Women's health in midlife - a person-centered approach in primary care

-effects on mental, somatic, and urogenital symptoms, and quality of life

Lena Rindner

Department of Public Health and Community Medicine

Institute of Medicine

Sahlgrenska Academy, University of Gothenburg

UNIVERSITY OF GOTHENBURG

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lena.rindner@vgregion.se

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Department of Public Health and Community Medicine
Institute of Medicine
Sahlgrenska Academy, University of Gothenburg
Gothenburg, Sweden

ABSTRACT

Midlife women, from 45-60, enter new challenges in life with various impacts on health and quality of life. Mental and stress-related illnesses are common causes for attending primary health care (PHC) and long-term sick leave. Today there are few educational opportunities, support or care for life going through the natural ageing and topics related to this transition period, which often coincides with menopause transition (MT). The identification of the prevalence of symptoms, prognostic factors and evaluating interventions for preventing stress-related illnesses, long-term sick leave, improve quality of life, and gaining further knowledge, is motivated. The overall aim of the present thesis was to obtain knowledge about; I) prevalence and severity of somatic, urogenital and psychological symptoms measured with the Menopause Rating Scale (MRS), II) the effect of group education intervention based on topics related to menopause transition in midlife women with focus on somatic, urogenital, psychological and psycho-social health, III) prognostic factors for health-related quality of life and work ability, and IV) the effect of group education or person-centered individual support in PHC on mental health, quality of life and sick leave in women aged 45-60 with stress-related symptoms.

Study I
The aim was to estimate the prevalence of somatic, urogenital and psychological symptoms in women aged 45–55 attending PHC and evaluate factors associated with severe symptoms. One hundred and thirty-one women were included in this cross-sectional study. Data was obtained from two self-reported questionnaires, the MRS and the Montgomery-Asberg Depression Rating Scale (MADRS). The five most frequently reported MRS symptoms were; physical and mental exhaustion (73 %), depressive mood (66 %), sleep problems (66 %), hot flushes (66 %), and muscle, joint and sexual problems

(62 %). Moreover, more severe depression symptoms (MADRS) and increasing age were associated with more severe menopausal symptoms (MRS). A nomogram was constructed for assessing the probability for severity of menopause symptoms using these three factors.

Study II
This RCT, investigates whether group education about menopause transition to women in PHC can improve women's menopausal symptoms and mental health. Midlife women (n=131), aged 45-55 years, were randomized to group education (n=64) or no intervention (n=67). The group education included two sessions with topics related to menopause transition. The MRS and MADRS were filled in at baseline and four months later. Main outcomes were change in MRS and MADRS over the four months. The intervention group experienced a slight reduction in symptoms while the control group mostly experienced the opposite.

Study III
This 6-year longitudinal cohort study investigated prognostic factors for future mental, physical, and urogenital health, as well as work ability in a population of women aged 45–55 years. Sixty-five percent (n = 71/110) of the women included in Study I could be followed up at 6 years. Prognostic factors for later health-related quality of life (SF36), work ability (yes/no) and hypertension (yes/no) were analysed by multivariate regression analyses. Living with a partner was associated with a better chance for good health, and having tertiary education was shown to be associated with poorer mental health after six years.

Study IV
This RCT, with a two-factor design including 368 women, evaluated the effect of group education as well as person-centred support in a PHC context on mental health issues and quality of life in women aged 45-60 with stress-related symptoms. The women were allocated to four groups: 1, group education (GE) 2, GE and person-centered individual support (PCS) 3, PCS and 4, a control group. GE comprised four one and one half hour, weekly sessions, and PCS included five sessions with topics related to middle age, but adapted to the woman's individual situation and based on the woman´s narratives, needs, resources and beliefs. The effect of the interventions were followed up at 6 and 12 months after baseline.

Conclusion
This thesis has described and identified factors associated with the transition period in women between the ages of 45 and 60, identified prognostics factors for later work ability and quality of life, as well as positive effects on health-

related quality of life, physical, urogenital, and mental symptoms of a person-centered intervention using the district nurse's competence and assignment in PHC and an interdisciplinary collaboration with midwife.

Keywords
Menopause transition, menopause, women's health, mental health, urogenital health, quality of life, local oestrogen deficiency symptoms, stress, sleep, hypertension, vaginal dryness, social support, depression, mental illness, common mental disorders, district nurse, education, Menopause Rating Scale, primary health care, person centered care

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SAMMANFATTNING PÅ SVENSKA

Medelålders kvinnor, från 45–60, går in i nya utmaningar i livet och en period av stora bio-psykosociala förändringar med varierande inverkan på hälsa och livskvalitet. Psykiska och stressrelaterade sjukdomar är vanliga orsaker till besök i primärvården och långvarig sjukfrånvaro.
Idag finns det få utbildningsmöjligheter, stöd och behandling om det naturliga åldrandet och om ämnen relaterade till denna övergångsperiod, vilken ofta sammanfaller med klimakteriet. Identifiering av förekomst av symtom, prognostiska faktorer och utvärdering av insatser för att förebygga stressrelaterade sjukdomar och långvarig sjukfrånvaro och förbättra livskvaliteten är motiverande. Syftet med avhandlingen var att få kunskap om, I) prevalens och svårighetsgrad av somatiska, urogenitala och psykologiska symtom med frågeformuläret Menopause Rating Scale (MRS), II) effekten av grupputbildningsinsats baserat på ämnen relaterade till klimakteriet till kvinnor 45-55 år med fokus på somatisk, urogenital, psykologisk och psykosocial hälsa, III) prognostiska faktorer för hälsorelaterad livskvalitet och arbetsförmåga, och IV) effekten av grupputbildning och personcentrerat individuellt stöd i primärvården avseende mental hälsa, livskvalitet och sjukfrånvaro hos kvinnor i åldern 45–60 år med stressrelaterade symtom.

Studie I
Syftet var att uppskatta förekomsten av somatiska, urogenitala och psykologiska symtom hos kvinnor i åldrarna 45–55 i primärvården och utvärdera faktorer som är associerade med svåra symtom. I en tvärsnittsstudie inkluderades 131 kvinnor. Två självskattningsformulär användes, MRS och Montgomery-Asberg Depression Rating Scale (MADRS). De fem mest rapporterade MRS-symtomen var; fysisk och mental utmattning (73%), depressivt humör (66%), sömnproblem (66%), värmevallningar (66%), muskel- och ledproblem och sexuella problem (62%). Dessutom var allvarligare depressionssymtom (MADRS) och ökande ålder associerade med svårare menopausala symtom (MRS). Dessa tre faktorer användes för att konstruera ett nomogram för att bedöma sannolikheten för svårighetsgraden av klimakteriet.

Studie II
Syftet med studien var att undersöka om gruppundervisning om ämnen relaterade till klimakteriet för kvinnor i primärvården kan förbättra kvinnors menopausala symptom och minska depression. I en RCT-studie inkluderade totalt 131 kvinnor och randomiserades till gruppundervisning eller ingen intervention. Gruppinterventionen inkluderade två, 120 minuters utbildningssessioner med ämnen relaterade till klimakteriet. Två frågeformulär

MRS och MADRS besvarades vid baseline och fyra månader senare. Huvudresultat indikerade förändring i MRS- och MADRS-poäng efter fyra månader. Interventionsgruppen upplevde en liten minskning av symtomen, medan kontrollgruppen upplevde motsatsen.

Studie III
I en 6-årig longitudinell kohortstudie undersöktes prognostiska faktorer för framtida fysisk, urogenital och mental hälsa samt arbetsförmåga hos kvinnor 45–55 år. Sextiofem procent (n = 71/110) av kvinnorna som inkluderades i studie I kunde följas upp vid 6 år. Prognostiska faktorer för senare hälsorelaterad livskvalitet (SF36), arbetsförmåga (ja / nej) och hypertoni (ja / nej) analyserades med multivariabla regressionsanalyser. Studien indikerade att bo med en partner var förknippad med en bättre chans att ha god hälsa medan att ha högre utbildning visade sig vara förknippat med sämre mental hälsa efter 6 år.

Studie IV
I en RCT studie med en tvåfaktordesign inkluderade 368 kvinnor med syfte att utvärderade effekten av grupputbildning och individuellt personcentrerat stöd i primärvården på psykisk ohälsa och livskvalitet hos kvinnor i åldrarna 45–60 med stressrelaterade symtom. Kvinnorna fördelades i fyra grupper: 1), grupputbildning (GE) 2), GE och personcentrerat individuellt stöd (PCS) 3), PCS och 4), kontrollgrupp. GE bestod av fyra stycken en och en halv timmas sessioner och PCS inkluderade fem sessioner med ämnen relaterade till hälsan ”mitt i livet” som var anpassade till kvinnans individuella situation och baserat på kvinnans berättelser, behov, resurser och övertygelser. Effekten av interventionerna följdes upp 6 och 12 månader efter baseline.

Slutsats
Avhandlingen har beskrivit och identifierat faktorer associerade med övergångsåldern hos kvinnor mellan 45 och 60 år, identifierat prognostiska faktorer för senare arbetsförmåga och livskvalitet, samt visat positiva effekter på hälsorelaterad livskvalitet, fysisk, urogenital, och psykiska symtom av personcentrerat individuellt samtal där distriktssköterskans kompetens och hälsofrämjande uppdrag i primärvården används, samt ett interdisciplinärt samarbete med barnmorska.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals. Copyright belongs to the publisher or journals and are used with permission in this thesis.

I. Rindner L, Strömme G, Nordeman L, Wigren M, Hange D, Gunnarsson R, Rembeck G. Prevalence of somatic and urogenital symptoms as well as psychological health in women aged 45 to 55 attending primary health care: a cross-sectional study. BMC Womens Health. 2017 Dec 8;17 (1):128.

II. Rindner L, Strömme G, Nordeman L, Hange D, Gunnarsson R, Rembeck G**.** Reducing menopausal symptoms for women during the menopause transition using group education in a primary health care setting - a randomized controlled trial**.** Maturitas 2017 Apr:98: 14-19.

III. Rindner L, Nordeman L, Strömme G, Prembeck Å, Svenningsson I, Hange D, Gunnarsson R, Rembeck G. Prognostic factors for future mental, physical, and urogenital health and work ability in women, 45–55 years. A six-year prospective longitudinal cohort study. BMC Womens Health. 2020. 20:171.

IV. Rindner L, Nordeman L, Strömme G, Hange D, Gunnarsson R, Rembeck G. Effect of primary care education on mental health and quality of life in women 45-60 years with stress-related symptoms. A randomized controlled trial. (Manuscript)

CONTENTS

ABBREVIATIONS

AUC	Aera Under Curve
AUDIT	Alcohol Use Disorders Identification Test
CC	Complete Case
CG	Control group
CMD	Common mental disorders
CVD	Cardiovascular disease
DN	District Nurse
EMAS	European Menopause and Andropause Society
FMP	Final Menstrual Period
GE	Group Education
GI	Group Intervention
HADS	Hospital Anxiety and Depression Scale
HRQoL	Health Related Quality of Life
ICD-10	International statistical classification of diseases and related health problems
IQ	Inter Quartile Range
ITT	Intention-to-treat
LDL	Low Density Lipoprotein
LOD	Local oestrogen deficiency
MADRS	Montgomery-Asberg Depression Rating Scale
Md	Median
MHT	Menopause Hormone Therapy
MRS	Menopause Rating Scale
MT	Menopause Transition
MTE	Menopause Transition Education

OECD	Organisation for Economic Co-operation and Development
PCC	Person-centered care
PCS	Person-centered individual support
PHC	Primary health care
PP	Per-protocol
PSS-14	Perceived Stress Scale
QoL	Quality of Life
RCT	Randomized Controlled Trial
SD	Standard deviation
s-ED	Self-rated Exhaustion Disorder Scale
SF36	36-item Short Form Health Survey
PF	*Physical functioning*
RF	*Physical functioning*
GH	*General health*
SF	*Social functioning*
RE	*Role emotional*
VT	*Vitality*
MH	*Mental health*
PCS	*Physical component summary score comprising: PF, RP, BP, GH*
MCS	*Mental component summary score comprising: VT, SF, RE, MH*
SoS	The Swedish National Board of Health and Welfare
STRAW	The Stages of the Reproductive Aging Workshop
SWAN	Study of Women's Health Across the Nation
UI	Urinary incontinence
VAS	Visual analogue scale
VIF	Variance inflator factor
VMS	Vasomotor symptoms

WHO	World Health Organization

DEFINITIONS IN SHORT

Climacteric period	The period in life of natural ageing processes with hormonal changes from a reproductive to non-reproductive stage and is often used synonymously with peri-menopause.
Menopause	The last menstruation in a woman´s life and is known as the Final Menstrual Period (FMP), marked by the absence of menses for 12 months without a pathologic cause.
Menopause transition	A universal part of a natural ageing process in women's lives including a period of physiological changes. Defined as a period of about five years before and five years after the last menstruation, it marks the end of a woman's reproductive years including hormonal changes as well as bio-psycho-social changes.

MY JOURNEY

My interest in the subject awakened when I, in my clinical work as a district nurse in a primary health care centre, daily met women in midlife" with questions and thoughts about physical and mental symptoms. Many of these issues related to ageing and were natural changes in this phase of life, but gave rise to anxiety and ill health. The women did not feel ill but neither did they feel well, and did not know where to turn for care. I discovered a lack of response from health care to these women, and insufficient access to knowledge and information about this phase in their lives. I also discovered a lack of knowledge about care and treatment from a bio-psycho-social perspective for women 45-60.

Thoughts arose of a care unit providing information, discussions, and instruction such as schoolgirls receive about puberty, similar to my work as a school nurse. Starting something similar for women who have reached menopausal age could be beneficial, based on a bio-psycho-social approach. I was introduced to midwife Gunilla Strömme, who had similar thoughts about women's mental, urogenital, and somatic health in midlife and about illness prevention. To start a women's health clinic in PHC, we felt it necessary to confirm the need for such a clinic, which was the start of our research in this area: women's mental, urogenital and somatic health in midlife" from a bio-psycho-social perspective".

My interest in illness prevention and health promotion work is strong. The thesis evaluates the prevalence and prognostic factors as well as the effects of promoting health prevention and health factors in midlife by offering counselling, person-centered individual conversations, and education on topics related to menopause, based on a bio-psycho-social strategy for women 45-60 in primary care.

This thesis aims to improve knowledge about advice, support, and treatment for women 45-60 from a person-centered approach with a bio-psycho-social perspective, and with a health-promoting view of women's situations, mental, urogenital, somatic symptoms, and psychosocial health. Moreover, the aim was to improve women's quality of life and increase awareness of management strategies for mental, physical, urogenital, and psychosocial health.

Min resa

Intresset för ämnet väcktes när jag i mitt kliniska arbete som distriktssjuksköterska på vårdcentralen dagligen träffade kvinnor ”mitt-i-livet” med frågor och funderingar om fysiska och psykiska symtom, om förändringar i kroppen och om måendet. Många av dessa frågor tillhörde det naturliga åldrandet och var naturliga förändringar i denna fas i livet, men gav upphov till oro och ökad ohälsa för den enskilda kvinnan. Kvinnorna kände sig inte sjuka, men de kände sig inte heller bra och visste inte vart de skulle vända sig för att söka vård. Jag upptäckte bristande bemötande från vården och otillräcklig information om denna fas i livet. Jag upptäckte också att det fanns en kunskapsbrist om vård och behandling ur ett bio-psyko-socialt perspektiv till kvinnor i livsfasen 45–60 år.

