The Menopause. Symptoms, Use of Hormones and General Practitioners' Attitudes and Advice

Studies of a Norwegian Female Cohort and Norwegian General Practitioners.
The Menopause. Symptoms, Use of Hormones and General Practitioners' Attitudes and Advice

Studies of a Norwegian Female Cohort and Norwegian General Practitioners

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Dissertation for the degree Philosophia Doctor (PhD)
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B  HWC Study: Letter and Questionnaire Wave 7

Errata
Acknowledgements

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Summary

The treatment of symptoms associated with menopause and the prevention of chronic disorders among post-menopausal women have been intensely debated both in the medical community and in the public during the last five or six decades.

Before the “hormone therapy (HT) for prevention” era of the 1990s, an international debate on menopause and hormone therapy (at that time called hormone replacement therapy – HRT) as an example of medicalisation had taken place. From 1990 onwards, HT was generally advocated as a reliable prevention for chronic diseases among postmenopausal women, especially osteoporosis, coronary heart disease, urinary incontinence and also cognitive loss and dementia. During a short time span around the turn of the millennium, the evidence base for hormone therapy (HT – estrogen and estrogen/gestagen therapy) during and after the menopause changed profoundly. Results from randomized controlled trials and new results from observational studies showed that HT did not prevent cardiovascular disease and led to increased risk for breast cancer. The findings led to a complete reversal of the treatment recommendations. According to the Norwegian recommendations, the indication for HT is bothersome hot flushes with a negative influence on quality of life, and the treatment should be revised annually.

The general practitioners (GPs) in Norway prescribe about half of the HT medicaments and they are important discussion partners for women in this age. The first part of the thesis, the GP study, deals with the attitudes and knowledge among Norwegian GPs regarding HT after the new evidence was published and the changing of the Norwegian recommendations. What did the GPs think about their role in prescription, and how did they assess the risks and side effects of the treatment? Did the GPs give different advice to the women, and if so, which factors were associated with these differences? We also wanted to investigate the use of HT among female GPs themselves. A random sample of 400 GPs were in May 2004 invited to participate, and 289 (72 %) returned a completed questionnaire. Three of the questions were formulated as clinical examples where doctors were requested to give an opinion about whether they would advise using HT or not, and they could also give their own comments. The results are published in Paper I and II in the dissertation. In 2004, most Norwegian GPs were familiar with the current evidence base regarding the effects and side effects of HT, and that they followed the recommendations regarding indications and contra-
indications. A large majority of the respondents agreed to the statements that hormone therapy increases the risk of breast cancer, that it does not prevent myocardial infarction and that the most important reason to prescribe hormone therapy is bothersome hot flushes. Female GPs seemed better updated on some aspects of the treatment than male doctors, while at the same time 14 out of 17 (82 %) peri- and postmenopausal female GPs were using or had used such treatment. A majority of the GP’s agreed to the statement that HT improves sex life, and almost half of the GP’s believed that HT counteracts aging of the skin. The doctors were asked to agree or disagree to a statement that HT implies an undesirable medicalisation of a natural life phase in women. One third of the GPs agreed, while some more (44 %) disagreed and 24 % were neutral to the statement. None of the background factors (e.g. age or gender) predicted the standing on this question.

When doctors were requested to give an opinion on clinical examples, they were notably divided in their view on therapy or not. The attitude to HT (elicited through the medicalisation question) was the most important predictor for the advice given, and perception of indications, contraindications and effects of HT played a lesser role in the judgment. Those who did not agree to the medicalisation statement were most in favor of treatment.

In the second part of the dissertation, the HWC Study, the aim was to describe the natural course of menopause and the use of HT in a representative female cohort in Norway. A particular aim was to analyze symptom prevalence over time during the natural menopausal transition, and to investigate which health factors, life style and socio-economic factors that were associated with frequency of symptoms. Another aim was to determine the association between symptoms and self-rated health. We also wanted to investigate the use of HT in the Cohort; factors associated with use of HT and to which extent the use of HT were in line with the Norwegian 2003 recommendations. Finally, we wanted to study if symptoms reappeared after cessation of HT. The Cohort consisted of 2229 women aged 40-44 at baseline, and the women have received almost identical questionnaires approximately every second year. The material used in this study cover the first seven questionnaires (Waves 1 – 7; 1999 - 2010). Data for 2002 women (90 %) were eligible for analyses, and the results are published in Paper III and IV.
In a longitudinal analysis, 36% of the women reported daily hot flushes in one or more questionnaires, whereas 29% did not experience hot flushes at all. The prevalence of daily hot flushes increased from 2% at ages 41-42 to 22% at ages 53-54. Daily smoking and low education was associated with more hot flushes.

The two-year incidence of new HT users dropped significantly from 8.2% in 2002 to 4.3% in 2004 and remained stable despite increasing prevalence of symptoms in the cohort. Self-reported health was good or excellent for a high proportion and remained stable in the same period. 29% of the women reported use of HT during the observation period, and mean duration of HT use was 4.5 years. Odds of HT use were higher among women with daily hot flushes compared to those who never or rarely experienced them. After HT cessation, hot flushes were still present and the frequency did not differ from the untreated controls.

**Conclusions**

Norwegian GPs were generally aware of available evidence of effects and side effects of HT after 2002, and observed the recommendations with respect to indications and contraindications. The doctors’ attitude to the question of whether the treatment implies medicalisation was more crucial for the advice they gave than their perception of indications, contraindications and the effects of treatment, and was also important in the assessment of indications and contraindications. Such factors should be addressed when new clinical guidelines or recommendations are implemented.

The proportion of menopausal female GPs who used hormone therapy themselves was substantially higher in 2004 than the average for the female population in the same age group. This finding may imply that menopausal female GPs regarded the individual risk of treatment as low, and that most of them found the benefits of treatment greater than the risks. The finding is in line with other surveys. However, little research has been done to clarify reasons for the increased HT use among doctors.

An important finding in HWC was that the prevalence of bothersome symptoms was lower than in most other international surveys. Among healthy women, daily smoking was an independent risk factor for experiencing daily menopausal symptoms. This finding should encourage women to stop smoking.

Use of HT in the HWC was lower than documented in comparable Nordic and international studies for the same period. Even though the symptom burden increased for
every wave up to the last wave (Wave 7), the use of HT did not increase after 2002. Many women preferred to live without HT in spite of their bothersome symptoms. Those who reported most symptoms had higher risk for reporting bad or not so good health, but the symptom burden did not influence self-rated health in the cohort in general. Our study design does not allow inference as to whether individual women have been under-treated, but the stable distribution of self-rated health categories after 2002 does not indicate systematic under-treatment in the cohort. The indication for HT according to the guidelines is bothersome hot flushes with a negative influence on quality of life. Hot flushes was the strongest predictor for HT use, and together with the fact that self-rated health did not change in a negative direction, we conclude that HT use in HWC was largely in line with the recommendations.

