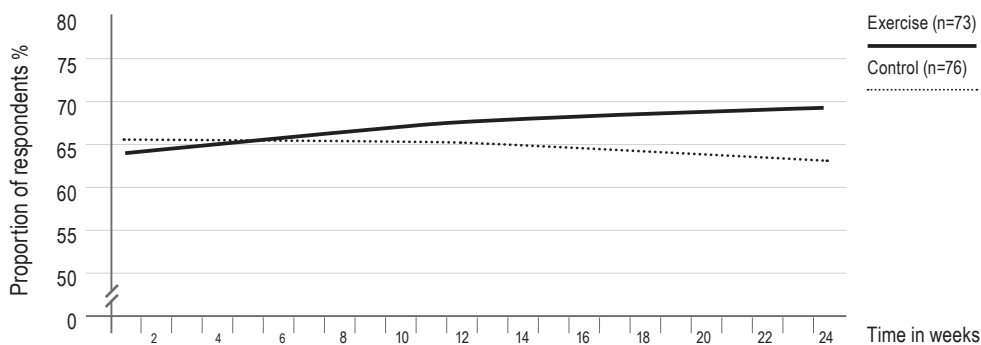
Figure 8b. Estimated proportion of responses with improved sleep quality. A multilevel ordinal regression model was constructed to analyse the effects of aerobic training on sleep quality.
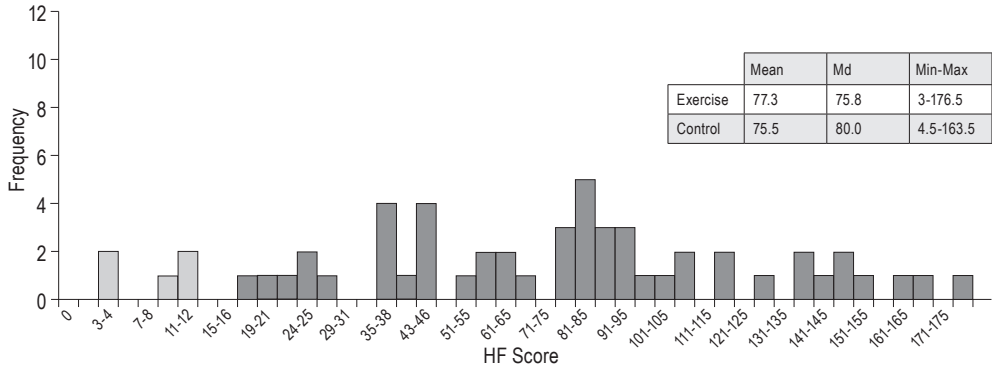
Within 24 weeks the women in the exercise group reported better sleep quality (OR=1.02, 95% CI=1.00-1.05, p=0.043) (Table 9). Hot flushes disturbing sleep decreased significantly more in the exercise group than in the control group (OR=0.96, 95% CI=0.93-0.99, p=0.004) (Table 9). At the end of the intervention it was found that when women had fewer vasomotor symptoms disturbing sleep a better quality of sleep was reported.

Table 9: Multilevel logistic regression (menopause symptoms) and multilevel ordinal regression (sleep quality) odds ratios (OR), 95% confidence intervals (CI) for 24 weeks (18,560-18,575 responses).

	Group		Week		Group x Week	
	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value
Menopause symptoms	1.53 (0.83–2.80)	0.17	0.99 (0.97–1.01)	0.45	0.96 (0.93–0.99)	0.004
Sleep quality	0.89 (0.57–1.40)	0.62	0.99 (0.98–1.01)	0.64	1.02 (1.00–1.05)	0.043

At 4-year follow-up HFScore was observed at three time-points. Figure 9 shows the distribution of HFScores (n=56) of the exercise and control groups at baseline, 2.5-year and 4-year follow-up. Hot flush frequency is multiplied by average severity according to the one-week hot flush diary. Each figure is illustrated with HFScores <13 points and ≥13 points and frequencies of HFScore. At baseline there were no differences in mean values of HFScores between groups, 77.3 points in the exercise group versus 75.5 points in the control group. The mean HFScore at 2.5-year follow-up was 26.9 in the exercise group and 40 in the control group and at the 4-year measurements they were 21.3 and 26 respectively. The columns show the HFScores at different time-points. When observing the HFScore points (EX 21.3, CON 26.0) and frequencies (HFScore=0, Frequency=12) at 4-year follow-up, it is possible to see the natural course among participants by the decreasing number of hot flushes.
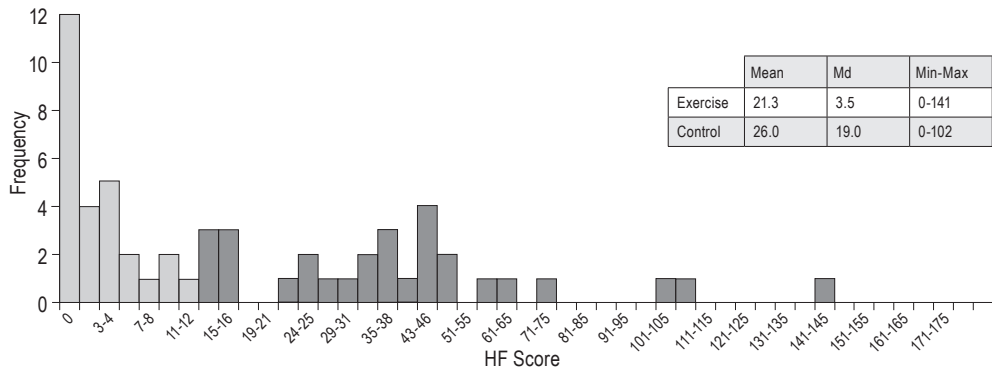
BASELINE

	Mean	Md	Min-Max
Exercise	77.3	75.8	3-176.5
Control	75.5	80.0	4.5-163.5

2.5 -YEARS

	Mean	Md	Min-Max
Exercise	26.9	15.0	0-154.5
Control	40.0	25.0	0-169.5

4 -YEARS

	Mean	Md	Min-Max
Exercise	21.3	3.5	0-141
Control	26.0	19.0	0-102
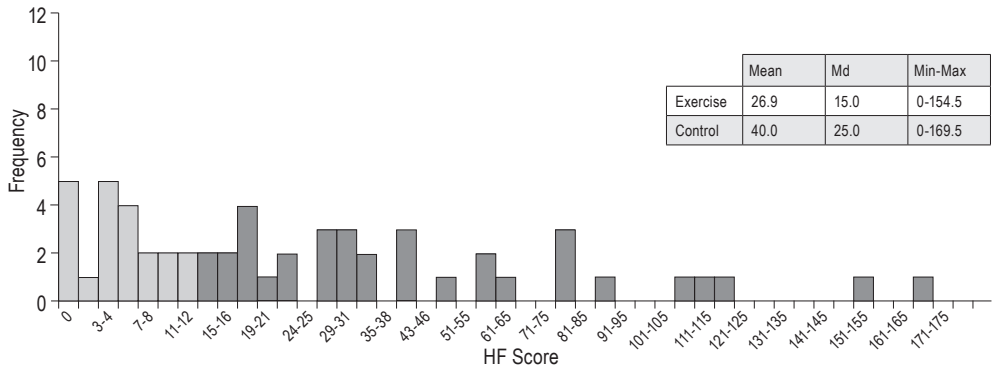
Figure 9. Distribution of HFScore (n=56) frequencies of <13 (light grey columns) and ≥13 (dark grey columns), mean and median in three time points, baseline, and 2.5 -years and 4 -years after the completion of the trial. Frequencies of HFScore appear in the respective colums.

The odds of the HFScore of at least 13 decreased by 7% in the exercise group and by 2% in the control group each month. This estimated difference in the slopes of time between the two groups was significant (p=0.049).

At 4-year follow-up women in the exercise group had a significantly improved HFScore, and there was a decrease in the proportion of women with HFScore of at least 13 points when compared to the women in the control group (Figure 10).
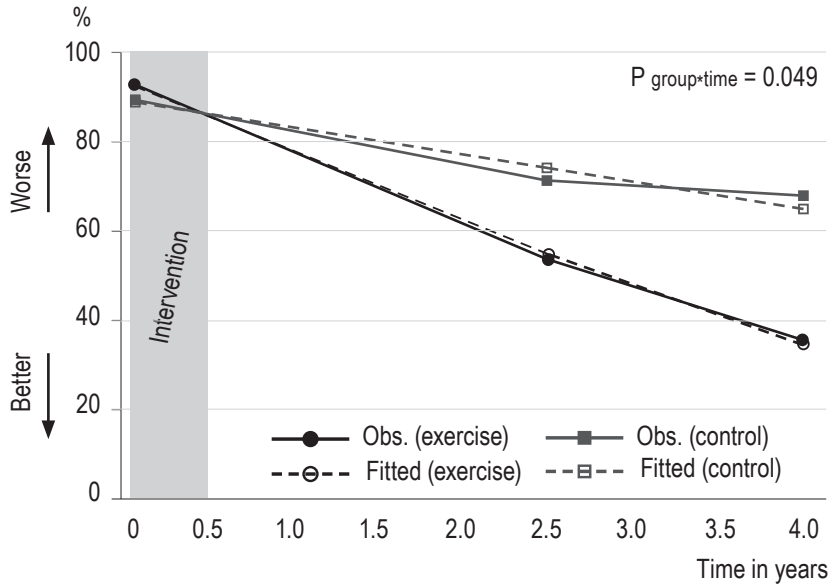
Figure 10. Proportions (%) of women with HFScore of at least 13 (n=56) during the intervention and at follow-ups. Observed probabilities, and fitted probabilities using multilevel mixed-effects logistic regression.

Table 10 shows the estimated odds ratios and their 95% confidence intervals in the three variables of HFScore. In the unadjusted model (Model 1) the estimated difference (interaction Group*time) in the slopes of time between the randomized groups showed an almost significant improvement in HFScore, i.e. a decrease in HFScore points, (OR 0.95; 95% CI 0.89 to 1.00) among participants in the exercise group compared to the control group. In an adjusted (for HT) model (Model 2), the result at HFScore ≥ 13 was borderline (OR 0.95; 95% CI 0.90 to 1.00). After additional adjustment for sleep quality (Model 3) the result showed a tendency to a significant result. At HFScore ≥22 and ≥35 the results did not show a statistically significant improvement.

Table 10. Multilevel mixed-effects logistic regression models of HFScore in unadjusted (Model 1), adjusted for HT (Model 2) and additionally adjusted variable for sleep quality (Model 3).

	Model 1		Model 2 *		Model 3**	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
HFScore ≥13						
Group	1.57 (0.28-8.96)	0.61	1.65 (0.27-10.2)	0.59	2.60 (0.31-21.6)	0.38
Time	0.98 (0.94-1.02)	0.28	0.97 (0.93-1.01)	0.13	0.98 (0.93-1.03)	0.34
Group*time	0.95 (0.89-1.00)	0.051	0.95 (0.90-1.00)	0.049	0.94 (0.88-1.00)	0.067
HT			4.52 (0.73-28.2)	0.11	2.76 (0.38-19.8)	0.31
Sleep quality					0.27 (0.07-1.00)	0.050
HFScore ≥22						
Group	1.39 (0.30-6.50)	0.68	1.43 (0.30-6.89)	0.65	2.18 (0.40-11.8)	0.37
Time	0.96 (0.91-1.01)	0.11	0.95 (0.91-1.00)	0.053	0.96 (0.92-1.01)	0.15
Group*time	0.95 (0.87-1.02)	0.16	0.95 (0.88-1.02)	0.15	0.94 (0.88-1.02)	0.13
HT			5.82 (0.34-98.8)	0.22	2.88 (0.15-53.9)	0.48
Sleep quality					0.20 (0.05-0.76)	0.018
HFScore ≥35						
Group	0.66 (0.17-2.52)	0.54	0.68 (0.17-2.73)	0.59	1.02 (0.22-4.85)	0.98
Time	0.90 (0.83-0.97)	0.005	0.88 (0.81-0.96)	0.005	0.90 (0.84-0.97)	0.007
Group*time	0.98 (0.90-1.08)	0.74	0.98 (0.88-1.08)	0.66	0.98 (0.90-1.07)	0.64
HT			48.1 (0.51-4556)	0.095	15.9 (0.26-962)	0.19
Sleep quality					0.15 (0.03-0.68)	0.014

*Model 2, adjusted for HT (use of hormone therapy at 4-year, 0=no, 1=yes)
**Model 3, additional adjustement for sleep quality at 4-year, (0=poor/ rather poor / not well, not bad, 1=good or fairly good)

6.   DISCUSSION

The aim of this study was to investigate the relationships between physical activity, menopause-specific and health-related quality of life and menopausal symptoms of women during menopause. In this study the participants who met the recommended level of PA had better quality of life and the study showed the importance of PA for physiological and psychological domains of quality of life in middle-aged women's lives. Aerobic exercise was found to reduce hot flushes disturbing sleep and improve quality of sleep. In addition, participants in the exercise group showed positive long-term effects on physical and mental dimensions of QoL and hot flushes four years after a 6-month exercise intervention.

6.1.   Physical activity and quality of life

A positive association was found between physical activity and quality of life along four WHQ dimensions - anxiety or depressed mood, somatic symptoms, memory/concentration and well-being when adjusted for education and BMI than was found among those who did not attain the recommended level. In addition, physically active women had better quality of life than inactive women after adjusting for self-perceived health, relative health and global quality of life. These results are consistent with an eight-year population-based follow-up study in Finland on the relationships between changes in QoL, menopausal status and PA , which found not solely physical activity, but also higher education and stable weight (BMI <25 kg/m²) to be associated with quality of life (Moilanen et al. 2012). This corroborates our study, where the results showed improvement in QoL dimensions after adjusting for education and BMI.

Aging women's lives are associated with diverse symptoms and complaints that may affect quality of life. According to longitudinal studies similar results with respect to physical activity and quality of life have been observed. Physical activity improves self-worth and affect, leading through this mechanism to improvement in quality of life among middle-aged women (Elavsky 2009). In a 9-year prospective longitudinal study it was found that exercise has beneficial effects on hot flushes and well-being. At baseline the participants were aged 45 to 55 years and had menstruated in the preceding three months, and they were followed up for annually by the interviews, fasting blood and physical measurements (Dennerstein et al. 2007).

In our survey the respondents were classified into two categories according to the recommendations for physical activity. The recommended target level for physical

activity is to engage in aerobic exercise on several days a week for at least 2h 30 min of moderate activity or 1h 15 min of vigorous activity (Fogelholm et al. 2005). Women who met the recommended level of PA benefited when self-perceived health, relative health, and global quality of life or WHQ dimensions were assessed.

Middle-age and menopausal transition may be a window to the future, since it may induce improvements in lifestyle. Also, menopausal women in the RCT changed their behaviour for six months in a more physically active direction, even though PA has been reported to decrease with age (Pedersen et al. 2009). Greater motivation for lifestyle modification could explain the increased physical activity. The evidence of menopausal women's physical activity suggests that exercise is a useful intervention strategy to alleviate menopause symptoms, and that exercise has various other benefits and is safe, with no side-effects (Guimaraes et al. 2011; Elavsky et al. 2012; Luoto et al. 2012; Stojanovska et al. 2014). Motivated attitude and perceived positive coping with daily life could encourage women to increase physical activity during the menopause.

6.2. The association between exercise, sleep and menopausal symptoms

The exercise intervention showed that aerobic training may reduce hot flushes that disturb sleep and improve the quality of sleep among women with vasomotor symptoms. The mobile phone-based diary also proved useful for data collection to monitor quality of sleep and menopausal symptoms, while it yielded much more information gathered during the intervention than can be collected by conventional methods.