Då kom tankarna om att det skulle finnas en mottagning på vårdcentralen där kvinnan får information, råd och stöd liknande den information som tonårstjejer får i skolan om pubertetsutveckling, likt den jag gav under mitt arbete som skolsköterska. Att starta något liknande för kvinnor som kommit i den ålder som ofta sammanfaller med klimakteriet kanske vore bra och utifrån ett bio-psyko-socialt perspektiv. Jag blev genom en genomsam kontakt presenterad för barnmorskan Gunilla Strömme. Hon hade liknande tankar som jag om hälsoförebyggande prevention för kvinnors somatiska, urogenitala och psykiska hälsa mitt-i-livet. För att starta en kvinnohälsomottagning på vårdcentralen behövde vi bekräfta behovet av en sådan mottagning och det blev starten för vår forskning inom detta område; ”Kvinnors somatiska, urogenitala och psykiska hälsa mitt-i-livet ur ett bio-psyko-socialt perspektiv”.

Mitt intresse för hälsoförebyggande och hälsofrämjande arbete är stort. Denna avhandling syftar till att förbättra kunskapen om råd, stöd och behandling för kvinnor 45–60 utifrån personcentrerad vård med ett bio-psyko-socialt perspektiv och med en helhetssyn på kvinnors situation, symtom och psykosociala hälsa. Genom att erbjuda grupputbildning och personcentrade individuella samtal utifrån ett bio-psyko-socialt förhållningsätt för kvinnor mitt-i-livet är förhoppningen att kunna förbättra livskvalitet, öka medvetenheten om copingstrategier och livsstil med positiv effekt på hälsan.

INTRODUCTION

Midlife is a natural phase in life, and a time of bio-psycho-social changes with major life events in a woman's life with various impacts on health (1, 2). From 45-60, women's physical and mental health show a marked decline (3-5) and long-term sickness, ill health and visits to primary health care (PHC) are more frequent than for men (6-10). Midlife often coincides with Menopause Transition (MT) which is a hormonal change in a woman's body and a period characterized by the ageing of the ovaries with a loss of function, and thus the end of fertility in women's lives (11, 12). Researchers have named the period as the "Window of vulnerability" (13).

Women's health in midlife

Women, 45-60 show an increased mental, physical, and urogenital illness in Sweden and in other OECD countries (1, 2, 14-18). Globally, depressive disorders account for close to 42% of mental disorders among women compared to 29% among men (19). About 85% of midlife women report at least one of the symptoms that usually indicate the presence of depressive disorders, vasomotor symptoms, or sleep disorders (15, 20, 21). Common mental disorders (CMD) such as depressive, anxiety and stress-related illnesses are common causes for women in midlife attending PHC, and risk for long-term sick-leave (22). Psychosocial factors have a strong impact on overall health, and many life events can influence and impact changes in personal and familiar relationships (1, 5, 15). Moreover, the history of impact life stressors, lifestyle and cultural traditions varies in the experience of symptoms (1, 16).

Prevalence of symptoms

About 60% of women 45 to 60 experience symptoms such as depression symptoms, cognitive symptoms, mental exhaustion, sleep problems, musculoskeletal pain, dry skin as well as hot flashes, night sweats, vaginal dryness, and loss of libido (1, 2, 21, 23-25). However, the prevalence of these symptoms vary globally.

Psycho-social health

Psycho-social changes of varying degrees occur during midlife. The changes often coincide with other changes in personal and social relationships such as caring for older parents, teenage children, or major life events such as parental death, children leaving home, or becoming grandparents (1, 15).

Personal attitudes to this period, a history of impacting life events, lifestyle and cultural factors will influence how this period of life is experienced (1). Psychosocial factors have shown to have a stronger connection to psychological symptoms than the stages of menopause (15).

Psychosocial factors around midlife show a strong association with psychological symptoms, mental health and impacting women's quality of life (5, 15, 16, 26, 27). Factors such as stressful life events, lifestyle, low social support, sleep problems, health problems, and relational problems can contribute to mental illness (5, 21).

Stress-related illness

For midlife women in Sweden severe stress-related illnesses such as exhaustion syndrome (ICD-10, F43.8A) and adjustment disorder (ICD-10, F43.2) are the most common mental disorders and cause of decreased quality of life (4, 9, 28, 29). The length of a stress load and the type of load are important to establish a diagnosis. Physical and mental symptoms preceded by a long period of stress exposure without adequate recovery and developed for at least six months are characterized by lack of mental energy, impaired function at work and social contexts. Mental symptoms such as difficulty concentrating, memory problems, difficulty coping with demands and time pressure, depression, anxiety, irritability, sleep disturbance, marked lack of energy and exhaustion are common. Moreover, physical symptoms such as pain, cardiovascular palpitations and gastrointestinal problems are also seen. If the stress load becomes prolonged, over six months, an adjustment disorder can turn into an exhaustion syndrome. Exhaustion syndrome is a consequence of prolonged stress without adequate recovery. These symptoms can occur in all mental illnesses, but fundamental to stress-related mental illness is a clear connection between external events and the patient's symptoms (30). Without external events, symptoms would not have occurred. Often the symptoms are natural reactions to external stresses. To avoid symptoms becoming long-lasting and worsening, many patients can be helped by problem-solving and short-term support (30).

Impact on work ability

Stress-related mental illness has a strong association with long-term sick leave for midlife women (9, 28, 29, 31, 32). Exhaustion syndrome (ICD-10, F43.8A) and adjustment disorder (ICD-10, F43.2) are the most common causes of long-term sick leave. Women have a 41 % higher risk to be affected by stress-related mental illness than men in Sweden (4, 33). After the age of 50 the risk for women being on sick leave increases, and then decreases after 60 (4). Adaptation disorders and stress reactions accounts for 66% of the increase in started sick leave in Sweden (4). Swedish women have a 25 % higher risk to go on sick leave than men, for psychiatric diagnoses the risk is 31 % higher, and for stress-related illness a 41% higher risk was seen (4, 33). Of the total number of women on sick leave, 31% are women 46-55 (4, 33). Women's share of total long-term sick leave over 90 days is 64 % (6). Long-term sick leave

increases at a faster rate among women, and the proportion of psychiatric illness diagnoses is increasing fastest (34).
It may be worthwhile to evaluate prognostic factors for health and work ability in a population of midlife women over time.

Health-Related Quality of Life

Quality of life according to the WHO is "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" (35). Quality of life is a subjective and broad concept including indicators of physical and mental health, level of education and employment, level of independence, access to recreation and leisure time, and social relationships (35).
Previous studies described the concept of health-related quality of life as a subjective perception as "the patient's evaluation of the impact of a health condition and its treatment on daily life" and "interferes with a woman's physical, emotional, social and material quality of life". Considering the concept of quality of life, health prevention should take into account the perception of the patient regarding severity of symptoms (35-37). Receiving social support, work ability, and balance in life are indicators of quality of life and associated with a higher quality of life and decreased risk of sick leave (3, 38-40). Psychosocial factors have a strong connection to quality of life in midlife when physiological and psychosocial changes of varying degrees occur (1, 15, 41).
To evaluate the women's health-related quality of life in midlife, the questionnaire Menopause Rating Scale (MRS) is one of the best age- and condition-specific health-related quality of life questionnaires (36, 42).

The transition

Transition is defined as a passage from one state of life to another such like puberty, pregnancy, becoming a parent, menopause or retiring (43, 44). A transition is an ongoing process and consists of a general structure of the changes that occur in three dimensions: *entry, passage and exit* (45). It can be defined as a process with changes in fundamental life patterns at personal and family levels, changes in identities, roles, relationships, abilities and patterns of behaviour (45, 46). During a transition, stress and anxiety can be experienced initially. Successful transition implies greater stability, indicating subjective wellbeing, the ability to cope with new roles, healthy relationships, and includes increased knowledge and new skills (43, 47). There are several factors that may impact the quality and consequences of the transitions such as attitudes, expectations, levels of knowledge, environment, mental and physical well-being (45). Therefore, these are important to understand and also awareness of the transition process in midlife and how it can impact life.

The menopause transition

The menopause transition (MT) is universal and part of a natural ageing process in women's lives including a period of physiological changes. The MT can be defined as going from "a reproductive phase to a non-reproductive" phase in life (12). Defined as a period of about five years before and five years after the last menstruation, it marks the end of a woman's reproductive years including hormonal changes as well as bio-psycho-social changes (2, 12, 16, 17). The transition between 45–60 can impact a woman's health in different ways (17). However, some women pass through this period with few or no symptoms, but for many women the transition is a troublesome time of life (23, 41, 48-50).

Menopause definition

Menopause is defined as the last menstruation in a woman´s life and is known as the Final Menstrual Period (FMP), marked by the absence of menses for 12 months without a pathologic cause (2, 11). FMP marks the cessation of the menstrual cycle and ovulation, and thus an end of fertility. This entails decreased oestrogen levels characterized by ovarian ageing and gradual loss of ovarian function (1, 2, 14, 15, 51). Women in developed countries usually live about a third of their lives after menopause.

The average age of menopause varies between countries from ages 47 to 51 (2, 23, 51). Mean age for entering menopause in Sweden is 51 (52). Smokers commonly enter menopause 2 years earlier than non-smokers.

Menopause can be divided into natural or induced menopause. The World Health Organization (WHO) described the natural menopause as "the permanent cessation of menstruation and loss of ovarian function activity".

Induced menopause implies the cessation of menstruation following surgery, for example, a hysterectomy or oophorectomy or by chemotherapy or radiation (12).
Menopause can be divided into premature and early menopause. Menopause before 45 is termed early menopause and menopause that occurs before 40 is termed premature menopause. Premature menopause means that ovarian failure occurs by natural or induced causes and affects 1% of women under 40 (53, 54).

Menopause transition stages and phases

To clarify the stages of the menopausal transition and female reproductive ageing the WHO and important international menopausal organizations have compiled classifications for female reproductive ageing and stages of menopause transition (12).
The Stages of Reproductive Ageing Workshop (STRAW +10) made a substantial contribution by means of a standardized seven-stage model describing the menopausal phases and reproductive status in healthy women (Figure 1) (2). This model STRAW +10, is now a recommended and standardized staging system criterion for defining the onset of each stage for the natural ageing of women (2).

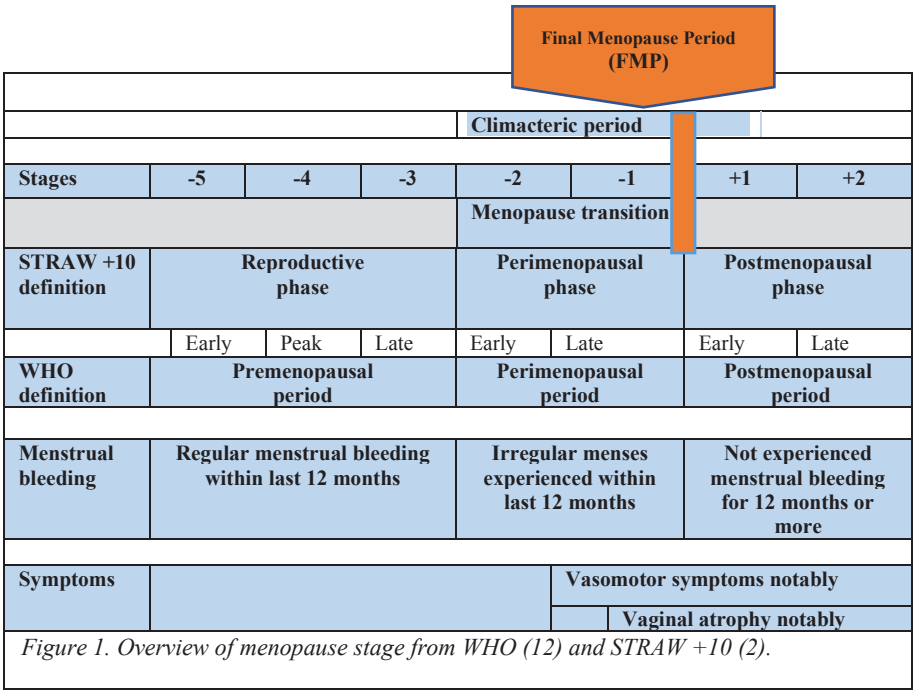

Figure 1. Overview of menopause stage from WHO (12) and STRAW +10 (2).

Reproductive period

The reproductive or premenopausal period, (Stages -5 to -3), comprise regular menstrual bleeding within the last 12 months (2, 12). In the late reproductive stage (Stage -3), when fertility begins to decline, changes and specifically shorter menstrual cycles are noticed (2).

Peri-menopause period

The perimenopausal or menopausal transition period: (Stages -2 to -1) comprise observation of irregular menses within the last 12 months, or the absence of menstrual bleeding for more than 3 but less than 12 months. The stage is divided by an early and late period. The early menopausal transition (Stage -2) is marked by increased changes in menstrual cycle length while the late menopausal transition (Stage -1) is indicated by the occurrence of amenorrhea of 60 days or longer. Most notable symptoms are vasomotor symptoms during this stage -2 to -1. "Peri-menopause" includes the time about five years before and after FMP (2).

Post-menopause period

The post-menopause period: (Stage +1 to +2), marks the end of the 12-month period of amenorrhea and is described as having not experienced menstrual bleeding for 12 months or more. Early post-menopause (Stage +1) included the 12 months after FMP and approximately lasts about 5 to 8 years after the FMP. Late post-menopause (Stage +2) continues throughout life. Vasomotor symptoms are noticeable during this stage and symptoms of vaginal atrophy become more increasingly prevalent (2).

Climacteric

Climacteric is the period in life of the natural ageing process with hormonal changes from a reproductive to non-reproductive stage, and the term is often used synonymously with peri-menopause (Figure 1) (12, 36).

Common signs and symptoms in midlife

The most globally prevalent reported symptoms during midlife causing reduction of the quality of life were mood changes, depressive symptoms, loss of energy, mental exhaustion, muscle and joint problems, dry skin, cardiovascular discomfort, sexual problems, sleep disturbances, urinary incontinence, and cognitive changes (1, 11, 15, 41, 55-57). These symptoms and conditions occurring in the age group 45–60 are not necessarily correlated to oestrogen levels and menopause but can be attributed to the menopause transition (11, 16). Of the women's reported symptoms and changes only vasomotor dysfunction and vaginal dryness were associated with hormonal changes due to decreased oestrogen levels and production (2, 58). Irregular bleeding, hot flashes and sweating, as well as symptoms due to dry mucous membranes have a clear connection to reduced levels of oestrogen menopause (59, 60). Women can experience various signs and symptoms due to decreasing oestrogen level protective effect and ageing (11).

Vasomotor symptoms

Vasomotor symptoms (VMS) affect about 70% of middle-aged women during peri-menopause and strongly impact physical, psychosocial, sleep and quality of life (16, 61). VMS remained longer than 7 years for more than half of the women and persisted 4.5 years after FMP (61). About 25-30% of women have severe symptoms starting well before FMP and continuing far into post-menopause (16). The symptoms could continue more than 10 years after FMP. More than 30 % experience moderate to severe hot flushes and seek treatment (36, 61).

Sleep

Sleep problems strongly affect quality of life and mental illness. The incidence of sleep disorders increased during and after menopause. About 40–60% perimenopausal and postmenopausal women reported greater sleep problems than premenopausal women. In late peri-menopause symptoms were most prevalent regardless of VMS (15). The prevalence of sleep problems greatly increases for women in midlife. Commonly reported problems were trouble falling asleep, disturbed sleep, and waking up early. Sleep disorders could affect duration, regularity, timing, and daytime sleep (16, 62, 63). Studies have not shown a direct physiological relationship or link between sleep problems and MT (15, 16). Other factors may contribute to poor sleep such as poor health and lifestyle, chronic pain, illness, mental disorders, and medication (15, 16, 64).