In line with other findings, we found that symptoms reappeared in most women after HT cessation. Further research is necessary to clarify in more detail the duration of treatment which may be necessary for symptoms to ware off.
Norsk sammendrag

Hormonbehandling av symptomer som er forbundet med menopausen og medikamentell forebygging av kroniske sykdommer etter overgangsalderen har blitt intensit diskutert de siste 5-6 tiårene, både i medisinsk fagpresse og i det offentlige rom.


Et tilfeldig utvalg av 400 norske allmennleger fikk i mai 2004 tilsendt et spørreskjema med spørsmål om effekter, indikasjoner, kontraindikasjoner, oppfatning av rolle og oppfatning av risiko ved HT. 289 leger (72 %) besvarte skjemaet. Tre av spørsmålene var formulert som kliniske eksempler der legene ble bedt om å angi om de ville gi råd om bruk av HT eller ikke, og de kunne også gi egne kommentarer i fri tekst.

Resultatene er publisert i Artikkel I og II i avhandlingen, og viste at flertallet av allmennlegene var kjent med den tilgjengelige dokumenterte kunnskapen om effekter og bivirkninger av HT. De fleste anga at de fulgte gjeldende anbefalinger med hensyn til indikasjoner og kontraindikasjoner. Et stort flertall av allmennlegene var enig i at HT øker risiko for brystkreft, at behandlingen ikke forebygger hjerteinfarkt og at plagsomme hetetokter er den viktigste indikasjonen for behandling. 14 av 17 (82 %) kvinnelige allmennleger som var i eller etter overgangsalderen anga at de brukte eller hadde brukt HT. Undersøkelsen viste også at et flertall av legene hadde tiltro til mer uspesifikke og mindre dokumenterte effekter av HT, slik som positiv effekt på seksuallivet og at HT motvirker aldring av hud. De anså allikevel ikke dette som viktige indikasjoner for behandling. Legene ble spurt om de mente at HT innebar en uheldig medikalisering av kvinners overgangsalder. En tredjedel av legene var enig i påstanden, noe flere (44 %) var ikke enig mens en fjerdedel var nøytral. Ingen av bakgrunnsvariablene (f.eks. alder eller kjønn) predikerte standpunktet legene inntok til dette spørsmålet. Et viktig funn var at legene var tydelig delt i spørsmålet om å anbefale behandling eller ikke i de kliniske eksemplene. Holdning til HT bruk, belyst ved spørsmålet om medikalisering var den viktigste faktoren som predikerte anbefaling om å bruke eller ikke bruke HT, mens oppfatning av indikasjoner, effekt og risiko ved behandlingen spilte mindre rolle. De som var uenige i påstanden om medikalisering var mer tilbøyelige til å anbefale behandling.

I den andre studien, *Kvinnekohorten i Hordaland*, var målsettingen å beskrive det naturlige forløpet av overgangsalderen og bruk av hormoner i en kohort av friske kvinner. Hvilke helse-, livsstils- og sosioøkonomiske bakgrunnsfaktorer er assosiert med hyppighet av symptomer, og er det sammenheng mellom symptomer og egenrapportert helse? Vi ønsket også å undersøke bruk av hormoner i kohorten, hvilke faktorer som var forbundet med hormonbruk og i hvilken utstrekning bruken var i samsvar med norske anbefalinger. Til slutt har vi ønsket å undersøke om symptomer kom tilbake etter at hormonbehandlingen ble avsluttet.
Kohorten besto av 2229 kvinner som var i alderen 40-44 år ved oppstart, og kvinnene har mottatt spørreskjema årlig eller hvert annet år fra 1999 til 2010. Data fra 2002 kvinner (90 % av kohorten) ble brukt i analysen, og resultatene er publisert i Artikkel III og IV i avhandlingen.

I den langsgående analysen anga 36 % av kvinnene daglige hetetokter og mye plager i en eller flere runder, mens 29 % av kvinnene anga lite eller ingen hetetokter overhodet. Forekomst (punkt-prevalens) av daglige hetetokter økte fra 2 % i alderen 41-42 år til 22 % i alderen 53-54 år. Røyking (registrert ved oppstart eller senere) og lav utdanning var forbundet med økt forekomst av daglige hetetokter i løpet av overgangsalderen.

Toårs insidens av HT-bruk (nye brukere, ikke bruk i forrige runde) sank fra 8,2 % i 2002 til 4,3 % i 2004 og forble stabil på dette nivået på tross av økende symptomer blant kvinnene. 29 % av kvinnene anga at de hadde brukt HT i løpet av observasjonsperioden. Gjennomsnittlig varighet av bruk var 4,5 år. Den viktigste faktoren som var forbundet med bruk av HT var opplevelse av daglige hetetokter. For de fleste kom symptome tilbake etter å ha sluttet med HT, og forekomst av symptomer var da ikke forskjellig hos brukere og ikke-brukere.

**Konklusjon**

Norske allmennleger var generelt godt oppdatert om kunnskapsgrunnlaget for HT etter 2002. Legens holdning til spørsmålet om medikalisering var mer avgjørende for de råd som ble gitt enn holdning til risiko, indikasjoner og kontraindikasjoner, og hadde også betydning for vurderingen av indikasjoner og kontraindikasjoner. Det kan tyde på at slike holdningsfaktorer er av stor betydning når nye behandlingsråd eller retningslinjer skal implementeres.

Andelen kvinnelige allmennleger som bruker HT var fortsatt høy i 2004 sammenliknet med kvinner generelt i samme aldersgruppe. Funnet kan innebære at kvinnelige allmennleger anser at den risikoen de selv løper ved å bruke HT er lav, og at de fleste av dem anser at fordelene ved behandlingen er større enn risikoen. Tilsvarende funn er gjort også i andre land, men er i liten grad blitt gjenstand for ytterligere forskning.

Et viktig funn i kvinnehohorten var at forekomsten av plagsomme symptomer var lavere enn i de fleste sammenliknbare internasjonale undersøkelser. Blant friske kvinner
var daglig røyking en risikofaktor for å bli plaget med hyppige hetetokter, og funnet burde oppmunte til røykeslutt.


Ytterligere forskning er nødvendig for å klarlegge mer detaljert hvor lenge behandlingen må vare før symptomene er over for de fleste, dersom den starter omkring menopause alder.
List of Papers


IV. Gjelsvik B, Straand J, Hunskår S, Dalen I, Rosvold EO. Use and discontinued use of menopausal hormone therapy in healthy women in Norway. The Hordaland Women’s Cohort (HWC) study. Accepted for publication in Menopause, the Journal of the North American Menopause Society.