Structured exercise training programmes have shown potential to reduce and alleviate vasomotor symptoms during menopause but the evidence is still insufficient (Daley et al. 2014). After a moderate intensity aerobic exercise session among women not using HT objectively and subjectively measured hot flushes decreased, although over a longer period, women with lower fitness levels reported more symptoms when they had more daily PA than usual (Elavsky et al. 2012). However, among Chinese menopausal women with vasomotor symptoms, no current HT users, 12 weeks of walking training was found to be effective in improving menopausal symptoms when compared to the control group (Zhang et al. 2014). The results for hot flushes disturbing sleep in our RCT are in line with this, while the difference between the exercise and control groups was apparent ten weeks after the beginning of the intervention and the women in the exercise group reported fewer hot flushes disturbing their sleep than women in the control group.

In our study during the intervention, approximately six weeks after the beginning

of the intervention an improvement in sleep quality was apparent among women in the exercise group. The odds for sleep improvement were 2% per week in the exercise group with a decrease of 0.5% per week in the control group. In the course of 24 weeks the women in the exercise group reported better quality of sleep than did than the women in the control group.

In an earlier study women with vasomotor symptoms were randomly assigned to yoga, exercise and usual activity groups, and in addition assigned randomly to a double-blind comparison of omega-3 or placebo capsules. The main purpose was to determine the efficacy of non-hormonal therapies for the improvement of menopause-related quality of life measured by MENQOL (Reed et al. 2014). The yoga intervention resulted in significantly greater improvement in MENQOL total scores at 12 weeks compared with usual activity group, but there were no group differences between exercise and usual activity or omega-3 and placebo. Statistically significant differences in MENQOL domains were observed for vasomotor and sexual domains in favour of the yoga intervention group. For exercise and omega-3 groups evaluation of the MENOL domains showed only a statistically significant result that favoured the exercise group for the physical domain of MENQOL at 12 weeks (Reed et al. 2014).

Stojanovska et al. (2014) showed in a narrative review that exercise intervention programmes have led to reduced menopausal symptoms, including somatic and psychological ones and to a lesser extent to sexual and vasomotor symptoms. These findings are in line with the findings from our population-based cross-sectional study in which vasomotor symptoms and sexual behaviour did not reach statistical significance among physically active women, while factors in somatic and psychological dimensions did.

Daley et al. (2007) using a postal questionnaire (n=2,399) examined the relationship between BMI, exercise participation, health-related QoL and vasomotor symptoms among women aged 46 – 55. The mean age of the women was 50.5 (SD 2.8), half of the respondents (n=1,206/2,399) were postmenopausal and the other half peri- or premenopausal. Regularly active menopausal women reported better health-related QoL than did less active women. No significant difference was found in vasomotor symptom scores between active and less active women. Furthermore, women with BMI within the normal range (BMI <25) achieved lower vasomotor symptom scores and better health-related QoL scores than obese participants (Daley et al. 2007). Our cross-sectional study also showed better QoL results among physically active women at the age of 49. Furthermore, in the follow-up study four years after the beginning of the trial an almost statistically significant improvement was seen in HFScore of at least 13 points among the women in the exercise group with BMI 26 kg/m².

Understanding the different effects of aging has also become more important in managing the daily tasks at work and in leisure time. The effects of PA on work ability and daily strain have been reported after our RCT. A 6-month exercise training

program had both short and long-term effects on women's work ability during menopause, but no significant effects on physical and mental strain during work (Rutanen et al. 2014). Geukes et al. (2011) using a questionnaire among healthy working population also demonstrated a negative association between menopausal symptoms and work ability.

6.3. The long-term effects of exercise on quality life and hot flushes

The results of the 4-year follow-up study showed that exercise intervention may have long-term positive effects on health-related QoL among the group of menopausal women with vasomotor symptoms. Women in the exercise group had higher probability of improvement in physical functioning dimensions of QoL from baseline to the end of 4-year follow-up. Overall, the results showed that women in the exercise group sustained their improved QoL on both physical health and mental health dimensions more often than did women in the control group. Thus it may be suggested that an aerobic training intervention for six months may have long-term positive effects on QoL dimensions among menopausal women. In the analyses at 4-year follow-up all initially randomized subjects were included in the statistical analyses, even if they did not participate in all measurements.

Findings from earlier studies have shown that taking physical exercise is associated with lower estimates of perceived severity of symptoms, and, in addition, that training moderates the psychological symptoms related to menopause (Elavsky 2009; McAndrew 2009). Mishra et al. (2003) in a two-year follow-up study found that certain domains of quality of life show a decline over time and that menopause affects physical aspects of general health and well-being. Furthermore, physical exercise has been proposed as an alternative to hormone replacement therapy decreasing symptoms for improving symptomatic women's quality of life. The benefits of exercise can also be more seen in general health and well-being. (de Azevedo Guimaraes AC et al. 2011; Elavsky et al. 2012; Luoto etal. 2012; Stojanovska et al. 2014; Grindler et al. 2015).

In our study positive long-term effects of exercise training on HFScore among menopausal women were observed four years after the beginning of the exercise intervention. Women in the exercise group had higher probability of belonging to the group with mild intensity of menopausal symptoms than did women in the control group. Women could change their behaviour towards a more active lifestyle during the intervention for six months and in a smaller group of women for four years after the training trial. Also, higher motivation to take regular exercise and for lifestyle changes could be a consequence of generally better health and better physical fitness. In addition, lectures once or twice per month during the intervention

supported the participants. Grindler et al. (2015) showed in their review that exercise was seen a near-ideal intervention for the prevention of many of the morbidities to which postmenopausal are prone. Exercise was found to promote longevity and increase women's functional life span and quality of life (Grindler et al. 2015).

Smith-DiJulio et al. (2008) in a longitudinal study found that a woman's sense of control over her life, and satisfaction with it and her ability to make use of the available social support predicted greater well-being during the menopause. This finding is consistent with our results, as we observed a slightly greater tendency for improved emotional well-being, vitality and mental health during the follow-up among the participants in the exercise group compared to the control group, even though the results did not reach statistical significance. In the course of time women in both the exercise and in the control group experienced fewer menopausal symptoms. This can be seen as a consequence of the natural course of menopause during which the hot flushes decrease. Our follow-up showed a clear decline in HFScore points, being at lowest four years after the beginning of the training trial.

6.4.   Strengths and limitations of the study

The strengths of the study are the cohort study with a relatively large number of study participants, the design of the randomized controlled trial with a fairly large sample size and the 4-year follow-up. The instruments for assessing menopause-related (WHQ) and health-related quality of life (SF-36) were valid and reliable. The WHQ questionnaire consists of both psychological and physical domains (Hunter 2003). The questionnaire is a valid instrument since test-retest reliability has been evaluated with a two-week interval for a sample of 48 women (Hunter 2003). Additionally, the questionnaire has been translated into Finnish (Hunter 2003, Zöllner et al. 2005). The WHQ also has a shorter version of the questionnaire and earlier studies have observed that the seven WHQ dimensions describe women's well-being just as well as the questionnaire with nine questions (Hunter 2003).

Adherence of the participants in the trial was good since the drop-out rate was low in both exercise (n=14) and reference (n=8) groups. Better adherence than expected is an important strength of the study. The response rate in the population-based survey was fairly good 52% (2,606 out of 5,000) and in the 4-year follow-up the response rate was 60%. Women with a minor interest in lifestyle change or women with severe vasomotor symptoms may account for their being non-responders.

The main strengths of the RCT and the follow-up study are also the repeated assessments of physical activity (at baseline, 6-month and 4-year follow-up), like-wise the prospective study design, which enabled us to analyse long-term differences between the groups. In addition, data collection by one-week diary for exercise

training, hot flushes and sleep quality, and the UKK 2 km Walk Test enabled us to compare results between baseline and 4-year follow-up. Few studies on women during the menopause have explored the changes between several time-points after an exercise intervention.

The major limitation of the study may be considered the lack of objective physical activity measurement in the cohort study, which would have supported the physical activity questionnaire, but PA measurement was not feasible at that time. However, the questions covered diverse types of physical activity during commuting and leisure time. More details of the intensity of PA were elicited with additional questions in five categories from "no regular exercise" to "strenuous exercise" (heavy sweating and/ or accelerated breathing such as jogging or running).

In the cohort study weight and height were self-reported by participants and therefore the results are not as reliable as they might have been if measured by a professional. The participants' own reports may have differed by some 0.5-1 kg and height by 1 cm from professional assessment (Dahl et al. 2010). In the RCT and the follow-up the assessments were performed by professionals. We concede the mobile-phone method for data collection as a weakness as it was not a validated instrument. The scale used in the evaluation of subjective sleep (scale 1-5) possibly lacked reliability since it had not been previously tested. The measurement of sleep was subjective and not as objective as actigraphy measurements. However, there were differences between the groups and thus the study was not underpowered.

The missing information on HFScore is a limitation in the 4-year follow-up study. From baseline (n=159) to 4-year follow-up only 56 women completed one-week hot flush diaries at all three time-points. The questionnaire was completed by 95 women at 4-year follow-up (response rate 60%), which can be considered quite an acceptable result.

Differences in the analyses between women who did not participate in the follow-up study and those who did were found in age, weight and smoking habits. This is in line with Daley et al. (2007), who showed obese women to report significantly higher vasomotor symptoms than women of normal weight, and that women who were not regularly active were more often smokers than were regularly active participants. According to a loss-to-follow-up analysis at 4-year follow-up there were significant differences in the exercise group between participating women (n=28) and those lost to follow-up (n=50) in waist (83.6; 91.3 cm, p=0.006) and BMI (25.2; 27.1 kg/m², p=0.040) among intervention women. Similar findings were not found in the control group, which indicates of a respondent bias restricted to the exercise group. This may have an effect to the results concerning the HFScore. The women (n=47, 28%) not participating in the follow-up studies were younger at baseline (53.0 years versus 54.5 years), they had a higher BMI (28.0 versus 26.3 kg/m²) and they were regular smokers more often (27%, in contrast to 12%) than participating

women. These observed differences may have influenced the findings in the 4-year follow-up study because the differences between the groups might possibly have been larger if all the participants of the 6-month training trial had participated in the follow-up measurements. The low participation may be due to the fact that the most active women are usually those who respond to questionnaires. The active women may have benefited even more from the available support, i.e. the interest in their well-being at follow-up measurements.

6.5. Implications for future studies

There still remain unanswered questions concerning the effects of aerobic training on alleviating the symptoms during the menopausal transition. The exercise-induced improvements in this study were at least moderate, since we could show positive changes in quality of life, hot flushes, physical fitness and body composition among menopausal women in the course of time. Also, a narrative review suggested that exercise is inexpensive, minimal risk and unambiguously beneficial, and is a goal for every woman during menopause to enhance lifelong wellness (Grindler et al. 2015).

According to the purpose of this study menopausal women may derive more from aerobic training regarding both general and vascular health, since aerobic training is beneficial to mental and physical health. Important factors that may affect health and well-being among women during the menopause are physical activity and high body weight. Both these factors can be modified by healthy dietary habits and exercise. Exercise is an appealing intervention because of the established and probable health benefits it may provide as a possible treatment for hot flushes. Long-term compliance with exercise recommendations during the menopause is a good opportunity to induce lifestyle modification.

Although exercise cannot be thought of as the only treatment for various psychological and physiological symptoms during the menopause, different exercise protocols including behavioural and cognitive therapy should be tested more for alleviating symptoms and offering an alternative to hormone therapy among aging women, likewise the use of novel technology during interventions, different forms of applications for supporting participants and automatic conversion of data into digital format for assisting the researchers.

7. CONCLUSIONS

According to the main findings of the study, the following conclusions may be drawn:

I

Women aged 49 who took the recommended amount of PA reported better menopausal and global quality of life. Our study confirmed the importance of an increase in physical activity for the psychological and physiological domains of middle-aged women's lives.

II

Aerobic training for six months was shown to have positive effects on menopausal symptoms. This study showed training to improve quality of sleep and to reduce nocturnal hot flushes among women with vasomotor symptoms during the menopause.

III

The women in the exercise group showed positive long-term effects on the physical and mental dimensions of quality of life four years after the beginning of the exercise intervention. Menopause is a window of opportunity for increasing physical activity and thereby improving future quality of life. This positive relation between physical activity and QoL is important, since an increase in physical activity may be associated with a lower future burden of chronic noncontagious diseases.

IV

Among the women with mild intensity of menopausal symptoms a difference between the exercise and control groups persisted until 4-year follow-up. Inspection of the HFScores showed that the menopausal women in the exercise group were still benefitting from the training four years after the beginning of the study.

ACKNOWLEDGEMENTS

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APPENDIX I

The mobile phone questionnaire
Pre-specified questions on hot flushes, sleep, and other symptoms

Questions in the morning

Date and time
Did you have night-time hot flushes? — 1 yes, 2 no
What were the hot flushes like? — 1 mild, 2 moderate, 3 severe
    Number of mild hot flushes?
    Number of moderate hot flushes?
    Number of severe hot flushes?
How were the disturbing hot flushes? — 1 not at all, 2 slightly, 3 somewhat, 4 rather a lot, 5 a lot
Did you have night sweating? — 1 yes, 2 no
How did you sleep last night? — 1 well, 2 fairly well, 3 not well, not bad, 4 rather poor, 5 poor
Did you get enough sleep? — 1 yes, 2 no
Did menopausal symptoms
disturb you last night? — 1 yes, 2 no

Questions in the evening

Date and time
Did you have day-time hot flushes? — 1 yes, 2 no
What were the hot flushes like? — 1 mild, 2 moderate, 3 severe
    Number of mild hot flushes?
    Number of moderate hot flushes?
    Number of severe hot flushes?
How disturbing were the hot flushes? — 1 not at all, 2 slightly, 3 somewhat, 4 rather a lot, 5 a lot
Did you have a headache today? — 1 yes, 2 no
    How disturbing was the headache? — 1 not at all, 2 slightly, 3 somewhat, 4 rather a lot, 5 a lot
Did you have mood swings today? — 1 yes, 2 no
    How disturbing was it? — 1 not at all, 2 slightly, 3 somewhat, 4 rather a lot, 5 a lot
Did you have dysphoria today? — 1 yes, 2 no
    How disturbing was it? — 1 not at all, 2 slightly, 3 somewhat, 4 rather a lot, 5 a lot
Have you been depressed today? — 1 yes, 2 no
    How disturbing was it? — 1 not at all, 2 slightly, 3 somewhat, 4 rather a lot, 5 a lot
Did you have dryness of the vaginal
mucosa today? — 1 yes, 2 no
    How disturbing was it? — 1 not at all, 2 slightly, 3 somewhat, 4 rather a lot, 5 a lot
Did you have problems with
micturition or urinary continence? — 1 yes, 2 no
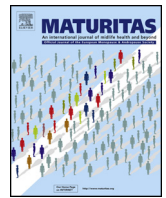   How disturbing was it? — 1 not at all, 2 slightly, 3 somewhat, 4 rather a lot, 5 a lot
Did you fall ill today? — 1 yes, 2 no
    What was it?
Any other information?

ORIGINAL PUBLICATIONS

Physical activity and menopause-related quality of life – A population-based cross-sectional study

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ABSTRACT

The aim of the research was to study the association between engagement in the recommended level of physical activity and quality of life (QoL) among middle-aged women.

In total, 2606 Finnish women aged 49 years responded to a postal questionnaire on lifestyle, quality of life, and health, wherein QoL was assessed with a shorter version of the menopause-specific Women's Health Questionnaire (WHQ). Proportional odds ratios (PORs) from ordered logistic regression models were used to test the association between the physical-activity and WHQ domains or three quality-of-life variables.

Physically inactive women had an increased probability of anxiety/depressed mood (POR 1.44; 95% confidence interval (CI) 1.26–1.65), of decreased well-being (POR 1.96; 95% CI 1.71–2.25), of somatic symptoms (POR 1.61; 95% CI 1.40–1.85), of memory/concentration problems (POR 1.48; 95% CI 1.29–1.70), and of vasomotor symptoms (POR 1.19; 95% CI 1.03–1.36) as compared to physically active women. Women with the recommended level of physical activity had a higher self-perceived health level, better relative health, and better global quality of life in relation to other women their age.

