JYU DISSERTATIONS 515

Dmitriy Bondarev

The Role of Physical Activity in the Relationship between Menopausal Status, Physical Performance and Mental Well-Being

UNIVERSITY OF JYVÄSKYLÄ
FACULTY OF SPORT AND HEALTH SCIENCES

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Esitetään Jyväskylän yliopiston liikuntatieteellisen tiedekunnan suostumuksella
julkisesti tarkastettavaksi päärakennuksen salissa C4
toukokuun 20. päivänä 2022 kello 12.

Academic dissertation to be publicly discussed, by permission of
the Faculty of Sport and Health Sciences of the University of Jyväskylä,
in Main Building, auditorium C4, on May 20, 2022, at 12 o'clock noon.

JYVÄSKYLÄN YLIOPISTO
UNIVERSITY OF JYVÄSKYLÄ

JYVÄSKYLÄ 2022

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ISBN 978-951-39-9139-5 (PDF)
URN:ISBN:978-951-39-9139-5
ISSN 2489-9003

Permanent link to this publication: http://urn.fi/URN:ISBN:978-951-39-9139-5

ABSTRACT

Bondarev, Dmitriy
The role of physical activity in the relationship between menopausal status, physical performance and mental well-being
Jyväskylä: University of Jyväskylä, 2022, 89 p.
(JYU Dissertations
ISSN 2489-9003; 515)
ISBN 978-951-39-9139-5 (PDF)

Middle adulthood is often characterized by an onset of a decline in physiological functioning and fluctuations in mental well-being. However, it also represents a time of high functioning in many areas of life. Among women, menopausal status may explain these confusing views. This study investigates physical performance and mental well-being among middle-aged women in relation to their menopausal status. It also explores the role of physical activity in the relationship between menopausal status, physical performance, and mental well-being.

The study utilized cross-sectional (n=1098) and longitudinal data (n=232) from the Estrogen Regulation of Muscle Apoptosis study, which involved Finnish (Jyväskylä area) women aged 47 to 55. Menopausal status (pre-, peri-, or postmenopause) was established by hormonal analysis and bleeding diaries. Perimenopausal women were followed-up until postmenopausal (mean follow-up time 15.6 months). Physical performance was assessed by muscle strength, muscle power, and walking. Positive (life satisfaction and positive affectivity) and negative (depressive symptoms and negative affectivity) dimensions of mental well-being and physical activity were assessed with questionnaires.

Handgrip strength and muscle power were lower in postmenopausal women compared to premenopausal women. The longitudinal data indicated a decline in knee extension strength and muscle power. Postmenopausal women reported greater levels of depressive symptoms than premenopausal women. Higher levels of physical activity were associated with greater knee extension strength and walking distance among peri- and postmenopausal groups and greater muscle power irrespective of menopausal status. After their menopausal transition, women with higher levels of physical activity showed a greater increase in handgrip strength but a greater decline in knee extension strength and power than less physically active women. Higher levels of physical activity were associated with lower level of depressive symptoms and greater level of positive mental well-being irrespective of the menopausal status. Of the investigated physical performance measures, only six-minute walking distance had an independent positive association with positive mental well-being.

High physical activity seems to enable a greater capacity to counteract the observed negative influence of the postmenopausal status on muscle strength and power and mental well-being. In addition, aerobic capacity related to physical performance has unique importance for positive mental well-being.

Keywords: menopause, physical activity, physical performance, mental well-being

TIIVISTELMÄ (ABSTRACT IN FINNISH)

Bondarev, Dmitriy
Fyysisen aktiivisuuden rooli vaihdevuosien tilan, fyysisen suorituskyvyn ja henkisen hyvinvoinnin välisessä suhteessa
Jyväskylä: University of Jyväskylä, 2022, 89 p.
(JYU Dissertations
ISSN 2489-9003; 515)
ISBN 978-951-39-9139-5 (PDF)

Keski-ikää luonnehditaan vaiheeksi, jolloin fyysinen toimintakyky heikkenee ja mielen hyvinvointi heilahtelee. Toisaalta se edustaa vaihetta, jolloin toimintakyky on monilla elämänalueilla parhaimmillaan. Naisten osalta näitä ristiriitaisia havaintoja saattaa selittää vaihdevuosien vaihe. Tässä tutkimuksessa selvitettiin keski-ikäisten naisten fyysistä suorituskykyä ja mielen hyvinvointia suhteessa vaihdevuosien vaiheeseen. Tutkimuksessa selvitettiin myös fyysisen aktiivisuuden roolia vaihdevuosien vaiheen, fyysisen suorituskyvyn ja mielen hyvinvoinnin välisissä suhteissa.

Tutkimuksessa käytettiin Estrogen Regulation of Muscle Apoptosis (ERMA) -tutkimuksen poikkileikkaus- (n=1098) ja pitkittäisaineistoja (n=232). Tutkimukseen osallistui 47–55-vuotiaita jyväskyläläisiä naisia. Vaihdevuosien vaihe (pre-, peri- ja postmenopaussi) määriteltiin hormonien ja kuukautispäiväkirjojen avulla. Perimenopausaalisia naisia seurattiin keskimäärin 15.6 kuukautta, postmenopaussiin asti. Fyysistä suorituskykyä selvitettiin lihasvoimaa, alaraajojen voimantuottotehoa ja kävelynopeutta mittaavilla testeillä. Mielen hyvinvoinnin myönteisiä (tyytyväisyys elämään ja positiivinen affektivisuus) ja kielteisiä (masentuneisuuden tuntemukset ja negatiivinen affektiivisuus) ulottuvuuksia sekä fyysistä aktiivisuutta arvioitiin kyselylomakkeilla.

Postmenopausaalisten naisten käden puristusvoima ja voimantuottoteho olivat heikommat kuin premenopausaalisten naisten. Postmenopausaalisilla naisilla oli enemmän masennusoireita kuin premenopausaalisilla naisilla. Korkea fyysinen aktiivisuus oli yhteydessä suurempaan polven ojennusvoimaan ja kuuden minuutin aikaiseen kävelymatkaan (kestävyyskunto) peri- ja postmenopausaalisilla naisilla sekä suurempaan lihasvoimaan vaihdevuosien vaiheesta riippumatta. Siirryttäessä perimenopaussista postmenopaussiin niiden naisten, joiden fyysinen aktiivisuus oli korkeampi, käden puristusvoima lisääntyi, mutta polven ojennusvoima ja voimantuottoteho heikkenivät enemmän kuin naisilla, joiden fyysinen aktiivisuus oli alhaisempi. Riippumatta vaihdevuosien vaiheesta korkea fyysinen aktiivisuus liittyi vähäisempiin masentuneisuuden tuntemuksiin ja runsaampaan myönteiseen hyvinvointiin. Kävelymatka oli yhteydessä myönteiseen mielen hyvinvointiin.

Korkea fyysinen aktiivisuus näyttäisi kumoavan postmenopaussivaiheen negatiivisia yhteyksiä lihasvoimaan ja -voimantuottotehoon sekä mielen hyvinvointiin. Lisäksi kestävyyskunnolla on ainutlaatuinen merkitys myönteiselle mielen hyvinvoinnille.

Avainsanat: vaihdevuodet, fyysinen aktiivisuus, fyysinen suorituskyky, mielen hyvinvointi

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ACKNOWLEDGEMENTS

This study was carried out at the Gerontology Research Center and the Faculty of Sport and Health Sciences in the University of Jyväskylä, Finland. My deepest gratitude goes to the supervisors of this thesis, Professor Sarianna Sipilä, Research director Katja Kokko, and Professor Taija Finni. Sarianna, you have taught me a great deal of being a diligent researcher, helping me to organize my thoughts in logical coherence and get rid of “exciting” ideas that can be stored in a drawer for the future. Despite my creativeness in slowing down my PhD studies, you inspired and guided me through every challenge to build my professionalism. I have never noticed anything like disappointment with my progress from your side, but instead only direct practical suggestions and solutions. Your positive attitude towards almost everything in the world and enthusiasm have been a huge motivation along my journey. Katja, thank you for your guidance, motivation, and immense knowledge. I always felt clearer regarding my next step in writing when I left your office. Taija, thank you for encouragement, insightful comments and stimulating discussions.

I am grateful for the financial support I have received for my PhD studies from the Faculty of Sport and Health Sciences, University of Jyväskylä and from the European Commission Horizon 2020. I was privileged to be a part of the “Physical Activity and Nutrition Influences in Ageing” project which was funded by European Commission Horizon 2020 Marie-Curie Innovative Training Network. I want to express my special gratitude to Professor Anna Whitaker for offering me the secondment opportunity in her research group in Birmingham and leading me working on diverse exiting projects. I thank my fellow group mates “PANINI boys” and its female counterpart: Justin Aunger, Evans Asamane, Andrea Cabbia, Paul Doody, Rizwan Tahir, Belina Rodrigues, Barbara Iadarola, Noémie Gensous, Shuk Yu Yeung and Keenan Ramsay. For three years we have worked close on various projects, prepared numerous presentations, and pitched our ideas. I hope that we will have a productive collaboration in our future research endeavour.

I warmly thank all my colleagues and students who have worked in the ERMA study. Without your efforts this PhD project would not been possible. In particular, I thank Senior researcher Vuokko Kovanen for organising ERMA project and Associate professor Eija Laakkonen for sharing knowledge with me and inspiring suggestions. I also owe a great debt of gratitude to Professor Urho Kujala and docent Pauliina Aukee for their valuable comments and help in answering reviewers’ comments during my work on manuscripts. I want to thank all my co-workers at the Gerontology Research Center, you taught me a lot both the academic and life issues during our coffee table conversations.

I sincerely thank the official reviewers University lecturer Laura Pulkki-Råback, PhD and Associate professor Mette Hansen, PhD for their efforts and valuable comments which helped to improve the thesis.

I also wish to express my sincere gratitude to a member of my thesis committee, Professor Taru Lintunen who introduced me to the scientific world of exercise psychology when I was a master’s student. I warmly acknowledge

Michael Freeman for language editing of the original papers and Senior lecturer Anne Viljanen for scientific editing of this thesis.

Finally, I dedicate this thesis to my whole family, who I know are most proud of this achievement. I know I can always count on your help and support.

Jyväskylä, April 2022
Dmitriy Bondarev

LIST OF ORIGINAL PUBLICATIONS

The dissertation is based on the following original publications:

I Bondarev D, Laakkonen E. K, Finni T, Kokko K, Kujala U. M, Aukee P, Kovanen V, Sipilä S. 2018. Physical performance in relation to menopause status and physical activity. Menopause 25(12): 1432-1441, doi: 10.1097/gme.0000000000001137

II Bondarev D, Sipilä S, Finni T, Kujala U. M, Aukee P, Laakkonen E. K, Kovanen V, Kokko K. 2020. The role of physical activity in the link between menopausal status and mental well-being. Menopause 27(4): 398-403, doi: 10.1097/GME.0000000000001490

III Bondarev D, Finni T, Kokko K, Kujala U. M, Aukee P, Kovanen V, Laakkonen E. K, Sipilä S. 2021. Physical performance during the menopausal transition and the role of physical activity. Journals of Gerontology Series A: Biological Sciences and Medical Sciences 76(9): 1587–1590, doi:10.1093/gerona/glaa292

IV Bondarev D, Sipilä S, Finni T, Kujala U. M, Aukee P, Kovanen V, Laakkonen E. K, Kokko K. 2021. Associations of physical performance and physical activity with mental well-being in middle-aged women. BMC Public Health 21, 1448, doi: 10.1186/s12889-021-11485-2.

As the first author of the original publications, taking into account the comments from the co-authors, the author of this dissertation formulated the research questions, prepared datasets for statistical analyses, performed all statistical analyses, and has taken the main responsibility of writing the manuscripts. In all studies I was privileged to use existing datasets.

ABBREVIATIONS

ANOVA	One-way analysis of variance
AMH	Anti-Müllerian Hormone
CES-D	Center for Epidemiologic Studies Depression Scale
CI	Confidence interval
ERMA	The Estrogen Regulation of Muscle Apoptosis study
FSH	Follicle-stimulating hormone
HT	Hormonal therapy
IGF-1	Insulin-like growth factor
I-PANAS-SF	The International Positive and Negative Affect Schedule Short Form
PA	Physical activity
STRAW	The Stages of Reproductive Aging Workshop

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1 INTRODUCTION

Around the world, people are reaching older ages than previous generations, prompting the WHO to announce a Decade of Action on Healthy Aging in 2020 (Beard et al., 2016). While aging is associated with a decline in physical performance and cognitive functioning, healthy aging is characterised by a low probability of disease and disability, high cognitive and physical functioning and active life engagement (Rowe & Kahn, 1997). Women have a longer life expectancy than man; thus, they account for a large proportion of aging society (Van Oyen, 2013). However, women's advantage in terms of life expectancy is counterbalanced by a disadvantage in terms of disabling conditions. Women have higher levels of disability, functional limitations and depression compared to men (Oksuzyan et al., 2010; Salk et al., 2017), which compromises healthy aging. Understanding the reasons for this is therefore a major public health goal.

Middle-aged women generally experience menopause between 47 and 52 years of age, which results in strong fluctuations in sex hormones such as estradiol and progesterone (Fiacco et al., 2019). Current knowledge suggests that the low estrogen levels that coincide with menopause may be among the key mechanisms behind muscle weakness and physical performance (Chidi-Ogbolu & Baar, 2019; Collins et al., 2019). Physical performance, including components such as muscle strength, muscle power and aerobic capacity, is an important factor for functional independence in older age. Furthermore, reproductive aging has far-reaching consequences for various systems which are also reflected in mental well-being. Absolute levels and fluctuations in gonadotropins and sex steroids have been suggested as possible predictors of mood disturbances and depressive symptomatology during perimenopause (Soares, 2013; Willi et al., 2021).

As a phase of life, middle adulthood is often characterised by an onset of a decline in physiological functioning and fluctuations in mental well-being; however, it also represents a time when people reach a peak in numerous areas, including career, earnings and emotional experience (Dobrow Riza et al., 2018; Lachman et al., 2015). From this viewpoint, middle adulthood could be considered a time of balancing growth and decline (Lachman et al., 2015). Thus, identifying factors that may compromise or balance physical performance and mental well-being in middle adulthood is essential to understanding how to maintain functional independence in old age.

Many of the adverse changes in physical performance and fluctuations in mental well-being experienced during menopause can be reduced by physical activity. However, compared to other age groups, physical activity in middle-aged women may be lower due to the influences of life circumstances, such as various transition events (Engberg et al., 2012) and hormonal factors related to menopause (Melanson et al., 2018). The association between menopause, physical performance and mental well-being has been often studied without considering participants' levels of physical activity. While menopause induces hormonal changes that may compromise physical performance and mental well-being, physical activity also elicits a hormonal response that has been shown to be positively related to both physical performance (Straight et al., 2015) and mental well-being (Elavsky, 2009). Consequently, the extant literature does not provide an opportunity to identify the potential role of physical activity in mitigating menopause-associated declines in physical performance and mental well-being. Before targeted interventions can be designed, it is important to understand the associations between menopausal status and physical performance and mental well-being considering participants' levels of physical activity.

Studying the role of menopause in physical performance and mental well-being is challenging because of numerous methodological issues. These issues revolve around defining the menopausal transition stages, comprehensive measurements of physical performance components and mental well-being dimensions, designing the study to disentangle aging effects from menopause and controlling for confounding factors such as levels of physical activity.

2 REVIEW OF THE LITERATURE

2.1 Midlife as a phase of life

Midlife is a phase which refers to the middle of a lifespan. In the literature, it encompasses a broad age range, most commonly ages 40 to 60 (Lachman, 2004). Although midlife includes a large portion of an individual's lifespan, it has been poorly studied compared to the earlier and later phases of life (Infurna et al., 2020; Lachman et al., 2015). This could be surprising, as more than a quarter of the population is now in their middle decades of life (Ritchie, 2019).

Middle-aged people are often at high professional levels and possess a great deal of care responsibilities related to next generations, children, older parents or spouses' parents (Infurna et al., 2020). The onset of midlife is only loosely characterised by age boundaries; rather, it is driven by the timing of transitional events (Infurna et al., 2020). The latter ones involve changes in career (seniority in one's field or mentoring), challenges related to family circumstances (e.g., merging caregiving for adult parents and parenthood and possibly grandparenthood), physiological changes (menopause) or changes in physical health (e.g., onset of chronic conditions). Middle-aged adults are often described as a sandwich generation who are balancing multiple intergenerational and social roles, undergoing life transition events and encountering challenges and opportunities (Lachman, 2004). In comparison with younger adults, middle-aged adults begin to experience age-related physiological changes, such as menopause among women, which has wide-ranging effects on women's lives and may affect mental health and physical functioning.

Mental and physical health problems may begin to accumulate in midlife (Roberts et al., 2015). For example, it has been demonstrated that severe psychological distress, clinical depression and anxiety are higher among middle-aged participants than among younger or older adults (Blanchflower & Oswald, 2012; Trollor et al., 2007). This difference is greater among women than men and among participants with low levels of education compared to those with high levels of education (Brody et al., 2018, p.4). Middle-aged participants also report an increased prevalence of multiple chronic diseases and lower physical functioning than younger adults (Peeters et al., 2013; Roberts et al., 2015).

Although midlife is often described as a phase of life that brings with it a decline in physiological and psychological functioning accompanied by challenges in social roles, there is also evidence that psychologically, midlife can be a rather satisfying stage of life (Kokko & Feldt, 2017; Lachman et al., 2015). Middle adulthood is often characterised by reaching a peak in relation to one's career, earnings, decision-making skills, control beliefs and emotional experience (Riza et al., 2018). From this perspective, middle adulthood is often viewed as 'the intersection of growth and decline' (Lachman et al., 2015), wherein there are gains in one area of life and declines in other areas.

In females, menopause occurs at middle age. Menopause, which is defined as the permanent cessation of menstruation as a result of the loss of ovarian follicular activity, occurs on average between the ages of 46 and 52 and signifies the end of a woman's reproductive life (Harlow et al., 2012; Schoenaker et al., 2014). The end of one's reproductive life has consequences for various physiological systems, such as bone and mineral metabolism (Sipilä et al., 2020), cognition (Maki et al., 2021), cardiovascular function (Novella et al., 2012) and muscle function (Juppi et al., 2020). All of these contribute to physical performance (Burger, 2006; Sowers & La Pietra, 1995). To investigate the role of menopause in physiological changes and to enable researchers to compare women across different menopausal transition stages (i.e., pre-, peri and postmenopause), a standardised staging system has emerged which defines the critical time points in the progression of reproductive life.

The Stages of Reproductive Aging Workshop (STRAW+10 guideline) (Harlow et al., 2012) proposed a system that divides women's reproductive aging into five stages before the final menstrual period and two afterwards (Table 1).

The premenopausal stage includes three substages: early, peak and late. Early premenopause is characterised by regular menstrual cycles. In the peak stage, menstrual cycles become less regular and shorter. The late stage demarcates the time when achieving a pregnancy is less likely than in previous years. The hormones produced by follicles in the ovary include Anti-Müllerian Hormone (AMH) and inhibin B, which are used as markers of ovarian reserve. AMH levels decline linearly, approximately 15 years prior to menopause, and they drop to very low levels approximately five years before menopause (Sowers et al., 2008), whereas inhibin B substantially declines to a nondetectable level 2 to 3 years before the final menstruation (Øverlie et al., 2005).

TABLE 1 The stages of reproductive aging (adapted from Harlow et al., 2012).

Stage	Substage	Menstrual cycle	Supportive criteria			Menopausal symptoms
			FSH	AMH	Inhibin B	
Pre-menopausal	Early	Regular - variable	<9.5 IU/L	-	-	None
	Peak	Regular	<17 IU/L	Low	Low	None
	Late	Regular - subtle change in flow/length	<17 IU/L	Low-variable	Low	None
Peri-menopause	Early	Variable	17 < 25 IU/L	Low	Low	Likely
	Late	Intervals of amenorrhea =>60 days	25-30 IU/L or >30 IU/L if occasional bleeding past 3 month	Low	Low	Likely
Post-menopause	Early	No menstrual bleeding during past 6 months or during past 3 months, or occasional bleeding	>30 IU/L or >39 IU/L, or >130 IU/L	Low	Low	Most likely
	Late	No menstrual bleeding for 12 months	Stabilizes	Very low	Very low	Increase in urogenital atrophy

AMH - Anti-Müllerian Hormone
FSH - Follicle-stimulating hormone

The perimenopausal stage comprises two substages: early and late perimenopause. They are characterised by variable cycle length and 60 or more days of amenorrhea, respectively. This variation in cycle length is associated with hormone secretory patterns that deviate from that of the premenopausal stage. Specifically, during early perimenopause, follicle-stimulating hormone (FSH) is more consistently elevated, and inhibin B and AMH are very low (Hale et al., 2009). In the late perimenopausal transition stage, menstrual cycles become highly irregular, and a lengthy period of amenorrhea coincides with a sharp increase in the rate of common menopausal symptoms in many but not all women (Augoulea et al., 2019; Woods & Mitchell, 2005). This stage is marked by the final menstruation.

The postmenopause stage comprises two stages: early postmenopause (first 5 years after) and late postmenopause. During postmenopause, FSH levels increase, and estradiol levels continue to decline approximately 2 years after the final menstrual period (Hale et al., 2007). However, these changes are at a significantly low magnitude in comparison with the perimenopausal phase; gradually, their levels stabilise permanently.

The onset of menopause and the menopausal transition in terms of its duration both have high interindividual variability (Woods & Mitchell, 2016). There are genetic factors and environmental factors, such as education, income and physical activity or other lifestyle choices that may influence the onset of menopause or the duration of perimenopause (Burger, 2006; Hyvärinen et al., 2021).

Menopause-related hormone fluctuations have been associated with a higher risk of menopausal symptoms (Finset et al., 2004). These symptoms are generally divided into somato-vegetative (e.g., sweating, hot flashes), psychological (e.g., tiredness, mood swings) and urogenital symptoms (e.g., vaginal symptoms, urinary track problems). The degree and prevalence of menopausal symptoms tend to increase as women enter the late premenopausal stage and progress through late perimenopause (Santoro, 2016). For example, peri- or postmenopausal women experience back or muscle pains, hot flashes, weakness and numbness significantly more often in comparison with premenopausal women (Moilanen et al., 2010).

Women experience menopausal symptoms in different ways; while some women may experience significant declines in well-being and may require a pharmacological treatment for menopausal symptomatology, other women may be relatively prone to certain types of symptoms or not experience symptoms at all (Woods & Mitchell, 2005). Factors that affect women's experiences of menopausal symptoms are biopsychosocial (Dennerstein et al., 2002); they could originate from individual perceptions of the menopausal transition or be influenced by their broader social and cultural context (e.g., demographic characteristic) or lifestyle (e.g., physical activity).

2.2 Physical activity in middle-aged women

Physical activity refers to any behaviour that involves movements that increase energy expenditure and includes planned or structured types of activities, such as exercise (Caspersen et al., 1985; Gabriel et al., 2017). Physical activity can be work-related, or it can occur during leisure time or between work and leisure (e.g., commuting). The exercise domain of physical activity typically has the aim of improving/maintaining physical performance (Gabriel et al., 2017).

Physical activity guidelines recommend that adults aged 18 to 65 participate in at least moderate aerobic activity 150 minutes per week or 75 minutes per week in more intense activities (Haskell et al., 2007; Izquierdo et al., 2021). Current physical activity guidelines also recommend participating in strength and flexibility exercises at least twice per week (Izquierdo et al., 2021).

In observational studies, overall levels of physical activity tend to gradually decline with age and are lower among women than men (Hallal et al., 2012; Husu et al., 2016). A cohort follow-up study across 22 years revealed that women were more likely to adhere to a consistently inactive rather than consistently active trajectory than their male counterparts (Barnett et al., 2008). However, these results are not always conclusive. For example, the Eurobarometer survey demonstrated that women are slightly more active than men. At the age of 40 to

55, women are less active than at the age of 55+ and are also less active in comparison with younger age groups (European Commission, 2018).

Physical activity is not stable over time, and discontinuity in physical activity may be triggered by various environmental or personal factors, including life events and transitions during the life course (Engberg et al., 2012). For example, in midlife, duties related to children, work or providing care for older parents may interfere with leisure time and reduce time which may be devoted to physical activity.

Physical activity may also be partially regulated by biological factors (Stubbe et al., 2006). Experimental animal studies have proven that physical activity among rodents differs based on sex and may be regulated by various hormonal pathways (Lightfoot et al., 2008). Additionally, observational studies among women have indicated a shift toward a more sedentary lifestyle and a decline in energy expenditure during the menopausal transition (Karine et al., 2013; Lovejoy et al., 2008). In addition, postmenopausal women on estrogen-containing hormone therapy have been demonstrated to be more physically active in comparison with women who were not on hormone therapy (Andersen et al., 2003), suggesting a relationship between estradiol and levels of physical activity.

Although the mechanism explaining how menopausal hormonal changes are linked to physical activity is poorly understood, some studies suggest that sex hormones may directly influence spontaneous daily activity (Lightfoot, 2008; Melanson et al., 2018). Studies with experimental animals have shown that removing ovaries leads to reduced wheel-running activity, while estradiol supplementation restores this activity to the same level as in control animals (Gorzek et al., 2007). Only limited data on this matter is available for women. In one study, women undergoing pharmacological suppression of ovarian sex hormones were divided into placebo and estradiol supplementation groups (Melanson et al., 2018). The study revealed that women with estradiol supplementation were more physically active than the control women during five months of treatment – the time when the maximal suppression of ovarian function was achieved by the drug. It is possible that the activation of the estrogen α-receptors pathway downregulates other physiological structures, most likely in the brain, which in turn increases levels of physical activity (Lightfoot, 2008).

In sum, levels of physical activity among middle-aged women may be lower than in other age groups, indicating specific factors that may influence it, including life circumstances and biological factors such as menopause.

2.3 Physical performance in middle-aged women

Physical performance represents a multidimensional construct which includes muscle strength, muscle power, agility, coordination, flexibility and aerobic capacity. Aging is accompanied by a progressive decline in physical performance

(Berthelot et al., 2019; Rantanen et al., 1998). This decline is reflected by dysfunctions in the neuromuscular system, which gradually restrict one's ability to carry out daily activities (Verbrugge & Jette, 1994), ranging from the essential activities of daily life (e.g., eating, bathing) to more complex social activities (e.g., walking, job).

2.3.1 Muscle strength

Muscle strength refers to a person's ability to overcome external resistance or to resist it through muscular efforts (tensions). Muscle strength depends on two factors, namely neurological and skeletal muscle factors, and it represents a complex interaction throughout the entire neuromuscular system (Enoka, 1988). This interaction occurs on the level of the motor cortex (excitatory drive), spinal cord (α-motoneuron excitability, motor unit recruitment and rate coding), neuromuscular transmission, excitation-contraction coupling pathways located within the muscle and muscle mass and architecture.

Cross-sectional studies across the adult lifespan have demonstrated that muscle mass and muscle strength are lower among older individuals compared to younger people from the third or fourth decade onwards (Faulkner et al., 2007; Janssen et al., 2000). A reported annualised rate of lower limb muscle strength decline for women aged 70–79 years was 2.6% (Goodpaster et al., 2006). Longitudinal studies suggest that the decline in muscle mass alone does not fully explain the age-associated decline in muscle strength and physical function in adults (Auyeung et al., 2014; Hughes et al., 2001). Both neurological and skeletal muscle factors are sites of age-associated decline in muscle strength. However, the loss of muscle mass contributes only 10% to the decline in muscle strength (Clark et al., 2006). In addition, an increase in muscle mass does not necessarily prevent an age-associated decline in muscle strength (Delmonico et al., 2009). This suggests that impairment in muscle strength with age is more closely related to concomitant impairments in neurological factors. A systematic review of the link between muscle strength or muscle mass and poor physical functioning or disability indicated that the number and magnitude of associations for low muscle strength are greater than for low muscle mass (Manini & Clark, 2012). Therefore, low muscle strength represents a greater relative risk for the development of disability in comparison with low muscle mass (Clark & Manini, 2008).

Strength measurements are often used for early screening to identify those with a greater risk of developing physical disabilities (Rantanen, 2003). Typically, strength measurements include the assessment of upper (e.g., handgrip strength) or lower extremities (e.g., knee extension strength), which is indicative of a participant's maximal voluntary force (measured as torque) during muscle contraction. Handgrip strength explains only 40% of the variance in low extremity strength (Bohannon, 2009), while low extremity strength has a greater functional connection to walking speed and physical functioning (Marsh et al., 2006). The maximal volitional activation of muscle occurs when all alpha-motor neurons innervating the muscle are stimulated with a maximum achievable discharge rate. Studies have demonstrated that older adults exhibit a deficit in the central activation of motor neurons in comparison with younger adults (Cannon et al., 2007; Stevens et al., 2003), suggesting that central neural drive can partially explain the age-associated decline in muscle strength. Furthermore, some age-related changes in the brain, primarily atrophy in the motor cortex (Salat et al., 2004) and the loss of myelinated nerve fibres (Marner et al., 2003), are likely linked to age-associated decline in muscle strength; however, no direct evidence has been published yet.

Muscular factors also contribute to lower muscle strength. Loss of muscle mass occurs due to a reduction in the synthesis rate of structural contractile muscle protein below the breakdown rate. Interestingly, although skeletal muscle mass declines in postmenopausal compared to premenopausal women, it has been observed that the rate of skeletal muscle protein synthesis is enhanced after menopause (Smith et al., 2014). The decline in muscle mass was most likely explained by the increase in skeletal muscle protein breakdown which coincides with estrogen deficiency following menopause, which in turn results in a net loss of muscle mass (Chidi-Ogbolu & Baar, 2019). This was suggested by the administration of hormone replacement therapy to postmenopausal women who had their lean body mass enhanced in comparison with the control group (Pöllänen et al., 2007)

In middle-aged women, menopause status has been proven to be a significant predictor of decreased lean body mass, leg lean mass and thigh muscle cross-sectional area (Juppi et al., 2020). These changes reduce muscle quality or muscle cross-sectional area relative to strength (McGregor et al., 2014). In addition, the accumulation of fat and connective tissue which has no contractile properties within the skeletal muscle is associated with lowered muscle strength (Delmonico et al., 2009).

2.3.2 Muscle power

Muscle power represents the capacity of the neuromuscular system to produce rapid muscle contraction, which is a product of force and contraction velocity. The maintenance of muscle power is an important factor for functional independence and may be more important than muscle strength in daily living activities, such as in sit-to-stand transitions or brisk walking (Bean et al., 2003). Measurements of lower limb muscle power may vary depending on the age of participants being tested and their health status. In middle-aged women, more direct measurements of muscle power can be achieved by employing a vertical jump aiming for maximal jump height (Bosco et al., 1983) or rapid knee extension in a power rig (Bassey et al., 1992). Other surrogate measures of muscle power are also available in the literature on middle-aged women, such as assessing sit-to-stand time or climbing stairs (Sowers et al., 2007).

In contrast to explosive knee extension in the power rig, vertical jumping requires eccentric–concentric muscle contraction, which involves the interaction of neuromuscular, sensory and cognitive function to efficiently coordinate the task (Andersen & Aagaard, 2006). For example, during vertical jumping, the rapid eccentric phase activates the extensor muscle spindle, which informs the central nervous system regarding a change in a muscle length (i.e., stretch-shortening cycle; Nikolaidou et al., 2017). In response, a stimulated motor unit contracts the extensor muscle while inhibiting the flexor muscle. At the same time, the Golgi tendon organ, which is coordinated by a higher-level motor control system, inhibits the activity of alpha motor neurons to exert muscle tension (Komi & Gollhofer, 1997). Muscle power starts to decline around 40 years of age in both women and men (Alcazar et al., 2020; Metter et al., 1997).

2.3.3 Walking

Walking is a complex task that involves the nervous system, musculoskeletal system and cardiorespiratory system (Hornyak et al., 2012). Performance in walking tests is indicative of various mobility actions in daily life. Depending on the duration of the tests, these measure walking time or speed (timed 4-meter or 10-meter walk) or aerobic capacity (e.g., walking distance within six minutes). Maximal walking speed reflects the complex ability of the neuromuscular system to increase walking speed above a 'comfortable' pace but without running. A sufficient walking speed suggests a potential reserve to adapt to varying environments and task demands (e.g., crossing streets, avoiding obstacles, chasing a bus). A study with well-functioning older adults revealed that maximum walking speed is associated with impairments in neuromuscular activation and force production (Clark et al., 2013). Performance in a six-minute walking distance test, in addition to the nervous system and musculoskeletal system, rely to a greater extent on aerobic capacity (Clark et al., 2013).

2.3.4 Physical performance and menopausal transition

Women tend to exhibit more rapid age-associated decline in physical performance than men, suggesting the influence of gender-specific factors (Peeters et al., 2013). One of the possible factors is hormonal changes due to menopause (Samson et al., 2000).

Several cross-sectional studies have demonstrated that postmenopausal women perform worse in handgrip strength than premenopausal women (Calmels et al., 1995; Cheng et al., 2009; da Câmara et al., 2015). However, in other studies, differences in muscle strength across menopause status groups were not observed (Bassey et al., 1996; Cooper et al., 2008). It should be noted that the above-mentioned studies have predominantly assessed physical performance relying mostly on one component, namely handgrip strength, while measurements of physical performance in low extremities have been scarce.

Few longitudinal studies have reported on the association between the menopausal transition and physical performance (Kurina et al., 2004; Sowers et al., 2007). One three-year study followed women in premenopausal to postmenopausal stages and observed a significant decline in pinch strength but a non-significant decline in handgrip strength (Kurina et al., 2004). Another study which followed pre- and perimenopausal women showed a significant decline in handgrip strength, sit-to-stand time and preferred walking speed over a five-year period (Sowers et al., 2007).

Age-associated decline in walking speed typically accelerates in late middle age, at around 60 years (Bohannon & Andrews, 2011; Himann et al., 1988). As performance in walking speed depends on inputs from several systems, it may be less sensitive to earlier declines in muscle strength that occur in middle age due to a compensatory mechanism from other systems. However, one cross-sectional study (da Câmara et al., 2015) showed that postmenopausal women had slower preferred walking speeds in comparison to premenopausal women. These researchers concluded that the role of menopause in physical performance is more pronounced in the musculoskeletal system as opposed to other systems, such as the cardiorespiratory system. However, this conclusion is made in perspective to walking performance. Other studies suggest a decline in lung function in relation to hormonal changes at menopause (Triebner et al., 2016, 2019). Thus, measurements of maximum oxygen consumption could reveal more clear link between menopausal status and aerobic capacity.

The relationship between walking distance and aerobic capacity has not been investigated in middle-aged women; however, aerobic capacity has been measured by other means. One longitudinal study reported no significant changes in maximum oxygen consumption for women during the menopausal transition during the course of a five-year observational study (Abdulnour et al., 2012). However, conflicting results show that menopause-related estrogen deficiency is associated with a reduction in cardiopulmonary function, which corresponds to the increase in oxygen requirements during exercise (Mercuro et al., 2006).

The role of estrogen in muscle strength has been demonstrated in studies in which postmenopausal women undergoing hormonal therapy containing estrogen or combined estrogen-progesterone supplements were compared with women who were not on hormonal therapy. One meta-analysis involving around 10,000 postmenopausal women showed that those women who were on hormonal estrogen therapy had greater muscle strength than those who did not use the therapy (Greising et al., 2009). Some studies provided evidence that exogenous estrogen improves muscle power more than muscle strength in postmenopausal women (Carville et al., 2006; Ronkainen et al., 2009; Sipilä et al., 2001).

Female sex steroids play important roles in maintaining skeletal muscle homeostasis and function (Collins et al., 2019; Sipilä et al., 2015). The neuromuscular system has multiple sites that express estrogen receptors; thus, estrogen may play a role in preserving muscle mass and quality, such as through apoptotic pathways (Collins et al., 2019) as well as through neural factors involved in muscle strength generation, such as neural drive or motor coordination (Ansdell et al., 2019). Sex steroids can also activate the IGF-1 (Insulin-like growth factor) pathway (Ahtiainen et al., 2012; Pöllänen et al., 2010), which controls the net balance of muscle protein turnover; in this way, they may influence muscle mass changes – one of the crucial determinants of muscle strength. Postmenopausal women exhibit a significantly lower expression of IGF-1 in comparison with premenopausal women (Ahtiainen et al., 2012). Therefore, there are several potential and most likely interlinked processes which affect the whole neuromuscular system in middle-aged women that may predispose them to decrements in muscle function and hence in physical performance.