*Papers are originally published in Norwegian in Tidsskrift for den Norske Legeforening. Norwegian and English version is published on the Journal’s web site.
Definitions and abbreviations

Definitions of the menopause

In everyday language, the menopause means end of menstruation – that is the cessation of regular or irregular vaginal bleeding and the end of the fertile ability– and is experienced by every woman reaching that age. The aging process of the ovum and the ovarium is accompanied by and determined by several hormonal changes, and is not yet fully understood and characterized. The term climacterium is used somewhat imprecise to include the period from the beginning of menopausal symptoms and more irregular bleeding occur, until bleeding has stopped and the symptoms have more or less disappeared. In order to communicate and discuss the process and the symptoms more precisely, it has been necessary to apply more precise definitions on the stages of female reproduction. The WHO issued a definition of menopause in 1981, later revised and evaluated by an international group of researchers in Korkylampi, Finland in 1986\(^1\). In this definition, the natural menopause called Final Menstrual Period (FMP) was defined retrospectively after 12 months of amenoré. Later revisions by the WHO Scientific group in 1996\(^2\) have added criteria to the definitions in order to clarify the nomenclature used in international research. The latest achievements have been proposals from the International Menopause Society in 1999 and the definition adopted by the Stages of Reproductive Aging Workshop (STRAW definition), Utah, USA 2001 (fig. 1)\(^3\). Here, the menopausal transition is divided in two stages and covers a variable space from the cycles become irregular (> 7 days different cycle length) until FMP occur. The early postmenopause runs four years from FMP and is followed by the late postmenopause. The term perimenopause includes the menopausal transition and the first year after FMP, and will for many authors cover the same idea as the concept climacterium.

The definitions below includes recommendations by the WHO in 1996 as well as the IMS-proposed addition of the term climacteric\(^2,4\).

1. **Natural menopause** is defined as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity. It is recognized to have occurred after 12 consecutive months of amenorrhea, for which there is no other obvious pathologic or physiologic cause. Menopause occurs with the final menstrual period (FMP), which is known with certainty only in retrospect ≥ 1
1. An adequate independent biologic marker for the event does not exist.

2. *Perimenopause* includes the period immediately before the menopause (when the endocrinologic, biologic, and clinical features of approaching menopause commence) and the first year after menopause. WHO advise the term *climacteric* to be abandoned to avoid confusion.

3. *Menopausal transition* covers a variable time space from the cycles become irregular (> 7 days different cycle length) until FMP occur.

4. *Postmenopause* is defined as the period dating from the FMP, regardless of whether the menopause was induced or spontaneous.

5. *Induced menopause* is defined as the cessation of menstruation that follows either surgical removal of both ovaries (with or without hysterectomy) or iatrogenic ablation of ovarian function (e.g., by chemotherapy or radiation).

6. *The climacteric* is the phase in the aging of women marking the transition from the reproductive phase to the nonreproductive state. This phase incorporates the perimenopause by extending for a longer variable period before and after the perimenopause.

7. *Premature menopause* ideally should be defined as menopause that occurs at an age ≥ 2 standard deviations below the mean estimated for the reference population. In practice, in the absence of reliable estimates of the distribution of age at natural menopause in populations in developing countries, the age of 40 years is frequently used as an arbitrary cut-off point, below which menopause is said to be premature.

The definition of menopause (and FMP) is in the thesis based on the self-reported cessation of menstruation, and this fact leads to several methodological problems. An (unknown) proportion of women experience menstrual bleedings after 12 months of amenorrhea, and this may result in a reassessment of FMP among these women. Also, the use of contraceptives (gestagen pills or IUD) often leads to cessation of menstruation without the other symptoms indicating that menopause has occurred. How women with simple hysterectomy should be regarded has not been clearly stated by the WHO definition. Therefore, these women are often excluded in studies or treated in separate groups. It is also worth noting that several studies indicate that women’s self-rating of
menopausal state often disagree with the menstruation-based definition\textsuperscript{7-13}. In epidemiological studies, investigators have chosen different strategies to overcome this\textsuperscript{14}. In our study, we decided to exclude the women who had undergone oopherectomy and/or hysterectomy, since we did not have access to hospital data, follow-up interviews or other ways to ensure if both ovaries or only one had been removed. In addition, studying the natural course of menopause was our primary interest. FMP and menopausal status were in our study established by means of last self-reported menstruation at least 12 months before the questionnaire was filled in, and no later reporting of menstruation.

\textbf{FIGURE 1}\textsuperscript{15}

Stages/nomenclature of normal reproductive aging in women. The stages of reproductive aging in women in relation to the final menstrual period, defined as Stage 0. Stage \(-5\): the early reproductive stage. Stage \(-4\): the peak reproductive stage. Stage \(-3\): the late reproductive stage. Stage \(-2\): the early menopausal transition. Stage \(-1\): the late menopausal transition. Stage +1a: the first year after the final menstrual period. Stage +1b: years 2 to 5 after menopause. Stage +2: the later postmenopausal years. Recommendations of Stages of Reproductive Aging Workshop (STRAW), Park City, Utah, July 2001. (Reprinted with permission from the American Society for Reproductive Medicine. \textit{Fertility and Sterility}, 2001, Vol. 76, No. 5, page 875).

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<th>+2</th>
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<td>Reproductive</td>
<td>Menopausal Transition</td>
<td>Postmenopause</td>
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<tr>
<td>Duration of Stage</td>
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<td>variable</td>
<td>Early</td>
<td>Late*</td>
<td>Early*</td>
<td>Late</td>
<td></td>
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<tr>
<td>Menses</td>
<td>variable to regular</td>
<td>regular</td>
<td>variable cycle length (\textasciitilde 28 days)</td>
<td>regular menstrual cycles after \textasciitilde 1 year</td>
<td>no menstrual cycles after \textasciitilde 4 years</td>
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<tr>
<td>Endocrine</td>
<td>normal FSH</td>
<td>\textasciitilde FSH</td>
<td>\textasciitilde FSH</td>
<td>\textasciitilde FSH</td>
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*Stage most likely to be characterized by vasomotor symptoms \textasciitilde elevated

Figure 1. STRAW definition of the normal reproductive aging in women. Reprinted with permission from \textit{Fertility and Sterility}, 2001, Vol 76, No 5, page 875.

\textbf{Abbreviations}

\textbf{AR} Absolute risk.

\textbf{ARR} Absolute risk reduction (risk difference or excess risk) is the difference between the control group’s event rate (CER) and the experimental group’s event rate (EER). The difference is usually calculated with respect to two treatments \(A\) and \(B\), with \(A\) typically a drug and \(B\) a placebo.

\textbf{BMI} Body Mass Index: weight(kg)/height(m)\textsuperscript{2}.