Physically active women showed higher quality of life in four menopause-specific WHQ dimensions and in global quality of life when compared to inactive women.

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1. Introduction

Middle-aged women's life is characterised by physiological and psychological changes that may have an impact on the various domains of quality of life (QoL) [1]. Physical activity (PA) is the most commonly explored domain, and many studies have shown a positive association between PA and QoL among middle-aged women [2–6]. On the other hand, physical activity raises body temperature and thereby could, at least in theory, increase the occurrence of vasomotor symptoms in menopause and decrease QoL [7]. Obesity has been found to be a risk factor during menopause, and evidence indicates that higher body-mass index (BMI) and levels of body fat are associated with greater vasomotor symptoms and hot flushes [8].

Mechanisms by which PA may increase QoL include psychological and social pathways, along with educational background as a modifying factor. Improved QoL might be explained by positive change achieved through improved physical self-worth [4,9]. In an 8-year follow-up study, women with higher education and a stable weight increased their physical activity and had improved QoL relative to that seen with the baseline questionnaire [4]. Another possible explanation involves associations among physical activity, mood, and weight. Maintaining or increasing one's level of physical activity during menopausal transition and post-menopause has been suggested to reduce various psychological symptoms [10].

The research reported on here is part of a population-based study in which the aim is to evaluate relationships among breast-cancer screening, various lifestyle factors, and QoL. The focus of our study is on exploring the relationship between physical activity and quality of life among menopausal Finnish women.
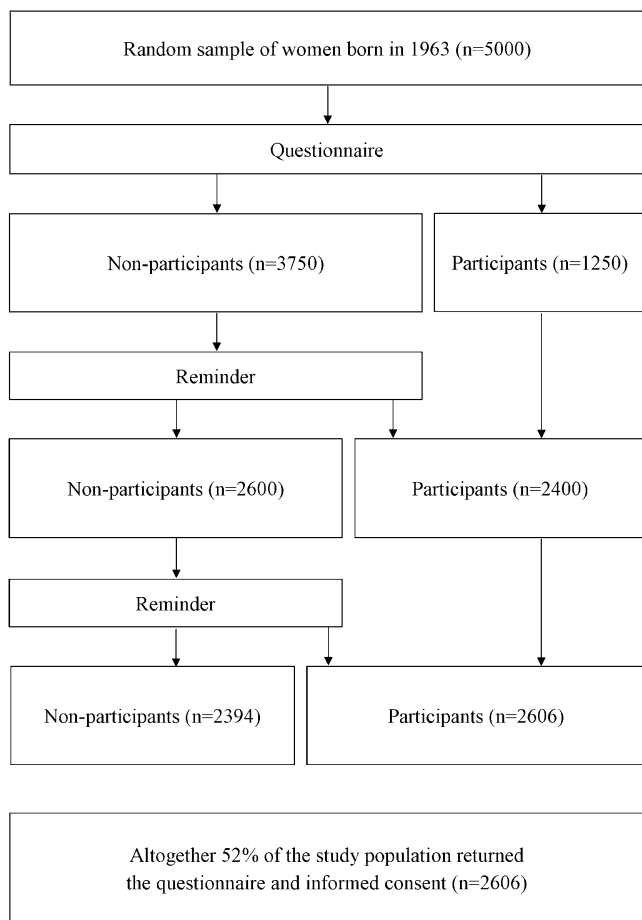
Fig. 1. Data collection and flowchart.

2. Material and methods

The study population, a random sample of 5000 women born in 1963, was obtained from the Finnish Population Register Centre. The Finnish Population Information System is a computerised national register that contains basic information about Finnish citizens and foreign citizens residing permanently in Finland. The Population Register Centre, tasked with directing and supervising population registration as well as with responsibility for the central register of population (the present Population Information System), was set up in 1969. The computer-based register was introduced in 1971. Individuals have been given a unique identifier, which allows linkage between individual registers.

In Finland, a population-based breast-cancer screening programme was fully implemented at the beginning of 1992 and has thereafter offered biennial screening for all Finnish women aged 50–59 years. The women were sent a postal questionnaire along with an informed-consent form in 2012, one year before their first invitation to mammography screening. After two reminders, 2606 women (52% of the study population) had returned the questionnaire and given informed consent (see Fig. 1). Nearly fourth of the participants (23%) did not have menstruation for 12 months and thus were postmenopausal. Third of the women (28%) were premenopausal with regular menstruation and 31% had irregular menstruation and thus were perimenopausal. In addition, 18% of women had no information about menstruation because of hormone replacement therapy.

The questionnaire included questions on education, occupation and work status, physical activity, height and weight, waist circumference, and quality of life. The options given for level of education

were primary, secondary (e.g., completion of secondary school or receipt of a college diploma), and higher (e.g., a bachelor's or master's degree) education. The data on occupation or type of work were classified into two groups, blue-collar and white-collar, where the former included, for instance, a worker with vocational training or a farmer's wife and the latter encompassed persons in higher positions but also lower-level white-collar workers.

The amount of physical activity was solicited via a question to which the subjects responded with how much exercise they did in a typical week. The women were asked to consider the previous 12 months and include any regular physical exercise performed weekly for at least 10 min at a time, with frequency expressed in days per week, total hours, and minutes in a week. The question on physical activity determines the intensity and frequency of physical activity including all types of exercise, which will continue at least 10 min at a time. Thus, we were not able to separate different types of exercise. The question was asked for each of five bands beyond 'no regular exercise', up to 'strenuous aerobic exercise' (heavy sweating and/or accelerated breathing, as in jogging or running). In addition, the women completed an item about the amount of strength training and balance training they received in a typical week (see Appendix 1). Physical activity was classified into one of two categories, on the basis of the UKK Institute's physical-activity recommendations for health and fitness [11].

Women who met the criterion of the recommended level of physical activity by being active several days a week with, in total, at least 2 h 30 min of moderate activity or 1 h 15 min of vigorous activity and, in addition, working to increase their muscle strength and improve their balance at least twice a week were classified as active, whereas those with less physical activity were considered inactive.

BMI was calculated from self-reported height and weight, and the participants were asked to measure their waist circumference below the ribs and at navel height. According to Han et al. [12], both being overweight and having a central fat distribution are associated with preventable ill health. Women with a waist circumference above 88 cm are 2.5–4.5 times as likely to display one or more major cardiovascular risk factors.

QoL was assessed with the Women's Health Questionnaire (WHQ), which addresses nine domains of physical and emotional experiences. The questionnaire was developed to evaluate changes experienced by women during the menopause transition and is standardised for women aged 45–65 years [13]. In our study, a shorter version of the WHQ instrument was used, investigating seven domains: anxiety/depressed mood, well-being issues, somatic symptoms, memory/concentration problems, vasomotor symptoms, and sleep problems. An eighth domain, sexual behaviour, was presented as an optional element [14].

Self-perceived health was assessed by means of a five-point scale (with the labels 'very good', 'good', 'average', 'poor', and 'very poor') and a three-point scale ('better than', 'worse than', or 'similar to' women of the same age) [15]. In addition, global quality of life was assessed with a 10-point visual analogue scale (VAS) ranging from the worst to the best possible quality (4). The rationale for using several methods in QoL assessment was that the methods complement each other and encompass many aspects of QoL (see Table 1).

2.1. Statistical analysis

Descriptive analysis was used to outline the characteristics of the participants by frequencies and proportions. Ordered logistic regression models (also known as proportional odds models) were used to analyse the association between WHQ domains or three life-quality variables (dependent variables) and physical activity

Table 1
Characteristics of the study population.

Education (missing: *n* = 11)	
Primary education	889 (34.3%)
Secondary education	981 (37.8%)
Higher education	725 (27.9%)
Occupation/type of work (missing: *n* = 130)	
Blue-collar	1186 (47.9%)
White-collar	1290 (52.1%)
Work status (missing: *n* = 43)	
Employed	2151 (83.9%)
Unemployed	149 (5.8%)
Student	49 (1.9%)
Retired	214 (8.3%)
Meeting of physical-activity recommendation* (no missing responses)	
No	1279 (49.1%)
Yes	1327 (50.9%)
Body-mass index (missing: *n* = 34)	
Under 25	1265 (49.2%)
25–29.9	784 (30.5%)
At least 30	523 (20.3%)
Waist circumference (missing: *n* = 186)	
Under 88 cm	1209 (50.0%)
At least 88 cm	1211 (50.0%)

* At least 2 h 30 min of moderate activity or 1 h 15 min of vigorous activity a week and muscle strength and, in addition, balance training at least two times a week.

(the independent variable). Models were adjusted for education and body-mass index.

Ordered logistic regression is used when the dependent variable is ordered and the cell count is adequate. Because of the sparseness of our data, we were not able to use the original scale, so the WHQ variables (range: 0–100) were broken down into 5–9 categories and the quality-of-life variables into 4–6 categories, respectively. This categorisation was based on the frequency distributions for the above-mentioned variables. We also tested the assumption of proportional odds (i.e., that the regression coefficients are constant across the various levels of dependent variable) for all models by employing the test of parallel lines.

In ordered logistic regression, an extension of binary logistic regression, the results can be expressed as proportional odds ratios (PORs) and 95% confidence intervals (CIs). Each POR may be interpreted as the effect of the variable on the odds of a higher-category outcome for WHQ and life-quality variables, higher being better.

The significance of all tests was determined to be at a *p*-value < 0.05, and data analysis was performed with IBM SPSS Statistics, version 21.

3. Results

The data came from 49-year-old female respondents to a postal survey (*n* = 2606). Nearly every third woman (28%) had a higher education, and about half of the women (52%) were white-collar workers. Most were employed (84%). Approximately half of the women (51%) were physically active – i.e., met the recommendation set forth in the physical-activity guidelines. That recommendation addresses two types of activity: aerobic training and muscle-strength training. The proportion of women who fulfilled the recommendation for both types of physical activity was 14.2%, and that for only one type was 36.7%. Since the results were similar no matter which type of physical activity was included, the types were not considered separately in the overall results. Half of the women were of normal weight (BMI < 25 kg/m^2) and had a waist circumference below 88 cm (see Table 1).

In the non-adjusted models, we found inactive women to have an increased probability of anxiety/depressed mood (POR 1.44; 95% CI 1.26–1.65), of lower well-being (POR 1.96; 95% CI

1.71–2.25), somatic symptoms (POR 1.61; 95% CI 1.40–1.85), memory/concentration problems (POR 1.48; 95% CI 1.29–1.70), and vasomotor symptoms (POR 1.19; 95% CI 1.03–1.36) relative to physically active women. For example, the odds for the combination of categories representing higher, rather than lower, levels of vasomotor symptoms were 1.19 times higher for the active than the inactive women when the other variables (education and BMI) were held constant in the model. The associations remained significant when education and BMI were taken into account in all dimensions except vasomotor symptoms (see Table 2). Women with the recommended level of PA had higher self-perceived health (POR 3.22; 95% CI 2.76–3.74), greater relative health (POR 3.42; 95% CI 2.91–4.02), and higher global quality of life (POR 1.91; 95% CI 1.65–2.20) in relation to other women their age (see Table 3).

4. Discussion

The cross-sectional study of 49-year-old women indicated that recommended levels of physical activity were associated with better quality of life along four adjusted WHQ dimensions – anxiety/depressed mood, well-being issues, somatic symptoms, and memory/concentration problems – among menopausal women. In addition, physically active women reported better quality of life when adjusted self-perceived health, relative health, and global quality of life were assessed.

Similar results with respect to physical activity and quality of life have been reported in studies with a longitudinal setting. A report on an eight-year population-based follow-up study from Finland stated that motivation to increase one's physical activity and lifestyle modification during menopausal transition may be an explanatory factor connected with improved quality of life [4]. Elavsky [9] found in a longitudinal study of middle-aged women that physical activity improved self-worth and affect, leading, through this mechanism, to improvement in QoL. A recently published review emphasises the role of physical activity in reducing menopause symptoms, including somatic and psychological ones [21].

In a Finnish population-based study, quality of life was found to be associated with higher education, stable or increased physical activity, and stable weight [4]. The results from our study were consistent with the findings of that earlier study. The eight-year follow-up study by Dennerstein et al. [16] found that increased BMI was associated with a decline in self-rated health. Whether this is because of awareness of the relationship between fatness and chronic disease is unknown. Elavsky [9] reported on a longitudinal study in which physical activity increased physical self-worth and positive affect that leads to improved quality of life.

Experimental studies have shown the effects of various type of exercise on quality of life among menopausal women. A Finnish trial compared quality-of-life effects of moderate-intensity aerobic training, mainly walking [6]. The participants were aged 43–63 years, were not using hormone replacement therapy at the time of the study, and had a sedentary lifestyle (with aerobic training less than twice weekly). The women were advised to walk four times per week for 50-min stints. The control group kept their exercise habits unchanged. Significant results were found for physical functioning, vitality, and the WHQ dimension of depression between the two groups [6]. A recent publication by Reed et al. [17] described attempts to ascertain the efficacy of yoga, exercise, and one's usual activity for the improvement of menopause-related quality of life (MENQOL) in women with vasomotor symptoms in a randomised controlled trial. Improvements were seen for MENQOL total and the vasomotor symptom and sexuality domain scores, and exercise showed benefits in the physical domain at 12 weeks. The study concluded that a 12-week yoga intervention

Table 2

Proportional odds ratios (PORs with 95% confidence intervals (CIs) and p-values) for seven aspects of WHQ as a function of physical activity (active versus inactive), where each POR may be interpreted as the effect of the variable on the odds of a higher-category (i.e., better) outcome for the WHQ and quality-of-life variables.

	Unadjusted model, ref. inactive			Model adjusted for education and BMI, ref. inactive		
	N	POR (95% CI)	p	N	POR (95% CI)	p
Anxiety/depressed mood	2588	1.44 (1.26–1.65)	<0.001	2547	1.31 (1.14–1.51)	<0.001
Well-being	2584	1.96 (1.71–2.25)	<0.001	2543	1.64 (1.42–1.89)	<0.001
Somatic symptoms	2584	1.61 (1.40–1.85)	<0.001	2544	1.39 (1.21–1.61)	<0.001
Memory/concentration	2586	1.48 (1.29–1.70)	<0.001	2544	1.29 (1.12–1.49)	<0.001
Vasomotor symptoms	2568	1.19 (1.03–1.36)	0.015	2527	1.12 (0.97–1.29)	0.13
Sleep problems	2573	1.11 (0.97–1.28)	0.13	2533	1.04 (0.90–1.20)	0.58
Sexual behaviour	2130	1.13 (0.98–1.32)	0.099	2095	1.10 (0.94–1.29)	0.22

Table 3

Proportional odds ratios (PORs with 95% confidence intervals (CIs) and p-values) for self-perceived health, relative health, and global quality of life as a function of physical activity (active versus inactive), where each POR may be interpreted as the effect of the variable on the odds of the subject showing a higher category for the output related to the WHQ and quality-of-life variables, with higher categories being better.

	Unadjusted model, ref. inactive			Model adjusted for education and BMI, ref. inactive		
	N	POR (95% CI)	p	N	POR (95% CI)	p
Self-perceived health[a]	2583	3.22 (2.76–3.74)	<0.001	2550	2.56 (2.19–3.00)	<0.001
Relative health[b]	2577	3.42 (2.91–4.02)	<0.001	254	2.60 (2.19–3.07)	<0.001
Global quality of life (VAS)[c]	2546	1.91 (1.65–2.20)	<0.001	2514	1.63 (1.40–1.89)	<0.001

[a] Four categories were used for the variable: 1 = very bad/bad, 2 = average, 3 = good, 4 = very good.
[b] 1 = worse than, 2 = similar to, 3 = better than.
[c] Because of the low number of observations, six categories were used for the variable: 1 = 1–4, 2 = 5–6, 3 = 7, 4 = 8, 5 = 9, 6 = 10.

improved menopause-related quality of life among sedentary women, although the effect was modest.