The decline in physical performance observed in middle-aged women may also be due to a decline in physical activity (Ward-Ritacco et al., 2014). Physical activity has been proven to be a significant factor that determines handgrip strength among women (Cauley et al., 1987; Cheng et al., 2009). However, researchers did not assess strength attenuation in relation to menopausal status among women of different physical activity levels.

2.3.5 Physical activity and physical performance

Physical activity and physical performance are functionally related concepts. Generally, although not always, increases in physical activity intensity and frequency lead to improved physical performance (Blair et al., 2001). The strength of this association varies immensely across individuals and is influenced by genetic control.

Physical activity has been shown to have numerous benefits for middle-aged women (Asikainen et al., 2004; Moilanen et al., 2012; Rantanen et al., 1992). There is a positive association between levels of physical activity in mid-life and physical performance in later life (Cooper et al., 2011; Patel et al., 2006). In a prospective cohort study, physically active participants in mid-life reported greater perceived physical function after eight years of follow-up in comparison with their sedentary counterparts (Hillsdon et al., 2005). Similarly, in a retrospective study, participants aged 74 who performed better on the Short Physical Performance Battery and had a greater ability to walk 400 meters recalled higher physical activity in mid-life compared to poorer performers (Patel et al., 2006). In the Women's Health Across the Nation study (Gabriel et al., 2017), women aged 42 to 52 years who maintained moderate and high levels of physical activity over 16 years exhibited better performance in walking tests, repeated chair stands and handgrip strength than the group whose physical activity was consistently low. These results suggest that physical activity during mid-life plays an important role in physical function in later life.

As physical activity is an effective tool for the maintenance of musculoskeletal health among middle-aged women (Akune et al., 2014), it is also important to understand which exercise parameters, such as intensity, frequency or type could be beneficial for physical performance. It has been proven that a greater amount of moderate to vigorous physical activity is associated with higher knee extension torque in middle-aged women (Hughes et al., 2001). Another study involving postmenopausal middle-aged women showed that higher daily step counts and duration of moderate to vigorous physical activity were associated with isokinetic knee torque and leg power (Straight et al., 2015). This study also revealed that there was no difference in lower extremity muscle power between women who accumulated 10,000 steps per day and those who did not reach that number of daily steps. It seems that the absolute amount of physical activity may be less important than intensity for the maintenance or developing muscle power.

Although habitual physical activity may decline in middle-aged women and exercise interventions may be implemented to counteract the reduction in physical performance in middle-aged women, the ability of postmenopausal women to respond to training stimuli to the same extent as younger women has been debated (Bassey et al., 1998; Parker et al., 2010). Older women exhibit a reduced myofiber hypertrophic response following a strength training program in comparison with man (Bamman et al., 2003). It has been suggested that a postmenopausal decrease in estrogen reduces the response to anabolic stimuli, such as resistance training (Hansen & Kjaer, 2014). However, previously sedentary middle-aged women showed significant improvement in cardiorespiratory fitness and leg strength after a 13-week Nordic walking intervention (Kukkonen-Harjula et al., 2007). It has also been suggested that hormonal changes in postmenopausal stage does not blunt training adaptation to exercise (Seidelin et al., 2017). A meta-analysis of randomised control studies (Asikainen et al., 2004) involving early postmenopausal women (50-65 years) investigated the effect of various exercise types on health-related fitness (body composition and bone strength, muscle strength and endurance, postural control, cardiorespiratory fitness and metabolic components). This meta-analysis showed that combined aerobic exercise (walking in addition to dance or cycling) improves more components of fitness than merely walking interventions. Furthermore, resistance training was effective in muscle strength improvements, while studies with high-impact training reported improvements in agility and cardiorespiratory fitness (Asikainen et al., 2004). Taken together, these results warrant additional research regarding the optimal amount and timing of physical activity during menopause for women considering their prior levels of physical activity.

2.4 Mental well-being in middle-aged women

2.4.1 The concept of mental well-being

Much of the research on mental well-being among middle-aged women has concentrated on clinical aspects or negative experiences related to menopausal symptoms and particularly depressive symptoms (Dennerstein & Soares, 2008). The World Health Organisation underlines that health is a 'state of complete physical, mental and social well-being and not merely the absence of disease or infirmity' (World Health Organization, 2005). In line with this definition of health, research has transitioned from examining psychological distress or aging-associated loss in function in the middle-aged population towards facilitating an improved understanding of positive experience and positive mental well-being (Brown et al., 2015; Lachman & Agrigoroaei, 2010). Mental well-being is viewed as a multidimensional construct which comprises both positive dimensions, such as general satisfaction with life and positive affectivity, as well as negative dimensions, such as mental distress and negative affectivity (Diener et al., 2002; Keyes, 2007). Positive mental well-being is linked to numerous important health outcomes spanning from better physical functioning to an increase in life expectancy (Lyubomirsky et al., 2005). Therefore, in addition to reducing distress, promoting positive mental well-being can be regarded as an important public health goal. Relative to a significant number of studies devoted to psychological distress in middle-aged women in menopausal transitions (Llaneza et al., 2012), using measures related to, for instance, depressive symptoms (Vesco et al., 2007), there is a paucity of research regarding positive mental well-being among middle-aged women.

Two theoretical frameworks – the hedonic and eudaimonic perspectives for capturing mental well-being - have emerged (Ryan & Deci, 2001). Hedonic well-being is related to positive affectivity and low negative affectivity, as well as a feeling of happiness and life satisfaction. Positive and negative affectivity are frequently measured using a scale called the International Positive and Negative Affect Schedule Short Form (I-PANAS-SF) (Thompson, 2007). Within this measure, positive and negative affect assess unique features of one's emotional state, showing only a modest association with each other (Steptoe & Wardle, 2012). With the exception of the emotional aspect of hedonic well-being, there is a cognitive component which builds on the appraisal of one's life satisfaction. The Satisfaction with Life Scale is a common tool to evaluate cognitive judgements regarding one's satisfaction with one's life (Diener et al., 1985).

The eudaimonic perspective relates to the process of self-actualising across the lifespan and forming a sense of meaning in life (Ryff, 1989). Self-actualisation can often be attained by exchanging short-term goals for a long-term perspective. In this sense, it could be conceptually distinct from a hedonic perspective, whereby one can report high eudaimonic well-being but also report low hedonic well-being. For example, in relation to middle-aged women, experiencing menopause could temporally influence one's emotional affective state, but at the same time, eudaimonic well-being could be unaffected.

While a prevailing view point is that these are two distinct theoretical frameworks, some studies have integrated these conceptualisations of mental well-being, which include affectivity and satisfaction and meaning in life (Keyes, 2007; Kokko et al., 2013; Seligman, 2012, p.16).

2.4.2 Mental well-being and menopausal transition

Available studies have revealed that there is no significant relationship between menopausal status and eudemonic well-being— such as purpose in life and self-acceptance (Abdelrahman et al., 2014; Deeks & McCabe, 2004). In contrast, there have been more studies on emotional aspects of well-being (hedonic well-being), and they have reported contradictory results, showing that some women may experience vulnerability in terms of affective mental well-being, while others do not (L. Brown et al., 2015; Smith-DiJulio et al., 2008; Steptoe & Wardle, 2012).

Depressive symptoms or psychological distress (negative mental well-being) have long been under scrutiny during the menopausal transition. Cohort studies such as the Study of Women Across the Nation or the Penn Aging Ovarian Study (Bromberger et al., 2001; Freeman et al., 2006) were instrumental in identifying sensitive periods for vulnerability to depressive or psychological symptoms during the menopausal transition. It has been proven that women are more vulnerable to depressive symptoms in the late perimenopausal stage than in the pre- or postmenopausal status (Bromberger et al., 2001; Stewart et al., 1992). The mechanism behind this vulnerability in the perimenopausal stage is not clear; however, one of the possible reasons is a fluctuation in estradiol levels, as it has been proven that women with greater estradiol fluctuations during perimenopause exhibit more severe depressive symptoms (Willi et al., 2021).

Dennerstein (1996) conducted a review of populational studies concerning the experiences of middle-aged women during the menopausal transition, in which he referred to mental well-being as encompassing both positive and negative affect (the emotional aspect of hedonic well-being). In this review, he posits that middle-aged women's well-being is largely unaffected by menopausal status but rather is a product of health status, psychosocial variables and life-style.

A more recent review which evaluated a connection between menopausal status and symptoms with hedonic well-being (affectivity, life-satisfaction) and eudaimonic well-being identified two studies that reported a significant association between menopausal status and positive mental well-being. However, five studies found no such association (Brown et al., 2015). This review also attempted to dissociate positive and negative mental well-being. The authors suggested that menopausal status may have a connection to negative but not to positive affect. For example, one study which defined well-being as a balance between positive and negative affect reported lower mental well-being in postmenopausal women compared to premenopausal women after four years (Dennerstein et al., 1997). However, after nine years, the mental well-being of these participants had improved due to a decline in negative affect (Dennerstein et al., 2002). This differential association between positive and negative mental well-being with menopausal status may indicate a compensatory mechanism wherein the positive aspect of mental well-being may be spared during the menopausal transition (Brown et al., 2015).

2.4.3 Physical activity and mental well-being

In addition to its connection to physical performance, physical activity is associated with higher mental well-being (Bragina & Voelcker-Rehage, 2018). Substantial evidence supports a positive relationship between physical activity and mental well-being in a variety of populations (Chekroud et al., 2018; Lovejoy et al., 2008; Netz et al., 2005); quite a few of the existing studies have investigated how physical activity contributes to mental well-being in middle-aged women. Much of the existing research that focuses on the link between physical activity and well-being is cross-sectional or interventional. Several meta-analytical reviews, however, have also been published (e.g. Buecker et al., 2020; Netz et al., 2005; Reed & Buck, 2009). This synthesised research focuses on either subgroups of populations (e.g., older adults) or specific types of exercise (e.g., aerobic) and reports a positive link between physical activity and positive mental well-being.

Middle-aged women in the middle and top percentiles of physical activity levels have been shown to report improved quality of life, in terms of both global and menopause-specific quality of life, and lower levels of depressive symptoms than women with low physical activity levels (Nelson et al., 2008). Positive changes in anxiety and depression (measured with the Hospital Anxiety and Depression Scale) were reported among previously sedentary healthy middle-aged women after a six-week prescribed moderate-intensity exercise program (Asbury et al., 2006).

Physical activity may influence mental well-being through different mechanisms which could be generally classified as neurobiological mechanisms (e.g., release of dopamine or serotonin), psychological mechanisms (e.g., improve of sense of mastery or positive affect) or behavioural mechanisms (e.g., quitting smoking and engaging in other health-related behaviours) (Bragina & Voelcker-Rehage, 2018; Lubans et al., 2016). Thus, physical activity characteristics, such as degree of sociality (performed alone or in a group), intensity and type of exercise (aerobic or strength) may differentially contribute to mental well-being. For example, moderate-intensity physical activity is positively associated with mental well-being, while there are conflicting results related to vigorous-intensity physical activity (Panza et al., 2017). Some evidence suggests that vigorous physical activity yields additional mental health benefits compared to those that result from moderate-intensity physical activity (Teychenne et al., 2008b). In the study with middle-aged women, vigorous physical activity was associated with a greater reduction in depressive symptoms than moderate activity alone (Pavey et al., 2013).

Types of physical activity may also influence mental well-being. A longitudinal study with middle-aged women who participated in four-month yoga and walking exercises revealed that physical activity facilitates improvements in positive affect and self-worth associated with greater satisfaction with life (Elavsky, 2009).

Some studies have attempted to identify a relationship between current levels of physical activity and mental well-being in later years. An Australian study with middle-aged women showed no significant association between baseline levels of physical activity and mental well-being after five years (Xu et al., 2010). In contrast, a Swedish study with middle-aged women indicated that higher levels of physical activity predicted mental well-being 24 years later (Blomstrand et al., 2009). However, the reverse relationship is also possible. A longitudinal study with Finnish middle-aged women demonstrated that mental well-being at age 42 was related to physical activity at age 50 but not vice versa, meaning that physical activity at age 42 did not relate to mental well-being at age 50 (Kekäläinen et al., 2019).

In women undergoing menopause, Nelson et al. (2008) showed that perimenopausal women with high and moderate physical activity levels had lower levels of depressive symptoms than their less physically active counterparts. Such results suggest that women with low physical activity levels may form a subgroup who is potentially vulnerable to a decline in mental well-being during menopause. The link between physical activity and mental well-being in women experiencing menopause may be rather complex, with mechanisms ranging from positive social interaction during physical activity to alleviating menopausal symptoms, which may also enhance their affective state (Elavsky, 2009). Habitual physical activity appears to act as a means of accumulating positive affective states over time, creating a psychological resource which is beneficial for a woman's ability to cope well and to feel in control of her menopausal symptoms (Kishida & Elavsky, 2015). However, another possible mechanism through which physical activity may exert its effect on mental well-being is by enhancing physical performance.

2.5 Physical performance and mental well-being

Despite the fact that physical activity and physical performance have a close functional relationship, physical performance may, independently from physical activity, be related to mental well-being. Two systematic reviews highlighted the role of aerobic fitness as a moderating factor of depressive symptoms (Kandola et al., 2019; Papasavvas et al., 2016). However, these reviews lack information about the physical activity levels of the participants; therefore, they could not disentangle the independent contribution of physical performance. Previously inactive middle-aged women participating in a six-week exercise program exhibited no improvement in cardiorespiratory fitness (indirectly measured oxygen consumption). However, they displayed a significant decrease in the depression subscale on the Hospital Anxiety and Depression Scale (Asbury et al., 2006).

A cross-sectional study showed (although not directly focused on this link) that more depressed individuals have lower handgrip strength (Ganasarajah et al., 2019). In one study with perimenopausal women as participants, various components of physical performance - muscle strength, cardiorespiratory fitness, speed-agility and flexibility - were assessed through self-reports (Aparicio et al., 2019). This study showed an association between greater levels of self-reported physical performance and reduced depression, anxiety, negative affect and greater optimism, positive affect and better sleep quality. As physical performance in this study was self-reported, and since it could be that those participants with greater well-being may tend to report greater physical performance (Sabourin et al., 2011), it is therefore important to investigate this relationship using comprehensive measurements of physical performance. Thus, identifying a unique contribution of physical performance to mental well-being merits additional research using objective measurements of physical performance components and controlling for physical activity.

In the present thesis, menopausal factors (status) were assumed to relate to both mental well-being and physical performance (Figure 1). On the other hand, the outcomes of physical activity affect both mental well-being and physical performance. Thus, the relationship between menopausal status and physical performance and between menopausal status and mental well-being may vary depending on levels of physical activity. Moreover, due to the close interrelationship between physical activity and physical performance, the link between physical performance and mental well-being independent of physical activity has also been investigated in the thesis.

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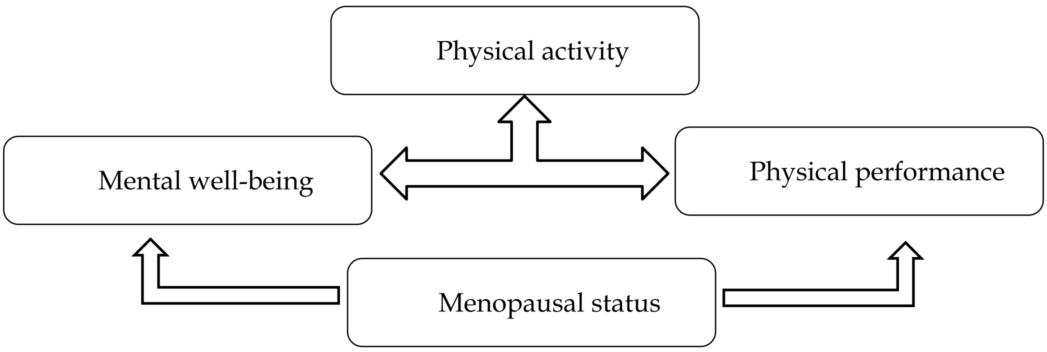


FIGURE 1 Interrelationship between physical activity, mental well-being, physical performance and menopausal status.

3 PURPOSE OF THE STUDY

The purpose of this study is to investigate physical performance and mental well-being in middle-aged women characterised by their menopausal status and to explore the role of physical activity in the relationships between menopausal status, physical performance and mental well-being. The specific research questions were as follows:

1. To examine the relationship between menopausal status and muscle strength and walking performance in cross-sectional (Study I) and longitudinal settings (Study III) and to investigate the role of physical activity in this relationship (Study I and III).
2. To examine the relationships between menopausal status and positive and negative mental well-being and to investigate the role of physical activity in this link (Study II).
3. To investigate the association between physical performance and dimensions of mental well-being in middle-aged women and to investigate the role of physical activity in this link (Study IV).

4 MATERIALS AND METHODS

4.1 Study design

This doctoral dissertation and the related original publications are based on the Estrogen Regulation of Muscle Apoptosis (ERMA) study (Kovanen et al., 2018). The ERMA study is a population-based cohort study which consists of data from women between 47 and 55 years of age living in the city of Jyväskylä (Finland) or neighbouring municipalities. The present thesis includes both cross-sectional (n=1098) and longitudinal study (n=232) designs. The flow chart is shown in Figure 2. Table 2 summarises research designs and variables utilised as outcomes and predictors as well as reports on sensitivity analysis across studies I-IV.

TABLE 2 Summary of the research design and variables utilised in the studies I-IV.

Study	*n*	Design	Outcomes	Predictors	Covariates	Sensitivity analysis
I	914	Cross-sectional	Physical performance: knee extension strength, hand grip strength, vertical jumping height, maximal walking speed, six-minute walking distance	Menopausal status; pre-, peri-, post-menopausal	Fat mass, body height, education, physical activity	Included age as an additional covariate
II	1098	Cross-sectional	Mental well-being: life satisfaction, positive affect, negative affect, depressive symptoms	Menopausal status; pre-, early peri-, late peri-, postmenopausal	Age, marital status, parity, employment status, self-reported mental disorder, use of psycholeptics and psychoanaleptics, menopausal symptoms	Included menopausal symptoms as categories (vasomotor symptoms; somatic or pain symptoms; psychological symptoms and urogenital symptoms)
III	232	Longitudinal	Physical performance: maximal isometric muscle torque, hand grip strength, vertical jumping height, maximal walking speed, six-minute walking distance	Menopausal status; early and late perimenopausal	Duration of hormone therapy	Performed with women (*n*=196) who did not use hormone therapy
IV	909	Cross-sectional	Mental well-being: life satisfaction, positive affect, negative affect, depressive symptoms	Physical performance: Knee extension strength, hand grip strength, vertical jumping height, maximal walking speed, six-minute walking distance	Body height, fat mass, menopausal status, menopausal symptoms, marital status, parity, employment status, self-reported mental disorders, use of psycholeptics and psychoanaleptics, and physical activity	

4.2 Participant enrollment

Women between 47 and 55 years of age living in the city of Jyväskylä or neighbouring municipalities were randomly selected from the Finnish National Registry administered by the Population Register Centre (Figure 2).

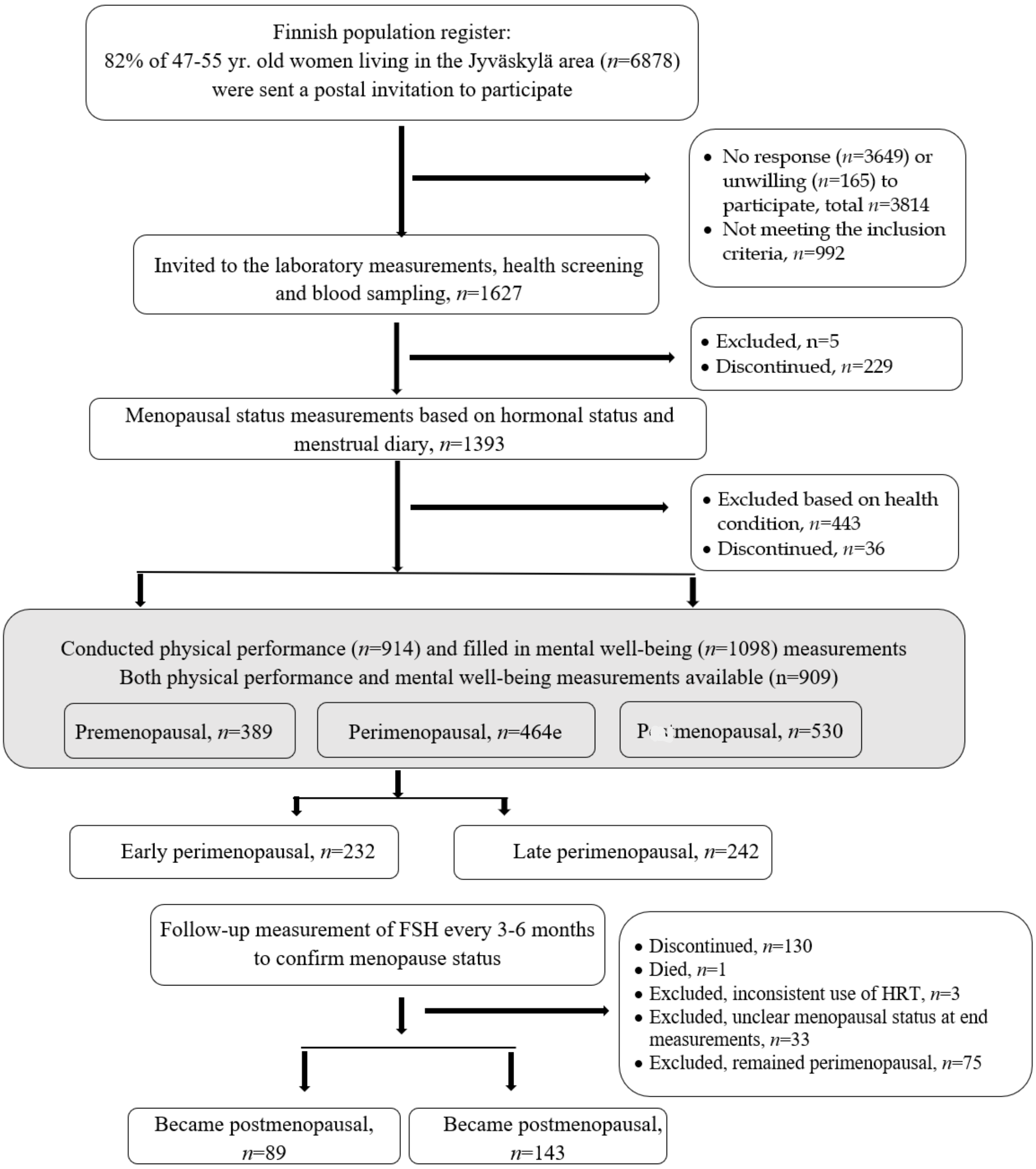


FIGURE 2 Enrolment of the study participants

The potential 6,878 participants were sent a postal invitation along with a consent form and questionnaire to evaluate their willingness and potential eligibility for participation in the study. The response rate was 47%. Based on the questionnaires that were received, participants were excluded if they used medications affecting ovarian function, including bilateral ovariectomy, oestrogen-containing hormonal preparations or other medications affecting ovarian function, had a self-reported body mass index of more than 35 kg/m^2, were pregnant or lactating, had been diagnosed with a mental illness or had conditions or had used continuous medications affecting their daily mental or physical functioning.

In the next step, eligible participants (n=1627) were invited to the laboratory, where they filled in the health screen questionnaire to estimate their safe participation in the physical performance measurements and to provide fasting blood samples. In the third step, participants submitted the completed baseline questionnaire, which was checked by the research assistant. Participants who reported unclear medical conditions were followed up through a medical examination to ensure their safe participation in physical performance measurements. Eligible participants were measured for body composition, physical performance and psychological/cognitive abilities. After the dropout of 36 participants and exclusion of 443 participants for health-related reasons preventing them from participating in the physical performance measurements, 1,098 eligible participants remained in the study and completed the well-being measurements. Participants who conducted at least one physical performance measurement acceptably (n=914) were included in the analysis in Study I, and participants who filled in the mental well-being questionnaire (n=1 098) were included in the analysis in Study II. Therefore, the dataset comprised of participants who had both baseline physical performance and mental well-being measurements available (n=909) was used in the analysis in Study IV.

Early and late perimenopausal women (who did not use progestogen-containing contraception or had no other conditions affecting their ovarian function or menstrual bleeding patterns) were invited to participate in the longitudinal part of the ERMA study, during which they were followed until reaching a postmenopausal state. During the follow-up, all participants kept a menstrual diary and provided blood samples at 3 to 6-month intervals until their postmenopausal status was confirmed. After their postmenopausal state was confirmed, they repeated the baseline measurements. The analysis in Study III comprises women whose performance in at least one of the physical performance measurements was acceptable in early or late perimenopause and after the follow-up when they were postmenopausal (n=232).

4.3 Ethical aspects

All participants provided written informed consent. The study protocol adhered to good clinical and scientific practice and the Declaration of Helsinki and was approved by the Ethics Committee of the Central Finland Health Care District (K-SSHP Dnro 8U/2014).

4.4 Measurements

4.4.1 Participants' characteristics

Body weight was measured with a digital scale, and height was measured with a stadiometer. BMI was calculated as weight (kg) divided by height squared (m^2). *Fat mass* was measured with an eight-point tactile electrode multifrequency bioelectrical impedance analyser [InBody (720), Biospace, Seoul, Korea] and presented as a fat mass percentage.

Information regarding socioeconomic status (i.e., age, education, marital status), health and use of medications was collected via a questionnaire. Participants' *level of education* was captured using a standard question and categorised as basic (primary and secondary school degrees), college (applied science degree, bachelor or nurse training) or university (master's degree or PhD) levels (Study I). In Study II, Study III and Study IV, the responses were classified as primary (primary school degree), secondary (secondary school degrees), and tertiary (applied science degree, bachelor's degree, nurse training, master's degree and PhD). *Marital status* was classified into three categories: single, married or living with a partner, divorced or separated or widowed. *Employment status* was categorised as either employed (including paid or self-employed job) or not regularly employed (studying, unemployed, work occasionally, retired, taking care of the home).

Parity was categorised as nulliparous, one or two children, and three or more children. *Menopausal symptoms* were assessed via a structured questionnaire, in which participants indicated whether they had any of the following menopause-associated symptoms: sweating, hot flashes, sleeping problems, headache, joint pain, tiredness, mood swings, vaginal symptoms, urinary track problems, sexual problems or any other symptoms. For the analysis, responses were grouped into a dichotomous variable (menopausal symptoms/no menopausal symptoms).

The presence of *musculoskeletal diseases or conditions* in Study I and *diagnosed mental disorder* in Study II were self-reported as yes/no. *Use of medications* that could influence mental well-being (Study II) was self-reported and coded according to the Anatomical Therapeutic Chemical Classification System (World Health Organization Collaborating Centre for Drug Statistical Methodology, 2017) as N05, psycholeptics and N06, psychoanaleptics.

In Study I, information about the use of *hormonal contraception,* such as the use of a progestogen-releasing intrauterine coil or other progestogen preparation (for contraception or to treat a gynecological bleeding disorder), was self-reported as yes/no.

4.4.2 Menopausal status

Systemic FSH and 17β-estradiol levels were measured from fasting serum samples collected between 8:00 and 10:00 AM. For the baseline measurements (for Study I and Study II datasets), if a woman was in her menstrual cycle, the data were collected during cycle days 1 to 5. For serum separation, blood samples were centrifuged for 10 minutes at 2.200x g. FSH and 17β-estradiol levels were measured with an IMMULITE 2000 XPi analyser (Siemens Healthcare Diagnostics, UK) using solid-phase, enzyme-labeled chemiluminescent competitive immunoassay.

The FSH and 17β-estradiol follow-up measurements were performed during two consecutive visits (control and final follow-up) and averaged to minimise the effect of daily fluctuations. Participants who started using hormonal therapy (HT) after the baseline measurements were assessed only during the final follow-up-visit.

Menopausal status was determined based on the analysis of bleeding diaries and serum concentrations of FSH according to the Stages of Reproductive Aging Workshop (STRAW+ 10) criteria (Harlow et al., 2012).

Group assignment according to menopausal status was as follows:

- Premenopausal (always if FSH <9.5 IU/L regardless of menstrual cycle or if reported regular menstrual cycle and FSH <17 IU/L; or if menstrual cycle information was incomplete FSH <15 IU/L);
- Perimenopausal (for Study I only) (always if FSH 17-30 IU/L or FSH 9.5-25 IU/L and reported irregular menstrual cycle, or FSH >30 IU/L and reported occasional menstrual bleedings during past 3 months, if menstrual cycle information was incomplete FSH 15-39 IU/L);
- Early perimenopausal group FSH 17-25 IU/L, if irregular menstrual cycle and FSH was 9.5 -25 IU/L;
- Late perimenopausal FSH 25-30 IU/L, if reporting occasional bleedings that had occurred during past 3 months even though their FSH value might exceed 30 IU/L;
- Postmenopausal (FSH >30 IU/L and no menstrual bleeding during past 6 months, or FSH >39 IU/L and no menstrual bleeding during past 3 months, or very high FSH (>130 IU/L) even if occasional bleeding still occurs; for users of progesterone-containing medication FSH >39 IU/L).

4.4.3 Physical activity

Current *level of leisure time physical activity* was assessed via a questionnaire on a seven-point scale (Hirvensalo et al., 1998), ranging from household chores to competitive sports and with items assessing leisure-time physical activity patterns. The questionnaire has been validated among middle-aged women (Hyvärinen et al., 2019).

The response options were as follows: (1) I do not move more than is necessary in my daily routines; (2) I go for casual walks and engage in light outdoor recreation 1 to 2 times a week; (3) I go for casual walks and engage in light outdoor recreation several times a week; (4) once or twice a week, I engage in brisk physical activity (e.g., yard work, walking, cycling) that causes some shortness of breath and sweating; (5) several times a week (3–5), I engage in brisk physical activity (e.g., yard work, walking, cycling) that causes some shortness of breath and sweating; (6) I exercise several times a week in a manner that induces somewhat strong shortness of breath and sweating during the activity; (7) I engage in competitive sports and maintain my fitness through regular training.

In Study I and Study II, the seven response categories were recoded to form three levels of physical activity: low (categories 1 and 2), medium (3 and 4) and high (5 and 7).

In Study III, which was longitudinal, to utilise the full information from the measurement of physical activity, and since options 1, 2, 3 and 7 yielded only 1, 4, 11 and 1 responses, respectively, we combined and classified responses into four categories: inactive (options 1, 2, 3), low physical activity (option 4), medium physical activity (option 5) and high physical activity (option 6 and 7).

4.4.4 Physical performance

Maximal isometric knee extension force, in Newtons (N), was measured in a sitting position with a knee angle set at 60° from full extension. The measurements were performed from the side of the dominant hand on a custom-made dynamometer chair (Good Strength; Metitur Oy, Palokka, Finland). Participants were encouraged to extend the knee to produce maximal force. In Study III, *maximal isometric muscle torque* was used to account for the height of a participant, which represents the same measurement as maximal isometric knee extension force but multiplied by the lower leg length, measured as the distance between the lateral joint line of the knee and the mid-line of force transducer around the ankle.

Handgrip force on the dominant side was measured in Newtons with the elbow flexed at an angle of 90° and the arm fixed to the armrest of the dynamometer chair. Participants were instructed to grip the handle as forcefully as possible. Grip was maintained for 2 to 3 s, and the peak value was taken for analysis.

Lower body muscle power was assessed by a countermovement jump on a contact mat. The countermovement jump describes the ability to elevate the body's center of gravity as fast as possible during a vertical jump (vertical jumping height). Vertical jumping height was calculated in cm based on flight time (t): (g × t2) ÷ 8 × 100 (Bosco et al., 1983). In all the above tests, three to five maximal attempts were performed, and best performance was recorded as the result.

Maximum walking speed was assessed over 10 m in a laboratory corridor, and walking time was measured with photocells. Participants were encouraged to 'walk as fast as they could'. The best time from two trials was taken as the result.

Aerobic capacity was assessed via the six-minute walking test. The test was conducted on a 20-m indoor track, and participants were instructed to complete as many laps as they could during 6 min. The distance covered in meters was used in the analysis.

4.4.5 Mental well-being

Depressive symptoms were assessed with the 20-item Center for Epidemiological Studies Depression Scale (CES-D) (Radloff, 1977). Participants were asked to rate the frequency of each symptom during the previous week. Each item was scored between 0 and 3, and a mean score for the 20 items was calculated. Higher scores reflect more depressive symptoms. In addition, to describe participants, a sum score ranging from 0 to 60 was calculated, and a score of 16 or above was considered to be a sign of potential clinical depression (Boyd et al., 1982).

Positive and negative affectivity was assessed with the International Positive and Negative Affect Schedule Short Form (I-PANAS-SF) (Thompson, 2007), comprising five positive affect adjectives and five negative affect adjectives. Participants rated each of these adjectives on a scale from 1 (does not describe me) to 5 (describes me very well). Average scores ranging from 1 to 5 were calculated for each affect scale, with higher scores indicating a higher tendency to experience positive or negative affectivity.

Global cognitive judgments of one's *life satisfaction* were measured using the five-item Satisfaction with Life Scale (Diener et al., 1985). Participants indicated the extent to which they agreed or disagreed with each of the five items on a scale ranging from 1 = strongly disagree to 7 = strongly agree. The mean score for the five items was calculated, with higher scores indicating more satisfaction with life.

4.5 Data analysis

Participants' characteristics have been indicated as means and standard deviations or as proportions. The differences in physical performance and mental well-being between the menopausal status groups, were analysed based on analysis of variance (ANOVA) with a post hoc Tukey test. For categorical variables, differences were tested with a Chi-square test. Categorical baseline characteristics between the early and late perimenopausal groups were compared using Chi-square tests or, in the case of continuous variables, via independent samples t-tests. For non-normally distributed data, a comparison was performed with the Mann-Whitney U test.

To investigate the differences in physical performance (Study I) and dimensions of mental well-being (Study II) across menopausal status groups, the multivariate linear regression modelling was used. In study I, the analyses were adjusted for body height, fat mass and education. In study II, age, marital status, parity, employment status, self-reported mental disorder, and use of psycholeptics, psychoanaleptics and menopausal symptoms were included as confounders.

The role of physical activity in the link between physical performance (Study I) or mental well-being (Study II) and menopausal status was investigated using the marginal means differences tests. This analysis allows one to compare the means across the menopause status categories (pre-, peri-, and postmenopausal) and across the physical activity (PA) levels (low, moderate, and high). In the case of categorical variables with more than two categories, the analysis of marginal means differences provides additional information beyond the full model with interaction (Robinson et al., 2013). The analysis was adjusted for the abovementioned confounders.

In the follow-up study, to evaluate the level of significance in the changes in physical performance during the menopausal transition, the general linear model with the interaction of perimenopausal group by time (as two time points, perimenopause and postmenopause) was used. Mean percentage changes in physical performance variables were calculated as [(follow-up – baseline)/baseline × 100]. The respective 95% confidence intervals were provided for mean percentage changes and mean values of each physical performance measurement. The analysis was adjusted for the duration of HT (days; entered in the model as a mean-centered variable).

To investigate the role of physical activity in the relationship between menopausal status and physical performance, we used the general linear model for repeated measures data with the interaction of baseline physical activity level group by time. If the level of significance was established, the Tukey test was employed to determine which physical activity group drove the significance. As 37 women started HT during the follow-up, we also conducted sensitivity analyses which included only those participants (n=196) who did not start HT during the follow-up.

To examine the association between the physical performance variables and dimensions of mental well-being, a step-wise regression model was employed (Study IV). In model 1, regression models were adjusted for body height, fat mass, menopausal status and symptoms, marital status, parity, employment status, self-reported mental disorders, use of psycholeptics and use of psychoanaleptics. While in the published manuscript related to Study IV, physical activity was formed into a three-level variable (low, medium and high), for the analysis in this doctoral thesis, physical activity was entered in a model as a discrete seven-item variable.

All analyses were performed with R, version 3.3.3 (Fife, D, 2017; R Core Team, 2016).

5 RESULTS

5.1 Participants' characteristics across menopausal status groups

Socioeconomic, anthropometric and health-related variables related to the participants categorised by their menopausal status are shown in Table 3 and Table 4. The participants were categorised into pre-, peri and postmenopausal groups in Study I. In Study II, the menopausal status groups were formed as follows: pre-, early peri-, late peri- and postmenopausal groups. In Study III, the participants were categorised into early and late perimenopausal groups. In Study IV, the analysis was performed without categorisation into menopausal status groups.