Muscle and joint pain

General stiffness and pain, including musculoskeletal, joint, and body pain, are commonly reported by women in menopause transition and increase during pre-menopause (65). Muscle and joint discomfort were, in a large mid-aged study, the most prevalent and severely rated symptoms, higher rated than vasomotor symptoms and appearing early in the pre-menopause (65). Muscle and joint discomfort impair quality of life and can persist 5 years beyond menopause. Women with depression and sleep problems have a greater risk for increased bodily pain (66).

Cardiovascular health

For women in midlife, the risk of incidence of cardiovascular disease (CVD) increases around menopause (57, 64, 67, 68). The protective effects of oestrogens have been suggested as a cause. Oestrogen levels change unfavourably for women after menopause with increased Low Density Lipoprotein (LDL) and decreased High Density Lipoproteins (HDL) (64, 69, 70). These changes contribute to a higher risk of CVD. Hypertension is an important risk factor for CVD and the onset often affects women in the early postmenopausal stage. The years around peri-menopause are accompanied by an increase in blood pressure and about 30 to 50% of women develop hypertension (>140/90 mmHg) before the age of 60 (71). Hence, it is important to increase women's awareness of cardiovascular risk factors (57, 68, 72).

Urogenital symptoms

Mid-life women with a prevalence of severe urogenital symptoms have a strong risk for decreased quality of life and mental illness during and after menopause transition (15).

Urinary incontinence

Urinary incontinence (UI) is often experienced during and after menopause transition (56). UI is defined as unintentional passing of urine when the bladder is under pressure, for example on physical exertion or when sneezing or coughing, and a sudden, intense urge to urinate followed by an involuntary loss of urine. UI is a common health problem especially in midlife women (56, 73). Nearly 50% of these women are affected by UI and the severity of leakage was shown to be related to a reduction in quality of life with a significant impact on women's physical and mental health (73, 74).

Vaginal atrophy and local oestrogen deficiency symptoms

Vaginal atrophy increased in MT, in pre- and early peri-menopause from 19% to 34% in the post-menopause stage and is a frequent symptom of postmenopausal women. Almost 50 % of all postmenopausal women have symptoms of local oestrogen deficiency (75). Symptoms of local oestrogen deficiency includes vaginal dryness, burning and pain during intercourse, itching, frequent urinary tract infections and urinary incontinence (76). It may cause sexual problems such as reduced sexual desire. However, changes in midlife women's daily lives, relationships and other above described stressors such as long-term stress may reduce sexual desire as well (5, 38, 76, 77).

Mental health

Mental health is the basis of our well-being, our health, and our ability to enjoy life and our ability to manage and solve life's ups and downs (19, 78, 79). Mental health means a life of value and not just the absence of illness or discomfort. The concept of mental health includes both good (positive) mental health and mental illness (negative) (5, 50). Good mental health is about being able to balance positive and negative emotions, to feel well and enjoy good social relationships. To master the various difficulties of life, good mental health is a basic resource (19, 79).

The dominating mental health problems for women is mental exhaustion with stress-related symptoms described earlier (5, 9, 13), depressive symptoms and anxiety. Depressive symptoms and anxiety are more common in late peri-menopause and post-menopause than in pre-menopause (1, 5, 13, 25, 80), also when adjusted for history of depression, poor sleep, and hot flushes (13, 80). Women with a history of depression have a 5 times higher risk for depression in peri-menopause (15). About 10 to 50 % of peri- and post-menopausal women reported mood changes (55). The menopausal transition is associated with an increased risk for new-onset depression and recurrence of previous depressive disorder (5). The risk for depression increases with age but a causal link between menopause and depression has not been clearly established (5, 13, 15, 17). Previous studies have shown that MHT can decrease depression symptoms in perimenopausal period (5, 25, 81, 82).

More than one in three women suffer from depression symptoms at some point in their lives (8, 10), and is a common reason for seeking PHC (6, 8, 9, 83). More than 70% of all patients with depression, anxiety or stress-related illness are treated in PHC and 20% are referred to a psychiatric specialist (7, 8, 84). About 65% of all antidepressant drugs are prescribed in PHC (8, 84).

Management in primary health care

Primary health care is the basis of health care and is defined by WHO as the core of healthcare, playing a key role worldwide with the goal of "better health for all" (85).

PHC is the frontline of care and where the population should first turn with their health and medical needs. Focus is on a person's long-term health, including medical assessments, treatment and follow-up of diseases not requiring hospitalization, and offers preventive measures, health-promoting services, and rehabilitation. One of the basic roles of PHC is primary prevention measures based on the patient's individual needs (84). To offer the patient quality and accessible PHC, defined as "safe, effective, patient-focused, knowledge-based, appropriate and equal and accessible" is the goal of PHC (84).

PHC assignment includes care and treatment for CMD and basic psychosocial and health-promoting disease prevention interventions, if there is no apparent need of hospital care specialists (86). Primary care handles the majority of sick leave for mental illness. To deal with mental illness with more than sick leave is important for early prevention and health promotion in PHC (33).

PHC is frontline care providing basic treatment for women with menopausal symptoms, and according to guidelines also basic pharmacological treatment such as MHT for midlife women(59, 60). It is a PHC responsibility which, based on the woman's subjective menopausal symptoms and experience of how symptoms affect quality of life, must be decisive when the woman together with the caregiver formulates treatment, plans and goals (60, 84). It is also the task of PHC to inform and offer MHT according to guidelines (59, 60) in cases of vasomotor menopausal symptoms, and in case of vaginal atrophy offer local MHT treatment, as well as offering basic examination and treatment and aids for urinary incontinence.

Another assignment for PHC is disease prevention and health promotion and should also offer non-pharmacological treatment such as person-centered support, individually or in groups on health-related risk and health factors, lifestyle changes independent of disease and health. Health prevention includes person-centered conversational support for mapping women's life situations, obstacles and resources, stressors, and health factors rimärvården. Midlife women may have contact with different caregivers in PHC depending on symptoms, were the district nurse’s and midwife’s competencies are important in this period of life. If an interdisciplinary intervention, including district nurse and midwife competencies in an interdisciplinary procedure with a person-centered approach can improve quality of life, needs further study.

District nurse

The district nurse (DN) traditionally has a key role and responsibility for health prevention work in PHC (10, 84, 87, 88). She/he works independently and is a support for people of all ages and health and medical conditions. The psychosocial aspect is an important perspective. DN is often the permanent care contact for patients at PHC providing continuity as well as the patient's need for coordination and safety (10, 84, 87, 89).
The district nurse has an independent and central role in public health work, where health promotion and disease prevention are aimed at people of all ages, both individually, for families, and in groups (87). The DN works with disease prevention through health promotion initiatives and public health work for people of all ages, from "the cradle to the grave". The task is focused on supporting the healthy and taking advantage of an individual's own resources. The importance of health work based on social and socio-cultural contexts and influence based on psychosocial conditions are imperatives in the district nurse's preventive care and health pedagogical approach (87). Promoting health and sound habits through lifestyle changes, as well as with health-promoting approaches, draws attention to how socio-economic and cultural differences affect health. In summary, the district nurse's work is based on a health-promoting, person-centered, and health pedagogical approach, with a perspective on natural development and ageing (84, 87-89).

Person-centered care

Person-centred care (PCC) emanates from theories of person-centredness, an ethical ground that guides our actions as professionals. PCC is based on a holistic view of the patients as persons with capabilities, responsible for their own lives (90-92). PCC in healthcare means building a partnership between the patient, her relatives, and the healthcare professionals involving the person as an active partner in care and treatment.

PCC contains three key concepts: *partnership, patient narrative and documentation* (93-96).

The concept of partnership is the most central part of PCC. Building the partnership involves sharing of information, and shared decision-making, and is based on mutual respect for each other's knowledge and expertise. Partnership means creating a trusting relationship where the patient feels safe and seen as the expert of her condition and its consequences. The starting point of the partnership is an invitation to the patient to share her narrative. The second concept of patient narrative entails listening to the patient's experience of the condition. PCC means seeing and meeting the whole person, not just the disease. The focus is on the content of the narrative where the patient's

experience, interpretation of their state of health, impact of symptoms on daily life, and available resources and opportunities, can contribute to an improved life situation. After listening to the patient's narratives, a health plan can be jointly constructed with content and strategies to achieve improved health.
The third component is documentation of the patient narrative in a health-plan, which serves at giving legitimacy to patient perspectives and safeguarding the partnership. The documentation should be a living document accessible to the patient and revised continuously (94, 96, 97).

Patient education

In primary care different methods of patient education are available to support the patient in actively participating in their lifestyle choices and providing support to improve quality of life, stimulate self-care and motivate lifestyle changes (98, 99). Education can be provided in several forms, two of which are group education and person-centred individual support as recommended in PHC.
Participation in group education can be an opportunity to exchange experiences and receive information (99, 100). Participants emphasize the value of "being with others" and "sharing experiences with others" as important factors, emphasizing the value of person-centered support for adaptation therapy for patients' different needs for better health and lifestyle changes (99, 101). Positive effects on knowledge, improved self-management strategies, and peer support in group education were shown from a previous overview publication (100, 102). The dialogue in group education can raise awareness of choices and consequences, create insight into behaviors and provide insight into the overall life situation to find the core of ill health (103). Research shows that participation in group education can increase opportunity to learn from others 'experiences, see their own experiences from a new point of view, gain new friends, reduce social isolation, and increase awareness of one's own state of health and needs. Moreover, participation increases awareness and insight into triggers regarding behavioral patterns and use of medication .
Research shows that group education for different populations have a health economic advantage compared to individual treatment . Most of the studies on depression, sleep, hypertension, and diabetes evaluating the effects of patient education often had no longer than a six-month follow-up (100, 104-110). Previous studies evaluating group education to midlife women with short follow-ups of four weeks to six months showed improved quality of life, and attitudes and knowledge towards menopausal symptoms (111-116). It may be worthwhile to evaluate long-term effects on physical, urogenital, and mental health as well as overall quality of life in a population of midlife women in a person-centered group education intervention on topics related to menopause transition.

Person-centred individual support is another method, deeper and more personal, where individual needs, narrative and resources are discussed one-on-one compared with group education. Support is based on needs and resources aimed to raise awareness on personal behaviour's possible effect on lifestyle, life events and health, and raising awareness of choices and consequences (100). Studies showed faster improved health-related quality of life in patients with hypertension, cardiovascular risk, unhealthy lifestyle habits or depressive symptoms after receiving person-centred support compared to a control group (104, 108, 109, 117).

There are few studies evaluating individual support and education with a follow-up longer than six months (117). Therefore, long-term follow-ups are warranted to evaluate long-term effects on physical, urogenital and mental health as well as overall quality of life in a population of midlife women in a person-centered support intervention on topics related to menopause transition.

Ethics

Study I, II, III: The studies were approved by the Regional Ethical Review Board in Gothenburg Sweden (registration number 041–09; T503–14)
Study II was registered in ClinicalTrials.gov with the registration ID: NTC02852811. Written informed consent was obtained from all participants and confidentiality was ensured.
Study IV: The study was approved by the Regional Ethical Review Board in Gothenburg Sweden (registration number 765-17, 2017-11-16). It was registered in ClinicalTrials.gov with the registration ID: NCT03663075. Written informed consent was obtained from all participants and confidentiality was ensured.

AIMS

General aims

The overall aim of this thesis was to estimate the prevalence of menopausal symptoms and evaluate factors associated with severe symptoms in women 45-60 in primary care, as well as identify prognostic factors for later unfavourable health development and ability to work. The aim was also to evaluate treatment methods and clarify which interventions have effects on women's health regarding somatic, urogenital, and mental symptoms during the life phase 45-60 years. In addition, the purpose was to investigate the effect of group education or person-centered individual support in primary care on mental health, quality of life, care needs and sick leave in women aged 45-60 with stress-related symptoms.

Specific aims

The specific aims of the included studies in this thesis were:

Study I
The aim of Study I was to estimate the prevalence of somatic, psychological and urogenital symptoms in women aged 45–55 attending PHC and evaluate factors associated with severe symptoms.

Study II
The aim of Study II was to investigate whether group education for women in primary health care (PHC) on the menopause transition could improve their physical and mental health.

Study III
The aim of Study III was to investigate prognostic factors for future mental, physical, and urogenital health as well as work ability in a population of women aged 45–55 years.

Study IV
The aim of Study IV was to evaluate the effect of group education as well as person-centred support in a primary health care context on mental health issues and quality of life in women aged 45-60 with stress-related symptoms.

PATIENTS AND METHODS

Study designs, selections of participants and inclusion criteria (I, II, III, IV)

This thesis consists of four empiric-atomistic (quantitative) studies. One cross-sectional study, one longitudinal cohort study and two randomised control trials (RCT). The overview is described in Table 1. Studies I, II and III were based on the same population, evaluating prevalence (I), group education (II) and prognostic factors (III). All patients were recruited from PHC settings in south-western Sweden. Women who wanted to participate and fulfilled the inclusion criteria were included.

Table 1. Overview of studies and study populations (I-IV)

	Study I	Study II	Study III	Study IV
Study design	Cross-sectional study	Randomised control trial	Longitudinal cohort study	Randomised control trial
Study population	n=131	Same study population as in Study I (n=131)	Same study population as in Study I and II	n= 368
		Intervention group (n=64) Control group (n=67)	Assessed at six years follow-up (n=71)	Group education (n=91) Group education and person-centered individual support (n=91) Person-centered individual support (n=93) Control group (n=93)

A cross-sectional study (I) was followed by a randomised control trial (II) in a group intervention followed by a six-year, prospective, longitudinal cohort study (III) (Figure 3). The women were consecutively recruited from March 2009 until December 2010 using recruitment posters when the women, for any reason, visited the PHC centers. The inclusion criteria were female gender, aged 45 to 55 and no impaired understanding of the Swedish language. The exclusions criteria were unwillingness to continue participate in the study and new onset of severe mental illness. No limitation was imposed on use of prescription drugs.

Study I
One hundred ten women were assessed. Women were invited to a district nurse and midwife at a PHC unit to fill in self-administrated questionnaires and demographic data. The self-administered questionnaires assessed the prevalence and severity of psychological, urogenital, and somatic symptoms and quality of life using the Menopause Rating Scale (MRS), and the severity of depressive symptom with the Montgomery-Asberg Depression Rating Scale (MADRS-S). The women also reported demographic data regarding age, educational level, family, and work status. The women were divided into two groups according to menopausal status categorized as still menstruating (pre/peri), or not menstruating for more than one year (post), to identify the prevalence of somatic, urogenital, and psychological symptoms. Differences between the groups were evaluated. A nomogram was constructed for predicting the probability of severe menopause symptoms.

Study II
One hundred ten women were assessed. In this randomised control trial (II), all patients were included from the cross-sectional Study I. The inclusion and exclusion criteria were the same as in Study I. Primary outcome effect measures were changes in somatic, urogenital, and psychological symptoms using (MRS) and depressive symptoms (MADRS). Outcomes were evaluated using both intention-to-treat and per-protocol analysis. The outcomes were assessed at baseline and were followed up four months later. Effect sizes were calculated for the clinical relevance of intervention effects.

Study III
At the 6-year follow-up (III), all women in Study I were contacted and those accepting participation were assessed (n=71). The same study protocol as in Study I was used and complemented with information on the women's health. New questionnaires were added such as frequency of sick leave days in the last 90 days, and health-related quality of life. The Short-Form Health Survey (SF-36) was used and current medication for hypertension, and cardiovascular history was documented. Menopause status was defined according to the criteria of the Stages of Reproductive Ageing (STRAW +10), and cardiovascular history, including hypertension or previous history of myocardial infarction, or cerebrovascular illness were complemented six years later.