In the study described here, the women were 49 years old when responding to the questionnaire. Therefore they were at least in the pre-menopausal phase. Respondents were classified into two categories in light of the recommendation for physical activity. The target level in the recommendation for physical activity is to engage in aerobic training several days a week for at least 2 h 30 min of moderate activity or 1 h 15 min of vigorous activity in all [11]. Women who met the recommendation benefited when self-perceived health, relative health, and global quality of life or WHQ dimensions were assessed.

Middle-aged women's life is associated with diverse symptoms and complaints that may be tied in with quality of life. Mishra et al. [18] found in their 2-year follow-up study that certain domains of quality of life show a decline with ageing and that the menopausal transition affects physical aspects of general health and well-being. Smith-DiJulio et al. [19] have reported that negative life events might predict decreased well-being in the menopausal transition but factors associated with that transition not. They also found that a woman's satisfaction with her life and ability to use social support predicted increased well-being [18].

Middle age and menopausal transition may be a window to the future, since it may induce lifestyle modification. Greater motivation for lifestyle modification could explain increased physical activity. In a study by Luoto et al. [6], women in menopausal transition took their behaviour in a more physically active direction even though physical activity has been reported to decrease with age [20]. The evidence of menopausal women's physical activity suggests that exercise is a useful intervention strategy for women's alleviation of menopause symptoms; in addition, exercise has various other benefits and is safe, with no reported side-effects [21].

The WHQ is a valid instrument of data collection for menopause-related quality of life, since it features questions about both psychological and physical domains [13]. The questionnaire's test–retest reliability has been evaluated with a 2-week interval for a sample of 48 women; all correlations were above 0.75, ranging from 0.96 to 0.78. Furthermore, it has been validated in the Finnish language [13,15]. In our study, seven sub-dimensions were used; menstrual symptoms and attractiveness were excluded, because previous studies have found that the above-mentioned seven WHQ dimensions describe women's well-being just as well as the full nine dimensions do [13]. Global quality of life was evaluated on the Ladder of Life scale: respondents were asked to evaluate their quality of life over the previous month on a 10-point scale, with 0 representing the worst possible QoL and 10 referring to the best possible QoL [4]. Another strength of the study was the size of the sample and the fact that the research was population-based.

A limitation of the study can be found in its lack of objective physical-activity measurement. However, the questions covered diverse types of physical activity during one's leisure time. Since the weight and height data were from the participants' own reports, the results are not as reliable as they might be with measurement by a professional. Self-reported weight differs by some 1 kg and height by 1–2 cm from professional measurements. In addition, the response rate was rather low: after two reminders, 2606 out of 5000 women, or 52%, answered. The low response rate may be explained by the low number of participants with a higher education (27.9%); in the longitudinal study [4], 40.8% fell into the higher-education group.

5. Conclusion

Middle-aged women who meet the recommendation stated in the leisure-time physical-activity guidelines reported better menopausal and global quality of life. Future research is necessary to clarify the relationship of quality of life with the long-term effects of objectively measured physical activity. Our study indicates the importance of an increase in physical activity for the psychological and physiological domains of menopausal women's life.

Contributors

Kirsi Mansikkamäki prepared the first version of the manuscript. Jani Raitanen was responsible for statistical analysis. All authors (Riitta Luoto, Jani Raitanen, Nea Malila, Tytti Sarkeala,

Satu Männistö. Sirpa Heinävaara) have participated in drafting of manuscript and approved the final version.

Competing interests

We declare that there are no competing interests related to the article.

Ethics

Study has received ethical approval from Helsinki Hospital District Ethics Committee. All participants gave written informed consent.

Appendix 1. Amount of physical activity

How much do you exercise in a typical week?			
Think about the last 12 months. Include any regular exercise that you do every week and that lasts for at least 10 minutes at a time. In sections 2 to 6, please indicate in the boxes how much of the exercise you do (days per week, total hours, and minutes in a week).			
If you do not exercise regularly every week, please choose option 1 and leave the other sections empty.			
1. No regular exercise every week			
	Days per week	Hours	Minutes
2. Slow-paced and easy aerobic exercise (No sweating or accelerated breathing – e.g., unhurried walking)			
3. Moderately fast aerobic exercise (Some sweating and/or accelerated breathing – e.g., fast-paced walking)			
4. Strenuous aerobic exercise (Heavy sweating and/or accelerated breathing – e.g., jogging or running)			
5. Strength training (For example, circuit training or gym training where exercises affecting various muscle group are repeated at least 8–12 times)			
6. Balance training (For example, Tai Chi, dance, ballgames, or balancing on one foot or on an uneven surface on all fours)			

The form used has been translated from the original Finnish here.

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Sleep quality and aerobic training among menopausal women—A randomized controlled trial☆

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ABSTRACT

Background: Menopause is associated with poor sleep quality and daytime sleepiness, which may lead to impaired quality of life and impaired functioning in daily activities.
Objective: To study whether exercise training improves sleep quality or decreases the amount of night time hot flushes among menopausal women with vasomotor symptoms.
Study design: A randomized controlled trial. Sedentary women ($N = 176$) aged 43–63 years with menopausal symptoms were randomized to a six-month unsupervised aerobic training intervention (50 min 4 times per week) or a control group. Both groups attended lectures on physical activity and health once a month.
Main outcome measures: Sleep quality and the amount of hot flushes disturbing sleep. The women reported daily via mobile phone whether hot flushes had disturbed their sleep and how they had slept (scale 1–5). Responses received by mobile phone over the 6-month period totaled on average 125 (5.2 per week) responses per participant.
Results: At baseline there was no difference between the groups in the demographic variables. Sleep quality improved significantly more in the intervention group than in the control group (OR 1.02; 95% CI = 1.0–1.05, $p = 0.043$). The odds for sleep improvement were 2% per week in the intervention group and a decrease of 0.5% per week in the control group. The amount of hot flushes related to sleep diminished ($p = 0.004$) by the end of the intervention.
Conclusions: Aerobic training for 6 months may improve sleep quality and reduce hot flushes among symptomatic menopausal women.

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1. Introduction

Regular aerobic exercise has been shown to reduce menopausal symptoms and improve health conditions among middle-aged women [1,2]. Among menopausal women sleep disturbances are common; 16–42% of premenopausal, 39–47% of perimenopausal and 35–60% of postmenopausal women have reported sleep disturbances [3]. It has been shown that vasomotor hot flushes and night sweats resulting in sleep disturbance may lead to depressive symptoms in these women [4]. Epidemiological studies indicate that exercise may be useful in improving sleep quality and in reducing daytime sleepiness [5–7]. However, the findings of long-term exercise studies are inconsistent: in a 4-month moderate-intensity walking and low-intensity yoga intervention no statistically significant effects on sleep quality were detected in symptomatic middle-aged women. The results moreover showed that both groups had fewer hot flushes [8]. In Turkish intervention study, 65 menopausal women participated in an aerobic training programme for 6 months, and the intervention group reported significantly fewer hot flushes and other menopausal symptoms [9].

Studies evaluating the effects of aerobic training on menopausal symptoms and sleep quality are rare, and the results have been contradictory [8,10–12]. In a 24-week walking trial for symptomatic menopausal women, the intervention did not alleviate most of subjects' symptoms, except sleep problems [13]. In our earlier study

CONSORT Flow Diagram

Fig. 1. Flow chart of the trial.

we reported results showing improved quality of life and fewer hot flushes among women in the exercise group than in the control group [14]. In reporting associations between hot flushes and subjective versus objective sleep disturbances findings may be due to varying methodologies in how sleep quality and patterns were ascertained [15]. The purpose of this study is to a report secondary analysis of the randomized trial concerning the question whether aerobic training improves sleep quality, or diminishes the amount of hot flushes among symptomatic menopausal women.

2. Materials and methods

With the approval of Pirkanmaa Hospital District Ethics Committee, we recruited 351 healthy Caucasian women via a newspaper announcement between January and March 2009. All women were screened for inclusion criteria through a telephone interview. All participants gave written informed consent. Details of the recruitment and participant selection have been reported previously [14]. From a total of 351 women, 176 participated in the study; 175 were excluded since they did not meet one or more of the inclusion criteria (Fig. 1). The duration of intervention was 24 weeks and the location of data collection was UKK Institute. Women were assigned to intervention and control groups by computer randomization. Envelopes including information on assigned group were delivered by research nurses [14].

The study was a secondary analysis based on a randomized controlled study and the main outcome measures were sleep quality and hot flushes disturbing sleep. The allocation ratio of the study was 1:1. Inclusion criteria for the study were: symptomatic (daily hot flushes), age 40–63 years, no current use or use in the past 3 months of hormone replacement therapy (HRT), sedentary (physical exercise less than twice a week), and 6–36 months since last menstruation. Women were excluded from the study if they were physically active (exercise ≥ 2 times per week, for at least 30 min each time) or had body mass index (BMI) over 35 kg/m^2 or had coronary heart disease or other disease preventing them from exercising. In addition, women who used medication for heart rate (β-blockers, sympathomimetics) were excluded. Menopausal status was verified by assay of plasma follicle-stimulating hormone (FSH), which had to exceed 30 IU/L [8].

2.1. Measurements

The outcome measures of the study were sleep quality and the amount of hot flushes disturbing sleep. The women reported daily via mobile phone whether hot flushes had disturbed their sleep and how they had slept (scale 1–5). Information on daytime and night-time hot flushes, aerobic exercise and sleeping was collected by mobile phone questionnaire twice a day during the trial. The Women's Health Questionnaire was used and reported in our earlier study [14] but was not integrated into the mobile phone

Table 1
Baseline characteristics among intervention and control groups. Values are shown as means ± standard deviations or frequencies and percentages.

	Intervention	Control	p^a for difference
N	83	86	
Age	54.2 ± 3.7	53.9 ± 3.8	0.60
University degree	20 (25.6%)	20 (24.7%)	0.89
Employed	66 (84.6%)	65 (78.3%)	0.31
Smoker or occasional smoker	13 (17.1%)	12 (14.8%)	0.70
Body mass index (kg/m^2)	26.1 ± 3.8	27.0 ± 4.5	0.19

[a] Differences between groups were tested by Student's t-test (continuous variables, normal distributions) or the chi-square test (dichotomized variables).

technology [16]. In the mobile phone questionnaire the women reported every morning whether hot flushes had disturbed their sleep (yes/no) and how they had slept. The mobile phone question was: "How did you sleep last night?" The sleep scale response options were scaled to the numbers, 5 = good to 1 = poor, responses were automatically transferred via 3G technology into digital format.

The power calculations for the study are based on the primary outcome measure of hot flushes as measured with the Women's Health Questionnaire [14]. Here we report secondary outcomes, namely hot flushes reported through a phone-based diary including frequency of hot flushes disturbing sleep and sleep quality.

Numbers of responses concerning the bothersomeness of menopausal symptoms or sleeping varied between 18,560 and 18,575 responses – on average there were 5.2 responses (3.3–6.0 responses per week). Table 2 presents the weekly frequencies of the responses (Table 2).

. Multivariate analyses were performed using individual responses. However, since the number of responses varied for each respondent, average number of responses per respondent (3.3–6.0 per week) was calculated, and used in the descriptive analysis of the data. The analysis method was multilevel logistic regression modeling, which can be performed with missing information on part of the responses. The analysis was unbalanced i.e. all respondents were included in the analysis although there were missing responses.

2.2. Exercise training

In the intervention group the exercise programme included aerobic training 4 times per week, with 50 min of exercise each time. The intensity of exercise was checked by ratings of perceived exertion (RPE) and participants were instructed to exercise at a level corresponding to 13–16 on a scale from 6 to 20, which corresponds to about 64–80% of maximal heart rate [17]. Ratings of perceived exertion (RPE) were used to check the intensity of aerobic training. Heart rate monitor belts were used to support RPE scale use. All participants were advised to exercise at 13–16 RPE and from the HR monitors we could ensure that the exercise had been strenuous enough. The HR monitors were also used in order to increase compliance. The women in the intervention group were advised to include at least two sessions of walking or Nordic walking (i.e. walking with poles or sticks, resembling cross-country skiing) while the other two sessions could include other aerobic exercise. Walking was mainly involved in the intervention because earlier trials have achieved positive effects on health among menopausal and post-menopausal women [18]. Nordic walking has also been observed to have a positive impact on training among 50–60 year old sedentary women [19].

Heart rate monitor belts (Suunto®, Memory Belt) were worn during all training sessions and the amount of exercise was reported by mobile phone. Heart rate ranges were not constructed for each participant because the monitors were used to confirm that the exercise was strenuous enough. Expenses arising from the use of mobile phones were covered during the trial. Exercise-based

injuries were monitored by means of questionnaires. No severe harm or adverse effects occurred during the trial.

2.3. Statistical analysis

Differences between groups at baseline were tested by Student's t-test for continuous variables when they were normally distributed. Chi-square test was used for dichotomized variables.

Ordinary logistic regression model assumes that the responses for the same individual are conditionally independent. However, serial dependence is expected between repeated responses recorded on the same individual in mobile phone questionnaire data and therefore a multilevel logistic and ordinal regression models were constructed to analyze the effects of exercise on sleep quality and menopause symptoms.

Using the latent-response formulation, the multilevel logistic regression model can be written as

$$y_{ij}^* = \beta_1 + \beta_2 x_{2j} + \beta_3 x_{3ij} + \beta_4 x_{2j} x_{3ij} + \varsigma_j + \varepsilon_{ij},$$

where x_{2j} represents group, x_{3ij} represents time in weeks, and $x_{ij} = (x_{2j}, x_{3ij})'$ is a vector containing both covariates, $\zeta_j \mid x_{ij} \sim N(0, \psi)$ and $\varepsilon_{ij} \mid x_{ij}, \zeta_j$ has a logistic distribution [20]. This model allow for a difference between groups at baseline (e.g. day one), linear changes in responses over time and the difference in the rate of improvement between groups, which can be viewed as the intervention effect (interaction between group and time). Fig. 2 is based on multilevel logistic regression and multilevel ordinal logistic regression of primary outcomes and estimates the trend separately in intervention and control groups (Fig. 2).

Multivariate analyses were performed using individual responses. However, since the number of responses varied for each respondent, the average number of responses by respondent (3.3–6.0 per week) was calculated, and used in the descriptive analysis of the data, Table 2.

The analysis was unbalanced i.e. all respondents were included in the analysis although there were missing responses. The missing responses were not processed at all, because multilevel logistic regression modeling can perform the analysis of the information on part of the responses.

All analyses were performed using STATA software (version 12.0 for windows), StataCorp LP, TX, USA.

3. Results

Women participating to the trial were aged 54 years on average, a quarter of them had university degrees and the majority of them were employed. A small proportion of the participating women were smokers (15–17%) and average body mass index was 26–27 kg/m^2. There were no significant differences between the groups in any baseline characteristics (Table 1).