\textbf{CER} Control event rate: the number of events in the control group divided by the number of participants in the control group.
CHD  Coronary heart disease
CONOR  Cohort of Norway. A collection of health data and blood samples from several Norwegian health surveys with the purpose of investigating the causes of disease. Among these are HUSK and HWC.
CVD  Cardiovascular disease
DDD  Defined daily dose of a medication, according to international pharmaceutical standards.
$E_2$  Estradiol.
EER  Experimental group event rate. The number of events in the experimental group (typically the treatment group in clinical trials) divided by number in the same group.
EMS  European Menopause Society
ET  Estrogen Therapy: Treatment with estrogen only for women without an intact uterus.
FSH  Follicle stimulating hormone.
GP study  The general practice part of the Thesis: Questionnaire sent to 400 Norwegian GPs in April 2004.
GP  General Practitioner / Family Medicine Practitioner.
HERS  Heart and Estrogen/progestin Replacement Study.
HF  Hot flushes.
HRT  Hormone Replacement Therapy: Treatment with estrogen and/or estrogen-progestogen combination of peri- and postmenopausal women, in later years replaced by the notion HT (underneath).
HT  Hormone therapy: Treatment with systemic estrogen and/or estrogen-progestogen combinations for women during perimenopause and/or later.
HUSK  The Hordaland Health Study.
HWC study  The Hordaland Women’s Cohort part of the Thesis. The Cohort started in 1999, with baseline data from HUSK (Helseundersøkelsen i Hordaland) in 1997-98 when the women was aged 40-44 years. In 2010, the Cohort had finished seven questionnaires and reached the age of 53-57 years.
HWC  The Hordaland Women’s Cohort.
IMS  International Menopause Society
LH  Luteinizing hormone.
MWMHP  Melbourne Women’s Midlife Health Project, an Australian Cohort study.
MWS   Million Women Study.
NAMS  North American Menopause Society
NDA   Norwegian Drug Agency [Legemiddelverket].
NHD   Norwegian Health Directorate [Helsedirektoratet].
NIPH  Norwegian Institute for Public Health [Folkehelseinstituttet].
NMA   Norwegian Medical Association [Den norske legeforening].
NNH   Number needed to harm. The reciprocal value of absolute risk increase (1/ARI). The number that must be treated to cause one additional event (side effect, death or disease), compared with no treatment. F.ex. 125 women must be treated with HT in 10 years to cause one additional case of breast cancer.
NNT   Number needed to treat. The reciprocal value of absolute risk reduction (1/ARR). The number who must be treated by a given therapy to avoid one pre-defined event (death or disease), compared with no treatment.
NSAM  Norwegian College of General Practitioners [Norsk Selskap for Allmennmedisin], from 2006 NFA – [Norsk Forening for Allmennmedisin].
QoL   Quality of Life.
RRR   Relative risk reduction: calculated by dividing the absolute risk reduction by the control event rate (CER).
S/NS  Sweats/night sweats.
STRAW Stages of Reproductive Aging Workshop. An expert group putting forward a refined definition of the stages of the female reproduction and menopausal transition (STRAW definition), USA 2001.
SWAN  Study of Women’s Health across the Nation, a US based cohort study.
Regular GP Scheme. The health reform carried out in 2001 in Norway, giving every citizen the right to be listed as a patient by a GP who is employed by or having contract with the local municipality.
VMS   Vasomotor symptoms: hot flushes and sweats, night sweats.
WHI   Women’s Health Initiative Study.
WHO   World Health Organization.
Preface

In my clinical and professional work as a general practitioner (GP), I was for many years interested in the broad field of prevention, especially prevention of cardiovascular disease. This led me in contact with groups in the Norwegian College of General Practitioners (NSAM), and the discussion which took place in the 1990s and onward on the problems of medicalisation of large proportions of the population. During these years, there was an ongoing debate regarding individual-oriented prevention of cardiovascular disease, which was the main cause of death in the Norwegian population from 1960 and onwards. The controversies covered several areas, including the question of which risk level should be the threshold for initiating medical interventions, and what was the most cost-effective treatment. Often, doctors from primary care were opposed to secondary care specialists, and an important reason for this was the differences in perspectives. The GPs are confronted with mainly healthy people, and in the field of prevention should be more concerned about the factors which keep people healthy, while the organ specialist are more concerned about the diseases and the factors that may lead to sickness and death. In this field, also the industry plays an important role. Individual-oriented prevention is an enormous market. The greater proportion of the population that can be included in the market plans, the greater is the potential for profit.

As a member of the Reference Group for Cardiovascular Disease Prevention in The Norwegian College for General Practitioners, (I was also a member of the board and later also the president of the College) I was engaged in the work to produce sustainable guidelines for prevention in Primary Care\textsuperscript{15-18}. The board was concerned about the “risk epidemic” in a broader sense and initiated “The Risk Project”\textsuperscript{19}, supported by the Health Minister at that time. The Risk Project was an effort to focus on the side effects following interventions to reduce risk for future disease in the population.

For me, this also led to an interest in other areas of medicine where arguments for prevention of disease and health maintenance have been used to prescribe medication. An outstanding example of this is hormone therapy of women during and after the menopause.

In 2002, new evidence emerged which profoundly changed the scientific basis of hormone treatment of the postmenopausal woman. The results from the North American Women’s Health Initiative study showed that oestrogen and oestrogen-gestagen treatment did not prevent cardiovascular disease, as had been argued during the 1990s\textsuperscript{20}. Before this
evidence emerged, several indications had been given to advocate the prescription of HT, and there were very few arguments against the use of hormones. Many GPs in Norway had been a little reluctant, but the concerns about side effects of the treatment had gradually diminished over the years, with the growing evidence from epidemiological studies about the benefits of the treatment. Now – quite suddenly – the evidence changed.

After the WHI results were published, there were some media reports and discussions about the treatment in Norwegian newspapers, but the discussions were not very long-lasting. In the autumn of 2002, a question was raised in the Internet discussion forum for Norwegian GPs, EYR: “How does Norwegian GPs address the question of hormone treatment of the menopause?” The person behind this demanding question was Ivar Aursnes, professor of Pharmacotherapy at the University of Oslo, and nobody could answer his question. I discussed it with my co-authors of the first article, Per Hjordahl at the Institute for General Practice and Community Medicine and GP Elisabeth Swensen, who had been active in NSAM’s Risk Project.

In the first phase of the project, I wanted to find out how the GPs in Norway dealt with the new evidence. What did they think about indications, contraindications and risk after the publishing of the WHI results, and what kind of advice did they give to the women? This led to a questionnaire survey sent to 400 Norwegian GPs in 2004, the GP study of the project. Two articles were published in the Journal of The Norwegian Medical Association 21,22.