Study IV
Three hundred sixty-eight (368) women were assessed. Women were recruited by advertising in local papers from November 2018 until May 2019. The

inclusion criteria were: some form of mental and/or physical health problems such as depression, anxiety, gastrointestinal symptoms, muscular symptoms and/or cardiovascular symptoms, sick leave maximum of 30 days during the past two months, ability to understand and speak Swedish, no severe illnesses such as psychosis, severe depression, or dementia, not in palliative care, and no known current alcohol or substance abuse. The exclusion criterion was new onset of severe psychological stress or illness. Written informed consent was signed, and self-administrated questionnaires were distributed electronically or by ordinary mail. The primary outcome effect measures were the Alcohol Use Disorders Identification Test (AUDIT), SF-36, the Hospital Anxiety and Depression Scale (HADS), the self-rated Exhaustion Disorder Scale (s-ED), the Perceived Stress Scale (PSS-14), MADRS and MRS. Other included measure were age, educational level, family status and work status, visits to PHC and their cause (mental and/or physical), menopause status (bleeding pattern and use of hormonal contraception), Menopause Hormone Therapy (MHT), alcohol consumption using the Alcohol Use Disorders Identification Test (AUDIT), and presence of hypertension. The outcome measures were assessed at baseline, and at 6 and 12 months after baseline for comparison between groups.

Data collection (I, II, III, IV)

Included measurements are listed in Table 2.

Table 2. Overview of measurements used in Study I-IV

Measurements	Study I	Study II	Study III	Study IV
Personal data				
Work ability	X	X	X	X
Sick leave	X	X	X	X
Family status	X	X	X	X
Education level	X	X	X	X
Menopause status	X	X	X	X
Cardiovascular history			X	X
Pharamacological treatment				
Menopause Hormone Therapy				X
Hypertension treatment			X	X
Health measures				
The Perceived Stress Scale (PSS-14)				X
The Exhaustion Disorder Scale (s-ED)				X
The Hospital Anxiety and Depression Scale (HADS)				X
The Montgomery–Åsberg Depression Rating Scale (MADRS)	X	X	X	X
The Short-form health survey (SF-36)			X	X
The Menopause Rating Scale (MRS)	X	X	X	X
The Alcohol Use Disorders Identification Test (AUDIT)				X

Personal factors (I, II, III, IV)

In studies I, II, III and IV, questions on age, education, family and work status, care need and contact PHC (only in Study IV), cardiovascular history (only in Studies III and IV), menopause status, use of MHT (only in Study IV), hormonal contraception (only in Study IV), pharmacological hypertension treatment (only in Studies III, IV), alcohol consumption (only in Study IV) and health status were registered in a standardized interview. In Study II the history was taken by a district nurse and midwife followed by group treatment.

Work status (I, II, III, IV)
Work capacity was categorised by work >1 hour per week or not working. The women also registered work/study status, sick leave full-time, sick leave part-time, disability pension (full-time), disability pension (part-time), unemployed full-time or unemployed part-time. Sick leave was registered by number of days on sick leave during the preceding 90 days (III).g

Menopause status (I, II, III, IV)
Menopausal status was used for registering stages of reproductive ageing. The criteria of the Stages of Reproductive Ageing Workshop (STRAW +10) were used to register menopausal status. The criteria involved the following stages; premenopausal - regular menses, perimenopausal women - irregularities >7 days from their normal cycle, and postmenopausal - no menses in the last 12 months (2). Questions about use of contraceptives and hormonal contraception affecting bleeding patterns was registered as having a hormonal spiral (IUD) or other hormonal contraceptive affecting bleeding patterns.

Cardiovascular history (III, IV)
Cardiovascular status was registered to gain an understanding of the presence of the history of cardiovascular illness in midlife women. The presence of hypertension was registered as: "never had high blood pressure, or had high blood pressure only during previous pregnancy, or think they have previously had hypertension unrelated to pregnancy, or currently has high blood pressure but unmedicated, or has high blood pressure and is on medication". The presence of cardiovascular history was registered as, "previous history of myocardial infarction or cerebrovascular illness".

Pharmacologic treatment
Menopause Hormone Treatment (IV)
Menopause Hormone Treatment (MHT) was registered as: application of MHT treatment local, or systemic administration, or not using MHT.

Hypertension treatment (III, IV)
Hypertension treatment was registered with questions about the presence of hypertension and treatment options.

Health measurements

The Perceived Stress Scale (PSS-14) (IV)

To assessed general stress, perceived as "unpredictable, uncontrollable, and overloading" PSS-14 was used (118). PSS-14 is a self-report questionnaire design to register generally perceived stress and to assess "the degree to which situations in one's life are appraised as stressful" and perceived as "unpredictable, uncontrollable, and overloading" and to identify risk for depression (118). The PSS-14 comprises 14 items with a five-point scale (0 to 4), where higher scores indicate a higher level of perceived stress symptoms. The questionnaire has good reliability and validity (118).

Exhaustion Disorder Scale (s-ED) (IV)

The self-rated s-ED was used to identify risk of developing exhaustion syndrome and risk of sick leave absence (119). The s-ED was developed in Sweden, based on the diagnostic criteria for exhaustion syndrome (ICD 10, code F43.8) regarding perceived stress and stress-related ill health. The form comprises four items with sub-items. Higher scores indicate a higher level of symptoms and risk of developing a clinical exhaustion syndrome. The questionnaire has good reliability and validity (119).

The Montgomery–Åsberg Depression Rating Scale (MADRS) (I, II, III, IV)

The MADRS is a validated questionnaire and was used to register the severity of depression symptom. This questionnaire was developed in the late 70s by British and Swedish researchers (120, 121). The MADRS consists of nine items, each scored from 0 to 6, with a maximum score of 54, where higher scores indicate more severe symptoms. The nine items are, 1) Apparent Sadness 2) Inner Tension 3) Reduced Sleep 4) Reduced Appetite 5) Concentration Difficulties 6) Lassitude 7) Inability to Feel 8) Pessimistic Thoughts and 9) Suicidal Thoughts. The total MADRS-S score was calculated according to the manual (English version). Foreign standards were interpreted as follows; 0-6 points essentially effortless, 7-19 points mild depression, 20-34 points moderate depression, > 34 points severe depression (121). The total MADRS-S score was calculated according to Swedish standards interpreted as follows; 0-12 points essentially effortless, 13-19 points mild depression, 20-34 points moderate depression, > 34 points severe depression (122).

The Hospital Anxiety and Depression Scale (HADS) (IV)

To examine anxiety and depressive symptoms, HADS was used (123). The HADS consists of 14 items, seven items for anxiety (HADS-A) and seven for depression (HADS-D) graded on a 4-point scale (0 and 3 points) where higher scores indicate a higher level of symptoms. The cut-off score of 8 is suggested to indicate possible clinical anxiety and depression (124). The questionnaire has good reliability and validity (124).

The Short-Form health survey (SF-36) (III, IV)

For health-related quality of life, SF-36 was used (125). The SF-36 consists of eight sub-scales: Physical Functioning (PF), Role-Physical (RF), Bodily Pain (BP), Mental Health (MH), Role-Emotional (RE), Vitality (VT), General Health (GH) and Social Functioning (SF). Scores for the sub-scales are between 0-100, a higher value indicates better perceived health. Two summary scores present an overall health index of mental and physical health (range 0–100): the Physical Component Summary (PCS) including PF, RP, BP, GG and the Mental Component Summary (MCS) including VT, SF, RE, MT. A higher value indicates better perceived health. The Swedish version of the questionnaire shows reliability and validity (125).

The Menopause Rating Scale (MRS) (I, II, III, IV)

The MRS was used to evaluate the prevalence and severity of menopausal symptoms and assess health-related quality of life in ageing women. The instrument is a self-administrated questionnaire developed in the early 1990s by Heinemann and validated in Sweden and has been translated into 25 languages (126). MRS consists of eleven items, categorised into three sub-scales reflecting; somatic symptoms - hot flushes, chest discomfort (irregular heart rhythm or feeling extra heartbeats), sleeping problems and muscle and joint problems; psychological symptoms - depressive mood, irritability, anxiety, and physical and mental exhaustion; and urogenital symptoms - sexual problems, bladder problems and vaginal dryness. Item ranged from 0 (not present) to 4 (1=mild; 2= moderate; 3=severe; 4=very severe). The MRS total score is the sum of obtained scores for each sub-scale. Severe menopausal symptoms were defined as values equal to or above 9 (somatic), 7 (psychological), 4 (urogenital), and 17 (total) (127, 128).

The Alcohol Use Disorders Identification Test (AUDIT) (IV)

The AUDIT was used to identify alcohol consumption, drinking behavior and risk habit (129). The AUDIT is self-administrated containing ten items categorized into three domains: consumption, addiction, and alcohol-related harm. Scores above the cut-off limit of 6 points for women indicate risky drinking habits (129).

Randomization procedure (Studies II, IV)

In Study II, the women were allocated by randomization to group education or a control group. Sealed opaque envelopes were created by a random allocation sequence. Participants and investigators were not blinded to group allocation. All women were invited to a baseline consultation after randomization.
In Study IV, the women were randomized using block-randomization in blocks of four. This randomization sequence was transferred to sequentially numbered closed sealed opaque envelopes. A note inside allocated the women to Group 1: Group Education (GE), group 2: GE and Person-Centered individual support (PCS), group 3: PCS and group 4: Control Group. Participants and investigators were not blinded to group allocation.

Interventions (II, IV)

The educational program in Studies II and IV, The Menopause Transition Education (MTE) was designed and developed by a district nurse and a midwife based on MRS subjects. The content of the educational program is shown in Table 3. Session flow and follow-ups are shown in Figure 2.

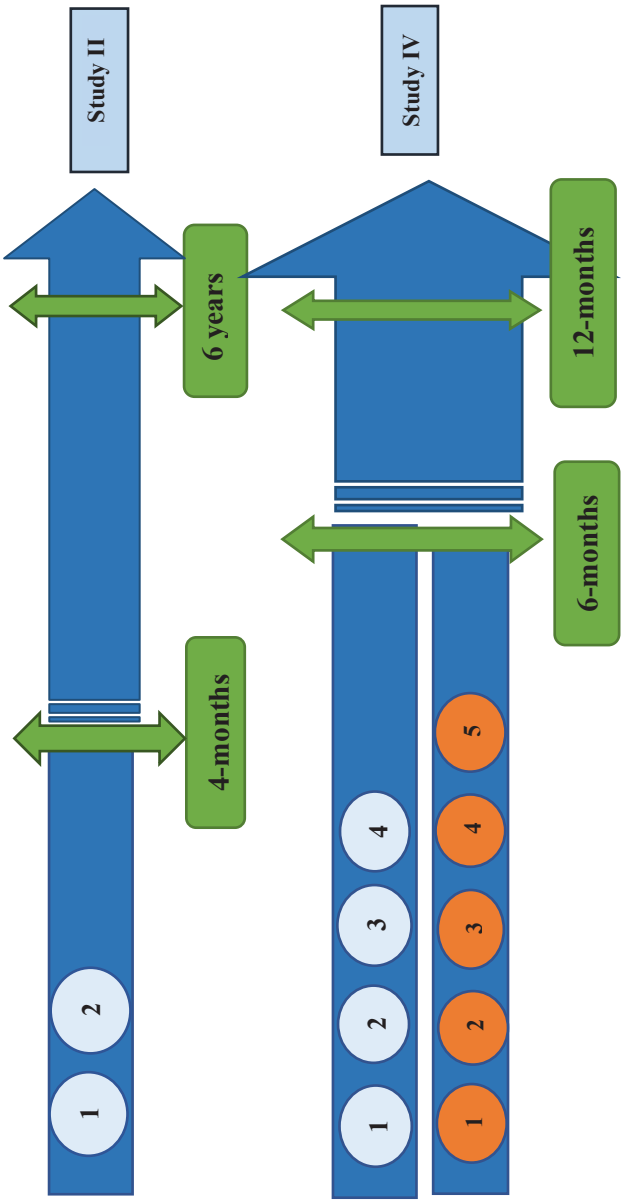

Figure 2. The session flow and follow-up, Studies II and IV

Table 3. Overview of topics in the person-centered interventions the Menopause Transition Education.

Session	Topics	Study II	Study IV
1	Definition of menopause transition, myths, epidemiology, physiology, bleeding disorders, hot flushes and sweating, local estrogen deficiency symptoms, incontinence, vaginal atrophy, osteoporosis	X	X
2	Cardiovascular health, - physiology, - risk and health factors, sleep, stress related illness, mental illness, social relationships, sexuality and desire	X	X
3	Specialization in the subjects of stress-related illness, depression, mental health, sleep and social relationships		X
4	Specialization in the subjects of stress-related and mental illness, social relationships, sexuality and desire. Recap and summary.		X
5	Last Individual session, contained a recap and summary		X

The educational program Study II

The group intervention consisted of two one-and-one half hour weekly sessions and took place within PHC. The second session took place the following week (Figure 2). Each group included 8–10 women and was supervised by a district nurse and midwife and consisted of sessions about topics related to menopause. Topics were related to physical, urogenital, mental, and psycho-social changes related to menopause as well as conversations aimed to clarify consequences of behavior, choices in life, and to stimulate desired behavioural changes.

The education, The Menopause Transition Education (MTE) was performed by a district nurse and a midwife based on MRS subjects. The educational program topics were: Session 1: A definition of menopause, general facts and myths about menopause, the menstrual cycle, menopause transition, local oestrogen deficiency symptoms including urogenital symptoms, osteoporosis and information about prevention, health promotion self-care and time for discussion and questions. Session 2 focused on cardiovascular risk and healthy factors during menopause, depressive symptoms, mental unhealth, stress, sleep, relationship, sexual health, and desire, as well as information on prevention and health promotional lifestyle factors to improve health. Time was allocated for discussion and questions (Table 3).

The control group
In Study II, the control group (CG) received the same education as the IG group four months later.

The educational program Study IV
The educational program focused on a person-centered approach in both group education and individualized treatment and were performed by a district nurse and midwife. The interventions contained information and discussions about biological processes as well as psychological and psychosocial aspects of menopause. Menopause transition as a natural part of life was emphasized and specific treatment options according to the guidelines were clarified. The topics were based on the MTE program from Study II, with greater focus on some subjects (Table 3). Prevention and health promotional lifestyle factors to improve health were discussed as well as lifestyle modifications to improve health.

Group education sessions (IV)
Group education comprised four one-and-one half hour weekly sessions including 12 to 16 women in the group sessions (Figure 2). The sessions were based on topics related to mental, urogenital, and physical changes as well as changes in psycho-social events aimed to impact lifestyle modifications to improve health (Table 3).

Person-centered individual sessions (IV)
Person-centered individual therapy comprised five, one hour, individually structured person-centered sessions, and were performed by a district nurse or midwife (Figure 2). The sessions were personal focusing on the participant's individual situation based on the woman´s narratives, needs, resources and beliefs. The topics were the same as in group education. (Table 3).

Control group
The control group received no intervention and were informed to seek advice wherever they wished outside the range of the study.

Statistical analysis (I, II, III, IV)

In all studies, (I, II, III, IV) the level of significance was $p < 0.05$. In Table 4, statistical tests are presented. The Statistical Package Software for Social Sciences (SPSS), Windows version 19.0, 22.0, 25.0 and 27.0 was used for statistical analyses in all study (I, II, II, IV). Analysis was by intention-to-treat and per-protocol in Study II and IV. Analysis complete case was also analysed in Study IV.

Table 4. Overview of statistical test included in the thesis.