Frequency of responses and proportion of responses reporting hot flushes or good sleep quality are shown in Table 2. As can be seen from the tables, the frequency remained at a similar level from week 2 to 21. The proportion of responses reporting hot flushes

Table 2
Frequency of responses, proportion of responses reporting hot flushes and good sleep quality.

| Week	Did hot flushes disturb your sleep last night?						How did you sleep last night?					
	Number of responses		Response/respondent		Proportion of "yes" responses (%)		Number of responses		Response/respondent		Well/fairly well proportion of responses (%)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
1	247	243	3.4	3.2	44.9	46.1	247	243	3.4	3.2	68.4	66.7
2	372	391	5.1	5.1	53.5	47.1	378	392	5.2	5.2	61.1	65.1
3	447	445	6.1	5.9	51.7	48.1	449	445	6.2	5.9	58.4	62.9
4	433	438	5.9	5.8	49.7	50.2	433	438	5.9	5.8	63.7	64.6
5	442	436	6.1	5.7	48.4	49.3	442	436	6.1	5.7	62.9	67.9
6	433	437	5.9	5.8	49.0	43.9	433	437	5.9	5.8	61.7	64.1
7	428	419	5.9	5.5	43.2	46.5	431	419	5.9	5.5	65.7	65.2
8	416	420	5.7	5.5	45.7	39.8	416	420	5.7	5.5	66.8	65.0
9	408	415	5.6	5.5	40.0	42.7	408	415	5.6	5.5	62.7	68.0
10	420	379	5.8	5.0	40.2	42.5	420	379	5.8	5.0	66.4	64.4
11	405	379	5.5	5.0	38.8	41.7	405	379	5.5	5.0	64.4	65.4
12	396	403	5.4	5.3	40.9	44.4	396	403	5.4	5.3	66.4	64.0
13	397	400	5.4	5.3	40.8	40.5	397	400	5.4	5.3	65.2	67.0
14	411	399	5.6	5.3	40.4	42.6	412	399	5.6	5.3	66.5	60.9
15	402	388	5.5	5.1	41.0	44.1	403	388	5.5	5.1	61.8	62.9
16	399	393	5.5	5.2	35.3	45.8	399	393	5.5	5.2	69.4	63.4
17	401	368	5.5	4.8	35.4	45.9	401	369	5.5	4.9	70.8	61.5
18	383	380	5.2	5.0	38.6	47.6	383	380	5.2	5.0	68.1	61.1
19	386	384	5.3	5.1	35.8	47.1	386	384	5.3	5.1	69.9	63.3
20	376	370	5.2	4.9	43.4	48.1	376	370	5.2	4.9	63.3	59.5
21	365	393	5.0	5.2	39.7	41.5	365	393	5.0	5.2	70.7	64.1
22	342	349	4.7	4.6	35.7	44.1	342	349	4.7	4.6	69.9	64.8
23	333	337	4.6	4.4	41.4	43.9	333	337	4.6	4.4	68.8	60.2
24	270	282	3.7	3.7	36.7	43.6	270	282	3.7	3.7	70.0	63.8
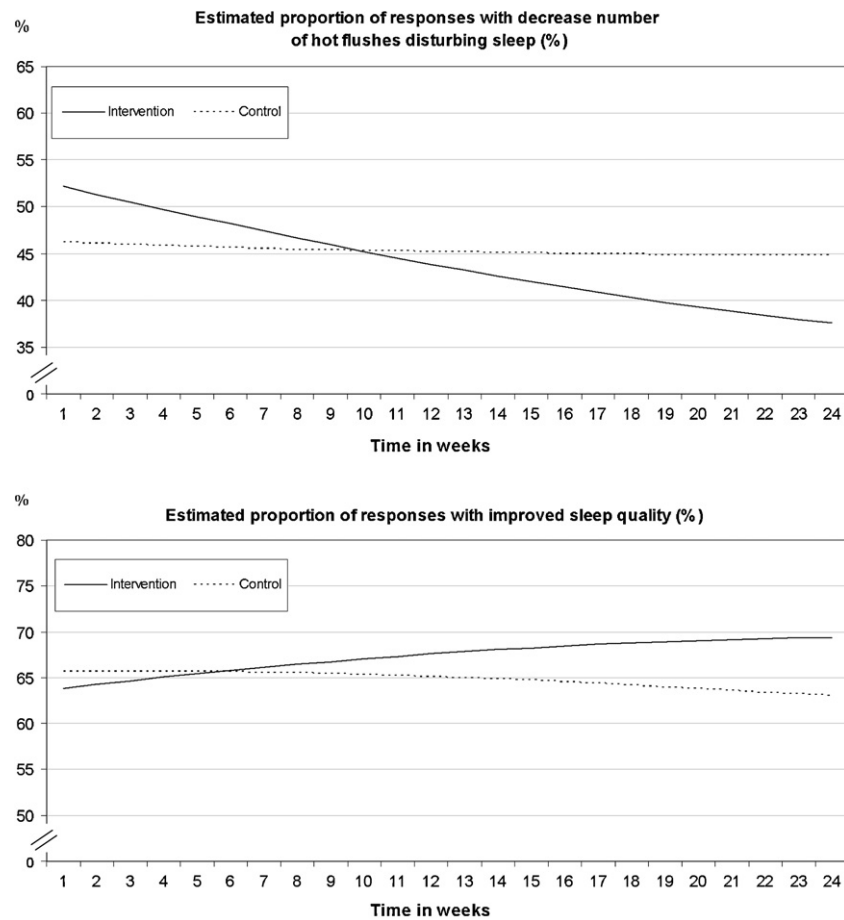
Fig. 2. Observed and estimated proportion of responses with improved sleep quality and number of hot flushes over 6 months.

varied between 3.2 and 6.1 per woman weekly and the proportion of responses reporting good quality of sleep between 3.2 and 6.2, respectively.

At baseline there was no difference between the groups in reporting poor quality of sleep ($p = 0.62$). Sleep quality improved significantly more in the intervention group than in the control group (OR 1.023; 95% CI = 1.001–1.046, $p = 0.043$) (Table 3). The odds for sleep improvement were 2% per week in the intervention group and a decrease of 0.5% per week in the control group. In the course of 24 weeks the women in the intervention group reported better sleep quality than the women in the control group and the development between groups was diverse and significant (Fig. 2). The differences between groups were apparent 6–10 weeks after the beginning of the trial, not only at 24 weeks. The modeling in Fig. 2 took into account the change in sleep quality and hot flushes disturbing sleep during the whole period (Fig. 2).

There were no-between group differences at baseline in hot flushes related to sleep ($p = 0.17$). After approximately two months the women in the intervention group reported fewer hot flushes disturbing their sleep than the women in the control group. Hot flushes decreased significantly more in the intervention group than in the control group (OR = 0.956, 95% CI = 0.926–0.986, $p = 0.004$) (Table 3).

In the present study the drop-out rate was fourteen participants in the intervention and eight in the control group, thus quite low. We also evaluated whether decreased vasomotor symptoms were associated with improved sleep quality by incorporating these variables into the same multivariate model (not shown in the tables).

The fewer vasomotor symptoms disturbed sleep, the better sleep quality was reported,

4. Discussion

Our study showed that an aerobic training intervention may improve sleep quality and reduce the amount of hot flushes causing disturbed sleep among middle-aged women. We used a novel method of daily mobile phone contact for data collection to monitor sleep quality and menopausal symptoms. This yielded much more information gathered during the intervention than can be collected by conventional methods.

The effect of aerobic training on sleep disorders among menopausal women has been contradictory. Among symptomatic middle-aged women walking or low-intensity yoga programmes in a 4-month randomized controlled trial resulted in no effect on sleep quality [8]. After controlling for the effects of physical activity, only menopausal symptoms were associated with overall sleep quality [8]. Earlier randomized intervention studies have shown that adults with moderate sleep complaints can improve their sleep quality by moderate-intensity exercise programme [21]. Longer exercise interventions and greater intensity may be needed to achieve greater improvements [21].

The strengths of our study include the randomized controlled trial design and fairly large sample size. Furthermore, participants' adherence was good since the drop-out rate was low in both intervention and control groups. Better adherence than expected is an important strength of the study. Aerobic training improved indicators of quality of life, such as physical functioning, physical role

Table 3
Multilevel logistic regression (sleep adequacy and menopause symptoms) and multilevel ordinal regression (sleep quality) odds ratios (OR), 95% confidence intervals (CI), z statistics[a] and p-values. Followed for 6 months (18,560–18,575 responses).

	Group			Week			Group × week		
	OR (95% CI)	z test	p-Value	OR (95% CI)	z test	p-Value	OR (95% CI)	z test	p-Value
Menopause symptoms	1.526 (0.831–2.802)	1.36	0.17	0.992 (0.971–1.013)	−0.75	0.45	0.956 (0.926–0.986)	−2.87	0.004
Sleep quality	0.890 (0.565–1.402)	−0.50	0.62	0.996 (0.981–1.012)	−0.47	0.64	1.023 (1.001–1.046)	2.02	0.043

[a] The z statistic is $\hat{\beta}/SE(\hat{\beta})$.

limitation and reduced hot flushes [14]. Intervention adherence was explored in our earlier study [14] by taking into account frequency of exercise sessions based on a heart rate monitor belt. In this analysis, improved quality of life (primary outcome) was dependent on exercise sessions realized. Thus, the better the adherence, the better the outcome, which may also be the case in to sleep-related outcomes. However, numbers of compliant women were small and this prevented a valid analysis of sleep and compliance in the trial.

Findings from another trial support the results as regards improved sleep but not hot flushes or night sweats after a 24-week exercise intervention among symptomatic midlife women not taking hormone therapy [13]. Likely as a consequence of the aerobic training in the middle of the intervention, sleep quality was better in the intervention group than in the control group. Another strength was that we used a novel method for daily data collection namely mobile phone and it was possible to obtain more information than when using paper-based questionnaire.

In the present study the women in the intervention group but not those in the control group reported better sleep quality and a reduction in menopausal symptoms at the end of the intervention. Consciousness of participating in the research project may have had an influence, such as the change in exercise habits in the control group, in which it was possible to attend monthly lectures on physical activity and health.

As weaknesses we concede that the mobile phone method was not a validated instrument for data collection. The scale used in the evaluation of subjective sleep (1–5) possibly lacked reliability, since it had not been previously tested. The assessment of sleep was subjective and not as objective as a sleep diary or actigraphy measurements, which were not available. Since our study was a secondary analysis of a primary study, there is uncertainty concerning the necessary power of the study to reveal sleep-related outcomes. However, there were differences between the groups and thus the study was not underpowered. Magnitude of improvement was perceived as a significant decrease in hot flushes. Our results are generalizable to the subgroup of women with verified menopausal symptoms, not to all menopausal women.

In the cross-sectional multicentre study an association was found between hot flush frequency and severity and objective evidence of disrupted sleep among postmenopausal women [15]. Actigraphy data collection was used but, it was found that subjective symptoms may be more important to patients than objective findings [15]. According to this the mobile phone questionnaire used in our study was a feasible and useful method for data collection.

The usability of the mobile phone for data collection was evaluated with the System Usability Scale (SUS) questionnaire two months after the intervention. The feasibility evaluation was based on the frequency of responses and open-ended questions [16]. The SUS score was 75.4 (range 0–100, N = 107) for all participants and mobile phone diary was found to be a feasible and usable tool for data collection in clinical trials [16]. Conventional methods have their limitations, since the subjective responses cover a short time frame whereas by mobile phone it is possible to elicit more information from a longer period and on-line. The present study was long, 6 months, which may have decreased participants' interest in responding to daily inquiries during the intervention.

4.1. Conclusions

Aerobic training may improve sleep quality and reduce hot flushes related to sleep disturbance among midlife women. In future studies related to quality of sleep during menopause, mobile phone methodology could be useful for data collection.

Contributors

Competing interest

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Ethical approval

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Open Access   **Research**

BMJ Open | Long-term effect of physical activity on health-related quality of life among menopausal women: a 4-year follow-up study to a randomised controlled trial

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ABSTRACT

Objectives: The aim of the study was to explore the long-term effects of physical activity intervention on quality of life (QoL) 4 years after an original randomised controlled trial (RCT).

Design: Cohort study after an RCT.

Setting: 95 of the 159 women from the original RCT participated in weight, height and waist circumference measurements, performed the UKK 2 km Walk Test and completed the SF-36 Health Survey questionnaire. Multilevel mixed regression models were performed in order to compare the original and current group in an RCT setting.

Participants: There were 159 participants in the original RCT; 2.5 years later, 102 of the women responded to a questionnaire and 4-year after the trial, there were 95 respondents. The inclusion criteria in the original RCT were: being symptomatic, experiencing daily hot flushes, age between 40 and 63 years, not using hormone therapy now or in the past 3 months, sedentary lifestyle and having last menstruated 3–36 months earlier.

Main outcome measure: Health-related QoL as measured with the SF-36 instrument.

Results: Women in the intervention group had a significantly higher probability of improved physical functioning (OR 1.41; 95% CI 1.00 to 1.99) as compared with women in the control group. In addition, women in the intervention group had higher odds of good role functioning (OR 1.21; 95% CI 0.88 to 1.67), physical health (OR 1.33; 95% CI 0.96 to 1.84) and general health (OR 1.14; 95% CI 0.81 to 1.62), relative to women in the control group, although the differences did not reach statistical significance.

Conclusions: Women in the intervention group showed positive long-term effects on physical and mental dimensions of QoL after 4 years.

Trial registration number: ISRCTN54690027.

Strengths and limitations of this study

- The core strengths of the study are its prospective study design and repeated assessments of physical activity behaviour at several time points after intervention.
- Our study underlines the importance of physical activity during menopausal transition.
- The response rate (59.7%) was low and women with an adverse lifestyle were more likely to be found among non-responders.

middle-aged women.[1] A positive association between physical activity (PA) and quality of life (QoL) has been explored in many studies.[2–7] PA has been associated with lower rates of cognitive and physical decline among postmenopausal women.[8] In addition, PA appears to have positive effects on work ability, both short and long terms.[9] Hormone therapy (HRT) is widely used as treatment for menopause symptoms, even though exercise has been deemed an alternative option for alleviating their symptoms and improving QoL in midlife.[1 10] In an 8-year follow-up study, PA has been found to be a significant factor among menopausal women who had stable weight or were highly educated.[4] Increasing one's level of PA during menopausal transition and the postmenopausal period or at least maintaining the recommended level has also been suggested to reduce various psychological symptoms.[11]

We previously reported results from our menopausal health and PA intervention randomised controlled trial (RCT)[6 12] examining aerobic training, and improved menopausal and health-related QoL among menopausal women. Women in the intervention group showed significantly larger decrease in the frequency of night-time hot flushes. These

INTRODUCTION

Many physiological and psychological signs and symptoms occur in the lives of

findings were based on information collected through mobile phone diaries. Additionally, the diaries pointed to better sleep quality among women in the intervention group as compared to those in the control group.[7] We also reported that the 6-month exercise intervention had effects on work ability 2½ years after the RCT.[9]

The aim of the follow-up study reported here was to explore the long-term effects of the PA intervention on QoL 4 years after the RCT.

MATERIALS AND METHODS

The study population consisted of a sample of women who participated in a follow-up 4 years after the beginning of the trial, which was in 2009.[6] The intervention study in 2009 was a RCT (ISRCTN54690027, http://www.controlled-trials.com/) in which the women were randomised into an intervention and a control group. Criteria for inclusion in the intervention study were: being symptomatic, experiencing daily hot flushes, age between 40 and 63 years, not using HRT now or in the past 3 months, having a sedentary lifestyle (with aerobic training under twice a week) and having last menstruated 3–36 months earlier. Women who were physically active (exercising two or more times a week, at least 30 min at a time); whose body mass index (BMI) was above 35 kg/m^2; or who had coronary heart disease, orthopaedic or other diseases preventing them from exercising, were excluded from the study. Further, women who were using medication influencing heart rate, or using β-blockers, were excluded, since they would have biased the results pertaining to heart rate. Menopausal status was verified via assay of plasma follicle-stimulating hormone (FSH exceeding 30 IU/L). Before the trial began, daytime and night-time hot flushes were recorded in a 2-week diary, with the women instructed to record a sensation of warmth, with or without concomitant sweating, as a hot flush, and the daily frequency of hot flushes before the intervention was estimated. During the intervention, the number of hot flushes, both daytime and night-time, was calculated. In total, 159 women participated in the study, and the duration of the intervention was 6 months.[6]

The women in the intervention group engaged in aerobic training four times a week, with 50 min of exercise each time. They were instructed to exercise at a level of about 64–80% of maximal heart rate, whereas the women in the control group were instructed to keep their PA habits unchanged. In the intervention group, at least two PA sessions had to consist of walking or Nordic walking, while the other sessions could include walking, Nordic walking, skiing, jogging, cycling, swimming, aerobics and/or gymnastics. The intervention primarily included walking because earlier trials showed it to have favourable effects on health among menopausal and postmenopausal women.[13] Information on hot flushes and aerobic training was collected via mobile phone questionnaires twice a day. Responses were automatically

transferred to digital format via 3G technology.[14] The SF-36 Health Survey questionnaire was used to measure health-related QoL. This questionnaire has been validated in Finland[15] and is known to be a reliable measure of QoL. It is composed of 36 items, addressing eight dimensions of QoL: physical functioning, physical role limitations, bodily pain, general health, vitality, social functioning, emotional role limitations and mental health.[6] The scores for each of the eight dimensions were transformed linearly to a scale ranging from 0 (maximal impairment) to 100 (best QoL).[6]

The first follow-up questionnaire was posted to the participants 2½ years after the intervention began, and 102 of the 159 women responded. Results from this follow-up questionnaire have been reported in earlier work.[9]

Four years after the beginning of the trial, the participants (n=159) were asked to take part in the second follow-up study. After this request, 95 of the women responded to the questionnaire and participated in the measurements. All the participants gave written consent. Weight, height and waist circumference were measured with lightweight clothing by staff of the UKK Institute, and the UKK 2 km Walk Test was performed.[16] The participants completed the SF-36 Health Survey questionnaire on health-related QoL, at home.[15] In addition, they carried a Hookie accelerometer for a week, in order to measure their daily PA. Also, the women were asked to take notes, in a 1 week diary, about the type and intensity of their PA, and to note the exercise time. Specific questions related to accelerometer use and the UKK 2-km Walk Test will be reported on in a separate article. In addition, the participants were asked to use a 1 week diary to note the number of daytime and night-time hot flushes experienced, the time they fell asleep and woke up, and their judgement of their sleep quality. A flow chart of the participants' data is shown in figure 1.