The postmenopausal women were older than the peri- (Tukey post hoc test $p < 0.001$) and premenopausal women (Tukey post hoc test $p < 0.001$); the late perimenopausal women were significantly older than the early perimenopausal women. In terms of education, only the postmenopausal group differed from other groups, having fewer women with a tertiary degree but a greater number of women with a primary degree. Perimenopausal women had higher body mass index than postmenopausal women (Tukey post hoc test $p=0.037$).

TABLE 3 Participants' characteristics across menopausal status groups (Study I and III).

Variables	Study I			Study III	
	Premenopausal *n*=233	Perimenopausal *n*=381	Postmenopausal *n*=299	Early peri-menopausal *n*=89	Late peri-menopausal *n*=143
Age, years, mean (SD)	50.6 (1.6)	51.2 (1.9)**	52.5 (1.8)**	51.2 (1.9)	51.8 (1.8)*
Education, *n* (%)	*n*=230	*n*=373	*n*=295	*n*=88	*n*=143
Primary	127 (55)	205 (55)	191 (64)	1 (1)	5 (3)
Secondary	26 (12)	49 (14)	42 (15)	16 (18)	28(20)
Tertiary	77 (33)	119 (31)	62 (21)*	71 (81)	110 (77)
Marital status, *n* (%)	*n*=231	*n*=377	*n*=297	*n*=88	*n*=143
Single	19 (8)	32 (9)	28 (9)	11 (13)	14 (9)
Married or registered partnership	181 (79)	290 (77)	215 (73)	65 (74)	109 (77)
Divorced, separated or widowed	31 (13)	55 (14)	54 (18)	12 (13)	20 (14)
Smoking, *n* (%)	—	—	—	*n*=88	*n*=142
Never	—	—	—	65 (73)	94 (66)
Former	—	—	—	21 (25)	35 (25)
Current	—	—	—	2 (2)	13 (9)
Musculoskeletal problems, *n* (%)	*n*=232 75 (32)	*n*=375 137 (36)	*n*=297 94 (31)	*n*=87 32 (37)	*n*=142 49 (34)
Use of hormonal contraception, *n* (%)	*n*=232 109 (47)	*n*=379** 116 (30)	*n*=298** 75 (25)	*n*=88 31 (36)	*n*=143 34 (24)

Using progestogens, n (%)	*n*=230 24 (10)	*n*=375 35 (9)	*n*=294 42 (14)	*n*=88 7 (8)	*n*=142 13 (9)
Physical activity, *n* (%)	*n*=232	*n*=378	*n*=298	*n*=88	*n*=143
Inactive	—	—	—	13 (15)	18 (13)
Low	36 (16)	64 (17)	59 (20)	21 (24)	34 (23)
Medium	140 (60)	248 (65)	181 (61)	36 (41)	70 (49)
High	56 (24)	66 (18)	58 (19)	18 (20)	21 (15)
Body mass index, kg/m²,	25.4 (3.2)	25.8 (3.8)*	25.1 (3.7)	25.3 (4.1)	25.7 (3.8)
Fat mass, %	21.2 (7.6)	22.5 (8.3)	21.5 (8.1)	—	—
17β-estradiol, nmol/L	0.62 (0.66)	0.32 (0.26)**	0.14 (0.29)**	0.46 (0.34)	0.25 (0.17)**
Follicle-stimulating hormone, IU/L	7.91 (3.54)	31.68 (20.73)**	82.97 (28.66)**	18.29 (4.99)	47.02 (20.65)**

* $p < 0.05$ compared to group premenopausal or to early perimenopausal
** $p < 0.001$ compared to group premenopausal or to early perimenopausal
Values given are n (%) for variables without units and mean (SD) for variables with units of measurements.

TABLE 4 Participants' characteristics across menopausal status groups (Study II and IV).

Variables	Study II				Study IV
	Premenopausal *n*=304	Early perimeno-pausal *n*=198	Late perimeno-pausal *n*=209	Postmenopausal *n*=387	Total sample n=909
Age, years	50.3 (1.67)	50.7 (1.81)*	51.6 (1.90)*	52.3 (1.98)**	51.5 (2.0)
Education, *n* (%)	*n*=304	*n*=198	*n*=209	*n*=387	*n*=898
Primary	5 (1)	3 (1)	7 (3)	9 (2)	17 (2)
Secondary	165 (55)	109 (55)	106 (51)	239 (62)	506 (56)
Tertiary	134 (44)	86 (44)	96 (46)	139 (36)	375 (42)
Marital status, *n* (%)	*n*=303	*n*=198	*n*=209)	*n*=385	*n*=906
Single	21 (7)	19 (10)	16 (7)	37 (10)	79 (9)
Married or registered partnership	242 (80)	148 (75)	164 (79)	278 (72)	687 (76)
Divorced, separated or widowed	40 (13)	30 (15)	29 (14)	70 (18)	140 (15)
Parity: number of children born	*n*=302	*n*=196	*n*=208	*n*=386	*n*=906
Nulliparous	35 (12)	25 (13)	26 (12)	53 (13)	110 (12)
One or two	178 (59)	114 (58)	113 (55)	219 (58)	512 (55)
Three or more	89 (29)	57 (29)	69 (33)	114 (29)	284 (33)
Employment status, *n* (%)					*n*=909
Employed	275 (90)	168 (85)	182 (87)	335 (87)	808 (89)
Not regularly employed	29 (10)	30 (15)	27 (13)	52 (13)	101 (11)
Self-reported mental disorders (yes)	*n*=303	*n*=194	*n*=209	*n*=385	*n*=903
	29 (9)	21 (11)	16 (8)	25 (6)	62 (7)
Depressive symptoms (CES-D ≥ 16[a])					—

	30 (10)	22 (11)	18 (10)	52 (13)	—
Users of psycholeptics (N05)	*n*=304	*n*=197	*n*=209	*n*=387	*n*=908
	9 (3)	7 (3)	3 (1)	7 (2)	17(2)
Users of psychoanaleptics (N06)	*n*=304	*n*=197	*n*=209	*n*=387	*n*=908
	26 (8)	19 (10)	13 (6)	30 (8)	67 (7)
Physical activity, *n* (%)					*n*=909
Low	50 (17)	37 (19)	30 (16)	81 (21)	159 (18)
Medium	174 (57)	124 (62)	145 (66)*	218 (56)	570 (62)
High	80 (26)	37 (19)	34 (22)	88 (23)	180 (20)
Menopausal symptom (yes)					*n*=907
	168 (55)	148 (74)*	172 (82)*	353 (91)**	702 (77)
Menopausal status, n (%)	—	—	—	—	*n*=909
Premenopausal					232 (25)
Early perimenopausal					182 (21)
Late perimenopausal					197 (22)
Postmenopausal					298 (32
Menopausal symptom (yes)	—	—	—	—	702 (77)
Body height, m	—	—	—	—	*n*=908
					1.6 (0.06)
Body fat mass, %	—	—	—	—	*n*=905
					30.5 (7.48)

Values given are n (%) for variables without units of measurement and mean (SD) for variables with units of measurement.
* $p < 0.05$ compared to group premenopausal
** $p < 0.001$ compared to group premenopausal
[a] Centre for Epidemiologic Studies Depression Scale

The use of progestogen-containing hormonal contraception was higher among premenopausal women than among the perimenopausal ($p < 0.001$) and postmenopausal groups (Tukey post hoc test $p < 0.001$).

The postmenopausal group had significantly greater estradiol and lower FSH levels than either the peri- or premenopausal group, and the perimenopausal group had greater estradiol and lower FSH levels than the premenopausal group (p for all comparison <0.001).

Postmenopausal women reported a significantly higher frequency of menopausal symptoms (Study II, Table 4) than the late peri- ($p = 0.025$), early peri- ($p < 0.001$) and premenopausal women ($p < 0.001$). In study II (Table 4), the PA distribution differed significantly only for the late perimenopausal group, which had a greater proportion of moderately physically active women than the premenopausal ($p = 0.032$) or the postmenopausal group ($p = 0.032$).

5.2 Menopausal status and physical performance (Study I, III)

Table 5 summarises the results for physical performance in relation to menopausal status. After accounting for the covariates, the postmenopausal participants had significantly weaker handgrip force (by -7%), and they had significantly lower vertical jumping height (by -6%) than the premenopausal participants (Table 5). No statistically significant differences between the study groups were observed in terms of walking performance.

TABLE 5 Relative differences (Study I, premenopausal as reference) and changes (Study III) in physical performance across menopausal status groups.

Comparisons between menopausal stages	Physical performance				
	Hand grip force, N	Maximum knee extension force, N (Study I)/torque, Nm (Study III)	Vertical jumping height, cm	Maximum walking speed, ms^{-1}	Six-minute walking test, m
Study I, Mean difference, % (95% CI)					
Perimenopausal	-0.7 (-3.7; 2.2)	1.1 (-2.5; 4.7)	-2.6 (-5.9; 0.6)	-1.2 (-4.1; 1.7)	-0.3 (-1.7; 1.0)
Postmenopausal	**-6.8 (-9.9; -3.7)**	-3.7 (-7.5; 0.1)	**-5.9 (-9.2; -2.5)**	-2.3 (-5.4; 0.7)	-0.1 (-1.5; 1.3)
Study III, Mean change, % (95% CI)					
Early perimenopausal	**-3.5 (-6.0; -1.1)**	**-4.1 (-6.5; -1.6)**	**-3.9 (-6.3; -1.6)**	0.1 (-1.5; 3.2)	**1.5 (0.4; 2.7)**
Late perimenopausal	-1.5 (-3.8; 0.8)	-1.6 (-4.2; 0.9)	**-2.2 (-4.2; -0.3)**	1.3 (-0.2; 2.9)	**2.5 (1.6; 3.3)**

Notes: CI = confidence interval;
Study I analysis is adjusted for fat mass, body height, education and physical activity;
Study III analysis is adjusted for the duration of hormone therapy use;
Values in bold indicate statistically significant results.

When participants were followed up from early perimenopause to postmenopause, a significant average decline was observed in handgrip force, maximum knee extension torque and vertical jumping height (Table 5). For the late perimenopausal participants, the average decline was significant only for vertical jumping height. There was no significant change in maximum walking speed in either the early or late perimenopausal participants. However, they improved their performance in the six-minute walking distance assessment during the menopausal transition.

5.3 Menopausal status and mental well-being (Study II)

Table 6 presents values related to the dimensions of mental well-being across the four menopausal groups. These values adjusted for the participants' age, marital status, parity, employment status, self-reported mental disorder, use of psycholeptics/psychoanaleptics and menopausal symptoms. Premenopausal women had lower rates of depressive symptoms than early peri- and postmenopausal women. No significant differences were observed between the menopausal status groups in relation to life satisfaction, positive affectivity or negative affectivity.

TABLE 6 Mental well-being dimensions by menopausal stages (Study II).

Variables	Premeno-pausal, *n*=302	Early peri-menopausal, *n*=196	Late peri-menopau-sal, *n*=208	Post-menopausal, *n*=387	*P values**
Depressive symptoms	0.68 (0.33)	0.74 (0.39)	0.72 (0.35)	0.75 (0.40)	0.019 Pre-E.Peri 0.038 Pre-L.Peri 0.534 Pre-Post 0.035 E.Peri- L.Peri 0.597 E.Peri-Post 0.974 L.Peri-Post 0.745
Life satis-faction	4.30 (1.12)	4.38 (1.05)	4.47 (0.98)	4.33 (1.17)	0.264
Positive af-fect	3.66 (0.61)	3.74 (0.64)	3.74 (0.63)	3.66 (0.63)	0.156
Negative affect	1.61 (0.46)	1.63 (0.50)	1.64 (0.51)	1.64 (0.54)	0.499

The analysis is adjusted for age, marital status, parity, employment status, self-reported mental disorder, use of psycholeptics and psychoanaleptics, menopausal symptoms.
Values given are means and standard deviations (SD)
Pre – premenopausal
E.Peri – early perimenopausal
L. Peri – late perimenopausal
Post – postmenopausal
*Post hoc Tukey test

5.4 Role of physical activity in the relationship between menopausal status and physical performance (Study I, III)

Figure 3 indicates the handgrip force, knee extension force and vertical jumping height values as a function of physical activity (PA) levels across the menopausal status groups.

For handgrip force, while cross-sectional comparisons did not reveal significant variation in physical activity levels among pre- peri- and postmenopausal women, longitudinal analyses showed that women with medium levels of PA at baseline exhibited a significant (-5.6%, 95% CI -7.9; -3.3) decline, and women with high PA displayed a significant improvement (3.4%, 95% CI 0.2; 6.7) over the menopausal transition.

For knee extension force, perimenopausal ($p<0.001$) and postmenopausal women ($p<0.001$) with high PA exhibited significantly greater performance than their less physically active counterparts. During the menopausal transition, women with medium PA showed a decline of -3.1% (95% CI -5.7; -0.5), and women with high PA displayed a decline of -6% (95% CI -9.6; -2.2). For vertical jumping height, pre- peri- and postmenopausal women with high PA showed significantly greater performance in comparison with women with low PA, respectively, $p=0.031$, $p<0.001$ and $p=0.014$. When perimenopausal women were followed up, women with medium PA showed a significant decline of -3.5% (95% CI -5.4; -1.6), and women with high PA had a decline of -4.0% (95% CI-7.4; -0.7).

For walking speed, no statistically significant differences were observed when comparing pre-, peri- and postmenopausal women across physical activity levels. Moreover, there were no statistically significant changes in walking speed when women were followed over the menopausal transition (Figure 4).

In terms of walking distance, perimenopausal women with high PA walked significantly longer distances during 6 min than women with low PA. Postmenopausal women with moderate PA walked longer distances than their low PA counterparts. In the longitudinal observation, women with low PA improved their walking distance by 2.3% (95% CI 1.1; 3.5), and women with medium PA also showed an improvement in performance of 2.6% (95% CI 1.5; 3.7).

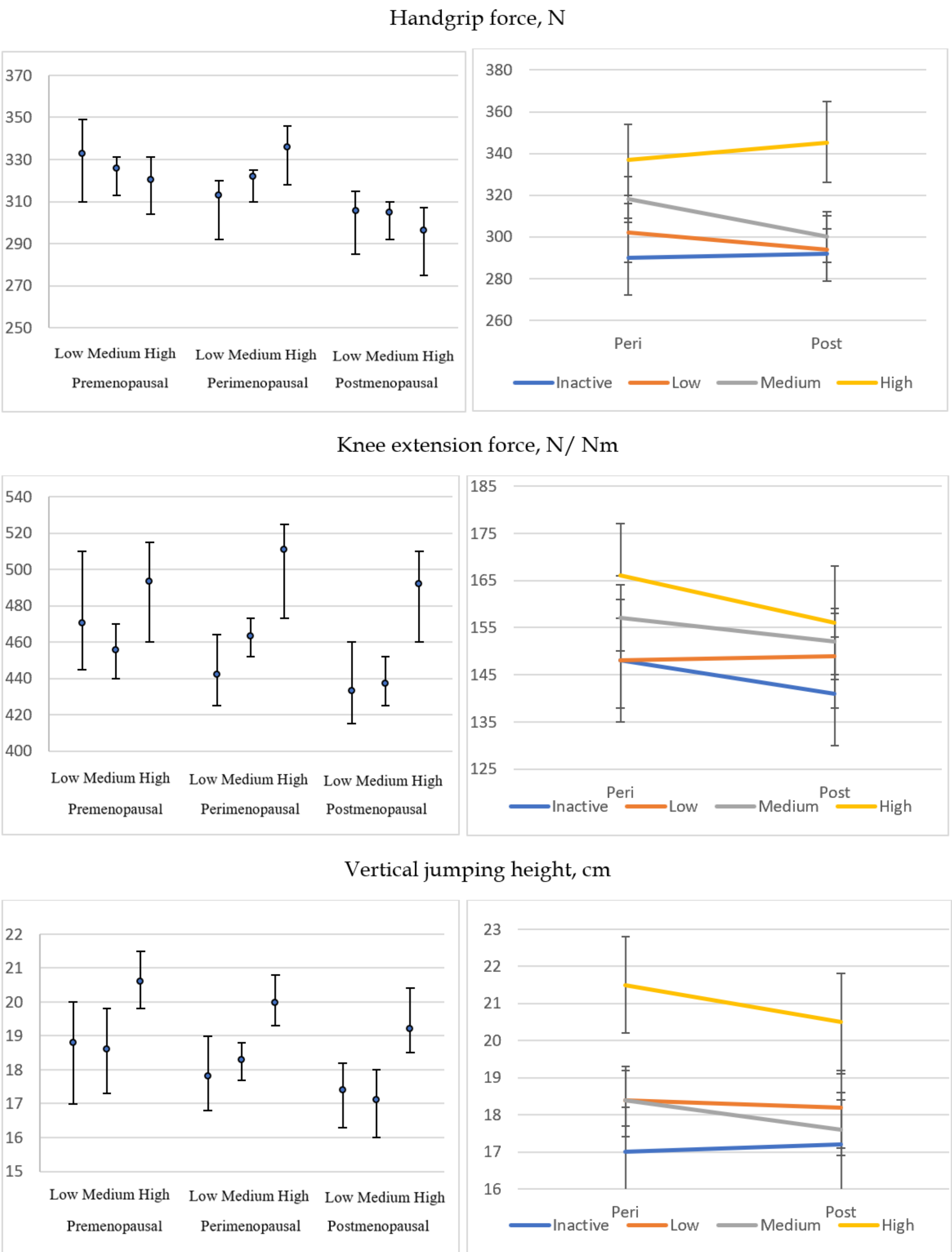
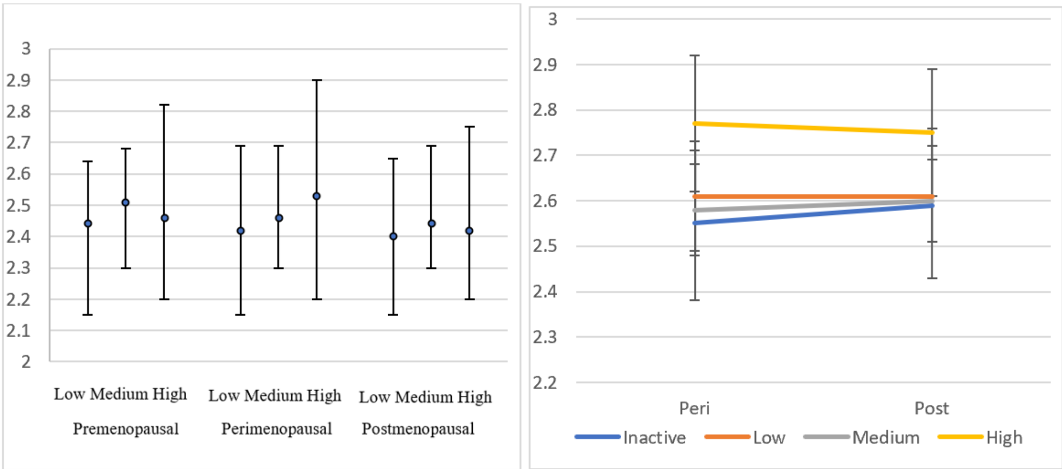


FIGURE 3 Muscle strength and power as a function of physical activity levels across menopausal status groups (left panel: cross-sectional data, right panel: longitudinal data).

Walking speed, m/s



Six-minute walking distance, m

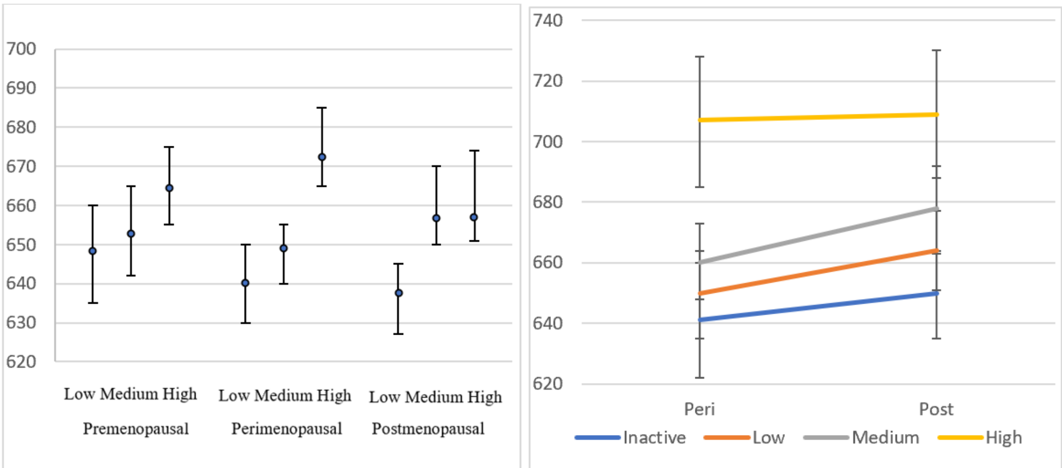


FIGURE 4 Walking performance as a function of physical activity levels across menopausal status groups (left panel: cross-sectional data, right panel: longitudinal data).

5.5 The role of physical activity in the relationship between menopausal status and mental well-being

Figure 5 illustrates the negative dimensions of mental well-being as a function of physical activity and menopausal status groups. Pre-, early peri- and postmenopausal women with low PA had significantly greater depressive symptoms scores than women with high PA in the same menopausal groups. Postmenopausal women with medium PA exhibited significantly fewer depressive symptoms than low PA women in a postmenopausal state. There were no differences in negative affectivity across the physical activity levels and menopausal status groups.

In terms of positive mental well-being, women with high physical activity levels scored significantly higher in positive affectivity than women with low physical activity levels in all four menopausal status groups (Figure 6). The same was true for life satisfaction, wherein women with high physical activity scored significantly higher than women with medium or low physical activity in the pre-, early peri- and postmenopausal groups.

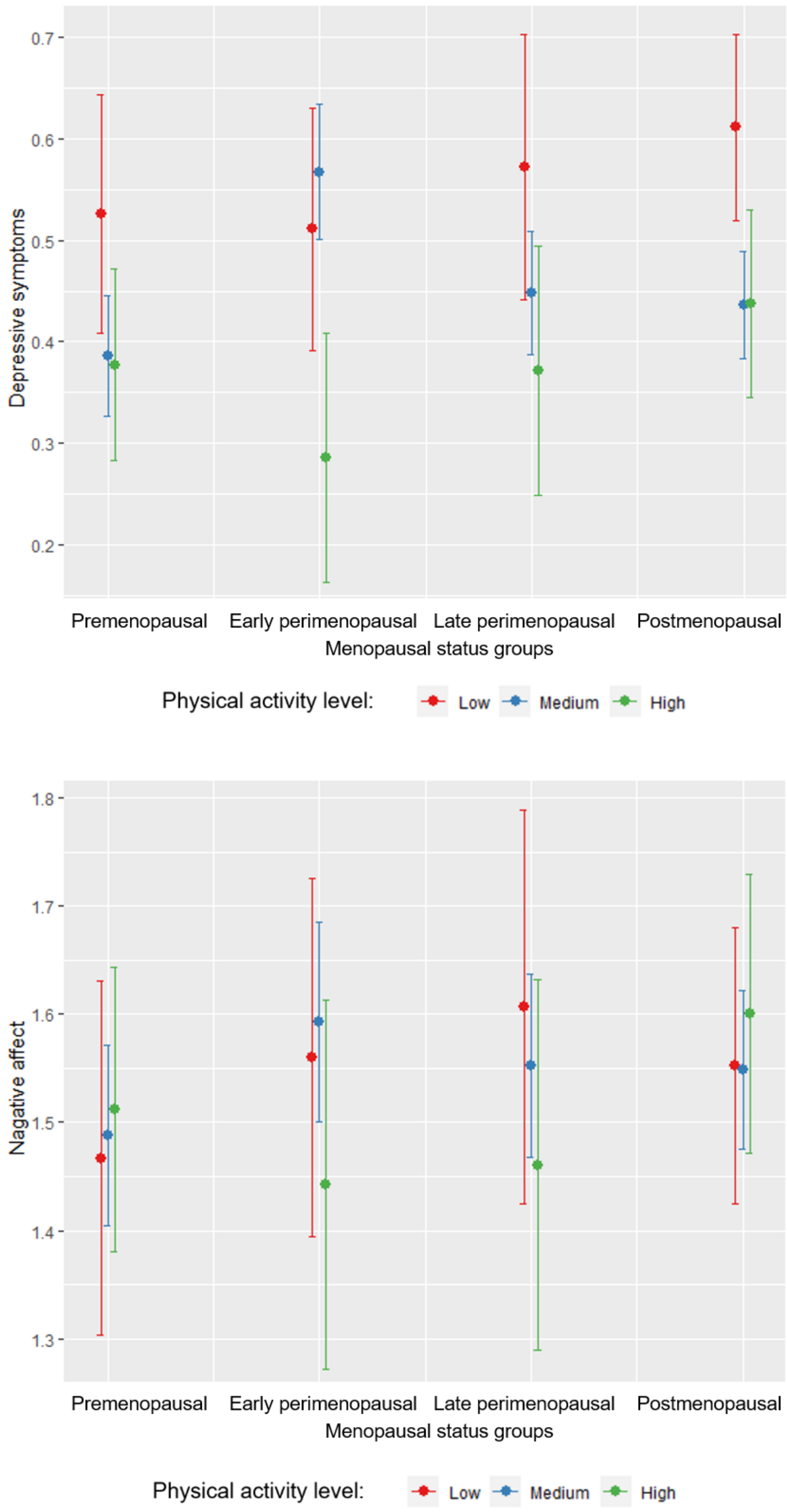


FIGURE 5 Negative mental well-being as a function of physical activity across menopausal status groups.

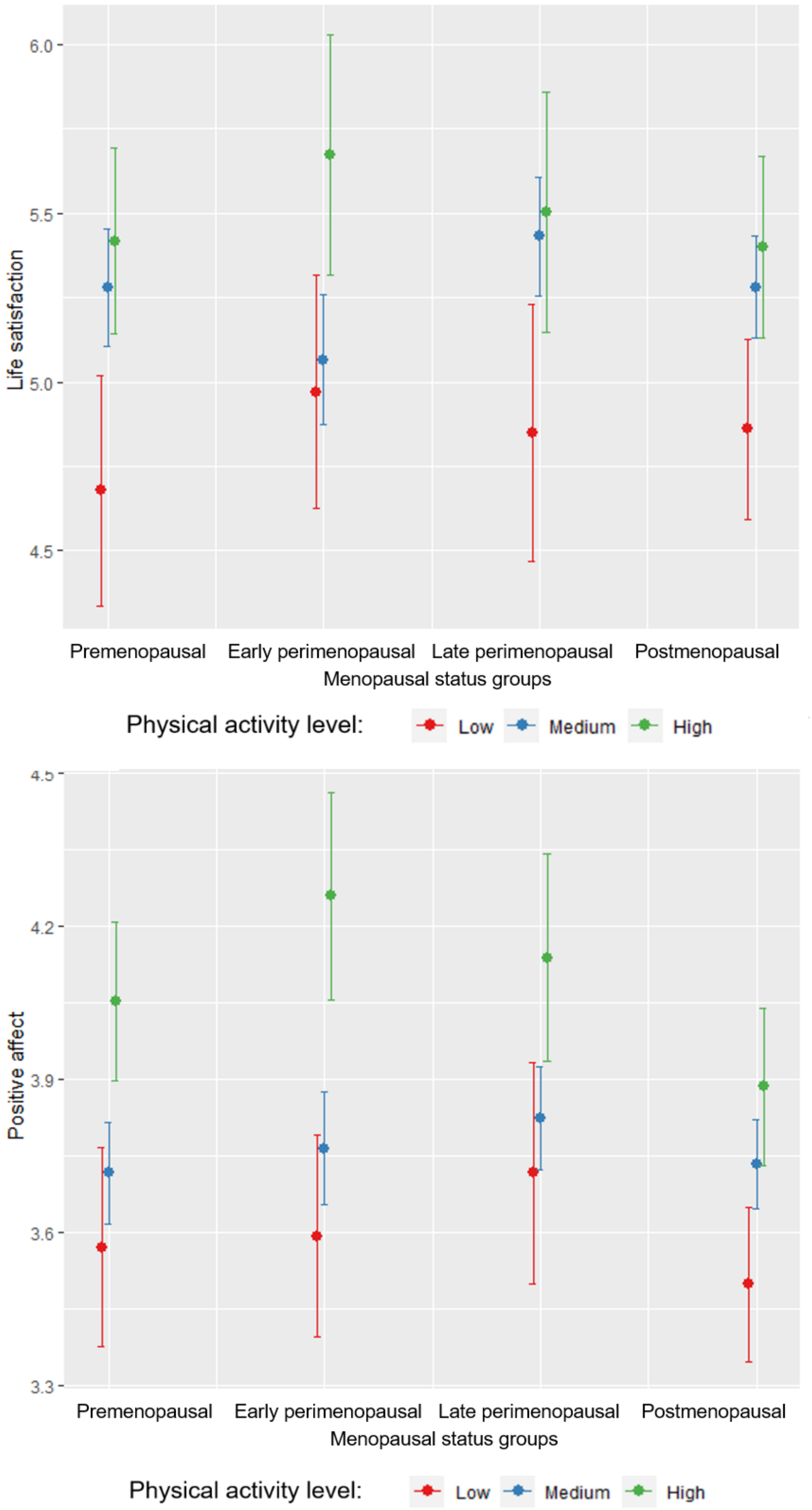


FIGURE 6 Positive mental well-being as a function of physical activity across menopausal status groups.

5.6 The role of physical activity in the relationship between physical performance and mental well-being

Given that physical performance and physical activity are functionally related concepts, we were interested in assessing whether physical performance, independent from physical activity, is associated with mental well-being. Therefore, the role of physical activity in this relationship was studied by adding physical activity to regression models in a separate step (Table 6).

Among dimensions of mental well-being, a significant association with physical performance emerged for positive mental well-being only, specifically for life satisfaction and positive affectivity. Six-minute walking distance was significantly associated with life satisfaction. Knee extension force, vertical jumping height, maximal walking speed and six-minute walking distance had a significant association with positive affectivity. However, when including physical activity in the regression models, these associations were no longer significant except for that between six-minute walking distance and positive affectivity. These results indicated that of the investigated physical performance measurements, only six-minute walking distance had independent positive associations with positive affectivity and life satisfaction.

TABLE 7 Significance of the regression coefficients for the association between physical performance and mental well-being (Study IV).

	Negative mental well-being				**Positive mental well-being**			
	Depressive symptoms		Negative affectivity		Life satisfaction		Positive affectivity	
	B	*p*	*B*	*p*	*B*	*p*	*B*	*p*
Hand grip	0.03	0.138	-0.01	0.902	-0.03	.664	-0.01	0.849
Hand grip + PA	0.03	0.118	0.01	0.898	-0.03	.597	-0.01	0.739
Knee extension	-0.01	0.536	-0.03	0.148	0.06	0.149	0.05	**0.041**
Knee extension + PA	0.01	0.968	-0.03	0.135	0.03	0.494	0.02	0.290
Vertical jumping height	-0.16	0.639	-0.58	0.245	0.57	0.587	1.23	**0.045**
Vertical jumping height + PA	0.06	0.873	-0.61	0.229	-0.19	0.860	0.64	0.294
Maximal walking speed	0.03	0.256	-0.01	0.745	0.10	0.194	0.09	**0.046**
Maximal walking speed + PA	0.04	0.164	-0.01	0.726	0.08	0.313	0.07	0.116
Six-minute walking distance	0.01	0.735	-0.01	0.920	0.19	**0.006**	0.16	**<0.001**
Six-minute walking distance + PA	0.02	0.355	-0.01	0.858	0.14	**0.040**	0.12	**0.003**

All coefficients are adjusted for height, fat mass %, menopausal status and symptoms, marital status, parity, employment status, self-reported mental disorders, use of psycholeptics, use of psychoanaleptics.
B, unstandardised coefficients; PA, physical activity.
Values in bold indicate statistically significant associations.

6 DISCUSSION

The aim of this thesis was to investigate physical performance and mental well-being in middle-aged women based on their menopausal status and to explore the role of physical activity in the relationships between menopausal status, physical performance and mental well-being.

The results demonstrated that handgrip strength and muscle power were lower in postmenopausal women compared to premenopausal women. This was confirmed by the longitudinal observations showing a decline in low limb muscle strength and power from early perimenopause to postmenopause. Associations between menopausal status and muscle strength and power were clearly stronger than for walking distance. High physical activity was associated with greater lower-body muscle strength during peri- and postmenopause and greater muscle power irrespective of menopausal status. Furthermore, in the peri- and postmenopausal groups, distance walked in 6 minutes was longer in the women with a high rather than low PA level. The longitudinal analysis showed that the women with a high level of PA exhibited a significant increase in handgrip strength but a greater decline in lower limb muscle strength and power than the medium, low or physically inactive women after the menopausal transition.

Postmenopausal women reported more depressive symptoms than premenopausal women. However, positive mental well-being (e.g., life-satisfaction and positive affectivity) was not associated with menopausal status. Physical activity was beneficial for mental well-being in middle-aged women irrespective of their menopausal status. Furthermore, aerobic components of physical performance contributed to positive mental well-being, independently from physical activity.

6.1 Association between menopausal status and physical performance

Study I revealed that handgrip strength and lower muscle power are lower in postmenopausal women than in premenopausal women. Furthermore, in longitudinal observations (Study III), muscle strength and power declined during the menopausal transition. Although several cross-sectional studies have shown that postmenopausal women performed worse in strength measurements than premenopausal women (Calmels et al., 1995; Cheng et al., 2009; da Câmara et al., 2015), other studies have reported no differences in physical performance across menopausal stages (E. Bassey et al., 1998; Cooper et al., 2008). The contradictions between studies could be due to different study designs and the use of various criteria for defining menopausal status. In a study by Cooper at al. (2008), menopausal status was assessed in women who were 53 years of age; thus, other age groups were excluded from the analysis. Bassey et al. (1998) employed self-reported bleeding patterns to categorise women by menopausal status, which may lead to misclassification (den Tonkelaar, 1997; Harlow et al., 2012). If they are on hormonal therapy, women may report regular menses and be categorised as premenopausal, or if their bleeding is minimal or absent, they can be misclassified as postmenopausal (Harlow et al., 2012). In the present study, we followed a recent STRAW criterion for the categorisation of participants according to menopausal status, relying on bleeding diaries and FSH measurements.

In the cross-sectional comparison, we observed lower handgrip strength and lower body muscle power in post- compared to premenopausal women. The follow-up data confirmed these findings. We observed an average decline of 2% to 3% in upper and lower extremities' muscle strength and power. In the present study, although menopausal status contributed to lower muscle strength and power, walking performance was not compromised by these menopausal factors. The results from Sowers and co-authors (2007) support our findings on the decline in muscle strength and power by reporting a significant decline in handgrip strength and sit-to-stand time. Contrary to our results, they also observed a decline in preferred walking speed based on a five-year follow-up (Sowers et al., 2007).

Typically, maximal walking speed begins to decline after 60 years (Himann et al., 1988). The participants in this study were younger; thus, a decline in walking performance may not yet be noticeable. In addition, although performance in walking speed depends on muscle strength, it also relies on cardiorespiratory and neuromuscular systems (Hornyak et al., 2012); thus, the contribution of diminished muscle strength may be compensated for. This may indicate that early menopause-associated changes occur in the musculoskeletal system rather than in the cardiovascular and respiratory system, as in the six-minute walking distance test, aerobic components play a significant role. This was supported by a longitudinal study with women aged 45 to 57 (median follow-up time is 9.7 y) which showed that postmenopausal women were more likely to self-report functional limitations in performing daily living activities, such as climbing stairs or walking, the performance of which mainly relies on the musculoskeletal system (El Khoudary et al., 2014).

In studies involving women using hormonal therapy, it has been demonstrated that women using estrogen or combined estrogen-progesterone therapy had greater muscle strength than those not using these therapies (Greising et al., 2009; Ronkainen et al., 2009). This suggested that the decline in muscle strength and power can most likely be attributed to wide-ranging alterations in hormones related to the menopausal transition.