Study design	Study I	Study II	Study III	Study IV
Chi square test with Yates's correction		X		
Fisher's exact test		X		
Mann Whithey U test		X		
Student's T-test		X		
Spearman correlation	X		X	
Multivariable linear regression				X
Multivariable logistic regression	X		X	X
Multivariable ordinal regression				X

Descriptive data (I, II, III, IV)

Group characteristics are presented with mean and standard deviations (SD), median and 25th and 75th percentile, median and interquartile range (IQ), or the number and percentage (%) were used.

Between group comparison (II, IV)

Changes between groups in baseline and follow-ups were calculated (Study II). Raw changes were transformed to improvement (coded as +1), worsening (coded as −1) or no change (coded as 0). For between group comparison the Student's t-test for unmatched groups and the Mann-Whitney U test was used for the raw changes. The Mann-Whitney U–test was also used for transformed changes (Study II). In Study IV, changes between baseline and follow-ups were calculated. Changes between baseline and follow-ups for nominal data are presented as a number (%) and changes in questionnaires are presented as the mean change Standard deviation (SD). Changes were also categorised into three categories: worsening, unchanged or improved (coded as -1, 0, +1) (Table 2 a-b, Study IV).

Prevalence of severe menopausal symptoms (I)

Estimates of the prevalence of somatic, urogenital, and psychological symptoms and depressive symptoms were described as numbers and proportions (Study I).

Logistic regression factors associated with severe menopausal symptoms (I)

To estimate the assessment factors associated with severe symptoms a binary logistic regression was made for each dichotomized MRS score. The mean value for the dichotomized MRS score was somatic symptoms ≥9=1/≤ 8 = 0, urogenital symptoms≥4=1/≤ 3 = 0, psychological symptoms ≥7=1/≤ 6=0 and total score ≥ 17 = 1/≤ 16 = 0. Independent explanatory variables in the regression were: age 45–55, work status; living with a partner, educational level, depressive symptoms score (MADRS ≥7 = 1/< 6 = 0). First, several unadjusted logistic regressions were performed to assess the associations between each of the independent and dependent variables of severe somatic, urogenital, psychological, and total symptoms in MRS. For zero order correlations significant variables were evaluated. Secondly, a forward stepwise multivariate (adjusted) logistic regression was made including the independent variables with a significant association to severe symptoms in MRS. To validate any multivariate logistic regression models the area under a curve (AUC) was performed (Study I). Lastly, to predict the probability of severe menopausal symptoms a multivariabel logistic model was transformed into a probability nomogram (Study I).

Nomogram (I)

To read the nomogram: 1) identify whether the patient has severe menopausal symptoms or no severe menopausal symptoms (MRS) >17, 2) affirm the patient's age and follow the corresponding line, 3) locate the depression score (MADRS) >7 and draw a horizontal line straight to the probability of severe menopausal symptoms axel and find the patient´s probability of severe menopausal symptoms (Study I).

Prognostic factors (III)

For all eight sub-scales of SF-36 a cut-off was introduced at the mean value for Swedish women aged 46–54 (125, 130). Being equal to or higher than the mean was coded as 1, and being lower coded as 0. Logistic regressions were used to identify prognostic factors. First, several multivariable logistic regressions were made to identify prognostic factors, one for each of the following dependent variables estimated at the 6-year follow-up: work ability, presence of hypertension and the dichotomization of the eight sub-scales in SF-36. The independent variables with a statistically significant association

with each of the dependent variables after six years were included in a stepwise multivariable logistic regression. Before logistic regression, multicollinearity was evaluated by the value of tolerance and variance inflator factor (VIF) between independent variables. Independent explanatory variables from the baseline measurement in the logistic regression were: age, working, living with a partner, having children living at home, education, work ability, any depression measured with MADRS ≥7, MRS somatic symptoms ≥9, MRS urogenital symptoms ≥4, MRS mental symptoms ≥7 and MRS total score ≥ 17, received active intervention (to adjust for any intervention given in the previous RCT) (Study III).

Two-factor analysis (IV)/

A two-factor design with four parallel arms was used and inferential statistical analysis was repeated for intention to treat (ITT), complete case (CC) and per protocol (PP) analysis (IV). Linear and ordinal regression were used for the effect of either intervention follow-ups (Table Supplemental 1, 2, 3, 4, study IV). Linear regression was first performed with mean change in SF-36, HADS, s-ED, PSS-14, MADR-S and MRS as the dependent variable. The dependent variables were transformed with Blom's rank-based method (131) when mean changes were not normally distributed (Table Supplemental 1 and 3, study IV). Independent variables were group education (GE), person-centered individual support (PCS), and the interaction between GE and PCS. All analyses were adjusted for age. The Beta coefficient in the linear regressions provides information about direction of effect and should not be interpreted as ranked data (Supplement Tables 1 and 3, Study IV). Multicollinearity were checked for assumptions for linear regression (Supplemental Tables 1 and 3, study IV). Next, ordinal regressions were performed. Changes in outcome variables were transformed coded as improvement +1, worsening -1 and unchanged as 0, and was used as the dependent variable. Independent variables were group education (GE), person-centered individual support (PCS) and interaction between GE and PCS. All analyses were adjusted for age regression (Supplemental Tables 2 and 4, Study IV).

Finally, in a summary table the results from linear and ordinal regressions were presented with statistically significant effects of any of the two interventions denoted with a + sign in at least one of ITT, CC and PP. A double + sign indicates a desired effect of intervention seen in two of the three statistical analyes and three + signs indicate a statistically significant effect in all three analyses. In analogue with this 1-3 minus signs indicate a statistically significantly undesired effect of the intervention. In the ordinal regression of the ITT analysis the odds ratio was also presented for any statistically significant effect. Some questionnaires estimate health while others estimate

symptoms. Desired effect in some outcome variables result in an odds ratio >1 while in others an odds ratio <1. To clarify, a desired effect always had an odds ratio >1 while an undesired effect always had an odds ratio <1, and was transformed in the summary table (Table 3, Study IV).

RESULTS

The present thesis will be available digitally. To avoid problems with publication of the results for Study IV these results are only presented briefly. The result tables for Study IV are presented in detail in the attached manuscript in the printed thesis. Therefore, Study IV with table numberings are according to manuscript number. Just the table number is presented otherwise.

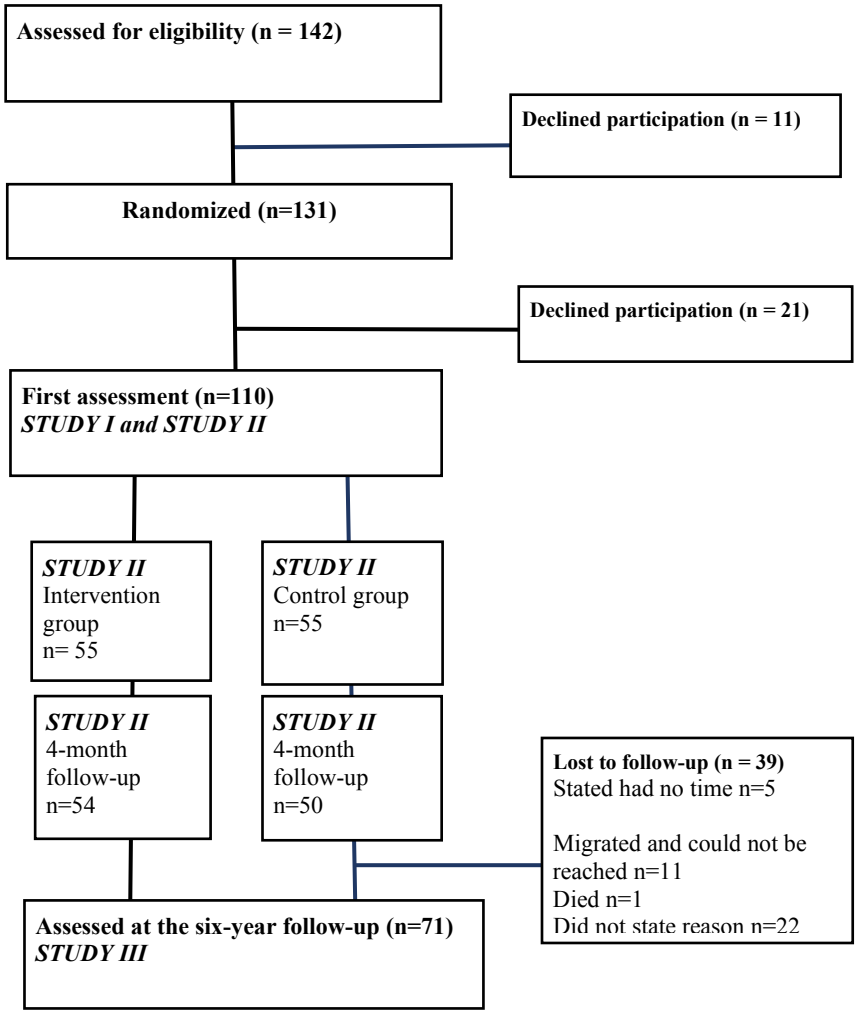

Figure 3. Participant flow Study I, II and III

Result Study I

One hundred and ten women age 45-55 were assessed (Figure 3) and the characteristics for total group and pre/peri- and postmenopausal group are shown in Table 5. The mean values for age were 50 (SD 3.0) for the total group for the group pre/peri 50 (SD 3.1), for the post group 52 (SD 3.0) (p=0.0049). Information about menopausal stage for menstruation was missing for 15% of the women due to contraceptive treatments with hormones, hysterectomy or not having provided a clear statement on menstruation (Table 5).

The post-menopausal group showed statistically significant more severe somatic symptoms (hot flushes, coronary discomfort, sleeping problems and muscle and joint problems) measured with MRS compared to the pre/peri-pausal group (p=0.033). Mean values for somatic symptoms (MRS) were 4.2 (SD 2.9) for the total group, the group pre/peri 3.9 (2.9) and for the post-menopausal group 5.1 (2.5) (p=0.033). No differences between groups were found for the psychological and urogenital symptoms in MRS or in depressive symptoms in MADRS (Table 5).

Table 5. Demography, depression, and symptom scores among women 45-55 years

	Total score (n=110)		Pre/peri[a] (n=69)		Post[b] (n=25)		P-value
Age (y)[c]	50 (3)		50 (3.1)		52 (3.0)		**0.0049**
Education (y)[d]							
Primary school (<9)	20 (18)		8 (12)		7 (28)		
Secondary school (10-12)	51 (46)		31 (45)		11(44)		**0.0065**
Tertiary school (>12)	39 (36)		30 (44)		7 (28)		
Work[d]							
In work	92 (84)		57 (83)		21 (84)		0.87
Family status[d]							
Living with a partner	98 (89)		61 (88)		23 (92)		0.62
MRS score[e]							
Somatic[f]	4.2 (2.9)	4.0 (2-6)	3.9 (2.9)	3.0 (2-6)	5.1 (2.5)	5.0 (4-7)	**0.033**
Urogenital[f]	2.5 (2.4)	2.0 (1-4)	2.2 (2.3)	2.0 (0-4)	3.2 (2.3)	2.0 (2–5)	0.091
Psychologcal[f]	3.8 (3.0)	3.0 (1-6)	3.9 (3.1)	3.0 (1-6)	3.8 (2.8)	4.0 (2-6)	0.90
Total[f]	10 (6.4)	9.5 (5-15)	9.8 (6.6)	8 (4-15)	12 (5.6)	11 (10-5)	0.068
Depression score[d,g]							
No	58 (53)		36 (52)		12 (48)		
Mild	45 (41)		29 (42)		11 (44)		
Moderate	7 (6.4)		4 (58)		2 (8)		0.54
Major	0 (0.0)		0 (0.0)		0 (0.0)		
Sumscore [h]	8.2 (5.9)	6.0 (4-12)	8.6 (6.0)	6 (4-13)	7.6 (5.6)	7 (4-11)	0.58

[a] Still menstruation
[b] No menstruation since more than one year ago
[c] First figure mean values (SD).
[d] n (%)
[e] Subscale and total Menopause Rating Scale (MRS) scoring. The reference values for the symptoms are follow: > 8 (somatic), > 6 (psychological), > 3 (urogenital) and >16 (total MRS) was defined as severe. First figure mean (SD) second figure median (25th and 75th percentile). Degree of severity of the MRS and its domains indicated; Total score; No, little (0–4), Mild (5–8), Moderate (9–16), Severe (17+), Psychological domain; No, little (0–1), Mild (2–3), Moderate (4–6),Severe (7+), Somatic domain; No, little (0–2), Mild (3–4);Moderate (5–8), Severe (9+), Urogenital domain; No, little (0), Mild (1), Moderate (2–3),Severe (4+).
[f] n 65
[g] Montgomery-Asberg Depression Rating Scale (MADRS) scoring.
[h] First figure n (%) First figure mean (SD) second figure median (25th and 75th percentile). International standards; 0-6 p no depression, 7-19 p, mild depression, 20-34 p moderate depression, >34 p severe depression.

For the total group MRS somatic score indicated mild symptoms, for urogenital and psychological score moderate symptoms (Tables 6). The five most frequently reported MRS symptoms were; physical and mental exhaustion (73 %), depressive mood (66 %), sleep problems (66 %), hot flushes (66 %), muscle and joint problems and sexual problems (62 %). The five most "severe to very severe" MRS symptoms were; sleeping problems (18 %), depressive mood (18 %), muscle and joint problems (12 %), physical and mental exhaustion (10 %) and sexual problems (9 %) compared with hot flushes (5 %) as were ranked ninth of eleven in the present series. In Table 6 the prevalence of menopause symptoms registered in MRS sub-scales are presented.
Depression symptoms (MADRS) indicated mild symptoms (Tables 3, Study I).

Table 6. Prevalence of menopause symptoms in Menopause Rating Scale (MRS) for Swedish women aged 45-55

Symptoms	None % (n)	Mild % (n)	Moderate % (n)	Severe % (n)	Very severe % (n)
Somatic[a]					
Hot flushes, sweating:	34 (37/109)	32 (35/109)	29 (32/109)	4.0 (4/109)	1.0 (1/109)
Heart discomfort:	52 (56/108)	28 (30/108)	19 (21/108)	-	1.0 (1/108)
Sleeping problems:	33 (36/108)	26 (28/108)	24 (26/108)	13 (14/108)	5.0 (5/108)
Muscle and joint problems:	38 (42/108)	21(23/108)	28 (31/108)	10 (11/108)	2.0 (2/108)
Psychological[a]					
Depressive mood:	33 (36/108)	26 (28/108)	24 (26/108)	13 (14/108)	5.0 (5/108)
Irritability:	41 (44/108)	37 (40/108)	17 (18/108)	6.0 (6/108)	-
Anxiety:	47 (51/108)	33 (36/108)	16 (17/108)	4.0 (4/108)	-
Physical and mental exhaustion:	27 (29/109)	44 (48/109)	19 (21/109)	8.0 (9/109)	2.0 (2/109)
Urogenital[a]					
Sexual problems:	38 (42/109)	33 (36/109)	20 (22/109)	5.0 (5/109)	4.0 (4/109)
Bladder problems:	50 (53/108)	34 (37/108)	12 (13/108)	3.0 (3/108)	2.0 (2/108)
Dryness of vagina:	53 (57/108)	28 (30/108)	12 (13/108)	5.0 (5/108)	3.0 (3/108)

[a] Higher value indicated more severe symptoms.

Factors associated with menopausal symptoms as measured with MRS.

More severe depression symptoms (MADRS) and increasing age were associated with more severe menopausal symptoms (MRS) (Table 7). Adjusted model accounted for approximately 39 % of the variance of menopausal symptoms (Nagelkerke R2) with area under curve (AUC) of 0.86 (CI 0.78-0.93, $p < 0.001$) (Table 7 and Figure 4).