STATISTICAL ANALYSIS

The characteristics of the study population are described best in terms of means and SEMs, or frequencies and percentages (table 1).

Multilevel mixed effects logistic regression models were constructed to account for the within-subject correlation between four time points. The odds model was used for analysis of the association between the outcomes both on the physical dimensions (physical functioning; role functioning, physical; freedom from pain; and physical health) and on the psychological dimensions (role functioning; emotional; vitality; emotional well-being; social functioning; general health; and mental health) over time and between the intervention versus the control group. Multilevel linear regression models could not be used, because the distributions of SF-36 variables were skewed or discrete. Since the conditions necessary for the use of multilevel ordinal logistic

Figure 1 Participant flow chart.
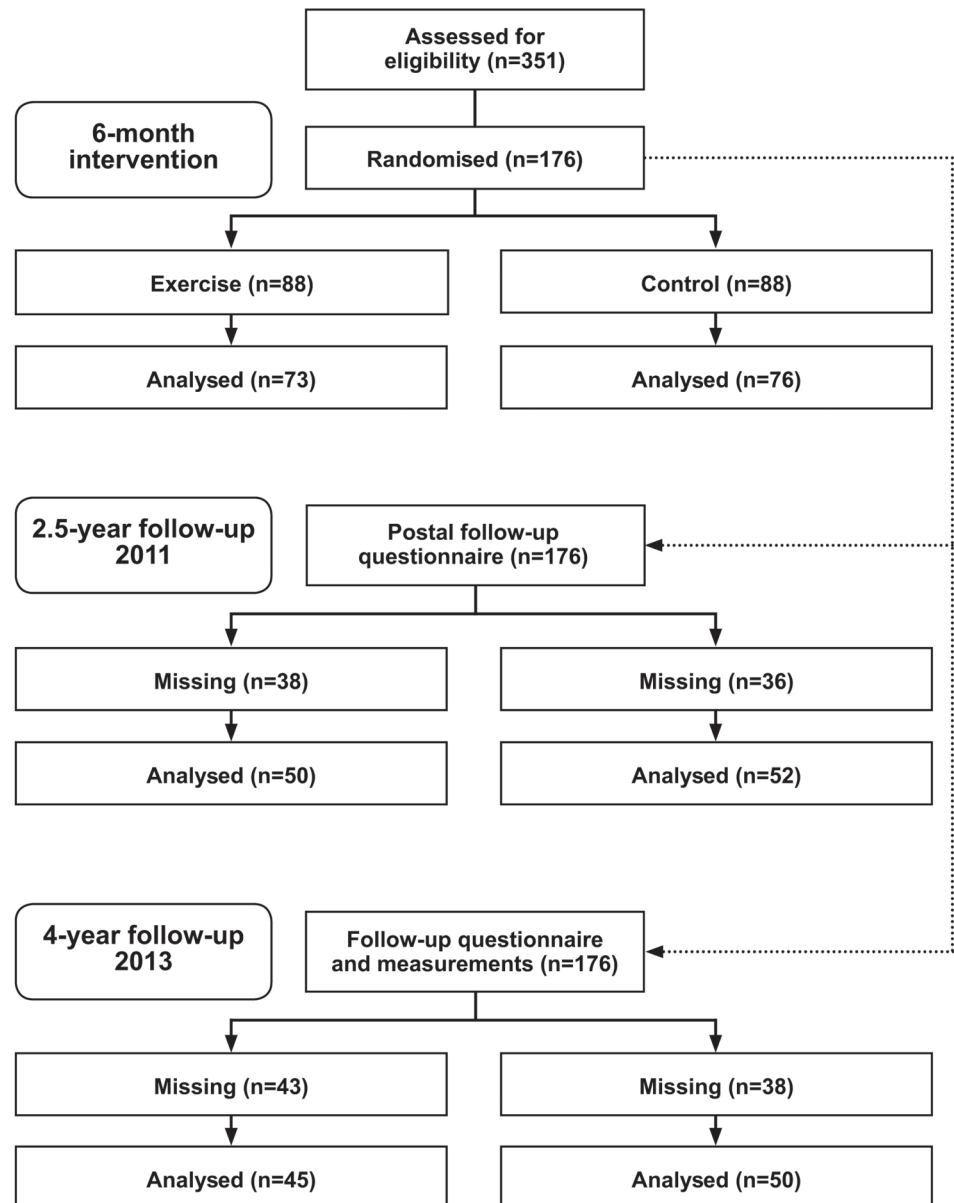
regression models were not met, these models could not be used either.

The multilevel model for dichotomous outcome y_{ij} at time i for person j can be expressed as

$$\text{logit}\{\Pr(y_{ij} = 1 | x_{ij}, \varsigma_j)\} = \beta_1 + \beta_2 x_{2j} + \beta_3 x_{3ij} + \beta_4 x_{2j} x_{3ij} + \varsigma_j,$$

where x_{2j} represents group, x_{3ij} represents time, $\mathbf{x}_{ij}=(x_{2j}, x_{3ij})'$ is a vector containing both covariates, and ζ_j is a person-specific random intercept. This model allows for a difference between groups at baseline β_2, and linear changes in the log odds of outcome over time with slope β_3 in the control group and slope $\beta_3+\beta_4$ in the intervention group. Therefore, β_4, the difference in the rate of improvement (on the log odds scale) between groups, can be viewed as changing over time between groups.[17] Also second-order and third-order functions of time were included in the model, for testing of whether

a model with a non-linear effect improved the fit. A likelihood-ratio test was used for models' comparison, to identify the model fitting best. The parameter estimates were presented as ORs with 95% CIs.

The proportions for the physical and mental dimensions of QoL by time are shown in figures 2 and 3. The outcomes of QoL dimensions were classified in two categories according to medians. Proportions of women having higher or equal score than median are shown in figures. Higher score defines more favourable health state. The Wilson score method without continuity correction:

$$\frac{(2np + z^2 \pm z\sqrt{(z^2 + 4npq)}}{2(n + z^2)},$$

where n denotes the sample size, p is a single proportion, q=1−p and z denotes the standard normal deviate

associated with a two-tailed probability α, was used to calculate the 95% CIs for the proportions in figures 1 and 2.[18]

The significance of all tests was determined to be at a p value <0.05, and data analyses were performed with Stata Statistical Software, Release 12 (from StataCorp LP, College Station, Texas, USA).

In these models, we used all available responses from women even if they had not responded to all points of data collection. As sensitivity analyses, we performed multilevel mixed effects logistic regression models also for women who responded to all four time points (N=75). We also analysed the results by using only the second follow-up (without 2.5 years follow-up).

RESULTS

Most of the participants (68%) were employed or part-time workers (9%) when the intervention began. Over the course of the 4 years, 7–20% of the women were in part-time employment.

The women participating in the 4-year follow-up were, on average, 58 years of age, and their mean BMI was 26–27 kg/m². In the follow-up, no significant change in BMI was observed. The proportion of women using HRT was higher at the 4-year follow-up point than before the intervention. In the follow-up, no significant differences were observed in use of blood pressure and cholesterol medication. Use of headache medicine and other painkillers, sedatives and sleeping pills, and antidepressants, decreased within the intervention group and also among those in the control group. The intervention and the follow-up showed increased use of vitamins and mineral preparations in the intervention group (from 55.1% to 68.9%) while in the control group their use declined (from 51.9% to 34.0%); these results are presented in table 1.

The women in the intervention group had a greater likelihood of improvement on the various QoL dimensions from baseline to the end of 4-year follow-up. Overall, the results show that women in the intervention group sustained their improved QoL more often than women in the control group did. Figures 2 and 3 show the proportions observed for the physical and mental dimensions of QoL.

With the follow-up measurements, we found that women in the intervention group displayed an improvement in physical functioning (OR 1.41; 95% CI 1.00 to 1.99) when compared with the control group. However, no significant differences were observed between groups for the other variables, as is indicated by table 2. Results for mental dimensions of QoL did not reach statistical significance (shown in table 3).

The women who did not participate in the 2½-year and 4-year follow-up studies (N=47, 28.1%) were younger at baseline (53.0 years, in contrast to 54.5 years), they had a higher BMI (28.0, in contrast to 26.3) and they were

Table 1 Characteristics (mean and SEM or frequency and percentage) of all participants

	Baseline		End of intervention		2½ Years		4 Years	
	INT	CON	INT	CON	INT	CON	INT	CON
N	78	81	75	80	50	52	45	50
Age, mean (SEM)	54.4 (0.42)	54.1 (0.41)						
BMI, mean (SEM)	26.4 (0.45)	27.2 (0.50)	25.2 (0.53)	26.2 (0.62)			26.0 (0.56)	26.6 (0.79)
Use of medicine in the past 7 days								
Hormone replacement therapy, N (%)	2 (2.6)	1 (2.8)	5 (6.7)	2 (2.5)	10 (20.4)	12 (24.5)	14 (31.1)	8 (16.0)
Blood pressure and cholesterol medicine, N (%)	16 (20.5)	12 (14.8)	12 (18.8)	12 (17.9)	13 (26.5)	16 (32.7)	10 (22.2)	11 (22.0)
Headache medicine and other painkillers, sedatives and sleeping pills, and antidepressants, N (%)	43 (55.1)	33 (40.7)	32 (50.0)	38 (56.7)	25 (51.0)	29 (59.2)	14 (31.1)	14 (28.0)
Vitamin and mineral supplements, N (%)	43 (55.1)	42 (51.9)	39 (60.9)	36 (53.7)	28 (57.1)	32 (65.3)	31 (68.9)	17 (34.0)

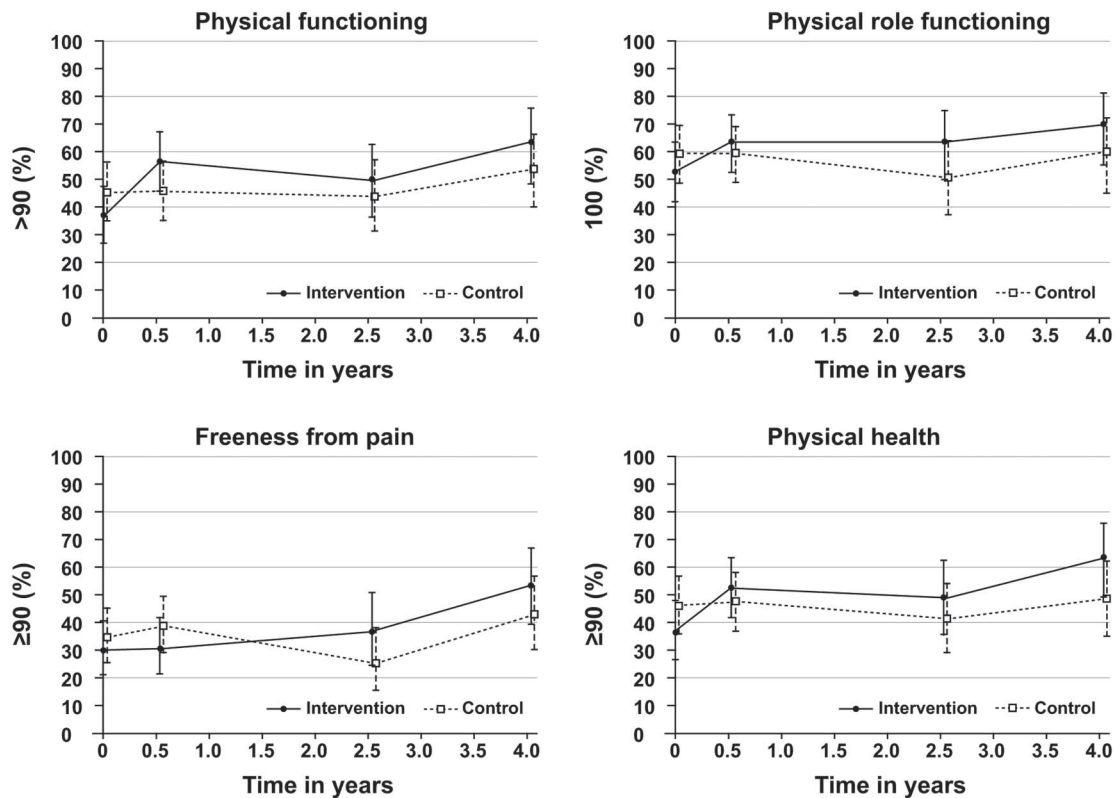BMI, body mass index; CON, control; INT, intervention.

Figure 2 Proportions for the physical dimensions of quality of life (QoL) by time. Outcomes of QoL dimensions were classified into two categories according to medians. Proportions of women having higher or equal score than median are shown. Higher score defines more favourable health state.

regular smokers more often (27.3%, in contrast to 12.0%) than the women who participated in the follow-up study.

As sensitivity analyses, we performed multilevel mixed effects logistic regression models also for women who responded to all four time points (N=75). When these women with non-missing responses were taken in the analyses, intervention women had significantly higher probability of improved mental health functioning (OR 1.96; 95% CI 1.13 to 3.40) as compared with control women (not shown in the figures or tables). Results from the models including only 4-year follow-up responses without 2.5 year responses were similar to the results in the current tables and figures.

DISCUSSION

The physical exercise intervention may have long-term positive effects on health-related QoL among the group of menopausal women experiencing daily symptoms of menopause. Women in the intervention group had a higher probability of improvement in physical function-ing dimension of QoL from baseline to the end of 4-year follow-up. Among a subsample of women who responded to both follow-up studies, significant results between the groups were found between mental health dimensions. Overall, the results show that women in the intervention group sustained their improved QoL on

both physical-health and mental-health dimensions more often than did women in the control group.

Findings from previous studies have shown that getting physical exercise is correlated with lower esti-mates of the perceived severity of symptoms and that exercise moderates the psychological symptoms asso-ciated with menopause.[19 20] Our study is in line with these findings both in physical and mental dimensions. A report on an 8-year population-based follow-up study from Finland[4] states that motivation to increase one's PA during menopausal transition might be an explanatory factor connected with improved QoL. According to that follow-up study, women whose PA increased or remained stable, had a higher probability of improved QoL than women whose PA decreased.[4] Elavsky[19] found, in a longi-tudinal study of middle-aged women, that PA was asso-ciated with self-worth and by this mechanism improved QoL. Furthermore, Stojanovska et al[1] recently published a review of the role of PA in reducing symptoms of menopause. They considered both somatic and psycho-logical dimensions. On the basis of their review, physical exercise has been proposed as an alternative to HRT, for improving the QoL of menopausal women.