Along the neuromuscular system, estrogen receptors are expressed at multiple sites. Estrogen may interact with both skeletal muscle factors and neurological factors that contributed to muscle strength (Collins et al., 2019). For example, the study with ERMA participants revealed mean appendicular muscle mass to be 4% lower in the postmenopausal than the premenopausal women (Juppi et al., 2020), suggesting that a loss of muscle mass around menopause may be one of the reasons for the decline in muscle strength. Estrogen may also play a role via neural factors involved in muscle strength generation, such as neural drive and motor coordination (Clark & Manini, 2008). For example, in the early follicular phase, when estrogen is low in comparison to the high-estrogen phases, motor unit discharge rates (Tenan et al., 2013) and voluntary activation (Ansdell et al., 2019) are lower. A recent study with a subsample of ERMA participants also proved that late perimenopausal women exhibited a greater reduction in their corticospinal inhibitory mechanism than early perimenopausal women, which may be implicated in coordinative motor activity (Pesonen et al., 2021). However, understanding the degree to which this may play a role in physical performance requires further investigation. It could also be noted that the menopausal transition is a time of instability in several hormones (e.g., FSH, estradiol, inhibin, progesterone); thus, it may be that no single hormonal change explains the decline in muscle strength and power.

6.2 Association between menopausal status and mental well-being

The present study showed that menopausal status, particularly postmenopause, is associated with greater depressive symptoms, but not with negative affectivity or positive mental well-being (i.e., life satisfaction and positive affectivity). In the present study, the peak in depressive symptoms was observed in the early perimenopausal and postmenopausal groups.

The observed prevalence of elevated depressive symptoms in the present study (around 10%) is similar to those reported previously in the middle-aged or older participants in Finland (Herva et al., 2006; Ruusunen et al., 2014).

Previous studies reported that some woman may experience vulnerability related to mental well-being (Brown et al., 2015; Smith-DiJulio et al., 2008; Steptoe & Wardle, 2012). It has been demonstrated that women are more vulnerable to depressive symptoms in the late perimenopausal stage than in the pre- or postmenopausal stage (Bromberger et al., 2001; Stewart et al., 1992). The nonsignificant difference between the pre- and late postmenopausal women in depressive symptoms was, however, somewhat unexpected. This may be due to the high variability in depressive symptoms in this group and/or to difficulties in establishing temporal continuity in the rate of depressive symptoms due to the use of a cross-sectional design. For example, Schmidt et al. (2004), in a longitudinal study using FSH measurements to validate menopausal status, showed that late peri- and early postmenopausal women had a similar risk of developing depression in comparison with premenopausal women (Schmidt et al., 2004). A recent study involving perimenopausal women with good and excellent mental health at the time of recruitment showed that greater estradiol fluctuations, but not absolute levels of estradiol, significantly predicted more depressive symptoms (Willi et al., 2021). Thus, because fluctuations in estradiol levels may occur in every menopausal transition state, this may explain the divergences in studies on the link between menopausal status and depressive symptoms.

In contrast to negative mental well-being (e.g., depressive symptoms), which fluctuated across the menopausal status groups, positive mental well-being was similar across the studied groups. Studies that have measured positive well-being have suggested that mental well-being may be more related to various social, psychological and health factors than to menopausal status per se (Smith-DiJulio et al., 2008; Woods & Mitchell, 2005). Positive mental well-being is linked to multiple outcomes, such as employment and family life, as well as health and longevity (Lyubomirsky et al., 2005; Steptoe & Wardle, 2012). Thus, positive mental well-being can be regarded as a resource that compensates for an increase in negative well-being in menopausal women (Brown et al., 2015).

6.3 The role of physical activity in the relationship between menopausal status, physical performance and mental well-being

The present study suggests that high physical activity may facilitate a greater capacity to counteract the negative influence of menopausal status on muscle strength and power. Furthermore, physical activity was also beneficial for mental well-being in middle-aged women irrespective of their menopausal status. Finally, we studied a possible link between physical performance and mental well-being and found that its aerobic component played a unique role in positive mental well-being.

Women with high levels of physical activity showed greater performance in terms of low body muscle strength and power as well as in walking distance compared to women with lower levels of physical activity. This was particularly evident at peri- and postmenopausal stages. Although in the longitudinal observation in handgrip strength, women with high physical activity showed an improvement during the menopausal transition, they also displayed a greater rate of decline in lower body muscle strength and power than their less physically active counterparts. At first glance, these results seem to be contradictory, as it was suggested above that greater physical activity enables a greater capacity to withstand the negative role of menopause in physical performance. Indeed, higher physical activity intensity and frequency has been proven to be beneficial for physical performance in middle-aged women (Chekroud et al., 2018; Straight et al., 2015). In accordance with these results, the present study proved that women with high physical activity had greater muscle strength and power than low and moderately physically active women.

However, it is not completely counterintuitive that the high physical activity group declined more than the other physical activity groups. First, there could be regression to the mean, because in the present study, women with high physical activity levels had greater baseline values in muscle strength and power than women with low physical activity levels. Consequently, they may display a greater reduction in physical performance than those women who already have low physical performance values. Secondly, high physical activity may lower estrogen levels (see e.g., meta-analysis by Ennour-Idrissi et al., 2019). Speculatively, in our study, participants with high physical activity levels may have experienced a greater decline in estrogen levels due to both menopause and high physical activity, which may eventually have affected their muscle strength and power decline. Another factor related to the estrogen level in peri- and postmenopausal women, is that the physical activity influences the size of the adipose tissue depots and thus this increases the production of estrogen in the adipose tissue depots (Thompson et al., 2012).

Specifically, the study by Bertone-Johnson et al. (2009) demonstrated that the relationship between physical activity level and estradiol had a U-shape in recreationally active postmenopausal women (Bertone-Johnson et al., 2009). Consistent with this, our participants with moderate physical activity level had the highest level of estradiol compared to women with other physical activity levels (Study III). High physical activity may distort the hormonal profile in perimenopausal women (De Souza et al., 2010). These results may indicate on the need to consider the optimal dosage and timing of physical activity for women with diverse histories of physical activity during the menopausal transition. They also prompt questions regarding whether interventions for promoting physical activity should primarily focus on leisure physical activity or on more structured and intensive exercise programs.

The present study also revealed that highly physically active women experience a lower frequency of depressive symptoms than women with low and moderate physical activity levels. Nelson et al. (2008) uncovered a greater level of depressive symptoms among less physically active peri- and postmenopausal women (Nelson et al., 2008). This was confirmed in our study, as in postmenopause women with high physical activity levels, we observed lower levels of depressive symptoms. It seems that when depressive symptomatology increased in peri- and postmenopausal stages, high physical activity became especially beneficial. However, due to the cross-sectional nature of the results, the reverse association is also possible. Women with greater levels of depressive symptoms may be less physically active (van Gool et al., 2003). For example, a longitudinal study with middle-aged participants indicated that greater mental well-being explained higher levels of physical activity rather than the opposite (Kekäläinen et al., 2019).

With respect to positive mental well-being, the present study showed that irrespective of menopausal status, women with high physical activity levels reported greater positive affect and were more satisfied with life than women with low physical activity levels. The mechanism which may explain the connection between physical activity and mental well-being is complex and may involve several possible avenues, from positive social interaction during physical activity or improving personal resources to reducing the experience of menopausal symptoms. Physical activity typically leads to an increase in positive affective states (Ekkekakis & Brand, 2019; Slaven & Lee, 1994). Regular physical activity may therefore help to accumulate positive affective states over time, which in turn serves as an important psychological resource to cope with the menopausal symptoms (Hobfoll, 1989; Kishida & Elavsky, 2015). However, because in the present analyses, a cross-sectional design was used and a mediation hypothesis was not tested, it could also be possible that physically active women experience fewer menopausal symptoms; by such a mechanism, they may have greater mental well-being than the less physically active women. The causality of the relationship between physical activity, menopausal status and mental well-being may require additional research, preferably with a longitudinal design.

Finally, because the present study revealed that physical activity attenuates menopause-related declines in muscle strength and power, while on the other hand, experiencing menopause leads to decreased physical activity (Lovejoy et al., 2008; Melanson et al., 2018), it became reasonable to investigate whether physical performance, independent from physical activity, is linked to mental well-being. Among the studied dimensions of physical performance, only the aerobic component was independently linked to positive mental well-being. Other dimensions of physical performance (low body muscle strength and muscle power, walking speed) were also associated with positive affectivity. However, their associations became non-significant in the presence of physical activity in the model. The results suggest that greater aerobic capacity could be regarded as a unique resource for mental well-being in middle-aged women. It is known that greater aerobic capacity is associated with better microvascular density, mitochondrial function and angiogenesis in the brain (Voss et al., 2016). Since aerobic capacity is also linked to positive mental well-being, it prompts speculation regarding structural and functional aspects in the brain, which may be related to mood states.

On a practical level, the reasonable questions that may arise from the findings regarding the unique role of aerobic capacity for mental well-being concern when and how aerobic capacity could be improved in women to enable them to have greater positive mental well-being during menopause. Some individuals may have a genetic predisposition to high aerobic capacity (Blair et al., 2001), and genotype may also play a role in the degree of improvement in aerobic capacity resulting from training (Sisson et al., 2009). There could also be specific causes of low aerobic capacity stemming from genetics, underlying medical conditions or life-style factors which are modifiable. However, a recent study with middle-aged women participating in combined aerobic and resistance exercise 3 days per week for 16 weeks showed that after the exercise program, women displayed significantly improved positive affect and decreased negative affect scores (Aparicio et al., 2021).

In addition, it could also be possible that women with greater positive affect are more physically active, or if they have greater aerobic fitness, this may enable them to be more physically active. Thus, further research is needed using other measurements of aerobic capacity (e.g. VO2 max) to confirm the direction of the association between aerobic capacity and positive mental well-being and factors that may influence them.

Other components of physical performance (low body muscle strength, muscle power, walking speed) were also associated with positive affectivity. However, when physical activity was present in the model, these associations were attenuated, except for six-minute walking distance. The results point to the benefits of physical activity for mental well-being. High levels of muscle strength and power may not be an important factor for greater well-being. In contrast, other aspects of participating in physical activity other than focusing on improvement in physical performance (except aerobic capacity) may become dominant. Aspects such as sense of coherence and mastery (Brown, 1991; Kekäläinen et al., 2018), which may be derived by women from participating in physical activity, can increase positive mental well-being. In line with this argument, previous studies have shown that while for men, better physical health predicted physical activity, for women, the social context of the physical activity had greater importance (Chipperfield et al., 2008; Teychenne et al., 2008a).

With respect to negative mental well-being, the present study showed no associations between the physical performance measurements and either dimensions of negative mental well-being, namely depressive symptoms or negative affectivity. Several systematic reviews have reported that cardiorespiratory fitness is linked to fewer incidents of depression among adults (Kandola et al., 2019; Papasavvas et al., 2016). However, these systematic reviews were not focused on the concomitant role of physical activity in the link between cardiorespiratory fitness and depressive symptoms. The results of the recent study showed that it is physical activity rather than physical performance that is linked to reduced depressive symptoms.

The current literature investigates either the link between physical activity and mental well-being (Bragina & Voelcker-Rehage, 2018; Buecker et al., 2021;

Lubans et al., 2016; Netz et al., 2005) or the link between aerobic capacity (cardiorespiratory fitness) and mental well-being (Kandola et al., 2019; Papasavvas et al., 2016). The present study extends this research to the investigation of the independent contribution of physical performance dimensions and physical activity to mental well-being.

6.4 Methodological considerations

This study utilised data from the ERMA study which includes both cross-sectional and longitudinal designs. The ERMA study is a population-based cohort study which consists of the data collected from women aged 47 to 55 years living in the city of Jyväskylä (Finland) or neighboring municipalities between 2016 and 2018. This age range represents the time when women may experience menopause. The study approached 82% of the population, and 47% responded to the invitation to participate in the study. The response rate was quite high, as in a similar study with middle-aged women, it was 25% (Mansikkamäki et al., 2015).

The final distribution of recruited women based on their menopausal status was comparable to the general population reported in the Finnish Health 2000 population survey conducted by the National Public Health Institute, Finland: 28% premenopausal (28% those in the ERMA-study), 48% perimenopausal (34% those in the ERMA study) and 24% postmenopausal women (38% of those in the ERMA study). However, there were a lower proportion of perimenopausal women and a slightly greater proportion of postmenopausal participants in comparison with the National Public Health Institute survey. This may be because perimenopausal women were also asked to participate in the longitudinal part; hence, they may consider this more time-consuming, or alternatively, they may experience a greater burden of menopause-related issues and thus decline their participation in the study.

The proportion of hormonal therapy users in Finland was reported to be 21% among women older than 45 years (consensus statement on menopausal hormonal treatment, the Finnish Medical Society Duodecim and the Academy of Finland). Those participants (14% in the ERMA study) were excluded from the ERMA study, because this may interfere with correct menopausal status categorisation and affect physical performance and mental well-being of participants.

Participants (4.3%) with a self-reported body mass index of more than 35 kg/m^2 were excluded from the ERMA study. This number is lower than the 14% of obese individuals reported for Northern European population (Gallus et al., 2015). It is possible that obese and severely obese individuals more frequently refrain from participation in the study. The non-respondents group in the ERMA study (those who discontinued participation after a response to the invitation with a filled-in questionnaire) contained proportionally more severely obese individuals than the group who continued to participate, namely 22% vs. 14%, respectively (Kovanen et al., 2018), thus indicating the self-exclusion of severely obese individuals.

In sum, the participants were randomly selected, and the sample was representative of relatively healthy, non-severely obese Finnish middle-aged women. The narrow age range allows us to better isolate menopause-related effects on physical performance and mental well-being. On the other hand, the study design restricts generalisation of the results to more heterogeneous populations (e.g., different races or obese individuals).

The strength of the study is the use of both cross-sectional comparison and longitudinal design. The longitudinal design allowed us to investigate changes in physical performance over the menopausal transition, which is a less researched area. Menopausal status was carefully categorised using menstrual diaries and hormonal analysis following the STRAW+10 guideline. This guideline recommends applying the criterion of 12 months of amenorrhea when defining the postmenopausal status. In this study, however, we applied a 6-month criterion for amenorrhea. This was necessary to ascertain the menopause status of around 1,000 participants during a reasonable time frame; while we also assessed FSH concentrations, this kept the potential misclassifications minimal. However, this may overestimate the number of postmenopausal women. If this is the case, then our findings on the diminished muscle strength after menopause is even more noteworthy.

In this study, the comprehensive measurements of physical performance (including upper and lower extremity muscle strength, muscle power, walking speed and walking distance) were utilised. Previous studies which assessed muscle strength in middle-aged women utilised a limited number of physical performance measurements (predominantly handgrip strength or sit-to-stand measurements). Another strength of the study is the inclusion of numerous potential confounders that may have a connection to physical performance or to mental well-being (e.g., education, duration of HT use, self-reported mental disorders, use of medications). Furthermore, in relation to mental well-being, previous studies mostly focused on the measurement of its negative dimension to capture depressive symptomatology in women undergoing menopause. In the present study, the use of measures capturing both positive and negative dimensions of mental well-being was employed, which may also be interpreted as a strength of the study.

Physical activity was assessed as a self-reported measure; thus, it may underestimate the number of highly physically active individuals (Cerin et al., 2016). The physical activity levels captured by the questionnaire used in the present study exhibited statistically significant correlations (ranging from 0.15 to 0.25) with accelerometer-measured moderate-to-vigorous leisure-time PA (Hyvärinen et al., 2019). The strength of the correlation is not high, which may suggest that self-reported physical activity and accelerometer-measured physical activity may capture somewhat different aspects. However, since the focus of the study was on the role of habitual physical activity, including gym or other indoor activities or cycling and running, which middle-aged women often engage in, self-reported physical activity would be a suitable option to reach that goal.

6.5 Implications for future studies

The present study demonstrated the role of physical activity in physical performance and mental well-being across menopausal stages. Although in this study we assumed that greater physical activity drives better physical performance and mental well-being, the relationship could be the opposite or even bidirectional. That is, women with greater physical performance or with greater well-being could be more likely to be engaged in physical activity. Thus, future studies may wish to investigate this alternative suggestion by exploring mediational models involving physical activity or physical performance.

As the present study revealed that physical activity is an important factor to consider in menopausal women and that this factor is modifiable, future studies may investigate how to promote physical activity among women undergoing menopause. High levels of physical activity have been proven to be particularly beneficial for physical performance and mental well-being; however, women with high physical activity also suffered more during the menopausal transition in terms of their decline in physical performance. It could be that prior levels of physical performance and physical activity may influence this relationship, which raises questions regarding optimal physical activity dosage and timing for women with diverse histories of physical activity around the menopausal transition.

Age-associated declines in muscle strength are to a greater degree related to neurological factors relative to declines in muscle mass (Clark & Manini, 2008). While several studies have uncovered a link between reductions in muscle mass and physical performance at menopause (Douchi et al., 2002; Sipilä et al., 2020), to date, only a limited number of studies have explored the link between menopause and neurological factors related to muscle strength. One such study showed that perimenopausal women had a reduction in corticospinal inhibitory mechanisms, which had implications for motor control (Pesonen et al., 2021).

Furthermore, the present study showed that declines in physical performance during menopause are around 2 to 3%. Few studies have been published regarding the clinical relevance of muscle strength or reduced power among women; those that exist were performed among old participants (e.g., Hicks et al., 2012). Therefore, the dearth of research in this area limits the conclusions regarding the clinical relevance of our findings. Future studies should investigate whether the relative decline in physical performance observed around menopause could be an indicator of clinical issues (e.g., incident mobility disability).

Finally, according to the Disablement process model developed by Verbrugge and Jette (1994), an impairment in neuromuscular function, which may coincide with the onset of menopause, gradually restricts one’s ability to perform daily activities and may lead to a disability later. Future studies may investigate the connection between menopause-associated declines in muscle strength and degrees of disability with advancing age.

7 MAIN FINDINGS AND CONCLUSIONS

The main findings and conclusions of the present study are summarized as follows:

1. Handgrip strength and muscle power were lower in postmenopausal women than in premenopausal women. In addition, muscle strength and power declined during the menopausal transition. No significant differences in walking performance were observed between the menopausal groups. Moreover, walking performance did not decline during the menopausal transition. These findings support earlier research findings which suggest that menopause predispose women to decline in muscle strength and power, especially in lower body muscles. As lower muscle strength and power are associated with slower walking speed and lower level of functioning in general, menopause-related changes may contribute to mobility impairment and disability that are common among women in their later life.

   In cross-sectional comparison, peri- and postmenopausal women with high level of physical activity had greater knee extension strength than their low physically active counterparts. In all menopausal groups, muscle power of participants with high level of physical activity was greater compared to less physically active counterparts. Moreover, perimenopausal women with high level of physical activity walked longer distance in 6 minutes than their less active counterparts. However, during the menopausal transition, a greater decline was observed in knee extension force and lower body muscle power among women with medium and high physical activity level compared to less physically active women. These findings are in line with earlier research findings in that women with higher level of physical activity have greater muscle performance than women with lower level of physical activity. However, targeted physical activity interventions aiming to improve muscle strength and power during the menopausal transition and thereafter may be among the most important future strategies to prevent strength and power decline and related mobility limitations and disabilities of aging women.

2. While postmenopausal women had a higher level of depressive symptoms compared to premenopausal women, positive mental well-being did not differ between women of different menopausal status. In all menopausal groups, high physical activity was associated with fewer depressive symptoms as well as higher scores in positive affectivity and life satisfaction. In postmenopausal women, also medium physical activity linked to respective dimensions of mental well-being. Consequently, physical activity was beneficial for mental well-being irrespective of menopausal status. The finding suggests that positive mental well-being could be considered as a resource to compensate for menopausal group difference in depressive symptoms. Physical activity could be a mean that promote mental well-being in women that experience menopause.

3. Greater physical performance was associated with higher scores for positive side of mental well-being. More specifically, better performance in all physical tests, except in hand grip, were associated with higher score in positive affectivity. In addition, greater distance walked in six minutes was associated with higher score in life-satisfaction. After taking into account the level of physical activity, the association between six minutes walking distance and life-satisfaction remained significant. This contribution was independent from physical activity level, which is, however, also had clear benefits for positive mental well-being. This implies that aerobic capacity may be considered as a resource for positive mental well-being.

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ORIGINAL PAPERS

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PHYSICAL PERFORMANCE IN RELATION TO MENOPAUSE STATUS AND PHYSICAL ACTIVITY

by

Bondarev D, Laakkonen E. K, Finni T, Kokko K, Kujala U. M, Aukee P, Kovanen V, Sipilä S. 2018.

Menopause. 25 (12): 1432-1441

DOI: 10.1097/gme.0000000000001137

Menopause: The Journal of The North American Menopause Society
Vol. 25, No. 12, pp. 000-000
DOI: 10.1097/GME.0000000000001137

Physical performance in relation to menopause status and physical activity

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Abstract

Objective: The aim of this study was to examine differences in physical performance (muscle power, muscle strength, aerobic capacity, and walking speed) across menopausal stages and potential of leisure physical activity (PA) to modify the impact of menopause on physical performance.

Methods: In this cross-sectional study, women aged 47 to 55 were randomly selected from the Finnish National Registry and categorized as premenopausal ($n=233$), perimenopausal ($n=381$), or postmenopausal ($n=299$) based on serum concentrations of follicle-stimulating hormone and bleeding diary. Physical performance was measured by knee extension force, handgrip force, vertical jumping height, maximal walking speed, and 6-minute walking distance. PA level was assessed by self-report and categorized as low, moderate, or high. Multivariate linear regression modeling was used for data analysis.

Results: After including fat mass, height, PA, and education in the model, the postmenopausal women showed 12.0 N weaker ($P<0.001$) handgrip force and 1.1 cm lower ($P<0.001$) vertical jumping height than the premenopausal women. There was no significant interaction between menopausal stage and PA on physical performance. The peri- and postmenopausal women with a high PA, however, showed better performance in the maximal knee extension strength and 6-minute walking test, and showed greater lower body muscle power than those with a low PA.

Conclusions: Menopause status is associated with muscle strength and power, whereas the association between menopause status and mobility/walking is clearly weaker. A high leisure PA level provides more capacity to counteract the potential negative influence of menopausal factors on muscle function.

Key Words: Aerobic capacity – Menopause status – Muscle power – Muscle strength – Physical activity – Walking.

Physical performance declines with aging. Low muscle strength and decline in the ability to produce force quickly (power) are associated with low walking speed and, further, with mobility limitations, disabilities,[1,2] and falls among older populations.[3,4] The pattern of decline in physical performance differs by sex, women showing more rapid decline than men during middle age.[5,6] This sex difference may be due to the hormonal changes that occur during the menopausal years.[7,8]

The mean menopausal age varies between 46 and 52.[9] During the menopausal transition, dramatic changes occur in the secretion of pituitary gonadotropins (follicle-stimulating hormone [FSH] and luteinizing hormone [LH]), ovarian steroids (estradiol and estrone), and inhibin B peptide. Based on data published by Rannevik et al,[10] 7 to 12 months after the final menstrual cycle, serum FSH concentration rises on average by 68%, with a concomitant decline of 60% and 32%, respectively, in estradiol and estrone concentrations, compared with the period 1 to 6 months before the final menstrual cycle. Owing to increased life expectancy, women spend one-third of their lives in a sex hormone-deficient state.

Received January 24, 2018; revised and accepted April 11, 2018.
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Funding/support: This study was supported by funding from the European Union's Horizon 2020 Research and Innovation programme under the Marie Sklodowska-Curie grant agreement No. 675003, and by the Academy of Finland (Grant Agreement 275323, Vuokko Kovanen).
Financial disclosure/conflicts of interest: None reported.
Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Website (www.menopause.org).
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Cross-sectional studies investigating differences in muscle strength across menopause status in middle-aged women have shown that postmenopausal women have lower strength and lower body muscle power than premenopausal women.[11-13] A 5-year follow-up study by Sowers et al[14] also showed that the decline in muscle strength is greater among middle-aged women characterized as postmenopausal compared with either pre- or perimenopausal women. Contradictory results, however, have also been published.[15-17] For example, the few studies that have investigated differences or changes in walking speed during the menopausal transition have reported mixed results. A cross-sectional study with 389 participants aged 40 to 65 reported no significant difference between pre-, peri-, and postmenopausal women in habitual walking speed,[13] whereas a follow-up study by Sowers et al[14] showed significantly greater decline in walking speed among middle-aged postmenopausal compared with either pre- or perimenopausal women.

Previous studies have predominantly defined menopause status according to self-reported bleeding data along with various criteria for menopause groups. This may blur the precise identification of menopause status and hence the association of menopausal factors with physical performance. In addition, earlier studies have used only a limited number of physical performance tests and thus not been able to capture a comprehensive range of physical performance dimensions, such as muscle power, muscle strength, aerobic capacity, and walking speed.

Physical activity (PA) is an important determinant of physical performance. In postmenopausal women, for example, it has been shown to be related to greater muscle strength.[8,17] Sex hormone deficiency during menopause may have an indirect effect on skeletal muscle through decreased spontaneous daily PA; in rodents, this has been shown to be reversed by estradiol replacement.[18] Moreover, earlier studies have shown a reduction in daily energy expenditure and a shift toward a more sedentary lifestyle during the menopausal transition.[19,20] Thus, the observed decline in physical performance during menopause may partially be an outcome of estrogen deficiency as well as the decline in the level of PA.

The purpose of this study was to investigate the association between physical performance and menopause status among middle-aged women and to test if this association varies with the level of PA. This study utilizes a comprehensive battery of physical performance tests, and categorization of menopausal groups was based on current guidelines, including serum hormonal analysis and bleeding diaries.

METHODS

Study design and participants

The study data were drawn from the Estrogenic Regulation of Muscle Apoptosis (ERMA) study.[21] Women aged 47 to 55 years living in the city of Jyväskylä or neighboring municipalities were randomly selected from the Finnish National Registry kept by the Population Register Centre

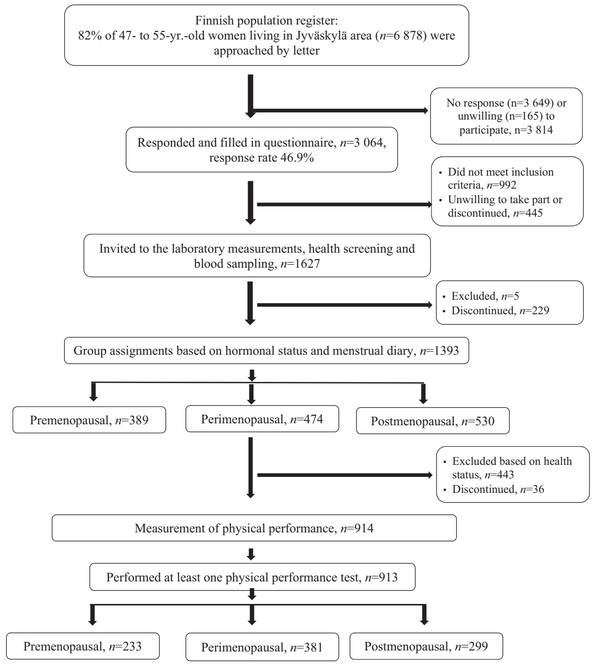

FIG. 1. Enrollment of the study participants.

(Fig. 1). Exclusion criteria were a self-reported body mass index (BMI) $>35\,kg/m^2$, being currently pregnant or lactating, conditions affecting ovarian function, including bilateral ovariectomy, estrogen-containing hormonal preparations (given orally or transdermally), or other medications affecting ovarian function, and chronic diseases or medications seriously affecting muscle function. A written invitation was sent to 6,878 potential participants. The response rate was 46.9%. Eligible participants ($n = 1,627$) were invited to the laboratory for a structural interview on their health status and to give fasting blood samples. Participants who had reported serious or unclear health problems were examined by a physician to ensure their safe participation in the physical performance measures. In total, 443 participants were excluded from the physical performance measurements for health and safety reasons. The present analysis only included women who performed at least one of the physical performance tests acceptably ($n = 913$).

All study participants provided written informed consent. The study was conducted in accordance with the guidelines for good clinical and scientific practice laid down by the Declaration of Helsinki and was approved by the ethics committee of the Central Finland Health Care District (K-SSHP Dnro 8U/2014).

Demographics, anthropometry, and body composition

Level of education was assessed by a single question and categorized as basic (primary and secondary school), college (applied science degree, bachelor, or nurse training) or university (master's degree or PhD) levels. *Marital status* comprised three categories: single, married or living with a partner, and divorced, separated, or widowed.

Body mass was measured with a digital scale and *height* with a stadiometer. *BMI* was calculated as body mass (kg) divided by height squared (m^2).

Fat mass was measured with an eight-point tactile electrode multifrequency bioelectrical impedance analyzer [InBody (720), Biospace, Seoul, Korea].

Physical activity

Current level of leisure PA was determined by a 7-point scale.[22] A similar seven-level scale has been validated with good outcomes against accelerometer-based PA and mobility variables.[23] The response categories were: (1) inactive, (2) light activity 1 to 2 times per week, (3) light activity several times per week, (4) moderate activity 1 to 2 times per week, (5) moderate activity several times per week, (6) high activity several times per week, and (7) competitive sports and related training several times per week. For the analysis, categories 1 and 2 were combined to indicate a low level of PA; 3 and 4 were combined to indicate a moderate level of activity; and 5 to 7 were combined to indicate a high level of PA.

Menopause status and health

Hormone assessments were performed from fasting serum samples taken between 8:00 and 10:00 AM, and in the women with a menstrual cycle, during cycle days 1 to 5. Serum was separated by centrifugation for 10 minutes at 2,200 × *g*. Systemic FSH and 17β-estradiol levels were immunoassayed using IMMULITE 2000 XPi (Siemens Healthcare Diagnostics, UK).

Participants' menopause status was determined based on systemic FSH and self-reported menstrual cycle (assessed by menstrual diary) after the Stages of Reproductive Aging Workshop (STRAW) criteria.[24] A detailed description of the categorization has been reported earlier by Kovanen et al.[21] In brief, the categories were premenopausal if regular menstrual cycle and FSH < 17 IU/L, perimenopausal if irregular menstrual cycle and FSH 9.5 to 30 IU/L, or if occasional menstrual bleeding occurred during past 3 months even if FSH >30 IU/L, and postmenopausal if no menstrual bleeding during the past 6 months and FSH >30 IU/L or no menstrual bleeding had occurred during past 3 months and FSH >39 IU/L. A few women who had very high FSH (>130 IU/L), but reported occasional bleeding, were also considered postmenopausal. For women with incomplete menstrual cycle information (eg, users of progestogen-containing medications), the categorization was based solely on FSH level and stricter cutoff values were applied (premenopausal: FSH < 15 IU/L, perimenopausal: FSH 15-39 IU/L, and postmenopausal: FSH >39 IU/L) to avoid potential errors due to gaps in the data. Participants self-reported their health problems, gynecologic status, and use of medications. Data related to parity, use of progestogen-releasing intrauterine coil, or other progestogen preparation for contraception, progestogen products (to treat gynecological bleeding disorders), as well as current and past smoking, presence of musculoskeletal diseases or conditions, hypertension, hypo- and hyperthyroidism were self-reported with a standard questionnaire.

Physical performance

Maximal isometric knee extension strength was measured in Newtons (N) from the side of the dominant hand in a sitting position on a custom-made dynamometer chair (Good Strength; Metitur Oy, Palokka, Finland) at a knee angle of 60° from full extension. The ankle was attached via a belt to a strain-gauge system. A belt around the pelvis was used to hold a participant to the chair. Participants were encouraged to extend the knee to produce maximal force.

Handgrip strength was measured in Newtons (N) on the dominant side by fixing the arm to the armrest of the chair with the elbow flexed at 90°. Participants were instructed to squeeze the handle as forcefully as possible. The contraction was maintained for 2 to 3 seconds and peak value was taken for analysis.

Lower body muscle power, that is, the ability of the neuromuscular system to produce the greatest possible force as fast as possible, was assessed as the height that the participant was able to elevate her body's center of gravity during a vertical countermovement jump (vertical jumping height) on a contact mat. Flight time (t) was measured, and vertical jumping height was calculated: $(g \times t^2) \div 8 \times 100$.[25]

In all tests, three to five maximal efforts were conducted and the best performance with the highest value was accepted as a result. In our laboratory, the coefficient of variation (CV) between two consecutive measurements with the same procedures has been 6% for knee extension force and handgrip force and 5% for vertical jumping height.[26]

Maximal walking speed was assessed for 10 m in a laboratory corridor. Five meters were allowed for acceleration, and the time was measured with photocells. Participants were advised to "walk as fast as possible, without compromising your safety". The fastest performance of two maximal walking tests was accepted as the result. In our laboratory, the CV for maximal walking speed has been 5%.[27]

Six-minute walking test was used to assess aerobic capacity. The test was performed on a 20-m indoor track, and participants were instructed to complete as many laps as possible within 6 minutes. The distance covered was used in the analysis.

Data analysis

To test differences in physical performance between the three menopausal stages, analysis of variance (ANOVA, *P* for trend shown in tables) was used with post hoc Tukey test (significant *P* values are shown in the text). For categorical variables, differences were tested with a Chi-square test.

The associations between menopause status and physical performance and the interaction effect of menopause status and PA on physical performance were analyzed using multivariate linear regression modeling.

Multiple regression analyses were conducted to examine the associations between menopause status and physical performance and the interaction effect of menopause status and PA on physical performance. A fully specified model for each performance variable, including main effects and an interaction term of menopause status with PA, was run.[28]

For the interaction analysis, a cross product of the three-level menopause status variable and the three-level PA variable was entered to the regression model as a categorical variable, resulting in four interaction terms for the model.

After performing fully specified multiple linear regression models, we observed that the interactions were nonsignificant in all the models predicting physical performance (the smallest P-value for knee extension force was 0.100, for handgrip force was 0.055, for vertical jumping height 0.445, for walking speed 0.474, for 6-min walking distance 0.261). Therefore, we excluded the interaction term from further analyses. The final tables include the models without the interaction terms.

The regression analyses were adjusted for body height and fat mass to take into account the size and composition of the total body[16,29] and also adjusted for PA and education. Body height and fat mass were entered into the models as mean-centered.[30] In addition, we repeated the analysis with the inclusion of chronological age (as mean-centered) and checked if this would meaningfully change the relationship between menopause status, PA, and the physical performance variables (see Table, Supplemental Digital Content 1, http://links.lww.com/MENO/A318 which illustrates age-adjusted regression models for knee extension, handgrip and vertical jumping height and Table, Supplemental Digital Content 2, http://links.lww.com/MENO/A319 which illustrates age-adjusted regression models for walking speed and distance). Standardized (β) and unstandardized (B) coefficients are provided for all models.

Despite the nonsignificant interaction effects of menopause status and PA on physical performance, we continued the analysis with the marginal means differences tests. Here, marginal means represent the means across the menopause status categories (pre-, peri-, and postmenopausal) and across the PA levels (low, moderate, and high) adjusted for height, fat mass, and education. Analysis of marginal means differences gives additional information not yielded by the full model with an interaction term,[31] especially in the case of an independent variable containing more than two categories.[32] Furthermore, this allowed us to test more specifically, whether the difference in physical performance of women with a low versus those with a high PA level increases when the menopause status progresses from pre- to postmenopause. The ANOVA and Chi-square analyses were performed using IBM SPSS Statistics 22.0 (SPSS, Chicago, IL). The regression and marginal means differences analyses were performed with R (www.r-project.org), version 3.3.3.

RESULTS

Demographics, anthropometry, body composition, and the level of PA of the sample across the three menopausal stages are presented in Table 1. As expected, the postmenopausal women were significantly older than the perimenopausal women (Tukey test $P < 0.001$), whereas the premenopausal women were the youngest (Tukey test $P < 0.001$). The mean difference in age between the pre- and postmenopausal groups was, however, less than 2 years. The postmenopausal group contained proportionally fewer women with a university degree and more women with a basic education than the premenopausal ($P = 0.005$) or perimenopausal ($P = 0.006$) groups. There was no difference between the groups in the level of PA.

No statistically significant differences were observed in body height or body mass between the groups. Body mass index was, however, lower in the postmenopausal than perimenopausal women ($P = 0.037$). No significant differences between the groups were observed in fat mass.