Table 7. Factors associated with menopausal symptoms as measured with Menopause Rating Scale (MRS) (n=109).

	Menopausal symptoms							
	Somatic symptoms >8		Urogenital symptoms >3		Depression symptoms >6		Total of symptoms >16	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Unadjusted								
Age[a]	1.1 (0.87-1.4)	0.46	1.2 (1.0-1.4)	**0.014**	1.1 (0.96-1.3)	0.15	1.2 (1.01-1.4)	**0.037**
Living with partner	1.0 (0.11-8.8)	1.0	1.8 (0.36-8.6)	0.48	1.3 (0.27-6.5)	0.74	4.3×10^8 (0.0-∞)	1.0
Working[b]	0.11 (0.026-0.47)	**0.0028**	0.55 (0.18-1.7)	0.29	0.21 (0.067-0.62)	**0.0051**	0.24(0.077-0.74)	**0.013**
Tertiary education[c]	0.50 (0.99-2.5)	0.40	0.44 (0.16-1.2)	0.11	0.83 (0.31-2.2)	0.71	0.75(0.26-2.1)	0.59
Depression[d]	3.4×10^8 (0.0-∞)	1.0	2.2 (0.91-5.5)	0.079	10 (2.8-37)	**0.00044**	31.6 (4.2-247)	**0.00099**
Menopause[e]	0.42 (0.48-3.7)	0.44	1.3(0.50-3.8)	0.53	0.61 (0.18-2.03)	0.42	1.1 (0.36-3.7)	0.82
Adjusted								
Age[a]							1.2 (1.0-1.5)	**0.041**
Depression[d]					10 (2.8-37)	**0.00044**	33 (4.2-270)	**0.00091**

[a] Odds Ratio for an increase in age of one year between 45-55 years
[b] Working more than one hour/week
[c] Primary school/ secondary school vv tertiary school
[d] Montgomery-Asberg Depression Rating Scale (MADRS) score ≥ 7
[e] Menopause one year after last menstruation

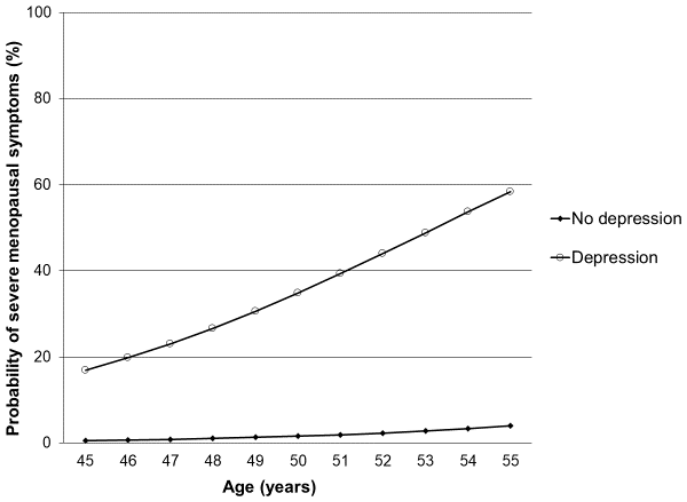

Figure 4. Study II Nomogram, the probability of severe menopausal symptoms among women. Depression = MADRS ≥7 (mild or moderate or severe depression). Severe menopausal symptoms = MRS ≥ 17. (Reprint permission of the publisher and journal)

Result Study II

One hundred and ten women were randomised to either the intervention group (IG) (n=55) or control group CG (n=55) (Figure 3). No significant baseline differences were found (Table 8).
In both groups, somatic symptoms (MRS) indicated mild urogenital symptoms (MRS) and psychological symptoms (MRS) and for total score moderate symptoms (MRS) at baseline (Table 8). Depressive symptoms (MADRS) indicated mild depression in both groups at baseline (Table 8).

Table 8. Baseline characteristics (n=110)

	Intervention group *n*=55		**Control group *n*=55**	
Age (y)[a,b]	50 (3.4)	50 (47-52)	50 (3.1)	51(48-53)
Education n (%)[b]				
Primary/ Secondary school (< 12 y)	33 (60)		38 (69)	
Tertiary school (>12 y)	22 (40)		17 (31)	
Be in work, n (%) [b]	45 (82)		47 (86)	
Living with a partner, n (%) [b]	51 (93)		47 (86)	
Average MRS scorec,[b]				
Somatic[d]	3..9 (2)	3 (1-6)[b]	4.5 (2)	5 (2-6)[b]
Urogenital[e]	2.2 (2)	2 (0-3)	2.9(2)	2 (1-4)
Psychological[f]	4.1 (4)	4 (1-6)	3.5 (3)	3 (1-5,3)
Total	10 (9)	9 (4-15)	11 (11)	11 (7-15)
Depression score[g,b]	8.3 (6.7-10)	6 (5.8)	8.3 (6.6-9.9)	7 (6.0)

a Age in years.
b First figure mean values (SD) second figure median (interquartile range).
c Subscale and total Menopause Rating Scale (MRS) scoring. The reference values for the symptoms are follow: > 8 (somatic), > 6 (psychological), > 3 (urogenital) and >16 (total MRS) was defined as severe. Degree of severity of the MRS and its domains indicated; Total score; No, little (0–4), Mild (5–8), Moderate (9–16), Severe (17+), Psychological domain; No, little (0–1), Mild (2–3), Moderate (4–6), Severe (7+), Somatic domain; No, little (0–2), Mild (3–4); Moderate (5–8), Severe (9+), Urogenital domain; No, little (0), Mild (1), Moderate (2–3), Severe (4+).
d Somatic symptoms - hot flushes, heart discomfort, sleeping problems and muscle and joint problems.
e Urogenital symptoms - sexual problems, bladder problems and vaginal dryness.
f Psychological symptoms - depressive mood, irritability, anxiety and physical and mental exhaustion.
g Montgomery-Asberg Depression Rating Scale (MADRS) scoring. First figure mean (SD), second figure median (interquartile range). International standards; 0-6 p no depression, 7-19 p, mild depression, 20-34 p moderate depression, >34 p severe depression

Differences between the groups four months after treatment.

At the four-month follow-up, the intervention group experienced a reduction in somatic, urogenital, and psychological symptoms (MRS) and depressive symptoms (MADRS) while the control group experienced the opposite. No statistically significant differences between groups in changed symptoms were seen in the intention-to-treat and per-protocol analyses (Table 9).

Table 9. Changes in menopausal symptoms and depression during four months.

	Mean change		SD[b]		*P* value[c]		
	IG[a]	CG[a]	IG	CG	T test	M&W	MWT
Menopausal Symptoms							
Somatic[e]	-0.13	+0.22	1.5	1.9	0.30	0.15	0.23
Psychological[e]	-0.13	+0.040	2.5	2.4	0.73	0.86	0.82
Urogenital[e]	-0.15	-0.080	1.8	1.7	0.84	0.41	0.32
Total score	-0.43	+0.42	4.1	4.1	0.30	0.29	0.46
Depressive symptoms[f]	-0.44	+0.10	5.0	4.8	0.58	0.48	1.0

[a] Number of women providing complete answers to both questionnaires. In Intervention group (IG) n= 54 and in Control group (CG) n = 55.
[s] Standard deviation of mean.
[c] *P* value for comparison of change between groups. *T* test= students t test; M&W = Mann Whitney´s test; MWT = Mann Whitney´s test using transformed data.
[e] MRS questionnaires with sub scales
[f] MADRS questionnaires total

Result Study III

Sixty-five percent (n = 71/110) of the women in Study I could be followed up after 6 years (Figure 3). The mean value for age was 50 (SD 3.1) at first assessment and background data are presented in Table 10. 63% of the women (34/54) were still menstruating. Information on menstruation due to contraceptive treatments with hormones, hysterectomy or not, provided a clear statement that menstruation had ceased in 24% (17/71).

Table 10. Participant Characteristics at First Assessment (n= 71)

	Mean (SD)	Median (IR)	N (%)
Age (y)[a]	50 (3.1)		
Education (y)[b]			
Primary school (≤ 9)			15 (21)
Secondary school (10-12)			31 (44)
Tertiary school (>12)			25 (35)
Work status/ Employment status[b]			
Currently working/studying[c]			61 (86)
Sick leave full-time			0 (0.0)
Sick leave part-time			0 (0.0)
Disability pension (full-time)			3 (4.0)
Disability pension (part-time)			2 (3.0)
Unemployed full-time			5 (7.0)
Unemployed part-time			0 (0.0)
Family status[b]			
Living with a partner			66 (93)
Children at home			17 (24)
Still menstruating[b,d]			34 (63)
Average MRS score[e]			
Somatic	4.3 (3.0)	4.0 (2-6)	
Urogenital	2.4 (2.5)	2.0 (0–4)	
Psychological	3.7 (3.1)	3.0 (1-6)	
Total MRS	10 (6.9)	9.0 (0-15)	
Average depression score[f,g]	7.3 (5.5)	6.0 (3-11)	

[a] First figure mean value (SD)
[b] n (%)
[c] Work more than one hour a week
[d] 34/54 are still menstruating. Information is missing in 17 women.
[e] Subscale and total Menopause Rating Scale (MRS) scoring. First figure mean (SD) second figure median (25th and 75th percentile). Degree of severity of the MRS and its domains indicated; Psychological domain; No, little (0–1), Mild (2–3), Moderate (4–6), Severe (7+), Somatic domain; No, little (0–2), Mild (3–4), Moderate (5–8), Severe (9+), Urogenital domain; No, little (0), Mild (1), Moderate (2–3), Severe (4+), Total score; No, little (0–4), Mild (5–8), Moderate (9–16), Severe (17+).
[f] Montgomery-Asberg Depression Rating Scale (MADRS) scoring. First figure mean (SD) second figure median (25th and 75th percentile). International standards; 0-6 p no depression, 7-19 p, mild depression, 20-34 p moderate depression, >34 p severe depression.
[g] Information is missing in 5 women (66/71).

Cardiovascular symptoms at the 6-year follow-up

Medication for hypertension was reported by 39 % (28/71). Three women reported hypertension but were not medicating. Four women were hypertensive during pregnancy. Five women stated myocardial infarction or cerebral haemorrhage.

Changes in health at the 6-year follow-up

At baseline the women reported moderate symptoms in MRS urogenital as well as psychological symptoms while somatic symptoms were reported as mild symptoms (Table 11). At the 6-year follow-up the severity of symptoms decreased in MRS somatic, mean changes, −0.23 (SD 2.5), urogenital score −0.52 (2.5) and total score −3.5 (5.6) while psychological symptoms (MRS) + 0.52 (3.0) and depressive symptoms (MADRS) + 0.38 (4.3) increased (Table 11). Four of 71 women stated part-time sick leave at six years compared with none at baseline.

11.Changes from baseline to the 6-year follow-up (n= 71)

Family status		
Children at home	-59 %	
Being in work[a]	-3 %	
Menopausal Symptoms[b]		
Somatic	-0.23	(2.5)
Urogenital	-0.52	(2.5)
Psychological	+0.52	(3.0)
Total MRS	-3.5	(5.6)
Depressive Symptoms[c,d]	+0.38	(4.3)

[a] Paid work at least one hour per week

[b] Menopause Rating Scale (MRS) subscale: Somatic symptoms - hot flushes, heart discomfort, sleeping problems and muscle and joint problems, Psychological symptoms - depressive mood, irritability, anxiety and physical and mental exhaustion, Urogenital symptoms - sexual problems, bladder problems and vaginal dryness, Total score - all subscales added. Higher score indicates more severe symptoms. Values are mean change (standard deviation)

[c] Montgomery-Asberg Depression Rating Scale (MADRS) scoring. Higher score indicates more severe symptoms.

[d,] Information is missing in 5 women (66/71).

Predictors for good health at the 6-year follow-up

Living with a partner and having tertiary education were the most important baseline predictors for health after six years (Table 12, 13 and 14). Having tertiary education was significantly associated with poorer mental health (SF36-MCS) 0.16 (CI 0.034–0.74) (p=0.019), vitality (SF36-VT) 0.18 (CI 0.035–0.87) (p=0.033), (CI 0.035–0.87), and social role functioning (SF36-SF) 0.12 (CI 0.28–0.50) (p=0.0051), (Table 12, 13 and 14). Living with a partner (yes/no) was significantly associated with increased physical role functioning (SF36-RF) 32 (CI 1.9–530) (p =0.016), social role functioning (SF36-SF) 21 (CI 1.3–320) (p= 0.031) and emotional role functioning (SF36-RE) (p=0.017) 29 (CI 1.8–460) (Table 12, 13 and 14).

Work ability at baseline predicted work ability after six years (Table 12, 13 and 14).

Table 12. Prognostic factors for good health, workability and presence of hypertension at 6-year follow-up

	Mental Health[a]		Physical Health[a]		Work ability		Hypertension[b]	
	(n=69) MCS SF36 ≥ 50		(n=69) PCS SF36 ≥ 50[b]		(n=71)		(n=71)	
Predictors	p-value	Effect size[c]	p-value	Effect size[c]	p-value	Effect size[c]	p-value	Effect size[c]
Age[d]	**0.0056**	1.5 (1.1-1.9)	0.67	0.96 (0.78-1.2)	0.46	1.1 (0.83-1.5)	0.13	1.2 (0.96-1.4)
Tertiary education	**0.019**	0.16 (0.034-0.74)	0.54	0.65 (0.17-2.6)	0.73	0.71 (0.10-4.8)	0.53	1.3 (0.40-4.4)
Work ability[e]	0.66	0.60 (0.061-5.8)	**0.017**	21 (1.7-250)	**0.0025**	51 (4.0-670)	**0.023**	0.12 (0.018-0.85)
Living with a partner	0.12	9.4 (0.56-160)	0.75	1.5 (0.13-17)	1.0	0.00 (0.00-∞)	0.80	1.1 (0.10-13)
Children at home	0.61	1.6 (0.28-8.3)	0.41	2.0 (0.39-11)	0.47	2.5 (0.22-28)	0.26	0.51 (0.11-2.4)
Depression[f]	**0.027**	0.15 (0.027-0.81)	**0.012**	0.16 (0.037-0.67)	0.50	2.2(0.22-22)	0.88	1.1 (0.30-4.3)
MRS								
Somatic[g]	0.95	1.1 (0.090-13)	1.0	1.0 (0.12-8.4)	0.44	0.34 (0.22-5.3)	0.57	0.55 (0.071-4.2)
Psychologic[g]	**0.0069**	0.035 (0.0032-0.40)	0.93	1.1 (0.23-5.1)	0.065	0.11 (0.011-1.1)	0.27	2.0 (0.45-9.2)
Urogenital[g]	0.47	1.9 (0.34-10)	0.71	1.3 (0.32-5.3)	0.32	4.1 (0.26-12)	0.84	0.96 (0.25-3.7)
Active intervention[h]	0.66	0.74 (0.19-2.8)	0.99	1.0 (0.29-3.4)	0.54	1.8 (0.27-12)	0.26	2.0 (0.61-6.3)
Nagelkirke R square		0.53		0.36		0.49		0.26
Hosmer-Lemeshow test	0.88		0.35		0.29		0.49	
Area Under Curve[g]	<0.001	0.87 (0.78-0.95)	<0.001	0.81 (0.70-0.91)	<0.001	0.87 (0.77-0.98)	<0.001	0.76 (0.64-0.87)
Omnibus test of model	0.00006		0.019		0.0005		0.12	