This first phase of the project led to an interest in the women themselves: Do we have valid information about the natural course of menopause among Norwegian women? How often and how long do women experience bothersome symptoms? Who use HT and for what, and have new guidelines changed practice? These are aspects of the menopause where precise information is valuable for the GP when giving advice to women in this age group. The second phase of the project consists of data from the Hordaland Women’s Cohort, a population-based cohort of 2229 women in the Hordaland County of Western Norway. In 2010, the Cohort had finished seven questionnaires and reached the age of 53-57 years. It was possible for me to contribute to the questionnaire in the seventh wave of the Cohort. Detecting symptoms and symptom burden during the menopausal transition, and use of medication among healthy women during this period of life were some of the aims of the Cohort.
After the publishing of the WHI results in 2002, HT had been continuously discussed in international medical journals, and new evidence has emerged also in the field of menopausal symptomatology. Although the evidence has been emerging, there are still many controversies and challenges for the clinicians. It is my hope and ambition that the results from these Norwegian surveys will contribute to the knowledge and clinical work done by the GPs and other doctors working with women in this age group, and for the women themselves.
Background

The written knowledge of female menopause goes back to the ancient Greeks. The Greek word *menopause* consists of the word “menos”, which means “month”, and “pause”, which means “cessation”. The literary meaning is “the cessation of monthly periods”. The word “climacterium” refers to steps in a ladder. During the history, there has been diverging perspectives regarding the menopause: should it be viewed as a step “up” or a step “down” the ladder? Previous medical literature had rather curious and speculative descriptions of the menopause, as this from 1887:

“The ovaries, after long years of service, have not the ability of retiring in graceful old age, but become irritated, transmit the irritation to the abdominal ganglia, which in turn transmit the irritation to the brain, producing disturbances in the cerebral tissue exhibiting themselves in extreme nervousness or in an outburst of actual insanity.” (Farnham AS, cited in 23).

In her dissertation, the Swedish GP Helene Ekström14 notes a shift of the view of the female climacteric in the last part of the 19th century. In the 18th century, physicians believed that the cessation of menstruation preserved the health of older women, and hot flushes were by some scientists seen as beneficial. The term “menopause” was introduced by the French physician Gardanne in 1821, at a time when the specialty of gynecology and obstetrics was formed in Europe. From the mid of the 19th century an increasing number of diseases and bothersome symptoms and conditions became associated with the menopause, and a perception of menopause as a negative event became prevalent24. Following the isolation of sex hormones in the 1920s and the syntetication of oestrogen in 1938, the menopause was defined as a hormone deficiency state and ultimately a disease25,26. Addressing the general public in 1966, the American gynecologist Robert Wilson in his famous book “Feminine forever” started the first wave of HT, at that time called hormone replacement therapy (HRT)27. The notion of menopause as a deficiency state, in which hormones should be replaced, came to dominate the medical discourse of menopause in the Western world. Naturally, this deficiency state also became associated with a wide variety of symptoms and diseases.

In addition to the biomedical perspective on menopause, many authors from the 1980s and onward add the sociocultural perspective, emphasizing the diversity of symptoms and experience of menopause in different parts of the world28. In 1986, an
international group of researchers met in Korpilampi, Finland, to discuss definitions of menopause and future research. According to this workshop, menopause is a biocultural event and modifiable by factors within the environment. The story women tell about menopause, both in regards to symptoms, the menstrual pattern and other aspects, differ between cultures. Interpretation of epidemiological research based on western notions about menopause is not necessarily valid in other cultural settings. For example, the hot flushes symptoms which are central in the western story of menopause, were sparsely reported among Japanese women.

These perspectives have been brought forward in the US based SWAN project, where symptoms and health factors among women of different ethnic origin in USA have been studied. The sociocultural perspective argues that the menopause not only should be viewed as a biological process inside the individual woman, with cessation of menstruation as the hallmark, but that menopause can be experienced and presented in many different ways, according to local beliefs and experiences. The sociocultural perspective focus on the process of aging per se, thus challenging the biomedical focus on effects of hormone depletion. These perspectives are important in the broad discussion of menopause, but also in a clinical setting, as most doctors see women with different ethnic background in their daily practice. An ideal of general practice is the holistic perspective, as general practice “deals with health problems in their physical, psychological, social, cultural and existential dimensions”. Taking other perspectives than the biomedical into the consultation can lead to lesser focus on pharmacological interventions.

Hormonal and tissue changes during the menopausal transition.

The hypothalamus - pituitary – ovarian hormonal axis is central in the mechanism of menopause, and is described extensively in the literature. Since it is not the theme for the dissertation, only a short outline is given here:

The starting point of the menopausal process seem to be depletion of ovums in the ovaries. The start of menopause is assumed to be programmed, starting around ages 45-50 in all regions of the world. It is also a specific process for human beings, and does not seem to take place in other mammals, except perhaps some female toothed whales. This contrasts the more gradual, slowly emerging natural aging of other tissues and species. The ovarian hypothesis suggests that most events in female reproductive life are directed by the size and quality of the follicle store. The crucial factors determining the start of menopause are the number of oocytes formed during intra-uterine life and the rate of
depletion of the follicle store (through maturation of ovums and degeneration of germ cells).

The hormonal changes during menopause are described in increasing details over the last decades. Both estradiol (E$_2$) and the peptide hormones Inhibin A and Inhibin B are produced in the ovarian granulosa cells, and the amount produced is influenced by the pituitary hormones FSH (follicle stimulating hormone) and LH (luteinizing hormone). Declining levels of Inhibin B (and A) is followed by increasing levels of FSH, and marks the start of the menopause. LH levels also increase, but less marked compared to FSH. Approximately two years prior to final menstruation date (FMP), the levels of FSH start to rise and levels of the sex hormone estradiol (E$_2$) begin to fall. The testosterone levels do not change significantly during the perimenopause. While the postmenopausal production of estradiol and progesterone virtually ceases, the ovary continues to secrete testosterone from the interstitial cells. In summary, there are great variations and complexity in hormone levels during the menopausal transition, and measurements of FSH or estriol are generally not reliable for characterizing the menopausal stages in the individual women.

**Menopause research**

Over the years, a wide variety of symptoms have been attributed to the menopause. Besides the classical vasomotor symptoms (hot flushes and sweats/night sweats), urogenital symptoms like vaginal dryness, pain during intercourse (dyspareunia) and varying degrees of incontinence are common. Sleeping problems, anxiety and depression are described, as well as fatigue, muscle and joint pain, drying of the skin, loss of energy, loss of libido and many other symptoms and problems. Breast tenderness is a symptom that decreases during the menopausal transition. This plethora of symptoms is reflected in several “check lists” and instruments for quantification of symptoms of the menopause, f.ex. Kuppermann index, Greene Climacteric Scale, Women’s Health Questionnaire, Menopause Rating Scale and others.