Table 2 shows the differences in gynecological and health status across the menopausal stages. Although all the

TABLE 1. *Demographics, anthropometry, and body composition across menopausal stages*

Variables	Premenopausal ($n = 233$)	Perimenopausal ($n = 381$)	Postmenopausal ($n = 299$)	P
Age, y	50.6 (1.63)	51.2 (1.92)	52.5 (1.89)	<0.001
Education	(n = 230)	(n = 373)	(n = 295)	0.014
Basic	127 (55)	205 (55)	191 (64)	
College	26 (12)	49 (14)	42 (15)	
University	77 (33)	119 (31)	62 (21)	
Marital status	(n = 231)	(n = 377)	(n = 297)	0.505
Single	19 (8)	32 (9)	28 (9)	
Married or registered partnership	181 (79)	290 (77)	215 (73)	
Divorced, separated or widowed	31 (13)	55 (14)	54 (18)	
Physical activity	(n = 232)	(n = 378)	(n = 298)	0.227
Low level	36 (16)	64 (17)	59 (20)	
Moderate level	140 (60)	248 (65)	181 (61)	
High level	56 (24)	66 (18)	58 (19)	
Height, m	1.66 (0.05)	1.65 (0.06)	1.65 (0.06)	0.126
Body mass, kg	70.2 (10.02)	70.3 (11.12)	68.4 (11.17)	0.056
Body mass index, kg/m^2	25.4 (3.28)	25.8 (3.86)	25.1 (3.79)	0.048
Fat mass, %	21.2 (7.6)	22.5 (8.33)	21.5 (8.14)	0.137

Values given are n (%) for variables without units and mean (SD) for variables with units.

TABLE 2. *Gynecological status and health across menopausal stages*

Variables	Premenopausal (n = 233)	Perimenopausal (n = 381)	Postmenopausal (n = 299)	P
Parity: number of children born				0.952
Nulliparous	28 (13)	43 (12)	39 (13)	
One or two	133 (57)	216 (57)	163 (55)	
Three and more	71 (30)	118 (31)	95 (32)	
Use of hormonal contraception	(n = 232)	(n = 379)	(n = 298)	<0.001
No user	88 (38)	209 (55)	166 (56)	
Former user	35 (15)	54 (15)	57 (19)	
Current user[a]	109 (47)	116 (30)	75 (25)	
Using progestogens	(n = 230)	(n = 375)	(n = 294)	0.101
No	176 (76)	276 (74)	198 (68)	
Former	30 (14)	64 (17)	54 (18)	
Current	24 (10)	35 (9)	42 (14)	
Smoking	(n = 231)	(n = 376)	(n = 297)	0.691
Never	153 (66)	249 (66)	202 (68)	
Former	64 (28)	94 (25)	75 (25)	
Current	14 (6)	33 (9)	20 (7)	
Musculoskeletal problems	75 (32) (n = 232)	137 (36) (n = 375)	94 (31) (n = 297)	0.352
Hypertension	27 (11) (n = 231)	57 (15) (n = 378)	39 (13) (n = 298)	0.474
Hypothyroidism	22 (9) (n = 232)	28 (7) (n = 378)	32 (10) (n = 298)	0.449
Hyperthyroidism	1 (1) (n = 232)	5 (1) (n = 378)	3 (1) (n = 298)	0.357
17β-Estradiol, nmol/L	0.62 (0.66)	0.32 (0.26)	0.14 (0.29)	<0.001
Follicle-stimulating hormone, IU/L	7.91 (3.54)	31.68 (20.73)	82.97 (28.66)	<0.001

Values given are n (%) for variables without units and mean (SD) for variables with units.
[a]Current users of estrogen-containing medication (given orally or transdermally) were excluded from this study, therefore the category "Current user" only includes users of progestogen-containing medications.

estrogen-containing hormonal contraceptive/therapy users were initially excluded, there were users of progestogen-containing hormonal contraceptive medications with a decreasing trend from the pre- to peri- and postmenopausal groups. The premenopausal group contained proportionally more current users of progestogen-containing contraception than the perimenopausal ($P < 0.001$) or postmenopausal ($P < 0.001$) groups.

No intergroup differences were observed in the proportions of users of progestogens, current smokers, musculoskeletal diseases or conditions, hypertension, hypothyroidism, and hyperthyroidism. As expected, the level of 17β-estradiol was significantly lower in the post- than perimenopausal women ($P < 0.001$) followed by premenopausal women ($P < 0.001$), whereas the level of FSH showed the expected reversed pattern ($P < 0.001$ for all comparisons).

Maximal knee extension strength decreased significantly across the three menopausal groups (Table 3). Specifically, the postmenopausal women were weaker than the perimenopausal ($P = 0.019$) or premenopausal ($P = 0.023$) women. The postmenopausal women had significantly lower handgrip strength compared with the perimenopausal ($P < 0.001$) and premenopausal ($P < 0.001$) women. Both the post- ($P < 0.001$) and perimenopausal ($P = 0.022$) women had a significantly lower jumping height than the premenopausal women. The postmenopausal women had a significantly slower maximal walking speed than the premenopausal women ($P = 0.024$). In the 6-minute walking test, the differences between the groups were not statistically significant.

The final adjusted models showed that menopause status was significantly associated with handgrip strength and vertical jumping height. The postmenopausal women were

TABLE 3. *Physical performance across menopausal stages*

Variables	Premenopausal	Perimenopausal	Postmenopausal	P
Knee extension strength, n	470 (100.9) (n = 199)	468 (93.6) (n = 328)	447 (90.4) (n = 262)	0.008
Hand grip strength, n	323 (60.5) (n = 233)	317 (61.6) (n = 377)	298 (54.2) (n = 297)	0.001
Vertical jumping height, m	0.20 (0.04) (n = 210)	0.19 (0.04) (n = 322)	0.18 (0.04) (n = 285)	0.001
Maximal walking speed, ms^{-1}	2.70 (0.49) (n = 232)	2.63 (0.48) (n = 375)	2.59 (0.39) (n = 297)	0.032
Six-minute walking distance, m	676 (58.8) (n = 214)	664 (64.2) (n = 345)	668 (58.5) (n = 280)	0.089

Values given are mean (SD).

TABLE 4. *Regression models and marginal means differences in isometric muscle strength and power, menopause status, and physical activity*

Model	Knee extension strength, N				Hand grip strength, N				Vertical jumping height, cm			
	Coefficients (SE)	*t*	*P*	*β*	Coefficients (SE)	*t*	*P*	*β*	Coefficients (SE)	t-value	*P*-value	β
Intercept	449.1 (11.8)				324.1 (6.7)				18.5 (0.4)			
Menopause status[a]												
Perimenopause	4.9 (8.3)	0.595	0.551	0.03	−2.5 (4.8)	−0.517	0.605	−0.02	−0.5 (0.3)	−1.578	0.114	−0.06
Postmenopause	−16.6 (8.7)	−1.906	0.057	−0.08	−12.0 (5.0)	−4.335	<0.001	−0.17	−1.1 (0.3)	−3.461	<0.001	−0.13
Physical activity[b]												
Moderate	7.0 (9.1)	0.768	0.443	0.04	1.6 (5.2)	0.305	0.761	0.01	0.2 (0.3)	0.691	0.490	0.03
High	53.7 (11.2)	4.784	<0.001	0.23	2.2 (6.4)	0.337	0.736	0.01	1.8 (0.4)	4.510	<0.001	0.18
Marginal means differences												
Premenopausal women												
Low PA (reference)	470.5 (18.6)				332.8 (10.2)				18.8 (0.6)			
Moderate PA	−15.0 (19.5)	−0.771	0.441	−0.06	−7.0 (10.8)	−0.647	0.517	−0.04	−0.2 (0.7)	−0.294	0.768	−0.01
High PA	22.9 (21.6)	1.060	0.289	0.06	−12.5 (12.3)	−1.015	0.310	−0.06	1.7 (0.8)	2.156	0.031	0.11
Perimenopausal women												
Low PA (reference)	442.2 (14.1)				313.0 (8.1)				17.8 (0.5)			
Moderate PA	21.0 (14.2)	1.480	0.139	0.10	8.9 (8.0)	1.101	0.2271	0.07	0.5 (0.5)	0.867	0.386	0.05
High PA	68.9 (17.9)	3.862	<0.001	0.19	23.0 (10.2)	2.244	0.025	0.10	2.1 (0.6)	3.180	<0.001	0.14
Postmenopausal women												
Low PA (reference)	433.4 (14.3)				305.4 (8.1)				17.4 (0.5)			
Moderate PA	4.0 (15.1)	0.267	0.789	0.02	−0.6 (8.6)	−0.062	0.946	−0.01	0.3 (0.5)	0.494	0.621	0.04
High PA	58.7 (18.4)	3.184	<0.001	0.15	−9.0 (10.7)	−0.843	0.398	−0.04	1.6 (0.6)	2.442	0.014	0.11

Coefficients, unstandardized coefficients (represent differences between reference and respective categories); SE, standard errors; *β*, standardized coefficient; PA, physical activity.
Regression models and marginal means differences analysis are adjusted for fat mass, body height, and education.
[a]Reference category is premenopausal group.
[b]Reference category is low physical activity level.

12.0 N weaker in handgrip strength than the premenopausal women. They also had 1.1 cm lower jumping height than the premenopausal group. In knee extension strength, the postmenopausal women were 16.6 N weaker than the premenopausal women, but the result did not reach statistical significance ($P = 0.057$). The 6-minute walking and maximal walking speed test results did not differ by menopause status after accounting for confounders (Tables 4 and 5).

Due to the significant interrelationship between age and menopause status ($r = 0.39$, $P < 0.001$), chronological age was not included in the final models as a confounding factor. The potential effect of age was, however, tested and found not to notably change the results. Briefly, in handgrip strength the postmenopausal women were 18.5 N weaker ($P < 0.001$) and in vertical jumping height the postmenopausal women had 1 cm lower jumping height ($P = 0.040$)

TABLE 5. *Regression models and marginal means differences in walking, menopause status, and physical activity*

Model	Maximal walking speed (ms^{-1})				Six-min walking distance, m			
	Coefficients (SE)	*t*	*P*	*β*	Coefficients (SE)	*t*	*P*	*β*
Intercept	2.45 (0.05)				642.3 (6.4)			
Menopause status[a]								
Perimenopausal	−0.02 (0.03)	−0.796	0.425	−0.03	−2.1 (4.5)	−0.463	0.643	−0.02
Postmenopausal	−0.05 (0.03)	−1.509	0.132	−0.06	−0.6 (4.7)	−0.135	0.892	−0.01
Physical activity[b]								
Moderate	0.04 (0.03)	1.082	0.280	0.05	11.4 (4.9)	2.286	0.022	0.09
High	0.05 (0.04)	1.141	0.254	0.05	23.3 (6.1)	3.800	<0.001	0.15
Marginal means differences								
Premenopausal women								
Low PA (reference)	2.44 (0.07)				648.4 (9.7)			
Moderate PA	0.07 (0.08)	0.912	0.362	0.08	4.3 (10.3)	0.425	0.671	0.04
High PA	0.02 (0.09)	0.315	0.753	0.04	16.0 (11.5)	1.380	0.168	0.08
Perimenopausal women								
Low PA (reference)	2.42 (0.06)				640.0 (7.8)			
Moderate PA	0.02 (0.06)	0.460	0.646	0.04	9.1 (7.8)	1.167	0.208	0.07
High PA	0.11 (0.07)	1.477	0.140	0.08	32.3 (9.8)	3.280	0.001	0.15
Postmenopausal women								
Low PA (reference)	2.40 (0.06)				637.6 (7.8)			
Moderate PA	0.04 (0.06)	0.638	0.523	0.05	19.1 (8.2)	2.329	0.020	0.13
High PA	0.02 (0.08)	0.327	0.743	0.03	19.4 (10.0)	1.930	0.053	0.09

Coefficients, unstandardized coefficients (represent differences between reference and respective categories); SE, standard errors; *β*, standardized coefficient; PA, physical activity.
Regression models and marginal means differences analysis are adjusted for fat mass, body height, and education.
[a]Reference category is premenopausal group.
[b]Reference category is low physical activity level.

than the premenopausal women (see Table, Supplemental Digital Content 1, http://links.lww.com/MENO/A318). No significant associations of knee extension strength, 6-minute walking distance and maximal walking speed with menopause status were observed (see Table, Supplemental Digital Content 1, http://links.lww.com/MENO/A318 and Table, Supplemental Digital Content 2, http://links.lww.com/MENO/A319).

After adjusting for body height, fat mass, education and PA, marginal means difference analysis (Tables 4 and 5) revealed that although the women with high PA, in general, performed better than those with low PA, the difference varied by menopause status. In all three menopausal groups, vertical jumping height was greater among the women with high compared with low PA. Among the perimenopausal women, higher PA was significantly associated with better performance in all the physical performance measures except for maximal walking speed. In addition to greater vertical jumping height, the postmenopausal women with high PA had greater maximal knee extension strength than those with low PA. In the 6-minute walking test, the postmenopausal women with moderate PA walked a significantly longer distance than those with low PA.

DISCUSSION

This study examined the difference in physical performance between menopausal stages and whether this difference varies with level of PA among 47- to 55-year-old women. After controlling for PA, education, body height and fat mass, the postmenopausal women had significantly lower handgrip strength and lower body muscle power production when compared to the premenopausal women. In all three menopausal groups, the women with a high PA level had greater muscle power production than those with a low PA level. Furthermore, in the peri- and postmenopausal groups, maximal knee extension strength was greater, and distance traveled in 6 minutes longer, in the women with a high compared with low leisure PA level.

Our results are in line with those of previous studies showing that postmenopausal women have lower handgrip strength than premenopausal women.[12,13] In this study, absolute handgrip strength showed a significant declining trend of 25 N. Moreover, after controlling for confounders, the postmenopausal women remained significantly weaker (by 12 N) than the premenopausal women. Earlier cross-sectional studies[15,16] reported no difference in handgrip strength across menopause status groups. The discrepancy between these studies and ours may be due to differences in the study design. Cooper et al[16] assessed menopause status when women were 53 years of age, leaving out other age groups. Bassey et al,[15] in turn, used self-reported bleeding regularity to assess menopause status, a criterion that could lead to misclassification. A longitudinal study,[17] however, reported a nonsignificant decline in grip strength of 0.93 kg (less than 10 N) in late perimenopause and of 1.04 kg (10 N) in postmenopause. The reason for the absence of significant changes in grip strength in this longitudinal study could be the relatively low proportion of women who become postmenopausal (around 12%) during the short 3-year follow-up.

In the present study, the postmenopausal women performed significantly worse in isometric knee extension strength; however, after adjustment for confounders, this result did not reach statistical significance ($P = 0.057$). To date, only a few studies have investigated low limb strength in women across menopausal stages. An earlier study showed no difference in isokinetic knee extension force between 45- and 50- to 59-year-old women.[11] Although these age groups correspond to the menopausal transition phase, an analysis based solely on age may inaccurately represent menopause status. In another cross-sectional study, no menopause status differences in isometric knee extension strength were observed.[15] Lower limb strength reflects daily PA level due to frequent loading of limb muscles during daily activities. It is thus possible that the moderating effect of PA weakens the association between menopause status and lower limb strength.

The present results found stronger evidence for a negative impact of the menopausal transition on handgrip strength than on isometric lower limb strength. This finding is supported by the longitudinal study of Sowers et al,[14] who followed pre- to perimenopausal women over a period of 5 years. They observed no significant changes in quadriceps isometric strength, but noted a significant decline in handgrip strength. In contrast to lower limb strength, which is more affected by environmental factors (eg, PA), handgrip strength may better reflect intrinsic vitality[2] and be less influenced by leisure PA. The earlier reported association between handgrip and disability[2] may be driven by a subclinical condition which later develops into disability and which may be exacerbated by menopausal factors.

Lower body muscle power is an important determinant of functional independence and has shown a stronger association than muscle strength with performance in daily tasks such as stair climbing, standing up from a chair and walking speed.[33] Our study showed that postmenopausal women have diminished muscle power in comparison to premenopausal women. Other studies that have measured performance in the chair rise test, which is a crude surrogate of muscle power, have reported no difference in performance across menopause status.[13,14,16] Bassey et al[15] measured leg extension muscle power in a rig but found no variation across the menopausal transition stages. The discrepancy between our results and those reported by Bassey et al[15] can be explained by differences in the menopause status classification and strength tests employed. Vertical jumping height, used in our study, is a weight-bearing test based on ballistic movements that also involves activity of the plantar flexor muscles, and hence better relates to everyday activities such as stair climbing. The present results suggest that menopausal factors such as estrogen deficiency may affect the mechanisms that earlier drive muscle power and later affect muscle strength. This finding is indirectly supported by studies of postmenopausal women on hormone therapy (HT) that have shown exogenous estrogen to have a greater influence on muscle power than on muscle force.[34]

Estrogens have an effect on multiple sites along the neuromuscular system, all of which contribute to the muscle strength and power output. These sites express estrogen receptors and therefore are most likely targets for estrogens regulation. We know that sex steroids activate the IGF-1 pathway[35] which controls the net balance of muscle protein turnover by activating protein synthesis and inhibiting protein degradation. It has been shown that postmenopausal women have significantly lower expression of IGF-1 compared with premenopausal women[36] which can predispose postmenopausal women to decrements in muscle function and quality.

Despite the differences observed across the three menopause status groups in muscle strength and power, no difference was observed in 6-minute walking distance. This may indicate that early menopausal changes affect the musculoskeletal system more than they affect the cardiovascular and respiratory system. A 5-year observational study[37] showed no decline in maximal oxygen consumption during the menopausal transition. In another study menopause-related estrogen deficiency was, however, associated with reduced exercise tolerance and impairment in maximal aerobic function.[38] Nevertheless, for our participants the walking test performed in our study is a more typical everyday activity than the incremental workload until exhaustion performed on a cycle ergometer used in that study.[38] Therefore, the aerobic capacity required to walk for 6 minutes either does not seem to be compromised by menopause, or if so, longer time is needed for the effect to become evident. This can be supported by a longitudinal study with women aged 45 to 57 (median follow-up time is 9.7 y) showed that postmenopausal women more likely self-reported functional limitations in performing daily living activities, such as carrying groceries, climbing stairs or walking; performance which mainly relies on the musculoskeletal system.[39]

Although the pre- and postmenopausal groups differed significantly in maximal walking speed, this difference was attenuated after adjusting for confounders. Studies with postmenopausal women on HT have shown higher maximal walking speed in HT users than nonusers,[34,40] suggesting that sex hormones play a role in the physiological systems governing performance during maximal walking. The age-associated reduction in walking speed accelerates after middle age, at around 60 years.[41] The fact that the oldest participants in the present study were early postmenopausal and younger than those in the above-mentioned studies may explain the inconsistency in maximal walking speed outcome between the women in the present study and those on HT in other studies.

Previous studies have shown that PA is a significant determinant of physical performance in postmenopausal woman.[8,17,42] In those studies PA has, however, been viewed as a controlling variable rather than a moderator. Our study, in turn, showed that irrespective of menopause status physical performance was considerably lower in women with a low than high level of leisure PA. Interestingly, we observed that the expected difference in physical performance between the low and high PA groups widened across the menopausal transition. For example, the difference between the low and high PA groups increased from 22.9 to 58.7 N in knee extension strength, and from 16 to 19.4 m in the 6-minute walking distance. These results suggest that PA may counteract the possible negative effect of menopausal factors on muscle strength and power: a higher level of PA may mean greater physical performance at the menopausal transition.

Earlier studies have shown that higher intensity and greater frequency of PA is associated with better physical performance in middle-aged women.[42-44] Consistent with these results, our study showed that in the peri- and postmenopausal groups, the women with high PA performed better in knee extension force and in lower body power production than those whose PA level was moderate or low. In the 6-minute walking test, moderate PA was, however, already sufficient to counteract the negative impact of menopause on muscle performance. These results prompt the question of whether interventions for promoting functional independence should primarily focus on habitual free-living PA or on more structured and intensive exercise programs.

The absence of a significant difference in maximal walking speed between the women with low and those with high PA across the menopause status groups shows that although women with low PA can walk at the same maximal speed as women with high PA, they are not able to maintain that speed over a longer time. Performance in maximal walking speed resembles usual walking and differences in PA level do not seem to significantly affect this in a middle-aged women population. The observation that PA modifies the effect of menopause status on physical performance needs to be studied further, as this may reveal a possible underlying mechanism that has consequences for functional independence in later life.

Strength and limitations

Unique to this study is the careful characterization of the menopause status of our participants following the STRAW criteria. Previous studies investigating the association of menopause status and muscle function have predominantly employed a self-reported menstruation questionnaire. Several studies have shown that although menopausal age can be fairly accurately measured by questionnaires,[45,46] some caution is warranted when menopause status is assessed retrospectively by self-report. Women who use hormonal contraception may, if they report regular menses, be misclassified as premenopausal or, if they do not bleed or bleeding is very minimal, be misclassified as postmenopausal. At the same time, some women with an irregular cycle but still premenopausal may be misclassified as peri- or postmenopausal.[47] The STRAW guidelines recommend applying the criterion of 12 months of amenorrhea when defining the postmenopausal state. Given our aim in this study of ascertaining menopause status for more than 900 participants within a reasonable period of time, and as we also assessed FSH concentrations, we decided to apply 6 months amenorrhea as the minimum requirement for categorizing a participant as postmenopausal. This may have led to some misclassification in the postmenopausal group. If so, our results may underestimate the differences between the postmenopausal and other groups.

Use of progestogen as well as thyroid dysfunction may influence bleeding patterns and ovarian function[48,49] and thereby these may interfere with the categorization by menopause status. In our study progestogen use and thyroid dysfunction was self-reported. Unfortunately, we do not have information on the dose and the length of use of progestogen medications. To avoid potential misclassification, for users with incomplete menstrual cycle information (eg, users of progestogen-containing medications) the more stringent cutoff criteria for the FSH level to categorize participants by menopause status was used in the present study. We also assumed that each participant who reported hypo- or hyperthyroidism receives treatment and thus have euthyroid range of serum thyroid hormone. In our sample, the distribution of those who reported use of progestogen and having hypo- or hyperthyroidism was equal across the menopause status groups. Therefore, it is unlikely that these conditions would influence the main results.

As expected, the pre-, peri-, and postmenopausal women differed in age, and hence it is reasonable to assume that, despite the narrow age range of the sample, the observed differences in physical performance between the groups were partly explained by aging. This is, however, impossible to test conclusively the aging effect separately from that of the menopause as aging and menopause are, by definition, intertwined. The inclusion of chronological age as a confounder in the multiple regression models attenuated the levels of significance of the associations between menopause status and the physical performance variables, but did not otherwise substantially change the results.

It should also be noted that self-reported PA may introduce some bias by underestimating the number of low and overestimating the number of high physically active individuals.[50] In our study, we used a questionnaire developed into a seven-level scale to enable the inclusion of physical activities performed for fitness and sports and household activities such as gardening, cleaning and housework.[22] An earlier validity assessment of the scale has shown it to be fairly accurate and to correlate significantly with accelerometer-based PA measurements.[23]

Our study is limited to nonsevere obese (BMI $<35\,kg/m^2$) individuals. Obesity and menopausal factors can act synergistically, which may worsen muscle functioning of obese middle-aged women.[51] Even though, we controlled the regression analysis for fat mass, we cannot generalize our results for obese individuals.

Furthermore, we used a reliable structured protocol to comprehensively measure physical performance. Our sample represents a large homogeneous cohort of relatively healthy Finnish women. This reduces the possibility for the analysis to be contaminated by unobservable potential confounders (eg, ethnicity, income or early-life stressors). On the contrary, this restricts the generalizability of the results to other more heterogeneous populations, particularly those in non-Western countries.

Although our discussion assumes that PA drives the difference in physical performance across menopause status, the possibility of a reverse relationship also exists. It is possible that better physical fitness enables women to be more physically active. To investigate this issue, longitudinal studies on premenopausal women followed up through the peri- and postmenopausal years with carefully characterized menopause status and a comprehensive battery of physical performance measures are needed.

CONCLUSIONS

This study showed that postmenopausal women had lower handgrip strength and lower body power production in comparison with premenopausal women after controlling for confounders. It seems that menopausal factors influence the mechanisms that govern general isometric strength and muscle power more strongly than performance in functional tests such as maximal walking speed and 6-minute walking. Importantly, leisure PA attenuates the menopausal-related declining pattern in physical performance: peri- and postmenopausal women with a high PA level had higher maximal knee extension strength and muscle power and they performed better in the six-min walking test than those with a low PA level. This suggests that leisure PA counteracts the possible negative effect of menopausal factors on muscle strength and power.

Acknowledgments: The authors thank all study participants and personnel of the Faculty of Sport and Health Sciences.

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II

THE ROLE OF PHYSICAL ACTIVITY IN THE LINK BETWEEN MENOPAUSAL STATUS AND MENTAL WELL-BEING

by

Bondarev D, Sipilä S, Finni T, Kujala U. M, Aukee P, Laakkonen E. K, Kovanen V, Kokko K. 2020.

Menopause. 27 (4): 398-403

DOI: 10.1097/GME.0000000000001490

Menopause: The Journal of The North American Menopause Society
Vol. 27, No. 4, pp. 000-000
DOI: 10.1097/GME.0000000000001490

ORIGINAL STUDY

The role of physical activity in the link between menopausal status and mental well-being

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Abstract

Objective: To examine the relationship between menopausal status and mental well-being, and whether this relationship varies as a function of physical activity (PA).

Methods: Based on a hormonal analysis and bleeding diary, women aged 47 to 55 were categorized as pre (n = 304), early peri (n = 198), late peri (n = 209), or postmenopausal (n = 387). Mental well-being was assessed using the Centre for Epidemiologic Studies Depression Scale, the International Positive and Negative Affect Schedule Short Form, and the Satisfaction with Life Scale. PA was self-reported and categorized as low, medium, and high. Associations between variables were analyzed using multivariate linear regression adjusted for age, marital and employment status, parity, self-reported mental disorder, use of psycholeptics and psychoanaleptics, and menopausal symptoms.

Results: Depressive symptoms were lower amongst the pre than postmenopausal women ($B = 0.07$, confidence interval 0.01-0.13). Menopausal symptoms attenuated these associations. Menopausal status showed no associations with life satisfaction, or with positive or negative affectivity.

Women with high PA scored higher on positive affectivity, and the pre, early peri, and postmenopausal women scored higher on life satisfaction ($B = 0.79$, $P < 0.001$; $B = 0.63$, $P = 0.009$; $B = 0.42$, $P = 0.009$, respectively) and scored lower on depressive symptoms ($B = -0.13$, $P = 0.039$; $B = -0.18$, $P = 0.034$; and $B = -0.20$, $P < 0.001$, respectively) than their low PA counterparts. The pre and postmenopausal women with medium PA scored higher on life satisfaction ($B = 0.54$, $P = 0.001$; $B = 0.038$, $P = 0.004$, respectively) than those with low PA.

Conclusions: Postmenopausal women reported marginally higher depressive symptoms scores compared with premenopausal women, but menopause was not associated with positive mental well-being. However, this association varies with the level of PA.

Key Words: Depressive symptoms – Life satisfaction – Menopausal status – Negative affectivity – Physical activity – Positive affectivity.

Video Summary: http://links.lww.com/MENO/A520.

The menopause, defined as the final menstruation, occurs between the ages of 46 and 52, and signifies aging of a woman's reproductive system.[1] Menopause-related hormonal changes begin several years before the menopause and are characterized by a gradual increase in follicle-stimulating hormone (FSH) and more rapid decline in systemic female sex steroids (estradiol and estrone) within 6 months around the menopause.[2] Reproductive aging among women has a far-reaching effect on the function of different body systems, and also on the psychological functioning and well-being among middle-aged and older women. Maintaining sufficient mental well-being is important for functioning

Received September 12, 2019; revised and accepted October 28, 2019.
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Funding/support: This study was supported by funding from the European Union's Horizon 2020 research and innovation Programme under the Marie Sklodowska-Curie grant agreement No 675003, and by the Academy of Finland (ERMA study grant agreement 275323, Vuokko Kovanen).

Financial disclosure/conflicts of interest: None reported.

Supplemental digital content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's Website (www.menopause.org).
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in later life, as it is associated with, for example, better health outcomes and survival.[3,4]

Menopause is an important life transition phase and has been suggested to be a time of increased vulnerability in well-being.[5] Although some cross-sectional studies have found no relationship between menopausal status and mental well-being,[6,7] other longitudinal studies have identified an increased risk for elevated depressive symptoms and negative mood in the transition phase of menopause.[8-10]

As midlife has traditionally been considered to induce psychological stress due to several competing social roles, such as care giving and work roles, and a cumulative number of losses,[11] the menopause literature has operationalized the measurement of mental well-being by focusing on its negative aspects. However, more recent studies indicate that, psychologically, midlife may be a rather satisfying stage of life,[12] characterized by a high level of mental well-being.[13] Thus, as a specific age-related transition in mid-adulthood, menopause may differentially influence both negative, and also positive dimensions of mental well-being.[14] Study of the relationship between menopausal status and mental well-being has been challenged by numerous methodological issues. These include a precise definition of menopausal status, the measurement of well-being, and the confounding influence of a prior level of mental distress and social circumstances.[15,16]

Despite the seeming changes in mental well-being associated with menopause and social circumstances, physical activity may attenuate the negative influence of both these factors. A longitudinal study in which middle-aged women participated in a 4-month exercise program showed, at 2-year follow-up, that physical activity positively influenced satisfaction with life through improvement in affect and self-worth.[17] Another cross-sectional study found that physically active middle-aged women reported better menopausal and global quality of life.[18] Moreover, physical activity alleviates some menopausal symptoms[19] and subsequently may weaken the negative impact of menopause on mental well-being. However, a decline in physical activity and a shift towards increased sedentary behavior, both of which have been observed during the menopause transition,[20,21] may be among the reasons for the adverse influence of menopause on mental well-being among low physically active women.

Although earlier studies consistently support a positive influence of physical activity on well-being and its dimensions in a variety of populations,[22-24] few of them have examined the simultaneous contribution to mental well-being of menopausal status and physical activity.

The aim of this study was to examine the relationship between menopausal status, and positive and negative dimensions of mental well-being, and whether these relationships vary as a function of physical activity.

METHODS

Study design and participants

This study utilized data from the ongoing Estrogenic Regulation of Muscle Apoptosis (ERMA) study.[25] In this study, women aged 47 to 55 years, living in the city of Jyväskylä and its neighboring municipalities, were randomly selected from the Finnish National Registry administered by the Population Register Centre (Fig. 1). A postal invitation was sent to 6,878 potential participants. Exclusion criteria were conditions or use of medications affecting ovarian function, including bilateral ovariectomy, estrogen-containing hormonal preparations or other medications affecting ovarian function, a self-reported body mass index (BMI) >35 kg/m^2, being pregnant or lactating, diagnosis of a mental illness, and conditions or use of continuous medications affecting daily mental or physical function. Eligible participants (n = 1,627) were invited to the laboratory, where 1,393 women filled in the health screen questionnaire and gave fasting blood samples. After dropout of 36 participants and exclusion of 443 participants for health-related reasons preventing them from participating in the further physiological measurements, 1,098 eligible participants remained in the study and completed the well-being measurements.

All participants provided a written informed consent. The study protocol followed good clinical and scientific practice, and the Declaration of Helsinki, and was approved by the Ethics Committee of the Central Finland Health Care District (K-SSHP Dnro 8U/2014).

Measurements

Menopausal status

Menopausal status was determined based on bleeding diaries and serum concentrations of follicle-stimulating hormone (FSH) following the Stages of Reproductive Aging Workshop (STRAW) criteria.[26] FSH assessments were performed from fasting serum samples which were collected between 8:00 and 10:00 AM. If the women had a menstrual cycle, then collection was performed during cycle days 1 to 5. Serum was separated by centrifugation for 10 minutes at 2.200×g. Systemic FSH was immunoassayed using IMMULITE 2000 XPi (Siemens Healthcare Diagnostics, UK).

A complete description of the grouping by menopausal status has been reported earlier.[25] In short, participants were assigned to the premenopausal group if they reported a regular menstrual cycle and had FSH <17 IU/L (M = 7.72, SD = 3.50), to the early perimenopausal group if they had FSH 17 to 25 IU/L, or, if they reported an irregular menstrual cycle, FSH >9.5 IU/L (M = 16.76, SD = 4.77), to the late perimenopausal group if they had FSH 25 to 30 IU/L, or, if they reported occasional menstrual bleeding during the past 3 months, FSH >30 IU/L (M = 44.90, SD = 19.96), and to the postmenopausal group if they reported no menstrual bleeding during the past 6 months and had FSH >30 IU/L, or reported no menstrual bleeding during the past 3 months and had FSH >39 IU/L (M = 82.48, SD = 28.82). For women with nonreported menstrual cycle information (eg, users of progesterone-containing medications), the categorization was based solely on FSH level, and stricter cut-off values were applied (premenopausal: FSH

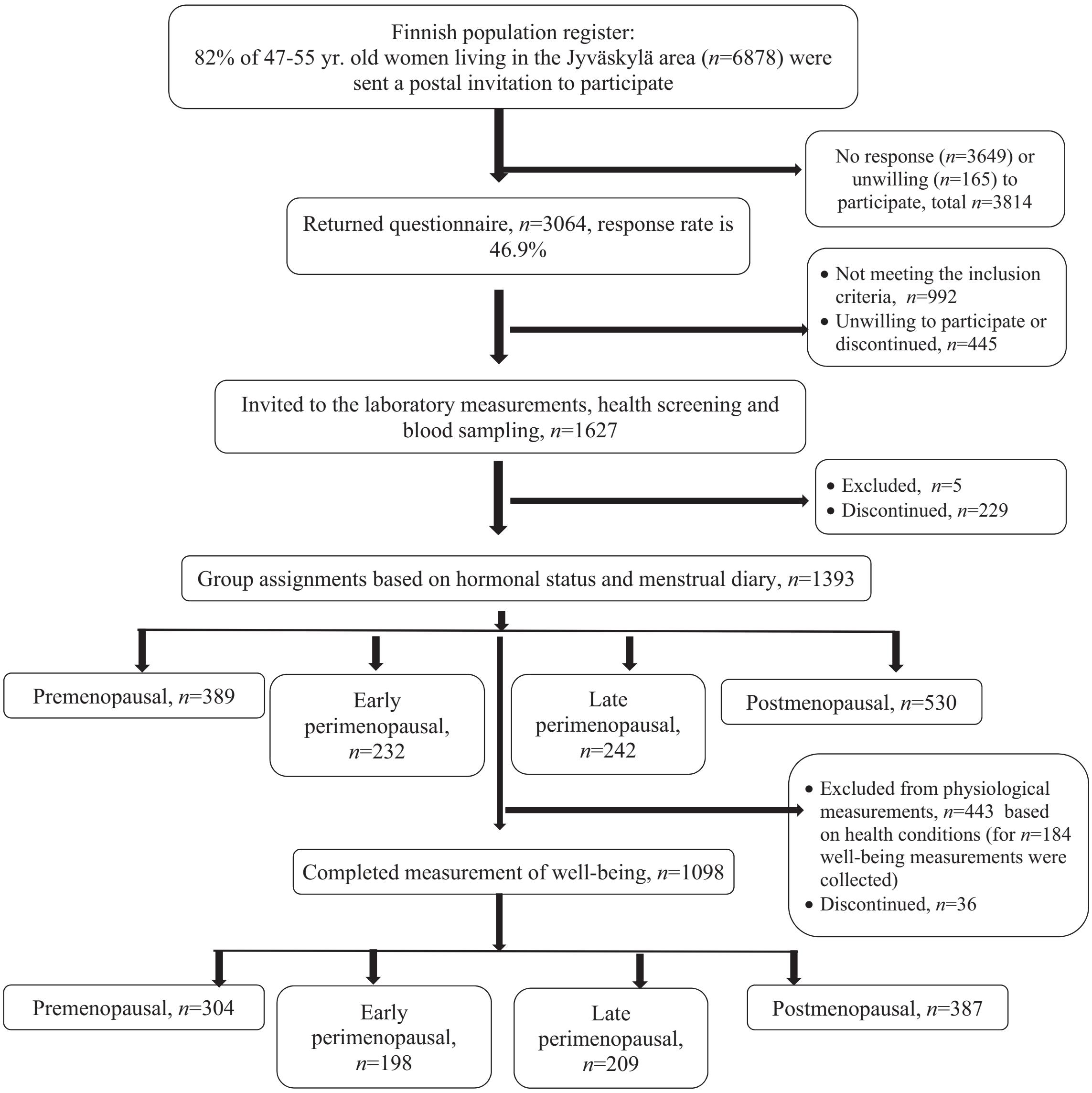

FIG. 1. Enrollment of study participants.

<15 IU/L, perimenopausal: FSH 15-39 IU/L, and postmenopausal: FSH >39 IU/L).

Menopausal symptoms

Menopausal symptoms were collected using a structured questionnaire which asked participants to indicate whether they had any of the following symptoms: sweating, hot flashes, sleeping problems, headache, joint pain, tiredness, mood swings, vaginal symptoms, urinary track problems, or sexual problems, or if they had some other symptoms. Based on the responses, four categories were formed: vasomotor symptoms; somatic or pain symptoms; psychological symptoms; and urogenital symptoms.[27] For the main analysis, we aggregated these responses into a dichotomous variable (has symptoms/no symptoms) to indicate if a woman was experiencing any of the menopausal symptoms.