[a] Cut of norm for Swedish women 45-54 years, SF36
[b] The part of the women stated having hypertension.
[c] Effect size is Odds Ratio and (95 % CI) for all predictors. First figure is p-value, second figure is predicted probability and CI, the odds ratio increase in score value.
[d] Odds Ratio for an increase in age of one year between 45-55 years.
[e] Working at least one hour/week.
[f] Montgomery-Asberg Depression Rating Scale (MADRS) score ≥ 7 indicating at least mild depression. Information is missing in 5 women (66/71).
[g] Menopause Rating Scale and total Menopause Rating Scale (MRS) scoring. Somatic symptoms - hot flushes, heart discomfort, sleeping problems and muscle and joint problems; Psychological symptoms - depressive mood, irritability, anxiety and physical and mental exhaustion; Urogenital symptoms - sexual problems, bladder problems and vaginal dryness. Higher score indicates more severe symptoms.
[h] The active group intervention is just as an adjustment and it is not the focus of this study

Table 13. Prognostic factors for good health estimated by the SF36 subscales Role Function, Physical Function, Vitality and Social Function at 6-year follow up

	RF (n=71) ≥ 84[a]		PF (n=70) ≥ 86[a]		VT (n=70) ≥ 68[a]		SF (n =70) ≥ 88[a]	
Predictors	**P-value**	**Effect size[b]**	**P-value**	**Effect size[b]**	**P-value**	**Effect size[b]**	**P-value**	**Effect size[b]**
Age[c]	0.60	1.06 (0.86-1.3)	1.0	1.0 (0.83-1.2)	0.12	1.3 (0.94-1.7)	0.078	0.12 (0.98-1.5)
Tertiary education	0.12	0.34 (0.089-1.3)	0.78	0.83 (0.22-3.1)	**0.033**	0.18 (0.035-0.87)	**0.0051**	0.12 (0.28-0.50)
Work ability[d]	0.065	7.3 (0.89–59)	**0.028**	8.7 (1.3-61)	0.21	5.5 (0.39-80)	0.62	1.6 (0.24-11)
Living with a partner	**0.016**	32 (1.9–530)	0.87	1.2 (0.12-11)	0.60	0.47 (0.027-8.1)	**0.031**	21 (1.3-320)
Children at home	0.76	0.78 (0.16-3)	0.19	3.0 (0.59-15)	0.15	4.0 (0.61–26)	0.34	0.46 (0.91–2.3)
Depression[e]	0.077	0.28 (0.065-1.2)	**0.021**	0.20 (0.050-0.78)	**0.014**	0.092 (0.014-0.61)	0.11	0.31 (0.072-1.3)
MRS symptoms								
Somatic[f]	0.51	0.45 (0.043-4.7)	0.96	0.96 (0.15-6.2)	0.47	2.6 (0.19-36)	0.23	0.25 (0.025-2.4)
Psychologic[f]	0.45	0.56 (0.12-2).5)	0.88	1.1 (0.25-5.2)	1.0	0.00 (0.00-∞)	0.25	0.40 (0.085-1.9)
Urogenital[f]	0.65	1.4 (0.32-6.2)	0.47	1.7 (0.42-6.6	0.64	1.5 (0.26-8.7)	0.29	0.46 (0.11-2.0)
Active intervention[g]	0.059	3.0 (0.85-1.04)	0.14	2.6 (0.73-9.4)	0.10	3.4 (0.78–15)	0.065	0.31(0.87-1.1)
Nagelkirke R square		0.38		0.27		0.57		0.40
Hosmer-Lemeshow test	0.63		0.47		0.91		0.80	
Area Under Curve[f]	0.031	0.65 (0.52-0.78)	0.015	0.68 (0.54-0.81)	0.005	0.70 (0.58-0.83)	0.000	0.82 (0.72-0.91)
Omnibus test of model	0.009		0.12		<0.001		0.006	

[a] Cut of for norm Swedish women age 46-54 years, SF36. SF36 subscales; Role function (RF), Physical function (PF), Vitality (VT) and Social function (SF). Higher score indicated better health.
[b] Effect size is Odds Ratio and (95 % CI) for all predictors. First figure is p-value, second figure is predicted probability and CI. The odds ratio increases in score value.
[c] Odds Ratio for an increase in age of one year between 45-55 years.
[d] Working more than one hour/week.
[e] Montgomery-Asberg Depression Rating Scale (MADRS) score ≥ 7 indicating at least mild depression. Information is missing in 5 women (66/71).
[f] Menopause Rating Scale and total Menopause Rating Scale (MRS) scoring. Somatic symptoms - hot flushes, heart discomfort, sleeping problems and muscle and joint problems; Psychological symptoms - depressive mood, irritability, anxiety and physical and mental exhaustion; Urogenital symptoms - sexual problems, bladder problems and vaginal dryness. Higher score indicates more severe symptoms.
[g] The active group intervention is just as an adjustment and it is not the focus of this study.

Table 14. Prognostic factors for good health estimated by the SF36 subscales Mental health, General health, Role emotional and Bodily pain at six years follow-up

	MH(n= 70) ≥ 80[a]		**GH (n= 70)** ≥ 75[a]		**RE (n= 71)** ≥ 87[a]		**BP (n= 69)** ≥ 71[a]	
Predictors	p-value	Effect size[b]	p-value	Effect size[b]	p-value	Effect size[b]	p-value	Effect size[b]
Age[c]	0.11	1.4 (0.94-2.0)	0.071	1.2 (0.98-1.5)	0.062	1.2 (0.99-1.5)	0.93	0.99 (0.82-1.2)
Tertiary education	0.47	0.52 (0.092-3.0)	0.14	0.37 (0.10-1.4)	0.085	0.25 (0.050-1.2)	0.88	1.2 (0.33-3.6)
Work ability[d]	0.64	2.1 (0.093-48)	**0.025**	18 (1.4-220)	0.82	1.3 (0.16-10)	0.14	4.3 (0.62-29)
Living with a partner	0.74	1.9 (0.060-58)	0.12	8.3 (0.59-116)	**0.017**	29 (1.8-460)	0.43	0.37 (0.029-4.5)
Children at home	0.94	1.1 (0.094-13)	0.47	1.7 (0.39-7.6)	0.97	0.97 (0.18-5.3)	0.98	0.98 (0.22-4.4)
Depression[e]	0.16	0.18 (0.017-1.9)	0.13	0.33 (0.080-1.4)	0.24	0.38 (0.075-2.0)	0.062	0.30 (0.083-1.1)
MRS symptoms								
Somatic[f]	1.0	0.00 (0.00- ∞)	0.73	0.67 (0.070-6.5)	0.64	0.59 (0.061-1.9)	0.98	0.98 (0.14-7.1)
Psychologic[f]	1.0	0.00 (0.00-∞)	0.37	0.46 (0.084-2.5)	**0.011**	0.11 (0.020-0.61)	0.99	1.01 (0.22-4.6)
Urogenital[f]	0.44	2.1 (0.32-14)	0.52	0.63 (0.16-2.5)	0.74	1.3 (0.23-61)	0.75	1.2 (0.33-4.6)
Active intervention[g]	0.89	1.2 (0.24-5.2)	0.87	9.1 (0.34-3.6)	0.25	0.43 (0.10-1.8)	0.55	1.4 (0.46-4.3)
Nagelkirke R square		0.35		0.33		0.40		0.22
Hosmer & Lemeshow	0.94		0.33		0.47		0.98	
Area Under Curve[g]	0.001	0.84 (0.75-0.94)	<0.001	0.79 (0.68-0.90)	<0.001	0.85 (0.75-0.95)	0.001	0.72 (0.60-0.85)
Omnibus test of model	0.13		0.029		0.010		0.28	

[a] Cut of norm for Swedish women 45-54 years, SF36. SF36 Subscales; Mental health (MH), General health (GH), Role emotional (RE) and Bodily pain (BP). Higher score indicated better health.
[b] Effect size is Odds Ratio and (95 % CI) for all predictors. First figure is p-value, second figure is predicted probability and CI. The odds ratio increase in score value.
[c] Odds Ratio for an increase in age of one year between 45-55 years.
[d] Working more than one hour/week.
[e] Montgomery-Asberg Depression Rating Scale (MADRS) score > 7 indicating at least mild depression. Information is missing in 5 women (66/71).
[f] Menopause Rating Scale and total Menopause Rating Scale (MRS) scoring. Somatic symptoms - hot flushes, heart discomfort, sleeping problems and muscle and joint problems; Psychological symptoms - depressive mood, irritability, anxiety and physical and mental exhaustion; Urogenital symptoms - sexual problems, bladder problems and vaginal dryness. Higher score indicates more severe symptoms.
[g] The active group intervention is just as an adjustment and it is not the focus of this study.

Result Study IV

Three-hundred and sixty-eight women 45-60 were randomised into four groups either Group I (GE) (n=91), Group II (GE/PCS) (n=91), Group III (PCS) (n=93) or Group IV (CG) (n=93) (Figure 1, Study IV). The mean values for age were 52 (SD 7.0) (Table 1, Study IV). Half of the women had tertiary school education 188/368 (51%), most were working (94%), living with a partner (79%), had children living at home (55%), and had non-risky alcohol consumption (90%) (Table 1, Study IV). Used MHT were reported from 15 % (56/368) divided in systemic administration 7% 26/368 and local administration 8 % (30/368). The study population at first assessment are presented in Table 1, Study IV.

Changes in health at 6 and 12 months.

At the 6-month follow-up, changes from baseline indicated a reduction in somatic, psychological, and urogenital symptoms (MRS) in all four groups (Table 2a, Study IV). Mental health was improved in all four groups (SF36, HADS, s-ED, PSS-14, MADRS) (Table 2a, Study IV).

At 12-months changes from baseline indicated a reduction in somatic, psychological symptoms (MRS) in all four groups. For the sub-scale urogenital symptoms (MRS) a reduction of symptoms were seen in group 2,3,4 (ITT-analyses) (Table 2b, Study IV). Mental health had improved or stabilized (SF36, HADS, s-ED, PSS-14, MADRS). At 12 months, a decrease in SF36 domain's physical function (PF) and bodily pain (BP) and SF36-PCS) was shown in Group 1 (Table 2b, Study IV).

The menopause status "had not had a period in > 12 months" was reported by half of the women 149/289 (49 %), had regular menstruation and 18 % (52/289) had irregular bleeding within the last 12 months from 12% (36/289). Hormonal contraceptives that may influence the bleeding pattern were reported from 12 % (36/289) (Table 2b, Study IV). MHT at the 12-month follow-up was reported by 28% 80/289 (Table 2b, Study IV).

Effect of GE and PCS at 6 and 12 months.

At the 6-month follow-up, a statistically significant positive effect in somatic, urogenital symptoms and MRS total score was showed in GE. At the 12-month follow-up this effect was lost but a positive effect was shown in mental health (SF36-MH, s-ED) (Table 3 and supplemental Tables 1-4, Study IV). At the 6-month follow-up, a statistically significantly positive effect in psychological, urogenital symptoms, MRS total score and mental health (SF-36-MH) was shown in PCS. At the12-month follow-up this effect was further reinforced (Table 3 and supplemental Tables 1-4, Study IV). When GE and PCS were combined additionally positive effects were shown in SF36-PF and MADRS at the 6-month follow-up. This effect of interaction was lost at 12-months.

DISCUSSION

The studies in this thesis have described and identified factors associated with the transitional period in women between 45 and 60 years of age and have shown positive effects on, somatic, urogenital and mental symptoms, and quality of life through a person-centered intervention in PHC.

At the first assessment the diversity and severity of symptoms was elucidated, and poor mental health was shown to be the most common symptom. More severe depression symptoms and increasing age were associated with more severe symptoms according to MRS (I). After six years it appears that midlife women living with a partner had a better chance for maintaining good health. Tertiary education was shown to be associated with poor mental health at a 6-year follow-up (III).

The effect of GE and PCS in PHC context showed that PCS on topics related to women 45-60 improved health-related quality of life, and reduced mental, urogenital, somatic, and stress-related symptoms with an effect lasting at least 12 months. These results suggest that PCS can improve health for midlife women and could be an effective intervention in PHC for improving women's health (IV).

Methodological aspects

Study design and study population (I, II, III, IV)

The present thesis was based on two observational studies and two RCTs. A cross-sectional study (I) was conducted to evaluate prevalence and severity of somatic, urogenital, and psychological symptoms measured with MRS in women 45-55 consulting PHC (I). A cross-sectional design could be considered when the purpose is to estimate prevalence and describe the severity of symptoms. All women were invited to a 6-year follow-up where 65% of participants could be included (III). The recruitment of participants in these studies aimed to reflect clinical practice.

Two RCTs (II, IV) were performed to assess the effect of an intervention performed in a PHC setting. In Studies II and IV, due to the character of the intervention the participants and investigators were not blinded to group allocation since they participated in the intervention.

Previous studies use different terms for menopause transition (16, 73, 77, 116, 132, 133). In the present thesis, the terms for the transitional period for women were; women aged 45–55 (III), middle aged (I, IV), menopausal women, and women during the menopause transition (II).

One hundred and thirty-one women were included in Studies I-III (Figure 3). These three studies were based on the same population, which is considered a strength as the women could be followed-up for a period of six years.

In Study IV participants were recruited by advertisement, which may have selected motivated women to participate in the study. However, approximately half of the included women had consulted PHC during the last two months at baseline suggesting that most of these women would have been included if we instead had used a consecutive enrolment in PHC. In this study, the women were followed up after 12 months, which is a longer follow-up period than in previous studies evaluating group education on topics related to middle-aged women (111-116).

Gender (I, II, III, IV)

This thesis includes only women, which may be considered a limitation, but the aim of the included studies was not to explore gender differences. The purpose of the included studies was to illuminate symptoms, identify prognostic factors for future health and interventions targeting topics relevant for the transition period for women 45-60.

Measurements (I, II, III, IV)

Validated self-reported questionnaires were used for assessment of symptoms, health, and quality of life in all included studied (I, II, III, IV). The questionnaires AUDIT, SF36, HADS, s-ED, PSS-14, MADRS and MRS used in this thesis have shown good validity and reliability in PHC population (118, 120, 125, 126, 129, 134, 135).

This thesis (I, II, III, IV) used the questionnaires MRS to measure quality of life and gain a profile of symptoms. The interventions were based on the MRS topics. MRS has been shown to be a better age- and condition-specific quality of life questionnaire for middle-aged women compared with SF-36 (42). Moreover, latest Swedish guidelines for menopause recommend using MRS (59). The SF-36 was included whereby it is a generic health-related quality of life measurement, which makes it possible to compare different populations regardless of condition.

MRS measures the severity of ageing symptoms and their impact on quality of life (42). Previous studies state that it can be used in PHC for the assessment of quality of life in a standardised way to guide treatment options (36). Furthermore, the MRS is showed to be a useful measure of treatment effect (27, 36).

In this thesis, a cut off score of 17 points in MRS was used for categorising women having severe menopausal symptoms, which has been previously recommended (126). How to define a cut off score for severe symptoms to treat menopausal symptoms and according to the woman's own perception are under discussion (36).

Interventions (II, IV)

In this thesis two RTCs were included. The educational programs structured in this thesis (II, IV) were based on the MRS sub-scales psychological, urogenital, and somatic. To our knowledge, this thesis is the first patient education program based on MRS items in Sweden in PHC on topics related to menopause transition to women aged 45-60 (II, IV).

In Study II, the control group was offered the same educational program as the intervention group after responding to Questionnaire II. Since the control group also received the intervention it is not possible to follow the effect of the educational program over time.

In Study IV, a two-factor design with four parallel arms and a high percentage follow-up, 78 % at six months and 79 % at twelve months, which is the main strength of this RCT.