The variety of symptoms that has been attributed to the menopausal transition was driven by a combination of researchers exploring a “new” field of medicine and a pharmacy industry promoting HRT for these complaints. The concept of a “menopausal syndrome” was introduced, to embrace many physical and psychological symptoms and diseases which could be linked to the menopausal transition and the age beyond it.
The studies of symptoms, health and health complaints during menopause have raised a number of important methodological considerations. In cross-sectional studies, it is not possible to disentangle age effects from effects of menopausal stage, or adjust for premenopausal health factors that can influence the results. In some prospective studies, age has been used as a proxy for menopausal stage. In that case, separation of the effect of aging from hormonal or physiological changes taking place during the menopausal transition and postmenopause is impossible. Secondly, the representativity of the selected participants is important. In many studies, self-recruitment based on symptoms has been used. Typical examples came from women seeking help for menopausal complaints. Studies based on representative, community based samples are important when the aim is to describe symptoms in the normal, healthy population. In addition, important confounding factors have to be dealt with, depending on the outcome of interest. As an example: when depression or psychological symptoms are addressed, the influence of age, important life events and vasomotor symptoms must be controlled for in the model.

Menopausal symptoms were typically studied in cross-sectional studies, many of which from menopause clinics, and the external validity of these studies was disputed\textsuperscript{43}. From late 1980s, longitudinal, population based studies were undertaken, contributing to more valid knowledge. Important contributions came from the Massachusetts Women’s Health Study\textsuperscript{11}. According to this study, the median age of menopause is 51.3 years and the normal range of the perimenopause is four years. The Australian Melbourne Women’s Midlife Health Project (MWMHP) explored associations between natural hormones and menopause, and found that the symptoms related to the menopausal transition were hot flushes, night sweats, dryness of the vagina and the disappearance of breast tenderness\textsuperscript{12,44}. The Canadian Manitoba Project studied the relationship between the menopausal transition and depression and other psychological factors\textsuperscript{45,46}. The study demonstrated that other life events like children leaving home, old parents getting sick or died, and other stress factors related to family life or diseases were more important factors associated with depression among women in these years. Also, results from British and Swedish cohort studies have contributed to more reliable results\textsuperscript{47,48}. Review articles from 1992 and onwards have summed up the results\textsuperscript{30,49-52}. Results from these studies vary considerably on many parameters, e.g. menopausal age, degree of symptoms, duration of symptoms, and medication use\textsuperscript{53-55}. Cultural and racial/ethnic differences may also explain some of the differences found in these studies\textsuperscript{54,56}. 
The Norwegian Menopause Project, led by the psychologist Arne Holte was a prospective cohort consisting of 1886 women, randomly selected in the Oslo area and followed from 1982 to 1986. The aim of this project was to study psychosocial factors and the menopause in a representative, prospective cohort of healthy women. Findings from this study included a factor analysis confirming that the vasomotor symptoms were the symptoms most consistently associated with menopause. Later, a second survey was derived from the cohort, consisting of 200 women randomly selected and followed from 1987 to 1992. The aim of the follow-up project was to study the hormonal changes during the menopausal transition, and to establish the relationship between hormones, gendered personality disposition and subjective complaints (such as hot flushes, musculoskeletal pain and psychological distress). 59 women formed the final substudy group in this study. Before menopause, hot flushes were associated with low levels of estradiol and high levels of FSH, while no such association was obvious later, and the hormonal changes observed in the women were difficult to assign to symptoms. Important contributions from the NMP were the methodology of a randomly selected, community based cohort design and the statistical methods used to separate symptoms due to physiologic changes during the menopausal transition from symptoms due to aging.

**Symptoms during the menopausal transition**

*The biological mechanism of VMS*

The vasomotor symptoms involve two biological systems: the core body temperature regulatory center in the central nervous system, and the peripheral vasculatory system of the body, regulated by the sympathetic nerve system.

The core body temperature is regulated between an upper threshold when sweating occurs and a lower threshold when shivering occurs. Sweating lowers the core temperature through heat loss when sweats vapor off from the body surface. The shivering creates heat through muscle work. Laboratory research has shown that HF often is proceeded by elevations in core body temperature. Hot flushes are triggered when the core body temperature crosses the upper limit of the thermo neutral zone, which seems to be greatly narrowed in women with bothersome symptoms. According to the same study, these women also have elevated levels of central noradrenergic activation compared to asymptomatic women. Peripheral estrogen levels are not associated with hot
flushes, and this fact supports the theory of a central nervous mechanism of HF. HF frequently occurs during sleep, and the researchers also found that HF in the second half of the night occurred after awakenings or arousals. Estrogen, clonidine (an $\alpha_2$-adrenergic agonist that reduce central sympathetic activity) and SSRI decrease sympathetic activity and have been shown to widen the narrowed thermo neutral zone of symptomatic women, while tryptophan depletion and yohimbine (an $\alpha_2$-adrenergic antagonist) tend to further narrow this zone and provoke VMS.

The role of the peripheral vascular system in VMS is to induce heat loss by vaporization of sweat and vasodilatation. This is controlled by cholinergic sympathetic neurons, but also local mechanisms may play a role.

Taken together, vasomotor symptoms (VMS) are body temperature dysfunctions that occur due to changes in gonadal hormones, but the exact mechanism by which the changing levels of hormones exert their effects on the temperature regulation is not fully understood.

Prevalence and incidence of VMS.

According to a recent meta-analysis, prevalence of symptoms peak 1-2 years after final menstrual period (FMP), when approximately 50 % (95% CI 42-58%) experience bothersome symptoms. At the same time, many women experience hot flushes many years before FMP, or they start to get symptoms several years after. The variety, frequency, duration and burden of symptoms vary from individual to individual.

The symptoms are reported by women all over the world, but the prevalence and demand for treatment differ between regions and cultures, and also between women of different ethnic background living in the same society or between countries in the same region of the world. The findings from a number of longitudinal cohort studies and cross-sectional studies are summarized in Table 1. The differences found in these studies probably have many reasons, including methodological such as different sample size, different populations with different representativity, and use of different questions and measuring tools. A number of factors have been shown to be associated with VMS, including genetic disposition, cultural and social factors, psychological factors, attitudes to menopause, stress, life style, diet, medication use etc., and very few of the surveys control for these factors.
Table 1. Prevalence of bothersome hot flushes and vaginal dryness in different regions of the world, according to a number of population based cohort and cross-sectional studies.