Mental well-being

Depressive symptoms were assessed with the 20-item Center for Epidemiological Studies Depression Scale (CES-D[28]). The participant rated the frequency of each symptom during the previous week. Each item was scored from 0 to 3, and a mean score for the 20 items was calculated. Higher scores indicate more depressive symptoms. This mean score was used in the main analyses. In addition, for descriptive purposes, a sum score ranging from 0 to 60 was calculated, and a score of 16 or above was used to indicate a sign of potential clinical depression.[29]

Positive and negative affectivity was assessed with the International Positive and Negative Affect Schedule Short Form (I-PANAS-SF[30]) with five positive affect adjectives and five negative affect adjectives. Participants were asked to rate each of these adjectives on a 5-point scale (from ''does not describe me'' to ''describes me very well'') according to the extent to which each describes the way they usually feel. Mean scores ranging from 1 to 5 were calculated for positive and negative affectivity. For both positive and negative effects, a higher mean score indicates a higher tendency to experience a positive and negative affectivity.

Global cognitive judgments of one's life satisfaction was measured using the 5-item Satisfaction with Life Scale.[31] Participants indicate the extent to which they agree or disagree with each of the five items on a 7-point scale ranging from 1 (strongly disagree) to 7 (strongly agree). The mean score for the five items, ranging from 1 to 7, was calculated, with higher scores indicating more satisfaction with life.

Physical activity

Current level of leisure physical activity was assessed on a 7-point scale[32] ranging from household chores to competitive sports, and with questions assessing leisure-time and physical activity patterns. The response options were: I do not move more than is necessary in my daily routines; I go for casual walks and engage in light outdoor recreation 1 to 2 times a week; I go for casual walks and engage in light outdoor recreation several times a week; Once or twice a week, I engage in brisk physical activity (eg, yard work, walking, cycling) that causes some shortness of breath and sweating; Several times a week (3-5), I engage in brisk physical activity (eg, yard work, walking, cycling) that causes some shortness of breath and sweating; I exercise several times a week in a way that causes rather strong shortness of breath and sweating during the activity; I do competitive sports and maintain my fitness through regular training. For the analysis, the response categories were combined to low level of physical activity (categories 1 to 3), medium level of physical activity (4 and 5), and a high level of physical activity (6 to 7).

Socioeconomic, lifestyle variables, and use of prescribed medications

Level of education was assessed by a question, and categorized as primary, secondary, and tertiary (applied science degree, bachelor's degree, nurse training, master's degree, and PhD). Marital status was categorized as single, married, or living with a partner, and divorced, separated, or widowed. Parity was categorized as nulliparous, one or two children, and three or more children. Smoking status defined participants as never, former, or current smoker. Participants' alcohol consumption was categorized as never or rarely (less than 1 unit/wk), weekly (1-5 units/wk), and often (more than 5 units/wk). Employment status was classified as either employed (paid or self-employed) or not regularly employed (studying, unemployed, working occasionally, retired, taking care of the home). Response options for self-rated health were poor, average, good, and very good. The latter two responses were merged into one category, labeled ''good and very good.'' For self-reported mental disorder, women were asked to indicate if they have (or have had) a mental disorder diagnosed by a physician as yes/no. Information on use of medications was collected and coded according to the Anatomical Therapeutic Chemical Classification System.[33] For this article, we report on use of N05 (psycholeptics) and N06 (psychoanaleptics) as medications that may influence mental well-being.

Data analysis

Participant characteristics are shown as means and standard deviations (SDs), or as percentages. To test differences in the studied variables between the groups, analysis of variance (ANOVA) was used with the post hoc Tukey test. For categorical variables, differences were tested with a chi-square test.

Multiple regression analyses were conducted to examine the association of menopausal status and different dimensions of mental well-being. To test if any of the socioeconomic and lifestyle variables were potential confounders in the relationship between menopausal status and mental well-being, we first ran a correlation analysis (Spearman's rho, r_s). We observed that marital status, parity, and employment status showed a significant association with the dimensions of mental well-being (r_s ranges from 0.070 to 0.185; P ranges from <0.001 to 0.003). Use of psycholeptics (N05), use of psychoanaleptics (N06), self-reported mental disorders, and menopausal symptoms showed a positive association with depressive symptoms ($r_s = 0.109$, $P < 0.001$; $r_s = 0.159$, $P < 0.001$; $r_s = 0.212$, $P < 0.001$; $r_s = 0.164$, $P < 0.001$, respectively) and a negative association with life satisfaction ($r_s = -0.094$, $P = 0.002$; $r_s = -0.067$, $P = 0.027$; $r_s = -0.148$, $P < 0.001$; $r_s = -0.006$, $P < 0.05$). Positive affectivity showed a negative association with the use of psychoanaleptics ($r_s = -0.108$, $P < 0.001$), self-reported mental disorder ($r_s = -0.172$, $P < 0.001$), and menopausal symptoms ($r_s = -0.122$, $P < 0.001$), whereas negative affectivity showed a positive association with these variables ($r_s = 0.115$, $P < 0.001$; $r_s = 0.172$, $P < 0.001$; $r_s = 0.110$, $P < 0.001$, respectively). Age, education, smoking, and alcohol consumption showed no significant associations with any of the mental well-being components. However, as the compared groups differed by age, we also included age as a confounder. The final model was thus adjusted for age, marital status, parity, employment status, self-reported mental disorder, use of psycholeptics (N05), use of psychoanaleptics (N06), and menopausal symptoms.

To investigate the role of physical activity in the relationship between menopausal status and mental well-being, we analyzed marginal means differences, that is, the means of categories across menopausal status and physical activity level adjusted for all the previously mentioned confounders. Analysis of marginal means differences gives additional information beyond the full model with inclusion of interaction terms, especially in the case of categorical variables with more than two categories.[34] In these analyses, in each menopausal status group, the women with medium and high physical activity were compared with those with low physical activity. All analyses were performed with R, version 3.3.3.[35,36]

RESULTS

The socioeconomic and lifestyle characteristics of the participants and their level of physical activity across the four menopausal stages are presented in Table 1. As expected, the postmenopausal women were significantly older than the

TABLE 1. *Participants' socioeconomic and lifestyle characteristics and information relevant to mental health by menopausal stages*

Variables	Premenopausal (n = 304)	Early perimenopausal (n = 198)	Late perimenopausal (n = 209)	Postmenopausal (n = 387)	*P*
Age, y	50.3 (1.67)	50.7 (1.81)	51.6 (1.90)	52.3 (1.98)	**<0.001** Pre-E.Peri 0.018 Pre-L.Peri < 0.001 Pre-Post < 0.001 E.Peri-L.Peri <0.001 E.Peri-Post <0.001 L.Peri-Post <0.001
Education	(n = 304)	(n = 198)	(n = 209)	(n = 387)	0.117
Primary	5 (1)	3 (1)	7 (3)	9 (2)	
Secondary	165 (55)	109 (55)	106 (51)	239 (62)	
Tertiary	134 (44)	86 (44)	96 (46)	139 (36)	
Marital status	(n = 303)	(n = 198)	(n = 209)	(n = 385)	0.560
Single	21 (7)	19 (10)	16 (7)	37 (10)	
Married or registered partnership	242 (80)	148 (75)	164 (79)	278 (72)	
Divorced, separated or widowed	40 (13)	30 (15)	29 (14)	70 (18)	
Parity: number of children born	(n = 302)	(n = 196)	(n = 208)	(n = 386)	0.926
Nulliparous	35 (12)	25 (13)	26 (12)	53 (13)	0.894
One or two	178 (59)	114 (58)	113 (55)	219 (58)	
Three or more	89 (29)	57 (29)	69 (33)	114 (29)	
Smoking	(n = 300)	(n = 196)	(n = 207)	(n = 385)	0.333
Never	194 (65)	136 (70)	131 (63)	260 (68)	
Former	90 (30)	47 (24)	55 (27)	98 (25)	
Current	16 (5)	13 (6)	21 (10)	27 (7)	
Menopausal symptom (yes)	168 (55)	148 (74)	172 (82)	353 (91)	<0.001 Pre-E.Peri < 0.001 Pre-L.Peri < 0.001 Pre-Post < 0.001 E.Peri-L.Peri 0.070 E.Peri-Post <0.001 L.Peri-Post **0.025**
Alcohol consumption	(n = 304)	(n = 198)	(n = 209)	(n = 387)	0.7447
Never or rarely (<1 units/wk)	100 (34)	90 (45)	88 (42)	129 (34)	
Weekly (1 to 5 units/wk)	145 (48)	94 (46)	104 (50)	193 (50)	
Often (>5 units/wk)	55 (18)	14 (9)	16 (8)	65 (16)	
Employment status	(n = 304)	(n = 198)	(n = 209)	(n = 387)	0.258
Employed	275 (90)	168 (85)	182 (87)	335 (87)	
Not regularly employed	29 (10)	30 (15)	27 (13)	52 (13)	
Self-rated health	(*n* = 304)	(*n* = 198)	(*n* = 209)	(*n* = 387)	
Good or very good	244 (80)	145 (73)	163 (78)	294 (76)	0.252
Average	57 (19)	52 (26)	43 (21)	85 (22)	
Poor	3 (1)	1 (1)	3 (1)	9 (1)	
Physical Activity level:	(n = 304)	(n = 198)	(n = 209)	(n = 387)	0.019 Pre-E.Peri 0.279 Pre-L.Peri 0.032 Pre-Post 0.338 E.Peri-L.Peri 0.338 E.Peri-Post 0.338 L.Peri-Post 0.032
Low	50 (17)	37 (19)	30 (16)	81 (21)	
Medium	174 (57)	124 (62)	145 (66)	218 (56)	
High	80 (26)	37 (19)	34 (22)	88 (23)	
CES-D ≥16	(n = 304) 30 (10)	(n = 198) 22 (11)	(n = 209) 18 (10)	(n = 387) 52 (13)	0.207
Self-reported mental disorders	(n = 303) 29 (9)	(n = 194) 21 (11)	(n = 209) 16 (8)	(n = 385) 25 (6)	0.260
Users of psycholeptics (N05)	(n = 304) 9 (3)	(n = 197) 7 (3)	(n = 209) 3 (1)	(n = 387) 7 (2)	0.397
Users of psychoanaleptics (N06)	(n = 304) 26 (8)	(n = 197) 19 (10)	(n = 209) 13 (6)	(n = 387) 30 (8)	0.620

Values in bold indicate statistically significant results.
Values given are n (%) for variables without units of measurement and mean (SD) for variables with units of measurement.
CES-D, Center for Epidemiologic Studies Depression Scale.

TABLE 2. *Mental well-being dimensions by menopausal stages*

Variables	Premenopausal (n = 302)	Early perimenopausal (n = 196)	Late perimenopausal (n = 208)	Postmenopausal (n = 387)	*P* for trend
Depressive symptoms, mean	0.42 (0.33)	0.51 (0.39)	0.46 (0.35)	0.49 (0.40)	**0.019** Pre-E.Peri **0.038** Pre-L.Peri 0.534 Pre-Post **0.035** E.Peri-L.Peri 0.597 E.Peri-Post 0.974 L.Peri-Post 0.745
Life satisfaction, mean	5.20 (1.12)	5.15 (1.05)	5.34 (0.98)	5.16 (1.17)	0.264
Positive effect, mean	3.80 (0.61)	3.82 (0.64)	3.83 (0.63)	3.73 (0.63)	0.156
Negative effect, mean	1.51 (0.46)	1.56 (0.50)	1.55 (0.51)	1.56 (0.54)	0.499

Values in bold indicate statistically significant results.
Values given are mean (SD).

late perimenopausal women followed by early perimenopausal women. The premenopausal women were the youngest.

No significant group differences were observed in the proportions of education, marital status, parity, alcohol consumption, smoking, employment status, and self-rated health. The postmenopausal women reported having menopausal symptoms significantly more often than the late, followed by the early peri and premenopausal women. The PA distribution differed significantly between groups, indicating that the late perimenopausal group included proportionally more medium physically active women. The distribution of signs of clinically relevant depressive symptoms, self-reported mental disorder, and the use of psycholeptics and psychoanaleptics was similar across the menopausal status groups.

The depressive symptoms score was significantly lower among the premenopausal than among early peri and postmenopausal women (Table 2). No statistically significant differences in life satisfaction or positive or negative affectivity were observed between the study groups.

A significant association between menopausal status and depressive symptoms was observed after controlling for age, marital status, parity, employment status, self-reported mental disorders, and use of psycholeptics and psychoanaleptics (Table 3). In the adjusted model for depressive symptoms, the early peri and postmenopausal women showed higher values than the premenopausal women. When menopausal symptoms were included in this regression analysis, the association between menopausal status and depressive symptoms remained, but was of a lower magnitude. No significant association of menopausal status with negative affectivity (Table 4), life satisfaction (Table 5), or positive affectivity (Table 6) was observed.

With respect to menopausal symptoms, we also performed sensitivity analyses in which we separately studied if different menopausal symptom classes would yield similar results to a

TABLE 3. *Multiple linear regression analysis for depressive symptoms as dependent variable*

	Depressive symptoms								
Predictors	Estimates	CI	*P*	Estimates	CI	*P*	Estimates	CI	*P*
(Intercept)	1.10	0.50 to 1.71	**<0.001**	1.03	0.44 to 1.62	**0.001**	1.04	0.46 to 1.63	**<0.001**
Early perimenopausal[a]	0.09	0.02 to 0.16	**0.009**	0.08	0.02 to 0.15	**0.016**	0.06	−0.01 to 0.12	0.084
Late perimenopausal[a]	0.06	−0.01 to 0.13	0.082	0.07	0.01 to 0.14	**0.032**	0.04	−0.02 to 0.11	0.222
Postmenopausal[a]	0.09	0.03 to 0.15	**0.003**	0.11	0.05 to 0.17	**<0.001**	0.07	0.01 to 0.13	**0.034**
Age	−0.01	−0.02 to −0.00	**0.045**	−0.01	−0.02 to 0.00	**0.042**	−0.01	−0.02 to −0.00	**0.022**
Married/partnership[b]	−0.04	−0.13 to 0.04	0.321	−0.02	−0.11 to 0.06	0.597	−0.03	−0.12 to 0.05	0.480
Divorced[b]	0.04	−0.06 to 0.14	0.459	0.05	−0.05 to 0.15	0.349	0.04	−0.05 to 0.14	0.379
Parity (1 or 2)[c]	−0.04	−0.11 to 0.04	0.307	−0.04	−0.11 to 0.04	0.340	−0.04	−0.11 to 0.04	0.338
Parity (3 or >)[c]	−0.10	−0.18 to −0.02	**0.020**	−0.08	−0.16 to 0.00	0.055	−0.07	−0.15 to 0.01	0.077
Not employed[d]	0.15	0.08 to 0.21	**<0.001**	0.12	0.05 to 0.18	**0.001**	0.12	0.05 to 0.18	**<0.001**
Self-reported mental disorders (yes)[e]				0.22	0.13 to 0.31	**<0.001**	0.22	0.13 to 0.30	**<0.001**
User of psycholeptics (N05)[f]				0.14	−0.01 to 0.28	0.064	0.13	−0.01 to 0.28	0.068
User of psychoanaleptics (N06)[f]				0.15	0.06 to 0.23	**0.001**	0.14	0.05 to 0.23	**0.002**
Menopausal symptoms (yes)[g]							0.12	0.06 to 0.17	**<0.001**
Observations	1,087			1,079			1,077		

Values in bold indicate statistically significant results.
[a]Reference category is premenopausal.
[b]Reference category is single.
[c]Reference category is nulliparious.
[d]Reference category is employed.
[e]Reference category is no mental disorder.
[f]Reference category is no user.
[g]Reference category is no symptoms.

TABLE 4. *Multiple linear regression analysis for negative affectivity as dependent variable*

	Negative affectivity								
Predictors	Estimates	CI	*P*	Estimates	CI	*P*	Estimates	CI	*P*
(Intercept)	1.45	0.62 to 2.28	**0.001**	1.37	0.55 to 2.19	**0.001**	1.39	0.57 to 2.20	**0.001**
Early perimenopausal[a]	0.05	−0.04 to 0.14	0.316	0.04	−0.05 to 0.13	0.414	0.02	−0.07 to 0.11	0.681
Late perimenopausal[a]	0.04	−0.05 to 0.13	0.367	0.05	−0.04 to 0.14	0.295	0.02	−0.07 to 0.12	0.624
Postmenopausal[a]	0.05	−0.03 to 0.14	0.217	0.06	−0.02 to 0.14	0.145	0.03	−0.06 to 0.11	0.536
Age	−0.00	−0.02 to 0.02	0.981	0.00	−0.02 to 0.02	0.953	−0.00	−0.02 to 0.02	0.921
Married/Partnership[b]	0.11	−0.02 to 0.23	0.086	0.12	−0.00 to 0.24	0.051	0.11	−0.01 to 0.23	0.066
Divorced[b]	0.10	−0.04 to 0.24	0.171	0.10	−0.04 to 0.24	0.147	0.10	−0.04 to 0.24	0.164
Parity (1 or 2)[c]	−0.01	−0.11 to 0.09	0.834	−0.02	−0.12 to 0.08	0.718	−0.02	−0.12 to 0.08	0.714
Parity (3 or >)[c]	−0.09	−0.20 to 0.02	0.125	−0.08	−0.19 to 0.03	0.147	−0.08	−0.19 to 0.03	0.178
Not employed[d]	0.14	0.05 to 0.23	**0.003**	0.11	0.02 to 0.20	**0.021**	0.11	0.02 to 0.20	**0.017**
Self-reported mental disorders (yes)[e]				0.30	0.17 to 0.42	**<0.001**	0.29	0.16 to 0.41	**<0.001**
User of psycholeptics (N05)[f]				−0.14	−0.35 to 0.06	0.166	−0.14	−0.35 to 0.06	0.162
User of psychoanaleptics (N06)[f]				0.11	−0.01 to 0.23	0.080	0.11	−0.02 to 0.23	0.092
Menopausal symptoms (yes)[g]							0.10	0.03 to 0.18	**0.008**
Observations	1,086			1,078			1,076		

Values in bold indicate statistically significant results.
[a]Reference category is premenopausal.
[b]Reference category is single.
[c]Reference category is nulliparious.
[d]Reference category is employed.
[e]Reference category is no mental disorder.
[f]Reference category is no user.
[g]Reference category is no symptoms.

model which included an aggregated menopausal symptoms variable. We observed that the results were very similar to those we obtained when using an aggregated variable for menopausal symptoms, although the strength of the association varied between different symptom classes. Therefore, we assume that the aggregated variable for menopausal symptoms was sufficient to consider in our analysis.

As shown in Table 7, in the pre and early perimenopausal women, the mean score for depressive symptoms was lower among those with high than those with medium or low physical activity, after adjusting for age, marital status, parity, employment status, self-reported mental disorder, use of psycholeptics and psychoanaleptics, and menopausal symptoms. Among the postmenopausal women, a medium or high physical activity level associated with lower scores on depressive symptoms scores than a low physical activity level. The differences in negative affectivity by menopausal status and level of physical activity were not statistically significant.

For positive mental well-being, particularly positive affectivity, women with high physical activity scored significantly

TABLE 5. *Multiple linear regression analysis for life satisfaction as dependent variable*

	Life satisfaction								
Predictors	Estimates	CI	*P*	Estimates	CI	*P*	Estimates	CI	*P*
(Intercept)	3.96	2.24 to 5.67	**<0.001**	4.04	2.33 to 5.75	**<0.001**	4.06	2.36 to 5.77	**<0.001**
Early perimenopausal[a]	0.02	−0.17 to 0.21	0.805	0.04	−0.14 to 0.23	0.644	0.08	−0.11 to 0.27	0.412
Late perimenopausal[a]	0.14	−0.05 to 0.33	0.155	0.12	−0.07 to 0.31	0.209	0.17	−0.02 to 0.36	0.088
Postmenopausal[a]	−0.00	−0.18 to 0.17	0.973	−0.03	−0.20 to 0.14	0.717	0.03	−0.15 to 0.21	0.749
Age	0.02	−0.02 to 0.05	0.375	0.02	−0.02 to 0.05	0.364	0.02	−0.02 to 0.05	0.333
Married/partnership[b]	0.48	0.23 to 0.73	**<0.001**	0.44	0.19 to 0.69	**0.001**	0.45	0.20 to 0.70	**<0.001**
Divorced[b]	−0.17	−0.46 to 0.12	0.250	−0.20	−0.48 to 0.09	0.185	−0.19	−0.48 to 0.10	0.196
Parity (1 or 2)[c]	0.16	−0.06 to 0.37	0.149	0.16	−0.05 to 0.37	0.143	0.16	−0.06 to 0.37	0.149
Parity (3 or >)[c]	0.29	0.06 to 0.52	**0.015**	0.25	0.03 to 0.48	**0.030**	0.25	0.02 to 0.48	**0.035**
Not employed[d]	−0.60	−0.79 to −0.41	**<0.001**	−0.54	−0.73 to −0.35	**<0.001**	−0.54	−0.73 to −0.35	**<0.001**
Self-reported mental disorders (yes)[e]				−0.50	−0.76 to −0.24	**<0.001**	−0.49	−0.75 to −0.23	**<0.001**
User of psycholeptics (N05)[f]				−0.51	−0.93 to −0.09	**0.018**	−0.50	−0.93 to −0.08	**0.019**
User of psychoanaleptics (N06)[f]				0.00	−0.25 to 0.26	0.970	0.02	−0.24 to 0.27	0.903
Menopausal symptoms (yes)[g]							−0.16	−0.31 to 0.00	0.052
Observations	1,087			1,079			1,077		

Values in bold indicate statistically significant results.
[a]Reference category is premenopausal.
[b]Reference category is single.
[c]Reference category is nulliparious.
[d]Reference category is employed.
[e]Reference category is no mental disorder.
[f]Reference category is no user.
[g]Reference category is no symptoms.

TABLE 6. *Multiple linear regression analysis for positive affectivity as dependent variable*

	Positive affectivity								
Predictors	Estimates	CI	*P*	Estimates	CI	*P*	Estimates	CI	*P*
(Intercept)	4.57	3.54 to 5.60	**<0.001**	4.72	3.71 to 5.73	**<0.001**	4.71	3.69 to 5.72	**<0.001**
Early perimenopausal[a]	0.05	−0.07 to 0.16	0.403	0.05	−0.07 to 0.16	0.422	0.07	−0.04 to 0.19	0.202
Late perimenopausal[a]	0.06	−0.06 to 0.17	0.331	0.05	−0.07 to 0.16	0.414	0.08	−0.03 to 0.20	0.151
Postmenopausal[a]	−0.03	−0.13 to 0.07	0.545	−0.05	−0.15 to 0.05	0.353	0.00	−0.10 to 0.11	0.980
Age	−0.02	−0.04 to 0.00	0.121	−0.02	−0.04 to 0.00	0.083	−0.02	−0.04 to 0.00	0.118
Married/partnership[b]	0.02	−0.13 to 0.17	0.813	−0.01	−0.15 to 0.14	0.927	0.00	−0.14 to 0.15	0.975
Divorced[b]	0.04	−0.13 to 0.22	0.635	0.02	−0.15 to 0.19	0.785	0.03	−0.14 to 0.20	0.760
Parity (1 or 2)[c]	0.02	−0.10 to 0.15	0.712	0.02	−0.10 to 0.15	0.746	0.02	−0.10 to 0.15	0.747
Parity (3 or >)[c]	0.08	−0.06 to 0.22	0.245	0.06	−0.07 to 0.20	0.376	0.05	−0.08 to 0.19	0.437
Not employed[d]	−0.18	−0.29 to −0.06	**0.003**	−0.13	−0.24 to −0.02	**0.024**	−0.13	−0.25 to −0.02	**0.020**
Self-reported mental disorders (yes)[e]				−0.38	−0.53 to −0.23	**<0.001**	−0.38	−0.53 to −0.22	**<0.001**
User of psycholeptics (N05)[f]				0.21	−0.04 to 0.46	0.102	0.21	−0.04 to 0.46	0.094
User of psychoanaleptics (N06)[f]				−0.09	−0.24 to 0.06	0.249	−0.08	−0.23 to 0.07	0.304
Menopausal symptoms (yes)[g]							−0.14	−0.24 to −0.05	**0.003**
Observations	1,087			1,079			1,077		

Values in bold indicate statistically significant results.
[a]Reference category is premenopausal.
[b]Reference category is single.
[c]Reference category is nulliparious.
[d]Reference category is employed.
[e]Reference category is no mental disorder.
[f]Reference category is no user.
[g]Reference category is no symptoms.

higher than women with low physical activity in all four menopausal status groups (Table 8). The same was observed for life satisfaction, where women with low physical activity scored significantly lower than women with medium or high physical activity in the pre, early peri, and postmenopausal groups.

DISCUSSION

This study examined the association between menopausal status and mental well-being, and the role of physical activity in this association, among 47 to 55-year-old women. Our data suggest that menopausal status is associated with negative mental well-being (ie, depressive symptoms), but not with negative affectivity or positive mental well-being (ie, life satisfaction and positive affectivity). The postmenopausal women reported more depressive symptoms than the premenopausal women. Furthermore, the pre, early peri, and postmenopausal women with high physical activity experienced depressive symptoms less often, were more satisfied with life, and had higher positive affectivity scores than their low physically active counterparts. Pre and postmenopausal women reporting medium physical activity were more satisfied with life than those reporting low physical activity. At the same time, the postmenopausal women with a medium

TABLE 7. *Marginal mean difference by menopausal stages and physical activity levels for negative well-being*

	Depressive symptoms			Negative affectivity		
	B[a]	CI	*P*	B[a]	CI	*P*
Premenopausal						
Low physical activity	1.39	0.72 to 2.05		1.12	0.17 to 2.06	
Medium physical activity	−0.09	−0.20 to 0.02	0.125	−0.00	−0.16 to 0.16	0.970
High physical activity	−0.13	−0.26 to −0.01	**0.039**	0.04	−0.14 to 0.22	0.686
Early perimenopausal						
Low physical activity	1.36	0.68 to 2.04		1.14	0.18 to 2.11	
Medium physical activity	0.05	−0.08 to 0.18	0.470	0.02	−0.17 to 0.21	0.858
High physical activity	−0.18	−0.34 to −0.01	**0.034**	−0.00	−0.24 to 0.23	0.967
Late perimenopausal						
Low physical activity	1.41	0.72 to 2.10		1.20	0.22 to 2.18	
Medium physical activity	−0.08	−0.22 to 0.06	0.266	−0.06	−0.25 to 0.14	0.590
High physical activity	−0.15	−0.32 to 0.03	0.102	−0.14	−0.39 to 0.11	0.281
Postmenopausal						
Low physical activity	1.52	0.83 to 2.21		1.16	0.18 to 2.14	
Medium physical activity	−0.21	−0.30 to −0.12	**<0.001**	−0.05	−0.18 to 0.08	0.446
High physical activity	−0.20	−0.31 to −0.10	**<0.001**	0.02	−0.14 to 0.17	0.816

Values in bold indicate statistically significant results.
[a]*B* coefficients for women with medium and high physical activity (PA) show the differences from the corresponding values of the women with low PA. All values are adjusted for age, marital status, parity, employment status, self-reported mental disorders, use of psycholeptics, use of psychoanaleptics, and menopausal symptoms.

TABLE 8. *Marginal mean difference by menopausal stages and physical activity levels for positive well-being*

	Positive affectivity			Life satisfaction		
	B[a]	CI	*P*	B[a]	CI	*P*
Premenopausal						
Low physical activity	3.98	2.83 to 5.12		2.76	0.82 to 4.70	
Medium physical activity	0.04	−0.15 to 0.23	0.695	0.54	0.21 to 0.87	**0.001**
High physical activity	0.34	0.13 to 0.56	**0.002**	0.79	0.43 to 1.16	**<0.001**
Early perimenopausal						
Low physical activity	3.91	2.75 to 5.08		3.13	1.16 to 5.11	
Medium physical activity	0.20	−0.02 to 0.43	0.080	0.12	−0.26 to 0.50	0.541
High physical activity	0.63	0.35 to 0.91	**<0.001**	0.63	0.16 to 1.11	**0.009**
Late perimenopausal						
Low physical activity	4.04	2.86 to 5.22		3.09	1.09 to 5.09	
Medium physical activity	0.11	−0.14 to 0.35	0.393	0.41	−0.00 to 0.82	0.052
High physical activity	0.37	0.07 to 0.67	**0.017**	0.42	−0.09 to 0.94	0.104
Postmenopausal						
Low physical activity	3.86	2.68 to 5.05		3.01	1.00 to 5.01	
Medium physical activity	0.26	0.11 to 0.42	**0.001**	0.38	0.12 to 0.65	**0.004**
High physical activity	0.35	0.16 to 0.53	**<0.001**	0.42	0.10 to 0.73	**0.009**

Values in bold indicate statistically significant results.
[a]*B* coefficients for women with medium and high physical activity (PA) show the differences from the corresponding values of the women with low PA. All values are adjusted for age, marital status, parity, employment status, self-reported mental disorders, use of psycholeptics, use of psychoanaleptics, and menopausal symptoms.

physical activity level experienced depressive symptoms less often and had higher positive affectivity scores than those with a low level of physical activity.

Previous studies measuring positive well-being or quality of life have suggested that mental well-being may be more affected by different social, psychological, and health factors than by menopausal status per se.[7,37] Studies on the negative dimensions of mental well-being have found an association between menopause and an elevated level of ill-being. For example, a longitudinal study with 405 participants followed for 4 years reported an increase in negative affect and decrease in positive affect in the first 2 years after the final menstruation.[38] When the follow-up was extended to 9 years with 226 of the same participants, the results showed a decline in negative, but not in positive mood. Consequently, well-being increased after the menopause transition.[39] In another cross-sectional comparison, the early perimenopausal women showed the highest rate of psychological distress, even after controlling for vasomotor symptoms and sleep difficulties.[40] Interestingly, a longitudinal follow-up study of the same cohort over 5 years reported an increase in depressive symptoms when women entered the early perimenopausal stage.[8]

Some studies highlight that women are more susceptible to the development of depression in the late perimenopausal stage than in the pre or postmenopausal stages.[40-42] However, when menopausal status was closely monitored employing FSH measures, the late peri and early postmenopausal women showed a similar risk for developing depression relative to the premenopausal level.[43] The fact that the postmenopausal status of our participants was established over a 6-month period may explain the peak observed in depressive symptoms in the postmenopausal group, as these women were in a relatively early postmenopausal stage. The nonsignificant difference between the pre and late postmenopausal women in depressive symptoms is, however, somewhat unexpected. It may be due to high variability in depressive symptoms in this group and/or to difficulties in establishing temporal continuity of a rate of depressive symptoms and changes in reproductive function due to the use of a cross-sectional design.

When we added menopausal symptoms to the regression models, the association between menopausal status and depressive symptoms remained only in the postmenopausal group. A similar observation has been made previously.[16] Closer scrutiny of a specific group of symptoms (eg, vasomotor symptoms, somatic or pain symptoms, psychological symptoms, and urogenital symptoms) yielded similar results. This suggests that the association between depressive symptoms and menopausal status may partially be explained by menopausal symptoms: that is, experienced menopausal symptoms may act as a mediator between a fall in estrogen levels and depressive symptoms. However, given that the fall in estrogen extends beyond menopause, it remains unclear whether estrogen deficiency is a primary cause of the elevation in depressive symptoms, as longitudinal studies have reported that depressive symptoms and negative mood return to premenopausal levels in postmenopause.[7,16]

In contrast to negative mental well-being (eg, depressive symptoms), which fluctuated across the menopausal status groups, positive mental well-being was maintained across the studied groups. Positive well-being is related to multiple outcomes such as employment and family life, and also health and longevity.[4,44] Thus, positive mental well-being can be viewed as a resource that compensates for an increase in negative well-being.[14]

Physical activity promotes higher quality of life both in middle-aged women[18] and during menopause.[45] Studies have reported a positive role of physical activity in decreasing anxiety and depression among menopausal women.[46,47] Our previous study with the present cohort[48] suggests further that physical activity attenuates the menopause-related decline in physical fitness, which, theoretically, may be linked to improvements in mental well-being.[49]

While much research effort has been expended on the direct link between menopausal status and mental well-being, less attention has been paid to the possible role of physical activity in this link. Slaven and Lee[50] assessed acute psychological response to exercise among menopausal women. They concluded that regularly exercising women reported a lower level of negative mood in comparison to non-exercising women irrespective of menopausal status. While this result may be explained by a transient reduction in anxiety following an exercise bout, our study, which assessed leisure physical activity, extends it to long-term differences in habitual physical activity. The present results showed that irrespective of menopausal status high physically active women showed better positive well-being. For negative well-being, however, we observed that the difference in depressive symptoms as a function of physical activity was more pronounced in the postmenopausal than pre- or perimenopausal women. Negative affectivity was the only dimension of mental well-being included in this study that was not linked to physical activity.

The same beneficial role of physical activity had been reported previously[19] showing that among the postmenopausal group only, highly physically active women had a lower level of depressive symptoms, perceived stress, and anxiety than the less physically active women. Moreover, in the ''late-transition group'' (late perimenopausal women), the level of depressive symptoms was highest among the ''moderately,'' but not highly active women. We observed a similar beneficial effect of physical activity with respect to depressive symptoms. Particularly, the postmenopausal women with a medium and high physical activity level had a lower level of depressive symptoms than their low physically active counterparts, whereas among the pre and perimenopausal women, such a difference was less clear. These results suggest that low physically active women form a subgroup potentially vulnerable to an increased level of depressive symptoms during menopause. However, the reverse relationship is also possible. That is, women with a higher level of depressive symptoms may be less physically active.[51] A longitudinal analysis, based on middle-aged women and men, showed that high mental well-being contributed to physical activity rather than vice versa.[52] It may also be the case here that low physical activity during early perimenopause[20] may partially be explained by a higher rate of depressive symptoms.

Positive mental well-being is not merely the opposite of negative mood, but has a specific independent and positive relation to health.[53,54] Our study suggests that, particularly during the early postmenopausal stage, a medium level of physical activity may be enough to maintain positive mental well-being. More focused research on physical activity intensity as a way of alleviating the menopause-related decline in mental well-being is needed.

The link between physical activity and mental well-being during the menopause transition is complex and may involve several mechanisms, ranging from positive social interaction and improving personal resources to alleviating menopausal symptoms that contribute to enhancing affective state. Our results suggest that physical activity may independently of menopausal symptoms help maintain positive mental well-being and counteract the possible negative influence of menopause on depressive symptoms. However, due to the cross-sectional study design, we cannot exclude the opposite association. That is, it is equally possible that physically active women experience a lower level of menopausal symptoms; if so, having a lower level of menopausal symptoms may explain the greater mental well-being found in the high physically active women. Consequently, the present results should be interpreted as demonstrating that while menopausal status, mental well-being, and physical activity are linked to each other, longitudinal data are required to reveal their specific causal and possibly cumulative associations.

Issues of causality aside, habitual physical activity may help the accumulation over time of positive affective states, which have been highlighted as an important psychological resource[55] and which may be beneficial for a woman's ability to cope well and to feel in control of her menopausal symptoms.[56] Thus, physical activity programs can be viewed as an alternative to hormonal therapy as they help to alleviate various psychological symptoms.[19] While hormonal therapy remains an effective treatment option in managing symptoms,[57] its use has declined substantially due to concerns and uncertainty about the possible link between hormonal therapy and risk for coronary heart disease, stroke, and breast cancer.[58] In addition, a majority of menopausal women have reported a desire for life-style change programs (eg, physical activity).[59] The present data extend previous findings on the importance of a medium or higher level of physical activity for maintaining physical fitness[48] and mental well-being during menopause.