Evaluating a person-centered individual or group educational intervention concerning issues relevant to midlife women with stress-related symptoms, is, as far as we know, the first in Swedish PHC. The contents of the interventions did not focus on hormones, but targeted natural ageing and topics related to the transition period for women 45-60.

Statistical analysis (I, II, III, IV)

In Study I, baseline values for a population of women 45-55 for prevalence of somatic, psychological and urogenital symptoms, and to evaluate factors associated with severe symptoms were measured with a multivariable logistics regression. To better complement the results and get an overview of the factors associated with severe symptoms a nomogram (Figure 4) was used and showed results of severe menopausal symptoms with an MRS > 17 points, age, and depression symptoms >7 points.

The MRS and MADRS were used in all the included studies. Both include items measuring anxiety and depression. However, MADRS contains several items without corresponding items in MRS. There is a significant overlap for MRS and MADRS, but also important differences. Spearmann's correlation coefficient was carried out to reinforce the fact that between MADRS ≥7 and MRS psychological sub-scale >6 the correlation is only 0.39 (n=108), which does not prohibit performing a regression analysis with these variables (I). Before logistic regression a multicollinearity test was carried out by exploring the value of the tolerance and VIF between independent variables (I, III, IV).
Study II has three possible approaches to analyse ordinal data, since treating observations measured by an ordinal scale, according to statisticians, vary (II). Using parametric methods such as a Student t-test, if data are normally distributed, are recommend by some statisticians. While others recommend that ordinal data always must be analysed using non-parametric methods. According to some statisticians the lack of equidistant scale steps such as for ordinal data is contradictory to the assumptions of simple subtraction, and consequently a change over time cannot be calculated. (II). We analysed the data using all three methods to ensure that this choice would not lead to incorrect conclusions. This approach has been used previously (44, 136, 137) (II).

Somatic, psychological, and urogenital symptoms and factors associated with severe symptoms in women (Study I).

Mental health

Study I indicated that among mental symptoms the most frequent and severe reported where depression symptoms (67 %), of which 17% reported "severe-very severe" symptoms. Physical and mental exhaustion were reported in 73 %, with ten percent reporting "severe-very severe" (Table 6). Depression and mental exhaustion are often related to prolonged high stress levels without adequate recovery. Psychosocial factors for the women have shown association with mental health and an impact on women's quality of life (13). Mental illness is the most common cause of long-term sick leave among midlife women in Sweden (6, 138). Early prevention for mental illness and mental exhaustion is recommended to reduce future sick leave (138-140). Hence, focus on preventive factors on women's mental health is important.

Sleeping problems

Sleeping problems together with depressive symptoms were the most prevalent (67 %, respectively), and of these 17% were reported severe to very severe symptoms (Table 5). Sleeping problems are a strong factor for the risk of developing mental ill-health affecting quality of life (15, 107). The incidence of sleep disorders increased for midlife women (63). Due to the high incidence of sleep problems and the strong link to mental illness, women's quality of sleep should be actively studied.

Pain

Musculoskeletal pain and stiffness are symptoms that usually affect midlife women (6, 141), and were one of the most common reported (70%), of which 11% had severe to very severe symptoms (Table 6). Muscle and joint pain are common causes of poor sleep quality and quality of life (21, 65, 142). In addition, pain and mental illness, are common causes of long-term sick leave in midlife women (3, 33, 143).

Cardiovascular symptoms

The risk for cardiovascular disease (CVD) increases from 45–55 years of age (57, 144). The present study indicated almost half of the women had cardiovascular problems and in accordance with previous studies reported heart discomfort (Table 6) (57, 67, 145). Moreover, risk may increase for mental illness from increasing stress factors and sleep problems (63, 72, 146).

Thus, increasing women's awareness of any cardiovascular risk factors is important (2, 57).

Urogenital symptoms and local oestrogen deficiency

A majority of women reported sexual problems, bladder symptoms and vaginal dryness of moderate severity (Tables 5 and 6). Moreover, bladder symptoms and vaginal dryness were reported from approximately half of the women (Table 6), which is consistent with previous studies (75). Local oestrogen deficiency (LOD) resulting in urinary incontinence (UI), vaginal dryness, burning and pain during intercourse, itching and frequent urinary tract infections, is a common cause of urogenital problems. Previous studies show that LOD symptoms and changes in women's daily lives and relationships may cause sexual problems and decreased sexual desire (76, 147, 148). Urogenital symptoms for midlife women have a strong impact on mental health and quality of life. Consequently, it is important to increase awareness of the symptoms of oestrogen deficiency, and of adequate treatment and relief of symptoms, and how various events and relationships in daily life impact health.

Early detection important but difficult

High prevalence of mental illness was shown in this study which is in line with previous studies (6, 13, 41, 55, 141). Furthermore, this study indicated that the prevalence of depression and menopausal symptoms seems to increase with age (Table 7 and Fig. 4). A previous study showed that long-term symptoms before seeking PHC were associated with delayed recovery, emphasizing the importance of identifying these symptoms. However, it can be difficult to detect depression symptoms while one third of women with depression symptoms only mention somatic symptoms when consulting PHC (141).

The transition between 45 and 55 years of age

The transition between 45 and 55 is a natural change in a woman's life. Some see this period as natural, while others see it as undesirable. This period includes major psychosocial changes such as children leaving home, ageing, parental care, changes in social relationships, and work (5, 13, 15, 38, 138, 149). Thus, social support can be valuable during this period (15). Therefore, it is important to pay attention to the symptoms experienced by women in midlife.

Group education for women about the menopause transition to improve their physical and mental ill-health (Study II).

Previous studies show that women's mental ill health and risk for long-term sick leave increases during menopause transition (55, 150). Therefore, education on a subject related to menopause transition could provide valuable health prevention input to women 45-55. This study indicated that it was possible and practical to organize group education around the topic of menopausal symptoms. For this group education the resources required were small. This intervention could be implemented as part of PHC's responsibility for health promoting activities.

Timing of education

Early detection and awareness of the symptoms of stress and poor mental health are important because delay involves risk for a prolonged recovery process (28). Previous studies have shown that girls in puberty maintain positive attitudes towards menstruation and the body if valuable information is provided just before the first menstruation (44). It is possible that early information about menopause transition is just as relevant for women about to enter menopause.

Prognostic factors for future mental, physical and urogenital health as well as work ability in women 45–55 (III).

This study (III) showed that better health 6 years later seems to be associated with living with a partner as compared to being single for women aged 45-55 with an impact on physical, social, and emotional role function (SF36) (Tables 12, 13 and 14).

Moreover, tertiary education seems to be associated with an increased risk of reduced mental health, vitality, and social role function (SF36) (Tables 12, 13 and 14). The level of education appears to be an important aspect to consider in health prevention work for women with poor mental health.

The ability to participate in social interaction in and outside the home as well as in daily life and work are important for mental health and preventing emotional problems (40).

The extent to which women live in an equal, friendly, harmless, and safe environment with their partner are social health factors and related to women's health. The ability to cope and solve problems and maintain a balance between work and leisure with time for recovery are other factors related to women's health. Previous studies show that women often have a higher level of education than men but a lower average income. Poorer general health and

anxiety problems were experienced more by women than by men (33). The results of our study seem to support that tertiary education was associated with future poorer mental health, lower vitality, and poorer social role functioning. Therefore, it is important for women to maintain an awareness of a healthy balance in life and to have realistic goals at work and at home. This intervention focused highly on social health factors impacting a woman's quality of life.

Tertiary education

Previous studies have often shown that mental problems and perceived poor health were attributed to people with less education compared to those with greater (88, 151). Women with less education had more sick leave compared to women with tertiary education (151). However, a dramatic change has occurred where the largest increase in sick leave has been in the group with longer education in the last 5 to 10 years (152). Factors appear to be high demands at work and at home, as well as psychosocial factors leading to increasing stress-related diagnoses in those with a tertiary education compared to women with a lower education (38, 40). The increased ill health of the highly educated women can also be related to greater exposure to certain risks, such as patriarchal systems that hinder women's progress in work, unreasonable burdens caring for others, imbalance between traditional administrations and realities in life and violence and sexual harassment at work (19, 33). Previous studies show a high increase of long-term sick leave caused by stress-related illness and depression among female academics (152).

This study appears to support the fact that tertiary education is associated with future poorer mental health, lower vitality, and lower social role functioning. Therefore, it is important to maintain women's awareness of a healthy balance in life and to have realistic goals socially and at work.

Living with a partner

Important factors for good mental health were social support and a successful marriage (153). Communication in a relationship may be a key to good health (154). Hence, it is important to be aware and inquire into marital status and partner relationships and the quality of relationships when discussing health issues with midlife women. Better mental health and quality of life were shown in happily married midlife women compared with women unhappily married and single women (153, 154). Higher marital quality and social support were shown to be associated with better health and a lower risk of mortality (153, 154).

The effect of group education and person-centred support in a primary health care context on mental health issues and quality of life (Study IV).

This study is the first in Swedish PHC evaluating an individual or group educational intervention concerning issues relevant to middle-aged women with stress-related symptoms. The contents of PCS and GE do not focus on hormones but target natural ageing and topics related to middle-aged women. In this RCT the intervention was led by district nurses and midwives working in PHC who often meet middle-aged women with stress-related symptoms. The interventions GE and PCS contained mental and psycho-social topics related to common psycho-social factors and events in the period of midlife as these factors have been shown to have a strong association with psychological symptoms and mental health impacting women's quality of life (5, 15, 16, 27) The interventions also included discussions about urogenital health such as symptoms and the course of local oestrogen deficiency due to a strong correlation to quality of life impacting the women's health. Menopause VMS such as hot flushes and sweating was discussed in the intervention as it affects 60-80% on middle-aged women and has been strongly related to reduced quality of life physically and psychosocially, impacting sleep and overall wellbeing (16, 61). In addition to the topic of VMS, these interventions also consisted of a discussion on the subject of cardiovascular risk-and health factors, and sleep problems. For midlife women, cardiovascular symptoms, and the incidence of CVD are increasing (57, 72, 144).

A person-centered approach was used in the interventions based on the women's narratives, needs and beliefs. The district nurse and midwife encouraged the women to use coping strategies for the process of changing thoughts and behavior to impact health and quality of life.

The PCS improved health and quality of life in middle-aged women at the short and long-term follow-up. The improvement was shown in all analyses (CC, PP, ITT) for urogenital, psychological, and total MRS, stress symptoms (PSS-14) and mental health (SF26-MH) at 6 and 12 months. At the 6-month follow-up depressive symptoms increased for GE and PCS (Table 3, Study IV). For PCS the result was the opposite at 12 months showing a decrease in depressive symptoms (MADRS). This result might be explained by the need for time to gain awareness of lifestyle consequences and to change thoughts and behavior (1, 15).

Health-related quality of life

These interventions led to improved quality of life measured with MRS. MRS could be used to show the impact of menopausal symptoms on quality of life and evaluate the severity of symptoms associated with menopause and assess treatment effect. This is an important effect since the signs and symptoms can affect women's quality of life by up to 80%, and about 42% reported symptoms as very serious. These interventions included dialogues reflecting somatic symptoms (sleep, hot flushes, heart symptoms and pain), urogenital symptoms (UI, LOD, sexual problems) and psychological symptoms (depression symptoms, irritability, difficulty concentrating, and mental and physical exhaustion) and psychosocial factors due to a strong correlation with quality of life and impact on women's health (5, 17, 27).

Mental Health

This study indicated improved mental health in both GE and PCS at the 12-month follow-up, which is an important result whereby women have a higher risk for mood changes (16, 27) as well during the menopause transition (5, 15). Experience of psychosocial factors has shown to have a much stronger association with psychological symptoms than the stages of menopause (1). PHC treats almost 70% of patients diagnosed with depression and stress-related disorders (7, 109).

Decreased mental illness might reduce the risk or development of a CMD, and the risk of experiencing life as uncontrollable and overloaded, and perceived mental stress, which has been shown in previous studies (119). GE and PCS contained mental and psychosocial topics related to midlife women due to psychosocial factors showing a strong association with psychological symptoms and mental health, and impacting women's quality of life (5, 15, 16, 27, 77).

Urogenital health

The intervention PCS improved urogenital symptoms, which is an important result since urogenital symptoms have a strong correlation with decreased quality of life and mental illness (16, 73). Previous studies have shown that symptoms of local oestrogen deficiency were experienced by half of all postmenopausal women (75, 76). Moreover, urinary incontinence (UI) is another common urogenital health problem among women and where approximately 50% of midlife women are affected by UI and the severity of leakage has a negative effect on quality of life (73).

Somatic health

PHC offers basic treatment for women with VMS and these interventions GE and PCS included dialogues on somatic symptoms in a person-centered approach. For midlife women, cardiovascular symptoms, and the incidence of CVD are on the rise (57, 72, 144) and previous studies have shown improved mental and physical health after person-centered education for patients with CVD risk (104, 108, 117). However, in this study somatic symptoms measured with MRS were not improved after 12 months.

District nurse role in primary health care

The interventions in this thesis are based on health prevention in women's natural ageing from 45-60 years of age, which is within the district nurse's competence and area of responsibility (88). The district nurse plays a key role, working independently, with responsibility for health prevention work in PHC based on a person-centered approach. She is a support for people of all ages "from the cradle to the grave", with naturally ageing and development, regardless of condition, where psychosocial aspects are an important factor (84, 87). Thus, the result of this thesis, including the use of MRS when screening for menopause symptoms and important prognostic factors for later health in middle-aged women and the intervention PCS, should be implemented using the district nurse’s competence for improving women’s health.

In summary, the district nurse's work is an opportunity to work with people of all ages, with varying health conditions, and promote the patient's physical and mental health, and social well-being based on a health-promoting, person-centered, and health pedagogical approach, with a perspective on natural development and ageing (84, 87, 88, 155).

CONCLUSION

The conclusion of this thesis is that the included studies have described and identified factors associated with the transition period in women between the ages of 45 and 60, identified prognostics factors for later work ability and quality of life as well as positive effects on health-related quality of life, physical, urogenital, and mental symptoms of a person-centered intervention in PHC.

The diversity and severity of symptoms can be elucidated with MRS, and mental ill health symptoms appears to be the most common, and more severe depression symptoms and increasing age were associated with more severe symptoms according to MRS.

It appears that midlife women living with a partner have a better chance to be in good health and having tertiary education was shown to be associated with poorer mental health after 6 years.

Individual person-centered support (PCS) on topics related to women 45-60 improved health-related quality of life, and reduced mental, urogenital, somatic, and stress-related symptoms with an effect lasting at least 12 months. These results suggest that PCS can improve health for midlife women and could be an effective intervention in PHC for improving women's health.

FUTURE PERSPECTIVES

This thesis concluded that poor mental health was shown to be the most common symptom in midlife women and more severe depression symptoms and increasing age were associated with more severe symptoms according to MRS. To prevent severe menopausal symptoms, we recommend that cardiovascular risk factors, musculoskeletal symptoms, urogenital problems, sleeping problems and mental health should be actively penetrated in midlife women aged attending PHC. Using the questionnaire MRS can generate a profile of menopause symptoms to evaluate the severity of ageing related symptoms and their influence on quality of life. Future studies could evaluate preventive intervention for women consulting PHC before the age of 45.

Living in a good relationship with a partner seems to be a strong factor for good perceived health, while tertiary education seems be a risk factor for poorer mental health 6 years later. To gain a deeper knowledge a qualitative study could illuminate this factor.

An individual person-centred support (PCS) on topics related to the transition period in midlife women improved health-related quality of life, and reduced physical, urogenital, mental, and stress-related symptoms with an effect lasting at least 12 months. Future research could evaluate an implementation process and health economics.

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