<table>
<thead>
<tr>
<th>Region</th>
<th>Study</th>
<th>N</th>
<th>Age span (yr)</th>
<th>Prevalence HF * (bothersome)</th>
<th>Vaginal dryness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finland</td>
<td>Moilanen 2010&lt;sup&gt;64&lt;/sup&gt;</td>
<td>1,427</td>
<td>45-64</td>
<td>38-54 %</td>
<td></td>
</tr>
<tr>
<td>Norway (NMP)</td>
<td>Holte 1991&lt;sup&gt;57&lt;/sup&gt;</td>
<td>1,886</td>
<td>45-55</td>
<td>45 %</td>
<td>22 %</td>
</tr>
<tr>
<td></td>
<td>Holte 1992&lt;sup&gt;58&lt;/sup&gt;</td>
<td>200</td>
<td>45-55</td>
<td>Very troubled 12 %</td>
<td></td>
</tr>
<tr>
<td>Denmark</td>
<td>Køster 2002&lt;sup&gt;63&lt;/sup&gt;</td>
<td>548</td>
<td>40-60</td>
<td>31-46-68 % (pre-, peri- and post-)</td>
<td></td>
</tr>
<tr>
<td>Sweden</td>
<td>Rödström 2002&lt;sup&gt;38&lt;/sup&gt;</td>
<td>1,462</td>
<td>38-60</td>
<td>68 % (early post)</td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td>Hunter 2011&lt;sup&gt;66&lt;/sup&gt;</td>
<td>10,418</td>
<td>54-65</td>
<td>54 % VMS Rating 4/10</td>
<td></td>
</tr>
<tr>
<td>Holland</td>
<td>Maartens&lt;sup&gt;67&lt;/sup&gt;</td>
<td>6,648</td>
<td>47-54</td>
<td>12-66 %</td>
<td>20-45 %</td>
</tr>
<tr>
<td>Australia</td>
<td>MWMHP Dennerstein 2000&lt;sup&gt;44&lt;/sup&gt;</td>
<td>438</td>
<td>45-62</td>
<td>39 % (any up to 52 %)</td>
<td>3-47%</td>
</tr>
<tr>
<td>Asia</td>
<td>Malaysia Dhillon&lt;sup&gt;68&lt;/sup&gt;</td>
<td>326</td>
<td>45-60</td>
<td>35-53 %</td>
<td>39-55 %</td>
</tr>
<tr>
<td>America</td>
<td>USA SWAN Gold 2006&lt;sup&gt;50&lt;/sup&gt;</td>
<td>3,198</td>
<td>42-59 Total</td>
<td>20 – 57 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>White</td>
<td>5-35 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Afro-American</td>
<td>12-50 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hispanic</td>
<td>12-30-12 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chinese</td>
<td>4-25-48 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Japanese</td>
<td>4-22-18 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MWHS McKinlay 1992&lt;sup&gt;11&lt;/sup&gt;</td>
<td>2,570</td>
<td>45-60</td>
<td>30-50 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Penn OAS Freeman 2001&lt;sup&gt;22&lt;/sup&gt;</td>
<td>438</td>
<td>35-47</td>
<td>26 % (any up to 79 %)</td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td>Kaufert 1992&lt;sup&gt;19&lt;/sup&gt;</td>
<td>469</td>
<td>45-55</td>
<td>14-40 %</td>
<td></td>
</tr>
</tbody>
</table>

*Prevalence from pre- through peri- to postmenopause
In Table 2, results from a systematic review and 2 meta-analyses are summarized\textsuperscript{53-55}. The frequency of bothersome VMS shows great variations. Most of the European surveys report VMS (hot flushes) in 50-75%. Since the burden of symptoms are usually not reported, and results are summarized both from longitudinal and cross-sectional studies, it is difficult to compare\textsuperscript{64-67}.

Table 2. *Vasomotor symptoms around the world. Results from a meta-analysis and 2 systematic reviews.*

<table>
<thead>
<tr>
<th>Country</th>
<th>No of studies</th>
<th>Longitudinal</th>
<th>N</th>
<th>Peak Duration</th>
<th>Duration</th>
<th>Bothering VMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Politi 2008\textsuperscript{55}</td>
<td>10</td>
<td>2</td>
<td>35,445</td>
<td>FMP+1 year</td>
<td>FMP+8 years</td>
<td>Up to 53 %</td>
</tr>
<tr>
<td>Woods 2005\textsuperscript{53}</td>
<td>12</td>
<td>12</td>
<td>18,255</td>
<td>FMP± 1 year</td>
<td></td>
<td>Up to 40 %</td>
</tr>
<tr>
<td>Freeman 2007\textsuperscript{54}</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>18-46 %</td>
</tr>
<tr>
<td>Europe</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>73 % (preval)</td>
</tr>
<tr>
<td>East Asia</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20-40 %</td>
</tr>
<tr>
<td>South East Asia</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25-80 %</td>
</tr>
<tr>
<td>Australia</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>16-55 %</td>
</tr>
<tr>
<td>Latin America</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0-67 %</td>
</tr>
<tr>
<td>South Asia</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>14-42 %</td>
</tr>
<tr>
<td>Africa</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>23-57 %</td>
</tr>
</tbody>
</table>

The question of when symptoms are most prominent during the menopausal transition has been evaluated in several of the longitudinal cohort studies. The cohort design is suitable for this question\textsuperscript{70}. The SWAN study found that across all ethnic groups, there was a significant increase in symptom prevalence from premenopause until postmenopause, with a peak incidence in late perimenopause\textsuperscript{50}. In the Australian MWMHP study, the frequency of bothersome hot flushes reached a maximum approximately two years after FMP, and 75% of the cohort reported bothersome hot flushes at some time during the transition\textsuperscript{12}. In this study, premenstrual complaints before the transition were associated with more VMS and other symptoms.

The duration of symptoms is not established, and probably the variation of duration is very great, as it is for prevalence per se. From the Australian Cohort study
MWMHP, the average duration of vasomotor symptoms was more than 5 years, longer than previously reported\(^49\). In a recent cross-sectional British survey among women aged 54-65, 90 % had experienced hot flushes/night sweats, with symptoms lasting on average 10 years for 54 % of the women\(^66\).

The prevalence of symptoms reported in these studies is of course confusing, both for the clinicians and the women concerned. From the clinician’s point of view, the prevalence and duration of bothersome symptoms and degree of influence on quality of life are the most relevant factors. The lack of relevant information regarding this in many of the studies mentioned above is a serious limitation in menopausal research.

**Factors associated with VMS.**

Factors associated with symptom prevalence and symptom burden are analyzed in a number of studies\(^30,48,60,64,71-74\).