Several limitations of this study should be noted. First, although we controlled for some important confounders (age, marital status, parity, employment status, self-reported mental disorder, use of psycholeptics and psychoanaleptics, and menopausal symptoms) related to well-being, we did not include other life events that may influence mental well-being. Second, the cross-sectional nature of the research design did not allow us to control for the initial levels of depressive symptoms or for the duration of the menopause transition, or for exposure to menopausal symptoms. All these factors may contribute to the level of the measured mental well-being variables.[10,16] In addition, menopausal symptoms were studied broadly as an aggregated entity. Although we also ran analyses in which different symptoms were included separately to check the robustness of the results, different menopausal symptoms (eg, vasomotor symptoms vs psychological symptoms) may differ in their influence on mental well-being, a possibility that was not fully captured by the present analysis. We assumed that physical activity contributes to improved well-being; however, the reverse or a bidirectional association is also possible. Therefore, further studies with a prospective design controlling for potential confounders are needed before these findings can be translated into effective interventions. Third, physical activity was assessed with a self-report questionnaire, which may cause underestimation of the number of low and overestimation of the number of high physically active individuals.[60] However, the questionnaire used captures diverse forms of leisure physical activity and has shown good outcomes when compared with accelerometer-based physical activity and mobility measures among middle-aged women who participated in this study.[61] In future studies, however, it would be useful to complement the present self-reported measurements of physical activity with accelerometer-based data to see if the observed benefits of physical activity for mental well-being are replicated.

The strength of this study is the careful categorization of menopausal status through the use of menstrual diaries and hormonal analysis following the STRAW+10 criteria. Many previous studies have assessed menopausal status using self-report questionnaires without hormone measurements and thus may have misclassified some participants, making it difficult to establish the role of menopause in well-being. In the present study, we consider the possibility of misclassification to be minimal.

Previous cross-sectional studies have reported on the relationship between mental well-being and menopausal status without controlling for self-reported mental disorders or use of medications that can influence mental well-being. As suggested by earlier longitudinal studies, a prior level of depressive symptoms may increase the rate of depressive symptoms during menopause[10,16]; our study contributes information about these important confounders to the existing models. Moreover, this study recruited a large homogeneous cohort of relatively healthy, nonseverely obese women, thereby reducing the possible influence of unobservable variables (such as ethnicity, income or access to health care).

CONCLUSIONS

This study showed that while menopausal status is associated with elevated depressive symptomatology, it does not compromise positive mental well-being (ie, life satisfaction or positive affectivity). A high level of physical activity, irrespective of menopausal status, was related to better mental well-being, particularly to a lower level of depressive symptoms and higher levels of satisfaction with life and positive affect. A medium level of physical activity was associated with higher satisfaction with life in the pre and postmenopausal women and with lower depressive symptoms and higher positive affectivity among the postmenopausal women. Thus physical activity might alleviate the potential negative influence of menopause on mental well-being. It would therefore be important to ascertain the causal links between menopausal symptoms, physical activity, and mental well-being.

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III

PHYSICAL PERFORMANCE DURING THE MENOPAUSAL TRANSITION AND THE ROLE OF PHYSICAL ACTIVITY

by

Bondarev D, Finni T, Kokko K, Kujala U. M, Aukee P, Kovanen V, Laakkonen E. K, Sipilä S. 2021.

Journals of Gerontology Series A: Biological Sciences and Medical Sciences 76 (9): 1587–1590

DOI:10.1093/gerona/glaa292

Journals of Gerontology: Medical Sciences
cite as: *J Gerontol A Biol Sci Med Sci*, 2020, Vol. XX, No. XX, 1–9
doi:10.1093/gerona/glaa292
Advance Access publication November 24, 2020

Research Article

Physical Performance During the Menopausal Transition and the Role of Physical Activity

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Received: May 19, 2020; Editorial Decision Date: November 11, 2020

Decision Editor: Anne B. Newman, MD, MPH, FGSA

Abstract

Background: To examine longitudinal changes in physical performance during the menopausal transition and the role of physical activity (PA) in these changes.
Methods: Based on follicle-stimulating hormone levels and bleeding diaries, women (47–55 years) were classified as early (n = 89) and late perimenopausal (n = 143) and followed prospectively until postmenopausal status, with mean duration of 17.5 and 13.8 months, respectively. Physical performance was measured by handgrip force, knee extension torque, vertical jumping height, maximal walking speed, and 6-minute walking distance. Physical activity was self-reported and categorized as inactive, low, medium, and high. Longitudinal associations of menopausal status, physical performance, and related changes with PA level were analyzed using generalized estimation equations adjusted for duration of hormonal therapy.
Results: A significant decline over the menopausal transition in handgrip force (−2.1%, 95% CI −3.8 to −0.4), knee extension torque (−2.6%, 95% CI −4.5 to −0.8), and vertical jumping height (−2.6%, 95% CI −4.2 to −1.1) and a significant increase in 6-minute walking distance (2.1%, 95% CI 1.4 to 2.7) were observed in the total sample. A significant interaction of PA by time was observed in handgrip force and in vertical jumping height. High PA women had greater increase in handgrip strength but greater decline in vertical jumping height than medium, low, and inactive women (all $p \le .001$).
Conclusions: Both early and late perimenopausal women show decline in muscle strength and power during the transition to postmenopause. Physical activity seems to influence physical performance during the menopausal transition but understanding the benefits of PA requires interventional studies.

Keywords: Longitudinal changes, Menopause, Muscle power, Muscle strength, Walking

Physical performance is essential for the maintenance of everyday functional capacity. Age-related decline in muscle strength and power are known causes of low walking speed, mobility limitations, and disabilities among older people (1). The rate of decline typically accelerates in the later decades of life; however, in women, this accelerated pattern may begin already in midlife due to hormonal changes occurring during the menopausal years (2,3).

The menopause, defined as the final menstruation, occurs on average between the ages of 46 and 52 depending on the population studied and signifies the end of a woman's reproductive years (4). Due to the ovarian failure, significant changes in the hypothalamo-hypophyseal control system become noticeable several years before menopause. This leads to a decline in a serum estrogen concentrations together with an elevation in follicle-stimulating hormone (FSH) levels (5). With the recent advancement in life expectancy, a significant proportion of women live in the postmenopausal state, with its accompanying physiology and pathophysiology, for almost one-third of their lives.

Female sex steroids play an important role in maintaining skeletal muscle homeostasis and function (6,7). We and others have shown that postmenopausal women have lower muscle mass, muscle strength, and muscle power than premenopausal women (8–11). However, no association between muscle strength and the menopausal transition stages has also been reported (12,13).

Only a few longitudinal studies have investigated the associations of the menopausal transition with physical performance. One such study investigated changes over 3 years from the premenopausal to postmenopausal stage and found a decline in pinch strength but not in handgrip strength (14). Another study showed a decline in handgrip strength, sit-to-stand time, and preferred walking speed in pre- and perimenopausal women followed up to postmenopause over a 5-year period (15). It is difficult to draw conclusions based on the existing studies, as they have reported only a limited number of physical performance measurements. Moreover, the conflicting results obtained for some measures of physical performance may be due to the use of self-reports on the menstrual cycle as the sole method of establishing menopausal status, as this protocol may in some cases lead to misclassification of menopausal status (16).

Physical activity (PA) is a significant factor in the physical functioning of middle-aged women (17,18). In our recent paper, we showed that a higher level of PA was associated with better physical performance and muscle mass in 47- to 55-year-old pre-, peri-, and postmenopausal women (8,11), indicating that higher levels of PA may, at least partially, slow down the loss of physical performance during the menopausal transition. However, at present, the complex interrelationship between the menopausal transition, physical performance, and PA has not been verified with longitudinal observations.

This longitudinal study thus extends the previously reported cross-sectional results on differences in physical performance at different menopausal stages (8), using data drawn from the population-based Estrogenic Regulation of Muscle Apoptosis (ERMA) cohort study (19). In the present study, menopausal status was assessed with bleeding diaries and hormonal measurements, allowing us to follow-up perimenopausal women prospectively until they became postmenopausal, an approach which provides a unique opportunity to examine changes in physical performance close to menopause and thereby reduce possible confounding factors. Thus, the aim of the study was (i) to assess changes in physical performance during the menopausal transition from the peri- to postmenopausal state utilizing a comprehensive set of measurements to assess physical performance, and (ii) to investigate whether these changes vary with the level of PA.

Method

Study Design and Participants

This study forms a part of the ERMA study (19). The present study flow chart is shown in Figure 1. Women aged 47–55 years living in the city of Jyväskylä and neighboring municipalities were randomly selected from the Finnish National Registry maintained by the Population Register Centre. An invitation to participate in the study was sent to 6878 potential participants. Women who self-reported a body mass index of >35 kg/m^2, being currently pregnant or lactating, having medical conditions affecting ovarian function

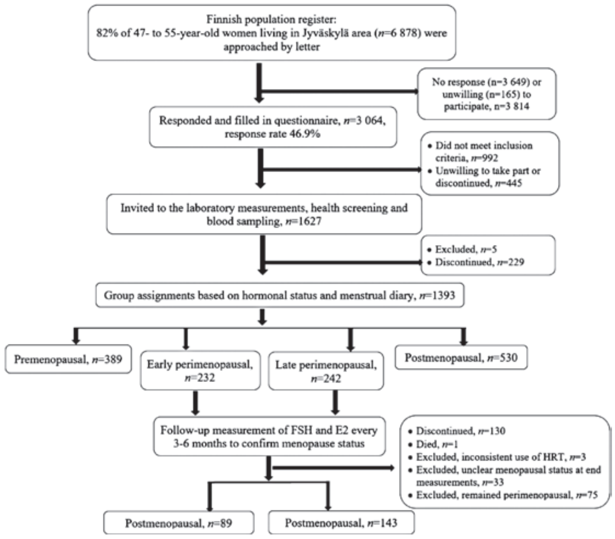

Figure 1. Recruitment of participants.

(such as bilateral ovariectomy), users of estrogen-containing hormonal therapy (HT) or other medications affecting ovarian function, or having health concerns or conditions that may affect skeletal muscle function or preclude them from participating in daily physical activities were excluded from the study. The response rate to the postal invitation to participate in the study was 47%. Eligible participants (n = 1627) were invited to the laboratory and 1393 women categorized as premenopausal, early perimenopausal, late perimenopausal, or postmenopausal based on self-reported menstrual bleeding and measured FSH levels. Of these, 232 women in the early perimenopausal stage and 242 women in the late perimenopausal stage were followed up until they reached postmenopause. During the follow-up, all participants kept a menstrual diary and gave blood samples: FSH and 17β-estradiol levels were measured approximately every 6 months in the early perimenopausal women and every 3 months in the late perimenopausal women until their postmenopausal status was confirmed. The analysis in the present study comprises women whose performance of at least one of the physical performance measurements was acceptable in early or late perimenopause and after the follow-up when postmenopausal (n = 232).

All study participants gave their written informed consent. The study was conducted in accordance with the guidelines on good clinical and scientific practice laid down by the Declaration of Helsinki and was approved by the ethics committee of the Central Finland Health Care District (KSSHP Dnro 8U/2014).

Measurements

Demographics, anthropometry, and body composition

Data on level of education, marital status, presence of musculoskeletal diseases or conditions, current and past smoking, use of a progestogen-releasing intrauterine coil, or other progestogen preparation (for contraception or to treat a gynecological bleeding disorder) were self-reported with a structured questionnaire. Age was calculated from date of birth to the date of the characterization of menopausal status.

Body mass was measured with a digital scale and *height* with a stadiometer. *Body mass index* was calculated as body mass (kg) divided by height squared (m^2).

Menopausal Status

Menopausal status was determined based on the analysis of bleeding diaries and serum concentrations of FSH following the Stages of Reproductive Aging Workshop (STRAW) criteria (20). A complete description of the grouping by menopausal status has been reported earlier (19). In brief, participants with FSH 17–25 IU/L were assigned to the early perimenopausal group and participants with FSH 25–30 IU/L were assigned to the late perimenopausal group. In addition, participants with irregular menstrual cycle were classified as early perimenopausal if their FSH was 9.5–25 IU/L. Participants reporting occasional bleedings that had occurred during past 3 months were classified as late perimenopausal even though their FSH value might exceed 30 IU/L (cutoff value for postmenopause).

Postmenopausal status was considered reached if no menstrual bleeding during the past 6 months was reported and FSH > 30 IU/L in 2 consecutive measurements. Participants with FSH > 30 IU/L during follow-up and no menstrual bleeding during the past 6 months were invited for check-up within a month of the last measurement, and if FSH remained >30 IU/L and no bleeding had occurred, were considered to be postmenopausal and invited to the laboratory to repeat the baseline muscle performance measurements. Follow-up time was calculated as the time between the initial hormonal measurements and the time when postmenopausal status was confirmed. The participants who started HT during the follow-up were invited to the physical performance measurements 6 months after starting HT.

Serum Hormone Measurements

Systemic FSH and 17β-estradiol levels were measured from fasting serum samples collected between 8:00 and 10:00 AM. At the baseline measurements, if a woman was in her menstrual cycle, the data were collected during cycle days 1–5. For serum separation, blood samples were centrifuged for 10 minutes at 2.200*g*. Follicle-stimulating hormone and 17β-estradiol level were measured with an IMMULITE 2000 XPi analyzer (Siemens Healthcare Diagnostics, Camberley, United Kingdom) using solid-phase, enzyme-labeled chemiluminescent competitive immunoassay. According to manufacturer's instructions FSH was determined using a monoclonal murine anti-FSH. The analytical sensitivity limit provided by the manufacture is 0.1 IU/L. Interassay coefficient of variation for the lower end of detection range is 2.9% with a precision value 6.8 ± 0.2 IU/L (mean ± *SD*); and for the higher end of the detection range is 3.9% with precision value 103 ± 3.2 IU/L. Accurate reportable range for E2 is 0.02–2 nmol/L.

The FSH and 17β-estradiol follow-up measurements were performed in 2 consecutive visits (control and final follow-up) and averaged to minimize the effect of daily fluctuations. Participants who started using HT after the baseline measurements were assessed only during the final follow-up visit.

Physical Activity

Physical activity was assessed by questionnaire on a 7-point scale (21) ranging from household chores to competitive sports and with items assessing leisure-time PA pattern. The instrument has previously been validated in middle-aged women (22).

The response options were: (1) I do not move more than is necessary in my daily routines; (2) I go for casual walks and engage in light outdoor recreation 1–2 times a week; (3) I go for casual walks and engage in light outdoor recreation several times a week; (4) Once or twice a week, I engage in brisk physical activity (eg, yard work, walking, cycling) that causes some shortness of breath and sweating; (5) Several times a week (3–5), I engage in brisk physical activity (eg, yard work, walking, cycling) that causes some shortness of breath and sweating; (6) I exercise several times a week in a way that induces rather strong shortness of breath and sweating during the activity; (7) I do competitive sports and maintain my fitness through regular training. As options 1, 2, 3, and 7 received only 1, 4, 11, and 1 responses, respectively, we combined and recoded them as follows: inactive (options 1, 2, 3), low PA (option 4), medium PA (option 5), and high PA (options 6 and 7).

Physical Performance

A detailed description of the measurement of physical performance has been given earlier (8). All measurements of physical performance were conducted at baseline and follow-up with the same procedure and equipment. Briefly, *maximal isometric knee extension force* was measured in a sitting position from the side of the dominant hand on a custom-made dynamometer chair (Good Strength; Metitur Oy, Palokka, Finland) with a knee angle set at 60° from full extension. Participants were encouraged to extend the knee to produce maximal force. To calculate *maximal isometric muscle torque*, the best attempt measured in Newtons (N) was multiplied by lower leg (lever arm) length (the distance between the lateral joint line of the knee and the midline of a cuff around the ankle).

Handgrip force on the dominant side was measured in Newtons with the elbow flexed at an angle of 90° and arm fixed to the armrest of the dynamometer chair. Participants were instructed to grip the handle as forcefully as possible. Grip was maintained for 2–3 seconds and the peak value taken for analysis.

Lower body muscle power was assessed by a countermovement jump on a contact mat. The countermovement jump describes the ability to elevate the body's center of gravity as fast as possible during a vertical jump (vertical jumping height). Vertical jumping height was calculated in cm from flight time (t): $(g \times t^2) \div 8 \times 100$ (23).

In all the above tests, 3–5 maximal attempts were performed and best performance taken as the result.

Maximum walking speed was assessed over 10 m in a laboratory corridor and walking time measured with photocells. Participants were encouraged to "walk as fast as they could." The best time of 2 trials was taken as the result.

Aerobic capacity was assessed by the 6-minute walking test. The test was conducted on a 20-m indoor track, and participants were instructed to complete as many laps as they could during 6 minutes. The distance covered in meters was used in the analysis.

Data on demographics, height, body mass index, and PA were obtained at the same time as the baseline measurements.

Data Analysis

Participant characteristics are shown as means and standard deviations or as percentages. The normality of distributions was tested with the Shapiro–Wilk test. Discrete baseline characteristics between the early and late perimenopausal groups were compared by chi-square tests or, in the case of continuous variables, by independent samples t test. For non-normally distributed data, comparison was performed with the Mann–Whitney U test.

The general linear model with the interaction of perimenopausal group by time was used to evaluate the level of significance in changes in physical performance during the menopausal transition. The analysis was adjusted by the duration of HT (days; entered in the model as a mean-centered variable). Mean percentage changes in physical performance variables were calculated as [(follow-up − baseline)/baseline × 100].

To investigate the role of PA in the link between menopausal status and physical performance, we used the general linear model for repeated measures data with the interaction of baseline PA level group by time. Tukey test was used for post hoc comparisons between groups.

A total of 37 women started HT during the follow-up. Therefore, the analyses were adjusted for the duration (days) of HT (entered in the model as a mean-centered variable). Because HT can influence neuromuscular function (24,25), and thus affect physical performance, we also conducted sensitivity analyses solely with the women (n = 196) who did not use HT (either estrogen-containing or progestogen-containing medications) during the follow-up (Supplementary Tables 1 and 2).

Due to high individual variation, changes in 17β-estradiol and FSH levels over the follow-up were calculated as the absolute differences between the baseline and follow-up measurements. These values were used in the correlation analysis (Pearson r) to see if the changes in the hormonal levels were associated with changes in physical performance. The correlation analysis was conducted for a subsample of women, excluding those who were using progestogen medication at baseline and those who started HT during the follow-up.

All analyses were performed with R, version 3.5.1. For significant chi-square values, a post hoc analysis was conducted using the fifer package for R. For repeated measures data the analysis was performed using package *ez* (to extract ANOVA values). Packages *geepack* and *emmeans* were used to calculate marginal means and respective confidence intervals for different groups across time points. All tests were performed at an a priori significance level of .05.

Results

Participants' demographic and health characteristics at baseline are shown in Table 1. The late perimenopausal women were slightly older than the early perimenopausal women. The level of 17β-estradiol was significantly higher and level of FSH significantly lower in the early peri- than late perimenopausal women. No between-group differences were observed in the other demographic or health characteristics.

Mean duration of follow-up was 17.6 (SD 8.5) months for the early peri- and 13.8 (SD 8.6) months for the late perimenopausal group (p < .001). A total of 40 women started HT during the follow-up from which 3 women were excluded due to the inconsistent reporting of HT use. Thus, 21 women in the early perimenopausal group and 16 women in the late perimenopausal group who started HT were included in the main analysis. The duration of HT varied from 2 to 337 days. The HT starters were significantly younger (50.6 years, SD 1.8), than those who did not start HT (51.8 years, SD 1.8, p = .001). There were no statistically significant

Table 1. Demographics, Health, and Gynecology at Baseline

Variables	Early Perimenopausal, n = 89	Late Perimenopausal, n = 143	Chi-Square Test, p Values
Age, years	51.19 (1.98)	51.85 (1.82)	**.010** (t test)
Education, n (%)	n = 88	n = 143	.516
Primary	1 (1)	5 (3)	
Secondary	16 (18)	28(20)	
Tertiary	71 (81)	110 (77)	
Marital status, n (%)	n = 88	n = 143	.813
Single	11 (13)	14 (9)	
Married or registered partnership	65 (74)	109 (77)	
Divorced, separated, or widowed	12 (13)	20 (14)	
Smoking, n (%)	n = 88	n = 142	.110
Never	65 (73)	94 (66)	
Former	21 (25)	35 (25)	
Current	2 (2)	13 (9)	
Musculoskeletal problems, n (%)	n = 87	n = 142	.727
	32 (37)	49 (34)	
Use of hormonal contraception, n (%)	n = 88	n = 143	.170
Nonuser	47 (52)	89 (62)	
Former user	10 (12)	20 (14)	
Current user*	31 (36)	34 (24)	
Using progestogens, n (%)	n = 88	n = 142	.384
No	62 (70)	108 (76)	
Former	19 (22)	21 (15)	
Current	7 (8)	13 (9)	
Physical activity, n (%)	n = 88	n = 143	.562
Inactive	13 (15)	18 (13)	
Low	21 (24)	34 (23)	
Medium	36 (41)	70 (49)	
High	18 (20)	21 (15)	
Body mass index, kg/m^2	25.35 (4.17)	25.70 (3.85)	.517 (t test)
17β-estradiol, nmol/L	0.46 (0.34)	0.25 (0.17)	**<.001** (t test)
Follicle-stimulating hormone, IU/L	18.29 (4.99)	47.02 (20.65)	**<.001** (t test)

Notes: *Current users of estrogen-containing medication (given orally or transdermally) were excluded from this study; therefore, the category "Current user" only includes users of progestogen-containing medications. Values in bold indicate statistically significant results.

differences at baseline between the HT starters and those who did not use HT in education (p = .418), marital status (p = .661), smoking (p = .706), musculoskeletal problems (p = .470), body mass index (p = .989), progestogen medication use (p = .385), or PA level (p = .228). There were also no significant differences between HT starters and nonstarters at baseline in 17β-estradiol level (p = .540) or in FSH level (p = .173).

In the early perimenopausal women, the level of FSH increased significantly from 18.3 (*SD* 5.0) to 64.8 (*SD* 30.7) IU/L (2.44, *SD* 3.47 IU/L per month) and in the late perimenopausal women significantly from 47.0 (*SD* 20.6) to 71.1 (*SD* 30.8) IU/L (1.69, *SD* 3.73 IU/L per month). The level of E2 declined significantly from 0.46 (*SD* 0.34) to 0.23 (*SD* 0.41) nmol/L (0.011, *SD* 0.04 IU/L per month) in the early perimenopausal women. In the late perimenopausal women, the level of E2 declined significantly from 0.25 (*SD* 0.17) to 0.21 (*SD* 0.31) nmol/L (0.002, *SD* 0.02 IU/L per month).

Table 2 shows the results of the physical performance tests for the whole sample and separately for the early and late perimenopausal groups. A significant decline over time was observed in hand grip strength (−2%), knee extension torque (−3%), and vertical jumping height (−3%) and a significant increase in 6-minute walking distance (2%). No significant interaction of perimenopausal group by time was observed in any of the physical performance variables.

Similar results were obtained when the women who were using progesterone medication at baseline and those who started HT during the follow-up were excluded from the analysis (Supplementary Table 1).

The correlation coefficients between changes in 17β-estradiol and FSH levels over the follow-up and changes in physical performance varied between r = 0.100–0.024 (p = .163–.757) for 17β-estradiol and r = 0.117–0.001 (p = .102–.993) for FSH.

Table 3 shows changes in the physical performance measures in relation to baseline PA level. A significant interaction of PA group by time was observed in handgrip force and vertical jumping height. In handgrip force a significant increase was observed in women with high PA, whereas a significant decline was observed in women with medium PA. Post hoc comparisons showed that, for the high PA women change in handgrip strength was significantly greater than for medium PA (p = .001), low PA (p < .001), or inactive group (p < .001). No significant differences in change in handgrip strength were observed when comparing medium PA group with low PA (p = .355) and inactive group (p = .151) or when comparing low PA group with inactive PA group (p = .527).

In vertical jumping height a significant decline was observed in women with medium and high PA, whereas physically inactive and women with low PA showed no changes. For high PA group the decline in vertical jumping height was significantly greater than for medium PA (p < .001), low PA (p = .001), or inactive group (p < .001). There were no differences in change in vertical jumping height when comparing medium PA group with low PA (p = .822) and inactive group (p = .232). Comparison of low PA group with inactive PA group also showed no differences in changes in vertical jumping height (p = .207).

No significant interactions of PA group by time were observed in knee extension torque and walking performance. A significant group effect was, however, observed in 6-minute walking distance: postmenopausal women with high PA had higher values than postmenopausal women who were inactive or had low PA (Table 3). Similar results were obtained when the women who were using progesterone medication at baseline and those who started HT during the follow-up were excluded from the analysis (Supplementary Table 2).

Discussion

We observed an average of 2%–3% decline in physical performance from early perimenopause to postmenopause. No changes were observed in walking speed, while distance travelled in 6 minutes had

Table 2. Changes in Physical Performance During the Menopausal Transition (time) in the Early and Late Perimenopausal Groups (groups)

	Time			ANOVA, p Values		
Variables, Group, n	Baseline, Mean (95% CI)	Post, Mean (95% CI)	Change, % (95% CI)	Time	Group	Time × Group
Hand grip (N)						
Total sample, n = 230	314 (306; 322)	305 (297; 313)	**−2.1 (−3.8; −0.4)**	**.002**	.681	.100
Early peri, n = 89	319 (307; 331)	306 (295; 318)	**−3.5 (−6.0; −1.1)**			
Late peri, n = 141	310 (300; 319)	304 (294; 315)	−1.5 (−3.8; 0.8)			
Maximum knee extension torque (Nm)						
Total sample, 193	155 (151; 160)	150 (145; 155)	**−2.6 (−4.5; −0.8)**	**<.001**	.810	.273
Early peri, n = 76	156 (149; 163)	149 (142; 157)	**−4.1 (−6.5; −1.6)**			
Late peri, n = 117	155 (148; 161)	151 (145; 157)	−1.6 (−4.2; 0.9)			
Vertical jumping height (cm)						
Total sample, n = 208	18.8 (18.3; 18.4)	18.2 (17.6; 18.8)	**−2.6 (−4.2; −1.1)**	**<.001**	.897	.241
Early peri, n = 83	18.9 (18.1; 19.8)	18.1 (17.3; 19.0)	**−3.9 (−6.3; −1.6)**			
Late peri, n = 125	18.7 (18.8; 19.3)	18.2 (17.6; 18.9)	**−2.2 (−4.2; −0.3)**			
Maximum walking speed (m/s)						
Total sample, n = 221	2.65 (2.55; 2.68)	2.63 (2.57; 2.69)	1.1 (−0.2; 2.40)	.656	.949	.420
Early peri, n = 87	2.62 (2.52; 2.73)	2.62 (2.53; 2.71)	0.1 (−1.5; 3.2)			
Late peri, n = 134	2.61 (2.53; 2.69)	2.64 (2.56; 2.71)	1.3 (−0.2; 2.9)			
Six-minute walking test (m)						
Total sample, n = 205	665 (656; 673)	667 (668; 686)	**2.1 (1.4; 2.7)**	**<.001**	.209	.178
Early peri, n = 81	672 (659; 686)	682 (667; 696)	**1.5 (0.4; 2.70)**			
Late peri, n = 124	657 (646; 668)	673 (661; 684)	**2.5 (1.6; 3.3)**			

Notes: CI = confidence interval. All analyses adjusted for the duration of hormonal therapy (HT) use. Values in bold indicate statistically significant results.

Table 3. Changes in Physical Performance During the Menopausal Transition (time) as a Function of Physical Activity (PA; groups)

	Time			ANOVA, *p* Values		
PA, Groups, *n*	Baseline, Mean (95% CI)	Post, Mean (95% CI)	Change, % (95% CI)	Time	Group	Time × Groups
Hand grip (N)				.16	**<.001**	**<.001**
Inactive, *n* = 31	290 (272; 309)	292 (279; 304)	3.9 (−2.0; 9.8)			
Low PA, *n* = 54	302 (288; 316)	294 (279; 310)	−1.9 (−5.3; 1.5)			
Medium PA, *n* = 104	318 (307; 329)	300 (288; 312)	**−5.6 (−7.9; −3.3)**			
High PA, *n* = 38	337 (320: 354)	345 (326; 365)	**3.4 (0.2; 6.7)**			
Maximum knee extension torque (Nm)				**<.001**	.190	.060
Inactive, *n* = 24	148 (135; 161)	141 (130; 153)	−2.6 (−9.7; 4.5)			
Low PA, *n* = 45	148 (138; 157)	149 (138; 158)	0.9 (−2.3; 4.1)			
Medium PA, *n* = 91	157 (150; 164)	152 (145; 159)	**−3.1 (−5.7; −0.5)**			
High PA, *n* = 30	166 (155: 177)	156 (144; 168)	**−6.0 (−9.6; −2.2)**			
Vertical jumping height (cm)				**.004**	**<.001**	**.003**
Inactive, *n* = 25	17.0 (15.7; 18.2)	17.2 (15.8;18.6)	−1.0 (−4.4; 6.4)			
Low PA, *n* = 49	18.4 (17.4; 19.3)	18.2 (17.1; 19.2)	−0.9 (−4.2; 2.2)			
Medium PA, *n* = 90	18.4 (17.7; 19.2)	17.6 (16.9; 18.4)	**−3.5 (−5.4; −1.6)**			
High PA, *n* = 36	21.5 (20.2: 22.8)	20.5 (19.1; 21.8)	**−4.0 (−7.4; −0.7)**			
Maximum walking speed (m/s)				.563	.226	.752
Inactive, *n* = 28	2.55 (2.38; 2.71)	2.59 (2.43; 2.76)	2.4 (−0.4; 5.3)			
Low PA, *n* = 52	2.61 (2.49; 2.73)	2.61 (2.51; 2.72)	0.9 (−1.7; 1.4)			
Medium PA, *n* = 100	2.58 (2.48; 2.68)	2.60 (2.51; 2.69)	1.2 (−0.9; 3.4)			
High PA, *n* = 38	2.77 (2.62: 2.92)	2.75 (2.61; 2.89)	0.3 (−2.4; 3.0)			
Six-minute walking test (m)				**<.001**	**<.001**	.150
Inactive, *n* = 25	641 (622; 660)	650 (635; 664)	1.4 (−0.6; 3.5)			
Low PA, *n* = 50	650 (635; 664)	664 (651; 677)	**2.3 (1.1; 3.5)**			
Medium PA, *n* = 93	660 (648; 673)	678 (663; 692)	**2.6 (1.5; 3.7)**			
High PA, *n* = 34	707 (685: 728)	709 (688; 730)	0.8 (−0.8; 2.5)			

Notes: CI = confidence interval. All analyses adjusted for the duration of hormonal therapy (HT) use. Values in bold indicate statistically significant results.

significantly improved at postmenopause. When analyzing the early and late perimenopausal groups separately, the decline in muscle strength was significant only in the early perimenopausal group, whereas in muscle power, both groups showed a significant decline during the menopausal transition. Women reporting a high level of PA showed a significant increase in handgrip strength but a greater decline in lower limb muscle strength and power than the medium, low, or inactive physically active women following the menopausal transition.

Although differences between pre- and postmenopausal women in muscle strength and power have been observed in cross-sectional studies (8,10), only a few longitudinal studies have investigated changes in physical performance during the menopausal transition (14,15). These studies showed a decline in handgrip strength in women transitioning from pre- to postmenopause over 3 and 5 years. The one study that provided measurements for components of physical performance other than grip strength found a nonsignificant postmenopausal decline in lower limb muscle strength but a significant decline in preferred walking speed and sit-to-stand time (15), contrary to our findings. Our study showed a significant decline in both lower limb muscle strength and power and no change or even an improvement in walking parameters.

The decline observed in muscle strength and power can most likely be attributed to wide-ranging alterations in hormones related to the menopausal transition. A meta-analysis showed that women using estrogen or combined estrogen-progesterone therapy displayed better muscle strength than those not using these therapies (26). This suggests that female steroids play an important role in muscle function. Estrogen receptors are expressed at multiple sites along the neuromuscular system (27), and thus estrogen may act in preserving of muscle mass and quality, for example, through apoptotic pathways (6) as well as through neural factors involved in muscle strength generation, such as neural drive and motor coordination (27). Our recent study with the ERMA participants showed mean appendicular muscle mass to be 4% lower in the postmenopausal than premenopausal women (11), suggesting that a loss of muscle mass around menopause may be one of the reasons for the decline in muscle strength.

The present analysis also showed a 2%–4% decline in muscle power that was significant in both early and late perimenopaual groups. Maintenance of muscle power is a crucial factor for functional independence and may be more important than muscle strength for active participation in daily activities (28). As power generation is based on muscle force and contraction velocity, both can be influenced by the menopausal transition. One of the candidates for the decline in muscle power is a mechanism in the central nervous system that governs the speed of motor unit recruitment. It has recently been demonstrated that rapid force development depends on the speed of recruitment and rate of discharge of motor neurons (29). There is also evidence that in the early follicular phase, when estrogen is low in comparison to the high-estrogen phases, motor unit discharge rates (30) and voluntary activation (31) are lower. These may be indicative of changes in excitability in the central nervous system during the menopausal transition.

Performance in walking speed and distance travelled in 6 minutes were not affected by the menopausal transition. In fact, we even saw an improvement in distance travelled during 6 minutes. Supporting our findings, the Montreal-Ottawa New Emerging Team (MONET) study found no changes in maximal oxygen consumption during the menopausal transition (32). In another study, however, postmenopausal women showed reduced exercise tolerance and impairment in maximal aerobic function as compared with age-matched premenopausal women (33). The improvement in walking distance, observed in our study, may be related to motivational factors. For healthy middle-aged women, the test is clearly submaximal as, unlike running or performing maximal strength and power measurements, it does not require maximum effort. This may give participants some latitude for improvement, especially if they remember their baseline results. On the other hand, there could also be a ceiling effect which may obscure discrimination in the functional performance between the 2 time points.

It is difficult to explicitly speculate the clinical relevance of our findings. Only very few studies have investigated the rate of the decline in muscle strength and the clinical outcomes and none, on our knowledge, among middle-aged women. One study among women aged >65 reported a 3-year decline of 1 kg in knee extension strength among those who developed incident mobility disability and that of 0.6 kg among those who did not (34). We observed an average decline of 0.7 kg among early perimenopausal group already after a relative short (an average of 1.5 years) follow-up period. This indicates that the rate of decline in muscle strength and power observed during the menopausal transition needs to be further investigated as a clinical sign in physical functioning decline.

Physical activity has been shown to be an independent determinant of physical performance in middle-aged women (18,35). For handgrip strength, women with high PA showed an increase in performance, whereas for lower limb strength and power we observed that women with a high PA level showed a greater rate of decline than those with a lower PA levels during the menopausal transition. In handgrip strength, the women with a medium PA level showed the highest rate of decline. Although the greater decline in lower limb strength and power among high physically active women may be due to regression toward the mean, this may also invite speculation as to whether the menopausal transition has a greater effect on women with high PA than women with low PA. Exercise intervention studies with predominantly postmenopausal women have shown that exercise is associated with a lower estrogen level (36), and thus women with high PA may show a greater decline in their hormonal level during the menopausal transition; this in turn may negatively affect muscle strength. In one study, women with moderate PA had a higher estradiol level than woman with low or high PA, suggesting a U-shaped relation between estrogen and PA (37). It is thus possible that high PA may disrupt the hormonal profile in perimenopausal women, especially when exercise is associated with low energy intake (38). This raises the question of the optimal dosage and timing of PA for women with diverse histories of PA during the menopausal transition.

Although we assumed that changes in serum sex steroids drive the changes in muscle strength, we did not observe significant correlations between changes in 17β-estradiol and FSH and changes in physical performance. Previous studies on this relationship have predominantly investigated postmenopausal women using HT (24,35,36). These studies reported conflicting results due to diversity in the type, dose, and duration of the exogenous hormones prescribed. The menopausal transition is a time of instability in several hormones (eg, FSH, estradiol, inhibin, progesterone), and thus it may be that no single hormonal change explains the decline in muscle strength.

This study has its limitations. Since our study did not include premenopausal women, our sample comprised women with a relatively short menopausal transition time (mean time to menopause of only 1.3 years during the follow-up). Despite the series of FSH measurements some women may have been categorized as postmenopausal too early due to fluctuations in hormone levels during the menopausal transition and due to the requirement of no menstrual bleeding over 6 months.

Physical activity may have changed during the follow-up and thus it may have differently influenced participants' physical performance. In the present study and with the methods used we could not track precisely at which point and for how long time during the follow-up our participants may have changed their level of PA. Therefore, the only baseline PA level was used in the models and PA during the follow-up period was not included in the models.

Moreover, PA was self-reported and included only leisure-time PA. This excludes occupational activities and may also exclude occasional light- and moderate-intensity PA. Self-reports are also subject to response bias. However, self-reported information on leisure PA may be more reliable than, for example, accelerometer-based measurements. The PA levels captured by our questionnaire have shown not especially high, but statistically significant correlations with accelerometer-measured moderate-to-vigorous leisure-time PA and both correlated equally with the physical performance measurements (22). Our analysis was limited to healthy and nonseverely obese participants, a choice which restricts the generalizability of the results to other populations.