Our study has its limitations, in the response rate (59.7%) and the fact that women with an adverse life-style were more likely to be found among non-responders. All initial participants were included in the analyses, even if they did not participate to the end of
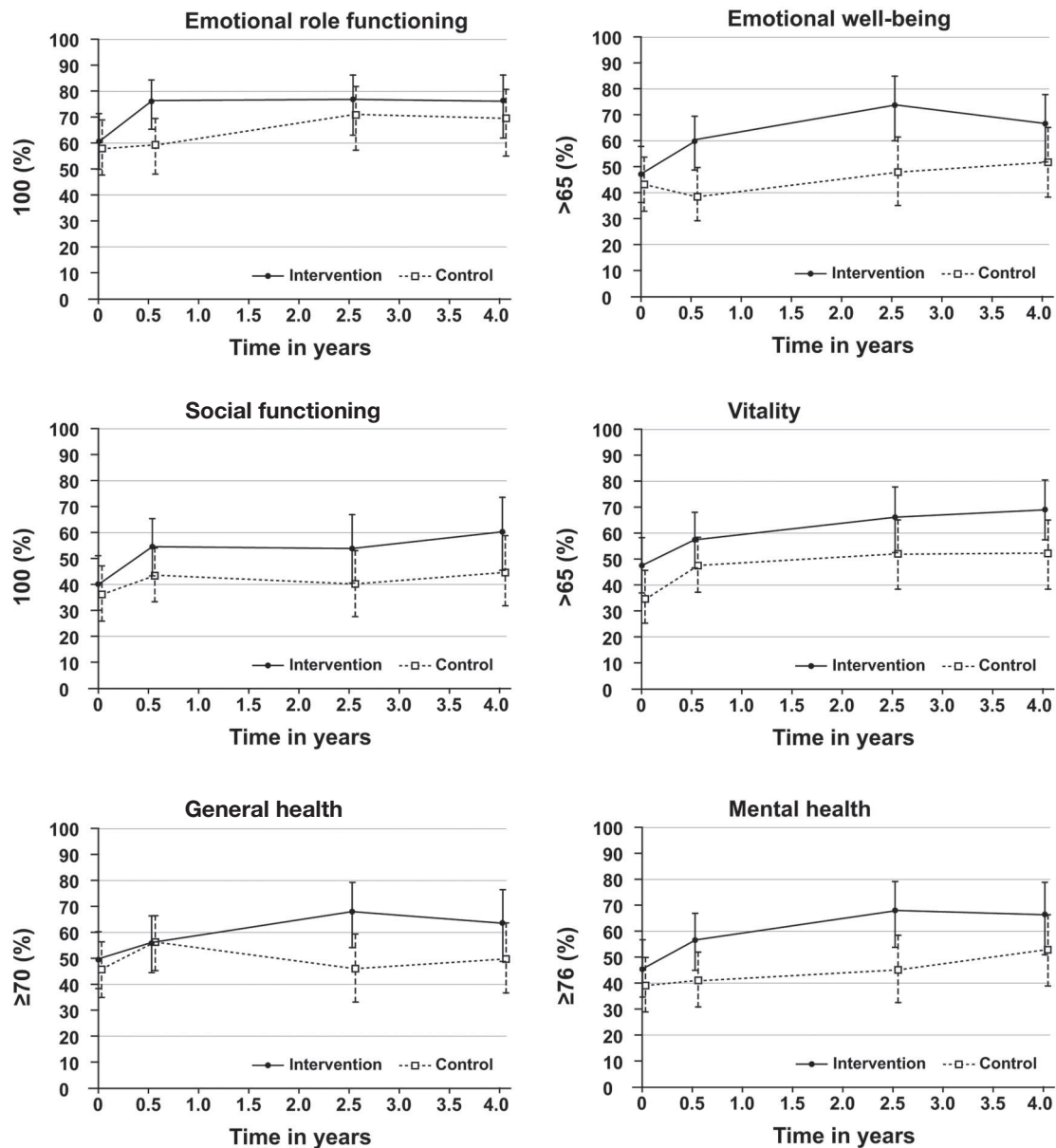
Figure 3 Proportions for mental dimensions of quality of life (QoL) by time. Outcomes of QoL dimensions were classified into two categories according to medians. Proportions of women having higher or equal score than median are shown. Higher score defines more favourable health state.

the intervention or the 2.5-year follow-up study. The results of the study showed a tendency towards increased QoL, although there were no statistically significant

differences for any cores on the physical and mental dimensions of QoL between the groups. Our findings are similar to those from a large multiethnic volunteer

Table 2 Multilevel mixed effects logistic regression, ORs and 95% CIs of physical dimensions of QoL

	Physical functioning	Physical role functioning	Freeness from pain	Physical health
N	159	159	159	159
Group$_{baseline}$	0.52 (0.17 to 1.61)	0.84 (0.33 to 2.12)	0.58 (0.22 to 1.54)	0.72 (0.28 to 1.81)
Time	1.03 (0.10 to 11.1)	0.93 (0.75 to 1.17)	1.07 (0.85 to 1.34)	0.97 (0.77 to 1.22)
Group×time	44.7 (1.45 to 1374)*	1.21 (0.88 to 1.67)	1.25 (0.90 to 1.73)	1.33 (0.96 to 1.84)
Time^2	0.86 (0.19 to 3.82)			
Group×time^2	0.11 (0.01 to 0.91)*			
Time^3	1.04 (0.82 to 1.32)			
Group×time^3	1.41 (1.00 to 1.99)*			
*p<0.05.				

Table 3 Multilevel mixed effects logistic regression, ORs and 95% CIs of mental dimensions of QoL

	Emotional role functioning	Vitality	Emotional well-being	Social functioning	General health	Mental health
N	159	159	159	159	159	
Group$_{baseline}$	1.74 (0.72 to 4.18)	1.93 (0.82 to 4.57)	2.50 (0.86 to 7.28)	1.46 (0.60 to 3.55)	1.04 (0.33 to 3.25)	1.98 (0.77 to 5.13)
Time	1.25 (1.00 to 1.57)*	1.28 (1.03 to 1.58)*	1.31 (1.03 to 1.67)*	1.10 (0.89 to 1.36)	0.98 (0.78 to 1.24)	1.29 (1.03 to 1.63)*
Group×time	0.93 (0.67 to 1.29)	0.97 (0.71 to 1.33)	1.02 (0.72 to 1.44)	1.05 (0.77 to 1.43)	1.14 (0.81 to 1.62)	0.97 (0.70 to 1.35)

*p<0.05.
QoL, quality of life.

cohort of postmenopausal women, in which self-reported PA was, for the most part, stable over 8 years of follow-up. There was approximately 0.3 metabolic equivalent (MET) of actual growth in recreational PA per year×8 years=2.4 MET h/week, which represented 30 min of brisk walking in this case.[21]

Loss-to-follow-up analysis showed differences between participants and those lost to follow-up. Non-responding women differed from responding women in their weight, age and smoking status. Respondents were lighter, older and were less often regular smokers than non-responding women. These differences might have had an effect on the findings in the follow-up study. If all of the original participants had been studied, the differences between the groups might have been larger. When limiting the analyses to women responding to both follow-up measurements, the results differed. Explanation for this may be due to the fact that conscientious women responding to questionnaires may have benefited even more from available support to be physically active. A follow-up study in itself can be considered an intervention, producing a non-differential support to the original groups in the RCT.

The core strengths of the study reported here are its prospective study design and repeated assessments of PA behaviour, which made it possible to examine the differences between groups in the follow-up.[17] Many studies have described PA patterns through the lens of cross-sectional data, while fewer studies have examined changes between several time points after an intervention. PA has been reported to decrease with age,[22] but contrary findings have also been reported. Earlier, our research group published the finding[6] that women in menopausal transition shifted their behaviour in the other direction. Therefore, increased PA could be explained by higher motivation for lifestyle changes during the menopausal transition. In a longitudinal study by Smith-DiJulio et al,[23] the researchers found that a woman's sense of control, of her life and satisfaction with it, and her ability to make use of the available social support, predicted greater well-being during menopause. This is consistent with our findings, as we observed improvement in vitality, emotional well-being and mental health during the follow-up, even though the results did not reach a level of statistical significance.

Our results may be generalised to menopausal women having daily vasomotor symptoms, such as hot flushes or sleep problems, according to the inclusion criteria in the original RCT.[6] Overall, our study underlines the importance of PA during menopausal transition. In addition, it supports the assumption that menopause can be seen as a window of opportunity, since it may motivate women to modify their lifestyle. Menopausal women should be encouraged to participate in regular exercise and supported in this endeavour through development of easily implemented home-based exercise programmes or incorporation of PA programmes into public-health initiatives.[10]

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CONCLUSION

Women in the intervention group showed positive long-term effects on physical and mental dimensions of QoL after 4 years. Menopause is a window of opportunity for increasing PA and thereby future QoL. This finding is important, since an increase in PA may be associated with a lower future disease burden.

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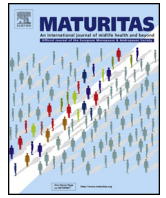
Hot flushes among aging women: A 4-year follow-up study to a randomised controlled exercise trial

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ABSTRACT

Objectives: The aim of this follow-up study was to explore the long-term effects of a 6-month trial of exercise training on hot flushes. The follow-up was 4 years after the exercise intervention ended.
Study design: A cohort study after a randomised controlled trial. Ninety-five of the 159 randomised women (60%) participated in anthropometric measurements and performed a 2-km walk test. Participants completed a questionnaire and kept a one-week diary on physical activity, menopause symptoms and sleep quality. The frequency of 24-h hot flushes was multiplied by severity and the total sum for one week was defined as the Hot Flush Score (HFScore). Multilevel mixed regression models were analysed to compare the exercise and control groups.
Main outcome measure: Hot Flush Score (HFScore) as assessed with the one-week symptom diary.
Results: The women in the exercise group had a higher probability of improved HFScore, i.e. a decrease in HFScore points, adjusted for hormone therapy (OR 0.95; 95% CI 0.90–1.00) than women in the control group at the 4-year follow-up. After additional adjustment for sleep quality, the result approached statistical significance at HFScore $\geq$ 13 with women in the exercise group. Women who had the least amount of hot flushes, HFScore < 13, benefited most from exercise during the 4-year follow-up when compared with women in the control group.
Conclusions: Women in the exercise group had positive effects on their HFScore 4 years after a 6-month exercise intervention.

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1. Introduction

Vasomotor symptoms are common during and after the menopausal transition; about 2/3 of menopausal women experience vasomotor symptoms or hot flushes to some degree [1]. Hot flushes are characterized by a sudden sensation of heat, flushing of the face and chest, sweating, and are often accompanied by anxiety and palpitations [2]. In addition, night sweats, dizziness, headaches, atrophic vaginitis, bladder irritability, mood changes, sleep disturbances, aches and pains are common menopausal symptoms [3,4]. Vasomotor symptom fluctuations are influenced by factors such as lifestyle, diet, climate, women's attitudes and societal role [3].

The most effective treatment to alleviate menopausal hot flushes is hormone therapy (HT) but the risks may outweigh the benefits [2] and alternative treatments are needed [5]. Since physical activity (PA) during leisure has positive effects on overall health, exercise training has been suggested as a useful way to alleviate symptoms and engage in a regular exercise program during and after menopause [6,7]. A population-based cross-sectional study with 49-year-old women (n = 2606) [8] responding to a postal survey indicated that fulfillment of exercise recommendations [9] was associated with better quality of life with four adjusted dimensions of Women's Health Questionnaire (WHQ) [10]—anxiety/depressed mood, well-being issues, somatic symptoms and memory/concentration problems [8]. However, the effects of training on menopausal symptoms remain contradictory [11]. One randomized moderate-intensity aerobic exercise intervention did not seem to decrease the risk of having menopause symptoms and may increase the hot flush severity [12]. Another

training studies examined the effectiveness of exercise on hot flushes or night sweats, among postmenopausal women, not using HT and exercise was not found to alleviate vasomotor symptoms but small improvements was observed in sleep quality, insomnia and depression [13,14].

In our RCT, we found that the frequency of hot flushes decreased after 6 months of aerobic training among women in the exercise group as compared to the control group [15,16]. Furthermore, training improved sleep quality and decreased sleep disturbing hot flushes [17]. A 4-year follow-up of our trial showed that women in the exercise group sustained improved QoL more often than women in the control group did [18].

The aim of the present report was to explore the long-term effects of the exercise intervention on hot flushes 4 years after the randomised controlled trial.

2. Material and methods

176 women were randomised to a 6-month exercise training trial (ISRCTN54690027), and 159 women continued until the end of the intervention [15]. Inclusion criteria were symptomatic women, with daily hot flushes, no current use of hormone therapy (HT), or having used it in the past three months, last menstruation 3–36 months earlier, aerobic training less often than twice a week for 30 min at a time. Women were excluded from the study if they were physically active; body mass index (BMI) was over 35 kg/m^2; or they had diseases preventing from training. [15].

The structured unsupervised 6-month aerobic training program included four weekly sessions, each 50 min. At least two physical activity (PA) sessions had to consist of walking or Nordic walking, while the other sessions could include other aerobic physical activity i.e. cycling, swimming, aerobics. Primarily walking was recommended because earlier trials have shown it to have favourable effects on health among menopausal and post-menopausal women [19]. The women in the control group were instructed to keep their physical activity habits unchanged. During the intervention information on hot flushes and exercise sessions was collected via mobile-phone questionnaires twice a day [20].

After the intervention, the first follow-up study was carried out as a questionnaire, which was posted to the participants 2.5 years after the beginning of the intervention, and 102 of the 159 women responded.

To the second follow-up, 4-years after the beginning of the intervention, 101 of the 159 women participated and written consent was obtained by all participants. Ninety-five responded to the questionnaire and attended in the measurements. The second follow-up study included the following measurements; weight, height, and waist circumference and estimation of aerobic power by the UKK two-kilometre Walk Test [21]. Furthermore, the women were instructed to wear Hookie® accelerometer (Traxmeet Ltd, Espoo, Finland) to record PA during one week.

At the 4-year follow-up the amount of hot flushes and sleep quality were recorded in a one-week diary. Number of daytime and night-time hot flushes and their severity; mild, moderate or severe were queried, and sleep quality was evaluated on a scale of one to five (from 1 = good to 5 = poor). The frequency of 24-h hot flushes was multiplied by severity [22]. The multiple of mild hot flushes was defined as one, that of moderate hot flushes two, that of severe hot flushes three, and the total sum for one week was defined as hot flush score (HFScore). When HFScores at baseline and 2.5-year and 4-year follow-up studies were analysed 30% of our women had a HFScore <13 points, 40% of women had a score <22 points and 50% <35 points. Therefore, HFScore was categorized as ≥13, ≥22 and ≥35 points.

2.1. Statistical analysis

The characteristics of the participants were described using means and standard errors of means (SEMs), or frequencies and percentages. Differences between the randomised groups were measured using *t*-test for continuous variables when they were normally distributed and Mann-Whitney test with non-normally distributed. Chi-square test was used with categorical variables.

Multilevel mixed-effects logistic regression models were constructed for within-participant correlation between three time points, at baseline, and after 2.5 and 4 years since the beginning of the intervention. These models were used for analysis of the HFScore over time and between the groups. The distribution of HFScore was skewed, thus multilevel linear regression models could not be used. These models included 56 women who had participated in three time points. The model was adjusted for HT and sleep quality, both of which were assessed at 4-year.