Among the strengths of the study is the longitudinal follow-up design and that we were able to comprehensively investigate changes in physical performance across different habitual PA levels during the menopausal transition. This study is a part of a large cohort study that, applying careful characterizations of menopausal status, is designed to capture changes that occur in women during menopause. The narrow age range of the present participants rendered the effect of chronological aging on physical performance minor in comparison with the effect of reproductive aging. Furthermore, our study employed comprehensive measurements of physical performance to capture different dimensions of strength (dynamic, isometric, endurance, power) which may vary according to the underlying physiology and be differentially influenced by changes in hormonal status.

Conclusions

The results of this longitudinal study showed that both early and late perimenopausal women show declines in physical performance during the transition to postmenopause. The decline is more pronounced for muscle strength and power than for walking performance. While women with high PA showed an increase in handgrip strength after the menopausal transition, they showed a greater decline than the medium, low, or inactive physically active groups in lower limb muscle strength and muscle power. Interventional studies are needed to establish whether PA benefits women during the menopausal transition.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

Funding

This study was supported by funding from the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement (PANINI No. 675003, S.S.); from the Academy of Finland (grant 275323 to V.K., grant 309504 to E.K.L.); and from the Ministry of Education and Culture of Finland (OKM/49/626/2017, OKM/72/626/2018, OKM/92/626/2019, K.K.).

Conflict of Interest

None declared.

Acknowledgments

The authors thank all the ERMA study participants and the staff members of the Faculty of Sport and Health Sciences who helped with the study.

Author Contributions

D.B., the corresponding author, compiled, analyzed, and interpreted the data and drafted the original manuscript. S.S., T.F., U.M.K., P.A., E.K.L., V.K., and K.K. designed, conceived, and supervised the entire study; S.S., V.K., and E.K.L. planned the ERMA study and obtained funding, P.A. was responsible for the gynecological data, and U.M.K. for the medical examination. All authors participated in the revision of the manuscript and read and approved the final version.

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IV

ASSOCIATIONS OF PHYSICAL PERFORMANCE AND PHYSICAL ACTIVITY WITH MENTAL WELL-BEING IN MIDDLE-AGED WOMEN

by

Bondarev D, Sipilä S, Finni T, Kujala U. M, Aukee P, Kovanen V, Laakkonen E. K, Kokko K. 2021.

BMC Public Health 21, 1448

DOI: 10.1186/s12889-021-11485-2

Bondarev et al. BMC Public Health (2021) 21:1448
https://doi.org/10.1186/s12889-021-11485-2

BMC Public Health

RESEARCH ARTICLE Open Access

Associations of physical performance and physical activity with mental well-being in middle-aged women

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Abstract

Background: To investigate whether physical performance is independently of physical activity (PA) associated with positive and negative dimensions of mental well-being in middle-aged women.

Methods: Data were drawn from the Estrogenic Regulation of Muscle Apoptosis (ERMA) study in which women 47 to 55 years were randomly selected from the Finnish National Registry. They ($n = 909$) participated in measurements of physical performance (handgrip force, knee extension force, vertical jumping height, maximal walking speed, and six-minute walking distance). Both mental well-being (the Centre for Epidemiologic Studies Depression Scale, the International Positive and Negative Affect Schedule Short Form and the Satisfaction with Life Scale) and PA were self-reported. Associations between variables were analysed using multivariate linear regression modelling adjusted for body height, fat mass %, menopausal status and symptoms, marital status, parity, employment status, self-reported mental disorders, and use of psycholeptics and psychoanaleptics. PA was then entered into a separate model to explore its role in the associations.

Results: In the adjusted models, significant positive associations of six-minute walking distance with positive affectivity ($B = 0.12$, $p = 0.002$) and life satisfaction ($B = 0.15$, $p = 0.033$) were observed. No significant associations were observed between physical performance and depressive symptoms or negative affectivity. PA was positively associated with positive affectivity and life satisfaction and negatively with depressive symptoms across all the physical performance variables.

Conclusions: Of the physical performance dimensions, aerobic component was associated with positive mental well-being independently of PA level. In relation to other physical performance components, the results point to the benefits of physical activity for mental well-being.

Keywords: Depressive symptoms, Life satisfaction, Negative affectivity, Positive affectivity, Physical performance, Middle-age women, Aerobic capacity

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Background

Mental well-being is a multidimensional construct with positive dimensions, such as general satisfaction with life and positive affectivity, and with negative dimensions such as mental distress and negative affectivity [1]. Higher mental well-being is associated with better health outcomes (e.g., fewer incidents of coronary heart diseases) and longer life expectancy [2, 3]. Although mental well-being has been shown to be relatively stable across the adult years [4], midlife is considered a life transition point at which the cumulative influence of several factors, including menopausal-related hormonal changes or personal life events, may influence mental well-being [5, 6].

Age-associated decline in physical functioning that results in mobility limitations or disabilities among older people [7] may also be related to low mental well-being [8]. It has been shown that women who transitioned through perimenopause to postmenopause had a decline in muscle strength and muscle power on average by 2–3%, which may suggest that the decline in physical functioning accelerates already during midlife [9, 10]. However, the physical performance of more physically active middle-aged women is greater than that of less physically active peers [11]. Since physical activity in middle-aged women is beneficially associated with both positive mental well-being [12, 13] and greater physical performance, mental well-being may also be higher in better physically performing middle-aged women.

Physical performance and physical activity have a close functional relationship. Despite considerable individual differences in the response to regular physical activity, in general, the higher the intensity and amount of physical activity, the better the physical performance [14]. However, the possible influence of physical performance and physical activity on mental well-being may stem from different sources. Physical activity may be linked to well-being through neurobiological (e.g., release of opioids), psychological (e.g., sense of mastery or emotions) or behavioural mechanisms (e.g., health-related behaviour) [15, 16]. Physical performance, in turn, acts as a mechanism in the relationship between physical activity and well-being [17] and may partially be a product of genetics or the amount of physical activity or other life-style choices. A meta-analysis of intervention studies on the link between physical activity and mental well-being showed that, at advanced ages, an improvement in physical performance induced by exercise interventions is related to improved well-being [18]. However, it has not been fully verified whether the level of physical performance plays a role in mental well-being. As middle adulthood in women coincides with a spontaneous reduction in physical activity that may be related to menopause-associated hormonal deficiency [19] and key personal life events [5], it would be useful to further investigate the independent role of physical performance in mental well-being for middle-aged women.

Thus, the aim of this study was to investigate whether physical performance – independent of physical activity – is associated with positive and negative dimensions of mental well-being, utilising a comprehensive set of physical performance measurements.

Methods

Study design and participants

This study is a part of the Estrogenic Regulation of Muscle Apoptosis (ERMA) study. The ERMA study is a population-based cohort study which consists of the data from women aged 47 to 55 years living in the city of Jyväskylä or neighbouring municipalities in Finland. A detailed description of participant recruitment has been reported earlier [20]. Briefly, an invitation to participate in the study was sent to 6878 women randomly selected from the Finnish National Registry (Fig. 1). Exclusion criteria were a self-reported body mass index (BMI) greater than 35 kg/m^2, pregnant women or lactating, medical conditions affecting ovarian function (e.g., bilateral ovariectomy, estrogen-containing hormonal preparations), or chronic diseases or medications that may significantly affect muscle function. Among the included participants, 2% reported use of psycholeptics and 7% use of psychoanaleptics medication. Their health status was followed by study physician and they were allowed to participate in the study.

Eligible participants ($n = 1627$) were assessed fasting blood samples in our laboratory and filled in the health screen questionnaire ($n = 1393$). Participants who had reported serious or unclear health conditions were examined by a physician to ensure safe participation in the physical performance measurements. The present analysis concerns women who performed at least one of the physical performance measurements acceptably and completed at least one mental well-being measurement ($n = 909$).

All participants gave their written informed consent. The study protocol followed good clinical and scientific practice and the Declaration of Helsinki and was approved by the Ethics Committee of the Central Finland Health Care District (K-SSHP Dnro 8 U/2014).

Physical performance

A detailed description of the measurement of physical performance – handgrip and knee extension force, low body muscle power, maximum walking speed and aerobic capacity – has been given earlier [11]. Briefly, *handgrip* and *maximal isometric knee extension forces* were measured in Newtons. Handgrip force was measured on the side of the dominant hand with the participant seated in an adjustable dynamometer chair (Good

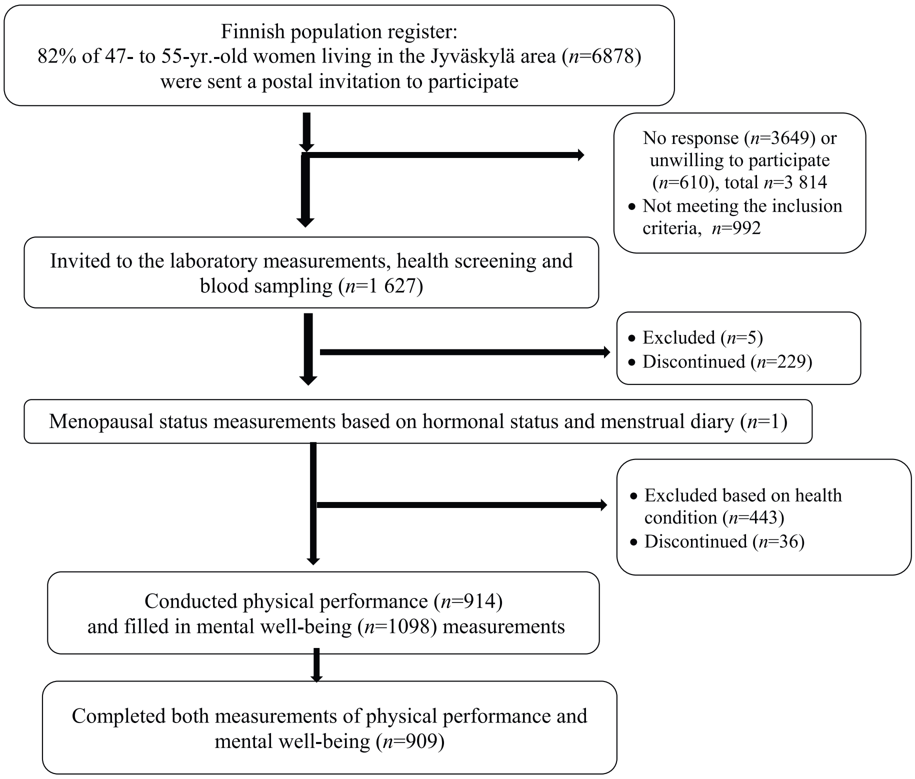

Fig. 1 Enrolment of study participants

Strength, Metitur, Palokka, Finland) with elbow flexed at 90°. The participants were instructed to squeeze the handle for 2–3 s to produce maximum force. Knee extension force was measured with the same dynamometer chair with a knee angle set at 60° from full extension. Participants were encouraged to extend the knee to produce maximal force.

Lower body muscle power was assessed by a vertical jump on a contact mat. Vertical jumping height was calculated in cm from flight time (t): $(g \times t^2) \div 8 \times 100$.

In all the above tests, three to five maximal attempts were performed and the best performance was taken as the result.

Maximum walking speed was measured over 10 m with the instruction to walk "as fast as possible" and timed with photocells. The fastest time of two trials, with self-selected rest of 30–60 s between trials, was taken as the result.

Aerobic capacity was assessed with the help of the six-minute walking test. The test was performed on a 20-m indoor track, and participants were encouraged to complete as many laps as they could within 6 min. The distance covered in meters was used in the analysis.

Mental well-being

Depressive symptoms were measured with the 20-item Center for Epidemiological Studies Depression Scale (CES-D [21]). Participants were asked to indicate how often they experienced each symptom over the past week. Each item was scored from 0 = seldom or never to 3 = almost all the time; a mean score for the 20 items was computed. Lower scores corresponded to lower depressive symptomatology.

The International Positive and Negative Affect Schedule Short Form (I-PANAS-SF [22]) was used to measure *positive and negative affectivity.* This inventory comprises five positive affect adjectives and five negative affect adjectives. Participants rated each of these adjectives on a scale from 1 = does not describe me to 5 = describes me very well. Average scores ranging from 1 to 5 were computed for each affective subscale, with lower scores indicating a lower degree to experience positive or negative affectivity.

Life satisfaction was measured with the 5-item Satisfaction with Life Scale which intended to evaluate global cognitive judgments of one's life satisfaction [23]. Participants indicated the degree to which they agree or disagree with each of the 5 items on a scale ranging from 1 = strongly disagree to 7 = strongly agree. The mean score of the scale for the five items was computed, with lower scores corresponding to lower satisfaction with life.

Physical activity

Level of leisure physical activity was measured on a seven-point scale assessing physical activity patterns from household duties, leisure-time physical activity to competitive sports. The PA questionnaire has been described previously and has been validated in middle-aged women [24]. Briefly, the response categories were: 1 = inactive, 2 = light activity 1 to 2 times per week, 3 = light activity several times per week, 4 = moderate activity 1 to 2 times per week, 5 = moderate activity several times per week, 6 = high activity several times per week, and 7 = competitive sports and related training several times per week. The seven response categories were recoded to form three levels of PA: *low* (categories 1 and 2), medium (3 and 4), and *high* (5 and 7), that were used as a variable for the analysis.

Background and adjusted variables

Age was calculated from date of birth to the date of the first laboratory visit. *Level of education* was measured with a single question and responces were grouped as primary (primary school), secondary (secondary school) and tertiary (applied science or bachelor's degree, nurse training, master's degree or PhD).

Body height was measured in meters by a stadiometer. *Body mass* was measured in kilograms with a digital scale with the participant wearing undergarments only.

Body fat was measured in percentage of body weight with a multifrequency bioelectrical impedance analyser (InBodyTM 720; Biospace, Seoul, Korea).

Menopausal status was measured based on monthly self-reported bleeding patterns and serum follicle stimulating hormone (FSH) concentrations according to the Stages of Reproductive Aging Workshop (STRAW) recommendations [25]. FSH measurements were conducted from fasting serum samples which were collected between 8:00 and 10:00 AM. For women in their menstrual cycle, the collection was performed during cycle days 1 to 5. For serum separation, a centrifugation of the blood samples was applied for 10 min at 2.200x g. Systemic FSH was measured using solid-phase, enzyme-labeled chemiluminescent competitive immunoassay (IMMULITE 2000 XPi, Siemens Healthcare Diagnostics, UK).

A detailed description of the categorisation by menopausal status has been reported previously [20]. Briefly, participants' menopausal status was characterised as *premenopausal* if they reported a regular menstrual cycle and had FSH values < 17 IU/L (M = 7.72, SD = 3.50); as *early perimenopausal* if they had FSH values from 17 to below 25 IU/L or if they reported an irregular menstrual cycle and had FSH values > 9.5 IU/L (M = 16.76, SD = 4.77); as *late perimenopausal* if they had FSH values in the range more or equal to 25 to 30 IU/L or if they reported occasional menstrual bleeding during the past 3 months and had FSH values > 30 IU/L (M = 44.90, SD = 19.96); and as *postmenopausal* if they reported no menstrual bleeding during the past 6 months and had FSH values > 30 IU/L or reported no menstrual bleeding during the past 3 months and had FSH values> 39 IU/L (M = 82.48, SD = 28.82).

Menopausal symptoms were assessed with a structured questionnaire to determine whether participants had any symptoms associated with menopause, such as: sweating, hot flashes, sleeping problems, headache, joint pain, tiredness, mood swings, vaginal symptoms, urinary track problems, sexual problems, or any other symptoms. For the present analysis, responses were recoded into a dichotomous variable (menopausal symptoms/no menopausal symptoms).

Marital status was assessed with the one question and responses were grouped as single, married or living with a partner, or divorced, separated or widowed. *Parity* was grouped as nulliparous, one or two children, and three or more children. *Employment status* was dichotomised as employed (paid or self-employed) or not regularly employed (study, unemployed, occasional job or retired). A diagnosed *mental disorder* was self-reported as yes/no. Information on the *use of medications* that could influence mental well-being (N05, psycholeptics and N06, psychoanaleptics) was self-reported and coded in accordance to the Anatomical Therapeutic Chemical Classification System [26]. The codes represent respective dichotomous variables – users or non-users.

Data analysis

Characteristics of the participants are shown as means and standard deviations or as percentages. Multiple regression analyses were employed to examine the association between the physical performance variables and dimensions of mental well-being. In model 1, regression models were adjusted for body height, fat mass percentage, menopausal status and symptoms, marital status, parity, employment status, self-reported mental disorders, use of psycholeptics and psychoanaleptics. In model 2, physical activity was added. These variables, deemed theoretically important, were justified based on our previous study with ERMA participants on various associations between physical activity, physical performance measurements, and mental well-being [11, 12]. All analyses were performed with R, version 3.3.3 and the package sjmisc [27]. *P*-values ≤0.05 were considered statistically significant. All categorical variables included in the adjustment were treated automatically as categorical variables in the regression analyses.

Results

The mean age of the participants was 51 (SD 2) years. More than half (56%) had secondary education and 42% had a tertiary degree (Table 1). Women were evenly distributed by their menopausal status. Most participants reported having experienced menopausal symptoms and

Table 1 Descriptive information on the participants

Variables	Total *n*	Mean (SD) or *n* (%)
Age, years	909	51.51 (2.05)
Education	898	
Primary		17 (2)
Secondary		506 (56)
Tertiary		375 (42)
Body height, m	908	1.62 (0.06)
Body mass, kg	908	69.73 (10.85)
Body fat mass, %	905	30.5 (7.48)
Menopausal status	909	
Premenopausal		232 (25)
Early perimenopausal		182 (21)
Late perimenopausal		197 (22)
Postmenopausal		298 (32)
Menopausal symptom (yes)	907	702 (77)
Marital status	906	
Single		79 (9)
Married or registered partnership		687 (76)
Divorced, separated or widowed		140 (15)
Parity	906	
Nulliparous		110 (12)
One or two		512 (55)
Three or more		284 (33)
Employment status	909	
Employed		808 (89)
Not regularly employed		101 (11)
Self-reported mental disorders (yes)	903	62 (7)
Users of psycholeptics (N05)	908	17 (2)
Users of psychoanaleptics (N06)	908	67 (7)
Physical activity level	909	
Low		159 (18)
Medium		570 (62)
High		180 (20)
Depressive symptoms, mean (SD)	908	0.46 (0.37)
Negative affect, mean (SD)	907	1.54 (0.50)
Positive affect, mean (SD)	908	3.78 (0.62)
Life satisfaction, mean (SD)	908	5.24 (1.07)
Hand grip strength, N	903	313.1 (59.6)
Knee extension strength, N	786	462.3 (94.6)
Vertical jumping height, m	813	0.19 (0.04)
Maximal walking speed (ms^{-1})	900	2.64 (0.46)
Six-minute walking distance (m)	835	669.1 (60.9)

Values given are n (%) for variables without units of measurement and mean (SD) for variables with units of measurement

were married or living in a registered partnership. More than half of the participants had one or two children and reported a medium level of physical activity. Nearly 90% were employed.

Depressive symptoms and negative affectivity

No significant associations between physical performance and depressive symptoms and negative affectivity were observed (Model 1, Tables 2 and 3). The results did not change after adding physical activity into the model (Model 2, Tables 2 and 3). However, physical activity showed a significant reverse association with depressive symptoms across all the physical performance predictors, indicating that, irrespective of physical performance, depressive symptoms were significantly lower in women with a self-reported medium or high physical activity level than in those with a low physical activity level. Physical activity was not significantly associated with negative affectivity.

Life satisfaction and positive affectivity

A significant positive association was observed between six-minute walking distance and life satisfaction (Model 1, Table 4). After adding physical activity into the model, this association remained significant (Model 2, Table 4). None of the other physical performance predictors were significantly associated with life satisfaction, although physical activity showed a significant positive association with life satisfaction for every physical performance predictor. This indicates that the physical performance of women with a medium or high physical activity level was also better than those with low physical activity.

Significant positive associations were observed between knee extension, vertical jumping height, maximal walking speed, six-minute walking distance and positive affectivity (Model 1, Table 5). When physical activity was added into the model, these associations were no longer significant, except for that between six-minute walking distance and positive affectivity (Model 2, Table 5). Similarly, with respect to life satisfaction, physical activity showed a significant positive association with positive affectivity across all the physical performance predictors. These results indicate that, independently, physical activity is significantly positively associated with positive affectivity. However, of the investigated physical performance predictors, only six-minute walking distance had an independent positive association with positive affectivity.

Discussion

The results showed that, among 47- to 55-year-old women, aerobic capacity (measured as six-minute walking distance) was, irrespective of physical activity, positively associated with life satisfaction and positive

Table 2 Associations of physical performance predictors with depressive symptoms

Predictors	Model 1			Model 2		
	B	*CI*	*p*	*B*	*CI*	*p*
Hand grip	0.03	−0.01 – 0.07	0.138	0.03	− 0.01 – 0.07	0.124
PA (medium level)[a]				−0.09	− 0.15 – − 0.03	**0.005**
PA (high level) [a]				− 0.14	−0.22 – − 0.06	**0.001**
Knee extension	−0.01	− 0.03 – 0.02	0.536	0.00	−0.03 – 0.03	0.950
PA (medium level) [a]				−0.09	− 0.16 – − 0.02	**0.011**
PA (high level) [a]				−0.16	−0.24 – − 0.08	**0.001**
Vertical jumping height	−0.16	− 0.85 – 0.52	0.639	0.02	−0.68 – 0.71	0.960
PA (medium level) [a]				−0.11	−0.18 – − 0.05	**0.001**
PA (high level) [a]				−0.15	−0.24 – − 0.07	**< 0.001**
Maximal walking speed	0.03	−0.02 – 0.08	0.256	0.04	−0.02 – 0.09	0.168
PA (medium level) [a]				−0.10	− 0.16 – − 0.03	**0.002**
PA (high level) [a]				−0.14	−0.22 – − 0.07	**< 0.001**
Six-minute walking distance	0.01	−0.04 – 0.05	0.735	0.02	−0.03 – 0.07	0.395
PA (medium level)[a]				−0.08	− 0.14 – − 0.01	**0.021**
PA (high level) [a]				−0.14	−0.22 – − 0.06	**0.001**

Model 1 adjusted for body height, fat mass %, menopausal status and symptoms, marital status, parity, employment status, self-reported mental disorders, use of psycholeptics, use of psychoanaleptics
Model 2 = Model 1+ physical activity
B unstandardised coefficients, *PA* physical activity
Values in bold indicate statistically significant results
[a]reference category is low physical activity level

Table 3 Associations of physical performance predictors with negative affectivity

Predictors	Model 1			Model 2		
	B	*CI*	*p*	*B*	*CI*	*p*
Hand grip	−0.00	− 0.06 – 0.05	0.902	− 0.00	− 0.06 – 0.05	0.903
PA (medium level)[a]				−0.01	−0.10 – 0.08	0.870
PA (high level) [a]				0.01	−0.10 – 0.12	0.857
Knee extension	−0.03	−0.06 – 0.01	0.148	−0.03	− 0.07 – 0.01	0.133
PA (medium level)[a]				−0.02	−0.11 – 0.08	0.764
PA (high level) [a]				0.00	−0.12 – 0.12	0.867
Vertical jumping height	−0.58	−1.55 – 0.40	0.245	−0.64	−1.64 – 0.35	0.207
PA (medium level)[a]				−0.01	− 0.10 – 0.09	0.898
PA (high level) [a]				0.02	−0.09 – 0.14	0.693
Maximal walking speed	−0.01	−0.09 – 0.06	0.745	−0.01	− 0.09 – 0.06	0.733
PA (medium level)[a]				0.00	−0.09 – 0.09	0.980
PA (high level) [a]				0.02	−0.09 – 0.13	0.765
Six-minute walking distance	−0.00	−0.07 – 0.06	0.920	−0.00	− 0.07 – 0.06	0.899
PA (medium level)[a]				−0.00	−0.10 – 0.09	0.966
PA (high level) [a]				0.01	−0.11 – 0.13	0.876

Model 1 adjusted for height, fat mass %, menopausal status and symptoms, marital status, parity, employment status, self-reported mental disorders, use of psycholeptics, use of psychoanaleptics
Model 2 = Model 1+ Physical activity
B unstandardised coefficients, *PA* physical activity
Values in bold indicate statistically significant results
[a]reference category is low physical activity level

Table 4 Associations of physical performance predictors with life satisfaction

Predictors	Model 1			Model 2		
	B	*CI*	*p*	*B*	*CI*	*p*
Hand grip	−0.03	− 0.14 – 0.09	0.664	− 0.03	−0.14 – 0.08	0.615
PA (medium level)[a]				0.36	0.18–0.54	**< 0.001**
PA (high level) [a]				0.51	0.29–0.73	**< 0.001**
Knee extension	0.06	−0.02 – 0.13	0.149	0.03	−0.05 – 0.11	0.449
PA (medium level)[a]				0.37	0.18–0.57	**< 0.001**
PA (high level) [a]				0.58	0.34–0.81	**< 0.001**
Vertical jumping height	0.57	−1.48 – 2.62	0.587	−0.12	−2.19 – 1.95	0.909
PA (medium level)[a]				0.40	0.21–0.59	**< 0.001**
PA (high level) [a]				0.57	0.33–0.81	**< 0.001**
Maximal walking speed	0.10	−0.05 – 0.25	0.194	0.08	−0.07 – 0.23	0.312
PA (medium level)[a]				0.36	0.18–0.54	**< 0.001**
PA (high level) [a]				0.52	0.29–0.74	**< 0.001**
Six-minute walking distance	0.19	0.05–0.32	**0.006**	0.15	0.01–0.28	**0.033**
PA (medium level)[a]				0.28	0.09–0.47	**0.004**
PA (high level) [a]				0.47	0.23–0.71	**< 0.001**

Model 1 adjusted for height, fat mass %, menopausal status and symptoms, marital status, parity, employment status, self-reported mental disorders, use of psycholeptics, use of psychoanaleptics
Model 2 = Model 1+ Physical activity
B unstandardised coefficients, *PA* physical activity
Values in bold indicate statistically significant results
[a]reference category is low physical activity level

Table 5 Associations of physical performance predictors with positive affectivity

Predictors	Model 1			Model 2		
	B	*CI*	*p*	*B*	*CI*	*p*
Hand grip	−0.01	−0.08 – 0.06	0.849	−0.01	−0.08 – 0.06	0.793
PA (medium level)[a]				0.19	0.08–0.29	**0.001**
PA (high level) [a]				0.45	0.32–0.58	**< 0.001**
Knee extension	0.05	0.00–0.09	**0.041**	0.02	−0.02 – 0.07	0.366
PA (medium level)[a]				0.15	0.04–0.27	**0.007**
PA (high level) [a]				0.41	0.28–0.55	**< 0.001**
Vertical jumping height	1.23	0.03–2.44	**0.045**	0.51	−0.69 – 1.71	0.403
PA (medium level)[a]				0.19	0.08–0.30	**0.001**
PA (high level) [a]				0.44	0.30–0.58	**< 0.001**
Maximal walking speed	0.09	0.00–0.18	**0.046**	0.07	−0.02 – 0.16	0.105
PA (medium level)[a]				0.20	0.09–0.30	**< 0.001**
PA (high level) [a]				0.46	0.33–0.60	**< 0.001**
Six-minute walking distance	0.16	0.08–0.24	**< 0.001**	0.12	0.04–0.20	**0.002**
PA (medium level)[a]				0.14	0.03–0.26	**0.011**
PA (high level) [a]				0.41	0.28–0.55	**< 0.001**

Model 1 adjusted for height, fat mass %, menopausal status and symptoms, marital status, parity, employment status, self-reported mental disorders, use of psycholeptics, use of psychoanaleptics
Model 2 = Model 1+ Physical activity
B, unstandardised coefficients, *PA* physical activity
Values in bold indicate statistically significant results
[a]reference category is low physical activity level

affectivity. Physical activity in turn showed a stronger association with positive mental well-being than that of physical performance assessed by muscle strength, muscle power and maximal walking speed. Physical performance was not associated with negative dimensions of mental well-being such as negative affectivity or depressive symptoms, whereas physical activity was associated with fewer depressive symptoms.

Although modest, the association of aerobic capacity with positive mental well-being was not attenuated when physical activity was included in the model. Although the association between physical activity and positive affect has been well demonstrated [28], studies have predominantly assessed short-term effects of physical activity on positive affect (e.g. after exercise interventions). In addition, physical performance level, which may play a role in affective responses to exercise [29], has often been overlooked in this relationship. Our study extends these results and provides evidence that in addition to regular leisure physical activity, aerobic capacity may have unique importance for positive mental well-being.

The fitness hypothesis holds that the beneficial effect of physical activity is due to gains in fitness [17]. It may be that, through regular physical activity, positive affective states accumulate over time [30] in parallel with improvements in aerobic physical fitness. Mechanistically, one biological pathway via which aerobic capacity may enhance positive affect is the greater oxidative capacity that results from improved mitochondrial function and angiogenesis, which in turn increases microvascular density in the brain [31]. This prompts speculation regarding structural and functional changes in the brain related specifically to mood state. However, due to the correlational study design, the opposite or bidirectional association is equally possible. Women with higher positive affect may be more physically active and hence fitter or their greater aerobic physical fitness may enable them to be more physically active.

Our results partially support those of the FLAMENCO study (the Fitness League Against MENopause Cost), which found a positive association between aerobic fitness and positive affect among perimenopausal women [32]. However, the same study also reported significant associations of self-reported muscle strength and speed-agility with positive and negative affect and depressive symptoms. This discrepancy could be explained by differences in the assessment methods. In comparison with performance-based measurements, self-reported physical performance may be less sensitive in identifying minor deficits in functioning because middle-aged participants may not yet recognize them.

Midlife represents a specific phase of life during which a reduction in physical activity can be expected [5, 19]. This may cause (or be a consequence of) vulnerability in mental well-being. Among middle-aged women, higher physical activity was associated with higher positive well-being and lower depressive symptomatology [12]. Thus, greater aerobic capacity may be viewed as a unique resource that helps to attenuate the effects of a decline in physical activity on mental well-being in middle-aged women.

Although aerobic capacity can be relatively quickly improved [33], it must be acknowledged that some individuals may have a genetic predisposition to high aerobic capacity [14]. In addition, genotype may also modify the association between physical activity and improvement in aerobic capacity [34]. This, however, raises the practical question of how to deal with individuals who have low aerobic capacity. Are there inherent reasons (such as an underlying medical condition) for low cardiorespiratory capacity or is it caused by modifiable factors (e.g., life-style choices) and correctable? Thus, our finding on the independent association of aerobic capacity and positive mental well-being, although promising for middle-aged women, merits further research (including other types of measurement of aerobic capacity) to confirm the direction of the association and identify the factors underlying it. Furthermore, it would be important to investigate, preferably using longitudinal data, competing models, where, for example, physical performance and physical activity were, alternatively, set as mediators.

In our study, other components of physical performance (low body muscle strength, muscle power, walking speed) were also associated with positive affectivity. However, these associations were attenuated after adjustment for physical activity. This result points to the role of physical activity in this association and may support the "mastery hypothesis", according to which participation in physical activity may instil a sense of coherence and mastery resulting in increased positive affect [35, 36]. This sense of mastery may not necessarily require a high level of muscle strength or power, and it may also be a function of other socio-psychological factors of participation in physical activity [37].

Our study showed no associations between any of the physical performance measurements and either negative affect or depressive symptoms. Several systematic reviews, although not focusing on the concomitant role of physical activity, have shown that cardiorespiratory fitness associates with lower incidents of depression [38, 39]. We found that physical activity, not physical performance, was associated with fewer depressive symptoms. One recent study of women aged 45–69 years living in Singapore found that those with high depressive symptoms (CES-D $\geq$ 16) had lower handgrip strength and lower body muscle power (5 repeated chair stands) than those with no depressive symptoms [40]. Interestingly, the above-mentioned analysis was adjusted for physical activity, and hence may suggest that handgrip strength and lower extremity functioning are factors independent of a high level of depressive symptoms. We analysed the association between depressive symptoms and handgrip strength as continuous variables rather than the association high and low muscle strength groups. It is possible that the associations between the groups, which were formed by categorising the participants into two levels of depressive symptoms and two levels of handgrip strength, may have resulted in overestimation of the results.

The results indicate that the link between physical performance and depressive symptoms found in our participants may be explained by level of physical activity. If so, this suggests that the women in our study potentially derived social or psychological benefit from participation in physical activity even in the absence of a gain in muscle strength, power or walking speed. In support of this argument, previous studies have found that better physical health predicted physical activity in men but not in women, for whom the social context of physical activity may provide additional psychological benefit [41, 42]. However, the absence of sex differences in the performance vs. social benefits of physical activity has also been reported [43].

The main limitation of this study is the correlational analysis, which precluded us from drawing conclusions on causality. Another limitation is that physical activity was self-reported, and thus the number of highly physically active participants may have been overestimated [44]. Our study is limited to participants with BMI < 35 kg/m2. Obesity and menopausal factors may synergistically influence physical performance among obese middle-aged women [45]. Although, we controlled our analysis for menopausal status and fat mass percentage, our results may not be generalized to severely obese individuals.

Among the strengths of this study is the comprehensive measurement of physical performance in a large cohort study. Previous studies investigating the associations between physical performance and mental well-being outcomes have predominantly assessed aerobic fitness to the relative neglect of other components of physical performance. Moreover, they have largely explored the association between physical performance and depressive symptoms (i.e., the negative dimension of mental well-being). Our study extends previous research by including both positive as well as negative dimensions of mental well-being. We were also able to include confounders known to have associations with mental well-being or physical performance in middle-aged women, including menopausal status, which was carefully categorised using menstrual diaries and hormonal analysis following the STRAW+ 10 criteria, self-reported mental disorders and use of medications. Our study participants represent a homogeneous group of relatively healthy, non-severely obese women within a narrow age range, thereby reducing the possible influence of unobservable variables while also reducing the results to be generalised to more heterogeneous populations.

Conclusions

This study, conducted among middle-aged women, revealed a positive association between aerobic capacity and positive mental well-being independently of the level of physical activity, although when physical activity was included in the analysis, the associations of the other components of physical performance studied (i.e., low body muscle strength, muscle power, walking speed) with positive affectivity were attenuated. Moreover, physical performance was not associated with the negative dimensions of mental well-being; instead, physical activity showed a stronger negative association with depressive symptoms. Thus, given the important role of physical activity for mental well-being found in this study, aerobic capacity may be considered a unique resource for positive mental well-being. However, the results warrant additional research to confirm the direction of the association and identify the factors underlying it.

Abbreviations

PA: Physical Activity; FSH: Follicle Stimulating Hormone; ERMA: Estrogenic Regulation of Muscle Apoptosis; BMI: Body Mass Index; CES-D: Center for Epidemiological Studies Depression Scale; I-PANAS-SF: International Positive and Negative Affect Schedule Short Form; STRAW: Stages of Reproductive Aging Workshop; FLAMENCO: the Fitness League Against MENopause Cost

Acknowledgments

The authors thank all the ERMA study participants and the staff members of the Gerontology Research Center and Faculty of Sport and Health Sciences who helped with the study.

Authors' contributions

DB, the corresponding author, compiled, analysed and interpreted the data and drafted the original manuscript. SS, TF, UMK, PA, EKL, VK, KK designed, conceived and supervised the entire study; SS, VK, and EL planned the ERMA study and obtained funding, PA was responsible for the gynaecological data, UMK for the medical examination and KK for the psychological measurements. All authors participated in the revision of the manuscript and read and approved the final version.

Funding

This study was supported by funding from the European Union's Horizon 2020 research and innovation programme under a Marie Sklodowska-Curie grant agreement (PANINI No 675003 to Sarianna Sipilä), the Academy of Finland (grant 275323 to Vuokko Kovanen, grant 309504 to Eija K. Laakkonen) and the Ministry of Education and Culture of Finland (OKM/49/626/2017, OKM/72/626/2018, OKM/92/626/2019 to Katja Kokko).

Availability of data and materials

The dataset generated and analysed during the current study is not publicly available due to being confidential but is available from the PI of the project (Eija K. Laakkonen) on reasonable request.

Declarations

Ethics approval and consent to participate
The study protocol followed good clinical and scientific practice and the Declaration of Helsinki and was approved by the Ethics Committee of the Central Finland Health Care District (K-SSHP Dnro 8 U/2014). All participants provided a written informed consent.

Consent for publication
Not applicable.

Competing interests
None.

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Received: 8 July 2020 Accepted: 9 July 2021
Published online: 23 July 2021

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