The multilevel model for dichotomous outcome of HFScore y_{ij} at time *i* for person *j* can be expressed as

$$logit\{\Pr(y_{ij} = 1|\mathbf{x}_{ij}, \zeta_j)\} = \beta_1 + \beta_2 x_{2j} + \beta_3 x_{3ij} + \beta_4 x_{2j} x_{3ij} + \zeta_j + \epsilon_{ij},$$

where x_{2j} represents group, x_{3ij} represents time, $\mathbf{x}_{ij} = (x_{2j}, x_{3ij})$ is a vector containing both covariates, and ζ_j is a person-specific random intercept, and ϵ_{ij} represents the occasion-spesific errors. This model allows for a difference between groups at baseline β_2, and linear changes in the log odds of outcome over time with slope $_{\beta3}$ in the control group and slope $\beta_3 + \beta_4$ in the exercise group. Therefore, $_{\beta4}$, the difference in the rate of improvement (on the log odds scale) between the groups, can be viewed as changing over time between the groups, [23]. The parameter estimates were presented as odds ratios (ORs) with 95% confidence intervals (CIs).

The statistical significance of all tests was determined to be at a *p*-value <0.05, and data analyses were performed with Stata Statistical Software, Release 12 (from StataCorp LP, College Station, Texas, USA). Additionally, loss-to-follow-up analysis was performed among the participating women (n = 56) and not participating (n = 103) at 4-year follow-up.

3. Results

Women who participated in all three time points and had measured HFScore (n = 56) were on average 58 years old, mean BMI was between 26 and 27 kg/m^2 and mean waist circumference varied from 86 cm in the exercise group to 90 cm in the control group, Table 1. The proportion of women using HT during the last 7 days at 4-year follow-up was 25% in the exercise group and 15% in the control group. Most of the participants were employed or part-time workers (71% exercise vs. 78% control). There were no differences in walking time or estimated VO$_2$max between the groups. Hookie® accelerometer PA assessment for one week showed no differences between the groups in proportion of time spent lying down and sitting, standing and light exercise and brisk and strenuous exercise. Table 1.

In Fig. 1. the distribution of HFScore, (hot flush frequency multiplied by average severity), is shown according to a one-week diary in three time points and in each figure is illustrated HFScores both <13, and ≥13 points, and frequences. At baseline the mean value of HFScore in the exercise group was 77 vs. 76 in the control group. The mean HFscore at 2.5-year follow-up was 27 in the exercise vs. 40 in the control group and at 4-year follow-up the mean values were 21 and 26, respectively.

The odds of HF Score at least 13 decreased 7% in the exercise group and 2% per month in the control group. This estimated difference in the slopes of time between the two groups was significant (p = 0.049). At 4-year follow-up women in the exercise group
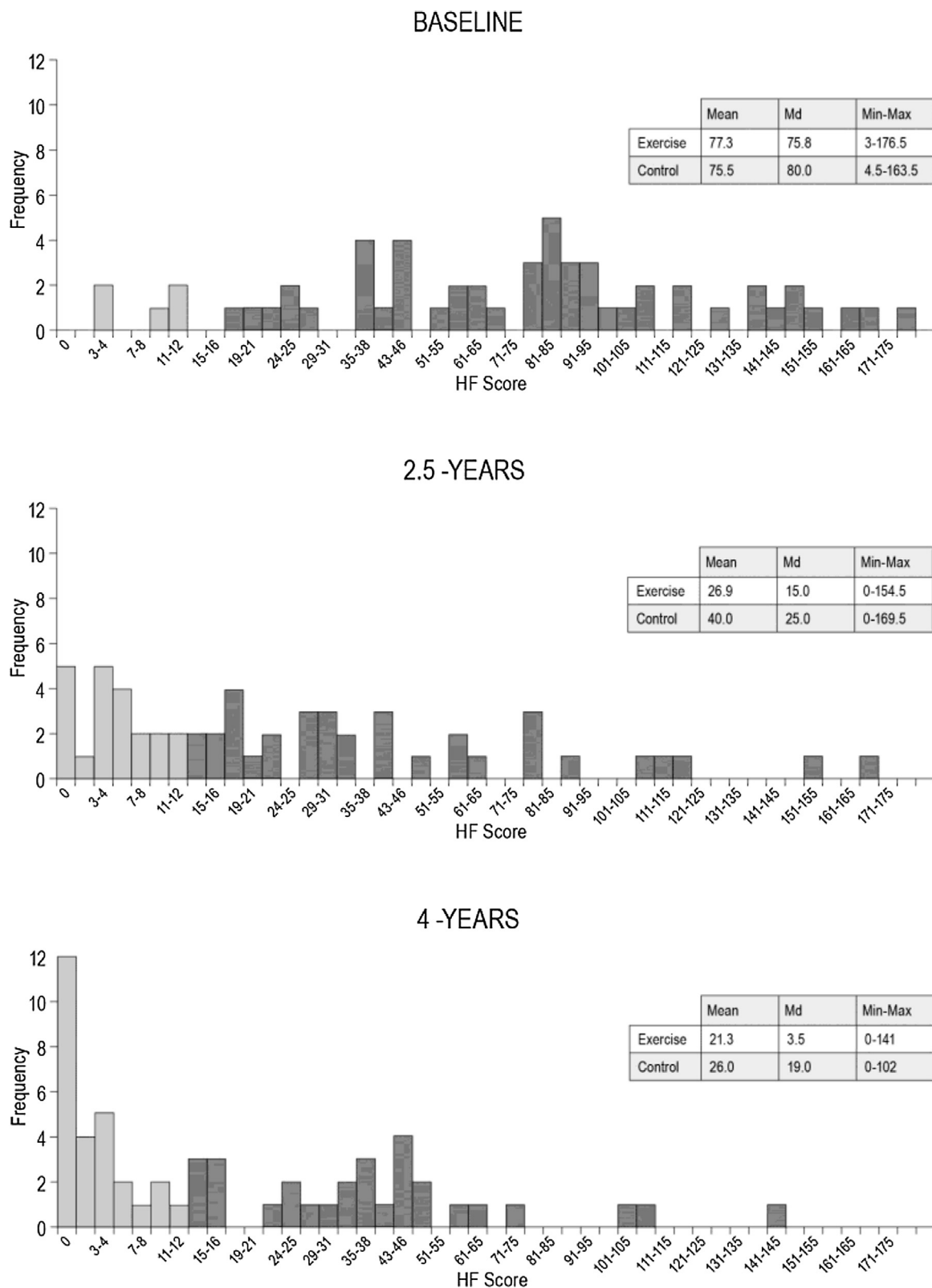
BASELINE

2.5 -YEARS

4 -YEARS

Fig. 1. Distribution of HFScore (n = 56) frequencies of <13 (light grey columns) and ≥13 (black columns), mean and median in three time points, baseline, and 2.5-year and 4-year after the beginning of the trial. In each column the frequences of HFScore are shown.

showed a significantly improved HFScore (p = 0.049), decrease in the proportion of women with HFScore at least 13 points, when compared to the women in the control group, Fig. 2.

The estimated odds ratios and their 95% confidence intervals in the three variables of HFScore are shown in Table 2. In the unadjusted model (Model 1) the estimated difference (interaction Group × time) in the slopes of time between the randomised groups

Table 1

Characteristics of participants with Hot Flush Score(HFScore)in three time points at 4-year follow-up in the exercise (n = 28) and control group (n = 28) (mean and SEM or frequency and percentage).

	Exercise (EX)	Control (CON)	p
N	28	28	
Age (y)	58.0 (0.7)	57.8 (0.7)	0.77[d]
Weight (kg)	69.6 (1.8)	71.9 (3.1)	0.51[d]
BMI (kg/m^2)	25.9 (0.7)	27.2 (1.0)	0.32[d]
Waist circumference (cm)	85.5 (2.5)	90.3 (2.9)	0.22[d]
Walking time (min)	16.6 (0.23)	17.2 (0.3)	0.10[e]
VO2Max (ml/kg/min), estimated[a]	32.1 (1.0)	30.6 (1.2)	0.33[d]
HT use during last 7 days (%)[b]	7 (25.0)	4 (14.8)	0.35[f]
Part-time or full-time work (%)	20 (71.4)	21 (77.8)	0.59[f]
Physical activity (accelerometer)			
Lying down and sitting (%)[c]	58.2 (1.6)	56.8 (1.6)	0.55[d]
Standing and light exercise (%)[c]	32.7 (1.6)	34.2 (1.4)	0.48[d]
Brisk and strenuous exercise (%)[c]	9.1 (0.5)	9.0 (0.9)	0.47[e]

[a] Oxygen consumption ml/kg/min.
[b] Hormone therapy.
[c] proportion (% of time) of one-week measurement.
[d] T-test.
[e] Mann–Whitney test.
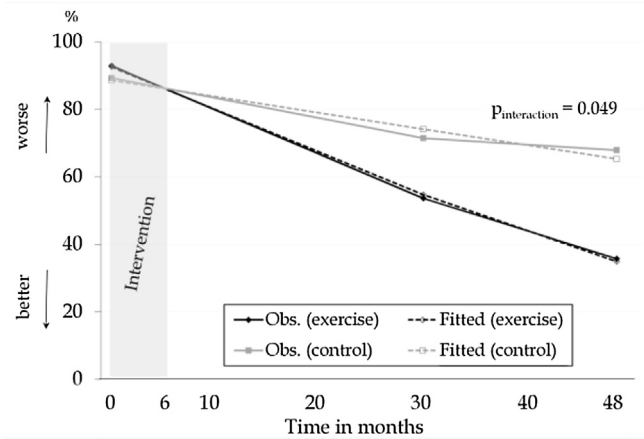[f] Chi-square test.

Fig. 2. Proportions (%) of women with HFScore at least 13 (n = 56) during intervention and follow-ups. Observed probabilities, and fitted probabilities using multilevel mixed-effects logistic regression.

showed close to a statistically significant improvement in HFScore, i.e. decrease in HFScore points, <13 (OR 0.95; 95% CI 0.89–1.00) among participants in the exercise group compared to the control group. In an adjusted (HT) Model 2 the result was borderline with OR 0.95; 95% CI 0.90–1.00. After additional adjustment with sleep quality, Model 3, the result showed a tendency to a significant result. At HFScore ≥22 and ≥35 the results did not reach a statistically significant improvement.

4. Discussion

The positive long-term effects of exercise training on HFScore, hot flush frequency multiplied by average severity, among the menopausal women was observed 4-years after the beginning of exercise intervention. Women in the exercise group had a higher probability of belonging to the group of HFScore ≥13 than women in the control group 4-years after the trial.

Structured exercise programs have shown the potential to reduce and alleviate vasomotor menopausal symptoms but the evidence still remains insufficient [11]. After a moderate intensity aerobic exercise acute bout, objectively and subjectively assessed hot flushes were decreased in women not using HT, although during a longer period women with lower fitness levels reported more symptoms when they had more daily moderate PA than usual [24]. However, among symptomatic Chinese menopausal women not using HT, 12-weeks of walking training was found to be an effective method to improve most of menopausal symptoms when compared to the control group [25]. Also in our 6-month aerobic training trial the frequency of night time hot flushes significantly decreased among the women in the exercise group [15,16]. Furthermore, we found significantly improved physical functioning (OR 1.41;95% CI 1.00–1.99) in 4-year follow-up study using SF-36 questionnaire on health-related quality of life [18].

The association between physical activity and hot flushes and night sweats remains contradictory while in recent randomised trials in previously sedentary women exercise training has not significantly alleviated bothersome hot flushes [13,14]. However,

Table 2

Multilevel mixed-effects logistic regression models of HFScore (n = 56)are shown in unadjusted (model 1), adjusted for Hormone therapy (model 2) and additionally adjusted variables for sleep quality (model 3).

	Model 1		Model 2[a]		Model 3[b]	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
HFScore ≥13						
Group	1.57 (0.28–8.96)	0.61	1.65 (0.27–10.2)	0.59	2.60 (0.31–21.6)	0.38
Time	0.98 (0.94–1.02)	0.28	0.97 (0.93–1.01)	0.13	0.98 (0.93–1.03)	0.34
Group × Time	0.95 (0.89–1.00)	0.051	0.95 (0.90–1.00)	0.049	0.94 (0.88–1.00)	0.067
HT			4.52 (0.73–28.2)	0.11	2.76 (0.38–19.8)	0.31
Sleep quality					0.27 (0.07–1.00)	0.050
HFScore ≥22						
Group	1.39 (0.30–6.50)	0.68	1.43 (0.30–6.89)	0.65	2.18 (0.40–11.8)	0.37
Time	0.96 (0.91–1.01)	0.11	0.95 (0.91–1.00)	0.053	0.96 (0.92–1.01)	0.15
Group × Time	0.95 (0.87–1.02)	0.16	0.95 (0.88–1.02)	0.15	0.94 (0.88–1.02)	0.13
HT			5.82 (0.34–98.8)	0.22	2.88 (0.15–53.9)	0.48
Sleep quality					0.20 (0.05–0.76)	0.018
HFScore ≥35						
Group	0.66 (0.17–2.52)	0.54	0.68 (0.17–2.73)	0.59	1.02 (0.22–4.85)	0.98
Time	0.90 (0.83–0.97)	0.005	0.88 (0.81–0.96)	0.005	0.90 (0.84–0.97)	0.007
Group × Time	0.98 (0.90–1.08)	0.74	0.98 (0.88–1.08)	0.66	0.98 (0.90–1.07)	0.64
HT			48.1 (0.51–4556)	0.095	15.9 (0.26–962)	0.19
Sleep quality					0.15 (0.03–0.68)	0.014

[a] Model 2, adjusted for HT (use of hormone therapy 0 = no, 1 = yes).
[b] Model 3, additional adjustment for sleep quality (0 = poor/rather poor/not well, not bad, 1 = well or fairly well.

there are many other reasons to encourage women to exercise and improve their health-related fitness; it is safe, well-tolerated and may improve subjective sleep quality, insomnia and depression all of which are related to hot flushes [13,14]. This is in line with our RCT in which aerobic training reduced sleep disturbing hot flushes and improved sleep quality among menopausal women at 6-month [17].

Limitations of our follow-up study include missing information of HFScore during follow-up. From baseline (n = 159) to 4-year follow-up only 56 of women completed one-week hot flush diaries in all three time of measurements. The questionnaire was filled in by 95 women at 4-year follow-up, and response rate to the questionnaire was 60% which can be considered as an acceptable result. According to a loss-to-follow-up analysis at 4-year follow-up there were significant differences in the exercise group between participating women (n = 28) and those lost to follow-up (n = 50) in waist (83.6; 91.3 cm, p = 0.006) and BMI (25.2; 27.1 kg/m^2, p = 0.040) among intervention women. Similar findings were not found among women in the control group, which indicates of a respondent bias restricted to the exercise group. This may have an effect to the results concerning the HFScore.

An important strength of our study is the prospective design which enabled us to analyze long-term differences between the groups. In addition, data collection by one week diary of hot flushes and sleep quality enabled us to compare results between baseline and the follow-up in two time points. Few studies in menopausal women have explored changes between several time points after an exercise intervention. We have previously showed that both physical and mental dimensions of QoL were better among women in the intervention group at 4-year follow-up after the beginning of aerobic training [18]. At 4-year follow-up the estimated VO$_2$max between groups showed a tendency towards better results but when VO$_2$max at baseline and follow-up were compared, no significant results were found among participating women. In this study the explanation for the positive effects of exercise on HFScore might be due that the natural course of menopausal symptoms, such as hot flushes, was shown as clear decrease by 4 year time.

We showed a positive long-term effect of aerobic training on improved status of hot flushes in a subgroup of women who participated in 6-month exercise intervention. Physically active lifestyle may offer an alternative to menopausal women in alleviating bothersome symptoms. Women should be encouraged to exercise regularly and to modify their lifestyle toward healthier choices during menopausal transition.

5. Conclusion

Among symptomatic women with mild intensity of menopausal symptoms a difference between the exercise and control group sustained until 4-year follow-up after the beginning of aerobic training, favoring the exercise group.

Conflict of interest

None declared.

Funding

Ethical approval

The study received ethical approval from the Pirkanmaa Hospital District Ethics Committee, Tampere, Finland.

Contributors

KM and RL prepared the first version of the manuscript. JR was responsible for statistical analysis. JR, C-H N, KK-H, ET, RR and RL participated in writing the manuscript and have approved the final version.

Provenance and peer review

This article has undergone peer review.

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