**Age and menopausal stage**

VMS are linked to age and menopausal stages. Several studies find that peak prevalence of symptoms appear in late perimenopause or in early postmenopause\(^73,75\). In a recent review including two longitudinal and eight cross-sectional studies with a total of 35,445 participants, the proportion of women reporting VMS increased sharply from two years before FMP and reached a peak prevalence one year after FMP\(^55\). According to these studies, the percentage of women reporting VMS returned to premenopausal levels approximately eight years after FMP. The median duration of VMS among symptomatic women was four years.

Also, the prevalence of vaginal dryness increase with age, but is not so closely linked to menopause. The overall prevalence of vaginal dryness in a Swedish study of 5,990 women aged 46-62 years was 21 %, reaching 34 % in the oldest age group\(^71\). The SWAN study reports a lower prevalence of vaginal dryness but with the same relation to age, from 8 % in the 42-45 year old age group to 20 % in the 52-55 year age group\(^73\).

**Smoking**

In several studies, smoking has been associated with more menopausal symptoms\(^72,73,76\). However, this was not found in a Swedish cohort study of women aged 49-53
years\textsuperscript{74}, nor in a recent study from Finland\textsuperscript{64}. Smoking have been found to have an anti-estrogenic effect\textsuperscript{77}, so an association between smoking and VMS during the menopausal transition is plausible.

**Physical activity**

The data is diverging. A 2007 Cochrane review on effects of exercise on menopausal symptoms referred to a number of observational studies with inconclusive results\textsuperscript{78}. Some studies report that physically active women have fewer VMS compared to less active\textsuperscript{64,72,73,79}. On the other hand, several cross-sectional studies have not found any association between physical activity and VMS\textsuperscript{76,80}. Also, a case-control study with 82 cases and 89 controls did not find any association between physical activity before FMP and later symptoms\textsuperscript{81}. The inconsistency of the results may have several reasons, e.g. different ways of reporting physical activity (frequency, intensity, self-reported, measured, assessment compared to other etc). The majority of these surveys are cross-sectional, so it is impossible to determine if women report fewer symptoms because they are active and feel better anyhow, or if women with more symptoms are less active because of their symptoms. According to a recent review, the role of aerobic exercise to reduce VMS is not established, but the evidence suggest that physical activity is associated with better QoL among symptomatic midlife women. Physical activity against menopausal symptoms is recommended by the North American Menopause Society and the Royal College of Gynecology and Obstetrics in the UK\textsuperscript{82}.

**Weight, BMI**

The role of BMI in relation to VMS is unclear\textsuperscript{82}. Higher BMI are in some studies associated with less VMS, while other cross-sectional and observational studies report an association between higher BMI and more hot flushes\textsuperscript{73,81,83}. In other, no association or fewer symptoms have been found\textsuperscript{84,85}. Adrenal androgens is converted to estrogen in adipose tissue\textsuperscript{86}, and higher BMI has therefore been thought to protect against hot flushes in the menopause. Again, the diverging results can be attributed to several factors, including the design (longitudinal or cross sectional, representativity), the way BMI are registered (self report or physical measurement), controlling (or not) for confounders and other risk factors, etc.
**Socioeconomic factors (income level, type of work, education)**

In the Australian MWMHP study, women reporting hot flushes at baseline were significantly more likely to not be in full- or part-time paid work\(^72\). In a cross-sectional analysis from UK, higher education (above 18 years) was associated with lower reporting of hot flushes\(^87\). The Swedish Woman’s Health in Lund Area study also found a lower risk for hot flushes related to high education, and among risk factors for hot flushes were part-time employment and unhealthy lifestyle\(^71\).

**Other symptoms**

Symptoms which have been associated with hormonal loss and the menopause include depression and mood alterations, sleep disturbances, reduction of libido and other symptoms related to sexual function, aging of skin and loss of energy and vitality – all of these symptoms should be targeted by HRT according to Wilson\(^27\). So are these symptoms associated with or caused by the hormonal changes during menopause? The evidence from longitudinal studies is sparse. According to the Australian MWMHP study, the most important factors influencing the sexual function was the prior level of sexual function, losing or gaining a sexual partner, feelings toward a partner, and also estriol levels\(^88\). Sexual response decreased with age, and vaginal dryness/dyspareunia increased with lower levels of estradiol. Testosterone was not associated with the aspects of female sexual functioning measured in this study. Prior sexual function and partner issues had larger effects on women’s sexual function than hormonal factors\(^89\). Aging are associated with decline in sexual function in several studies, as well as the length of the relationship with the partner\(^90\).

The diagnostic entity “female sexual dysfunction” with a suborder called “hypoactive sexual desire disorder” has been added to the American *Diagnostic and Statistical Manual of Mental Disorders* (DSM IV). Up to 43 % of the adult female population in USA are suffering from this condition, according to some enthusiastic researchers\(^91\). However, these conditions are controversial\(^92\), because it downplays the role of emotional and cultural factors, and does not encompass contemporary understanding of the complexity of women’s sexual responses\(^93\). Although some aspects of reduced sexual function can be attributed to medical conditions, like dyspareunia due to vaginal atrophy, many other aspects can be seen as sound adaption to altered life circumstances.
Is there a menopausal syndrome?

As mentioned above, the symptoms most consistently connected to menopause and the subsequent changes in hormonal status during the menopausal transition are the vasomotor symptoms (hot flushes and sweats/nights sweats) and vaginal dryness, and to some extent sleep disturbances. The many other symptoms and complaints that have been associated with menopause, like depression, fatigue, sleeping disturbances, musculoskeletal pain, decreasing sexual function etc are to a much lesser extent proven to be associated with menopausal stages and hormonal changes. Following this, the effect of HT on these symptoms is not established. Many assumed effects of HT, especially effects linked to sexuality, femininity and attractivity as a woman has been attributed to the notion that declining levels of oestrogen are the main cause of these common complaints, and not the result of aging per se.

The proposal of a specific menopausal syndrome, consisting of a cluster of symptoms in addition to the vasomotor symptoms, was put forward in the 1950’s. The existence of a syndrome has been debated internationally over many years, and is still questioned. Diseases such as osteoporosis, cardiovascular disease and Alzheimer’s disease have also been associated with hormone loss among women in contrast to men, but have not been considered part of a menopausal syndrome. Several epidemiological studies conducting factor analyses are consistent as to the significance of VMS as a specific symptom complex associated with the menopause, separate from other somatic complaints or psychological symptoms. The idea of a universal menopausal syndrome has now been rejected by most investigators in the field.

Age at menopause

In a recent European cross-sectional study, the question of increasing age at menopause was raised. The authors found a median age at natural menopause (women not undergoing surgery) of 54 year, considerably older than the median age of 50-51 years found in previous studies. Factors associated with lower age at menopause in the SWAN study were current smoking, lower education, being separated or divorced,
non-employment and history of heart disease, while more children, prior use of oral contraceptives and Japanese ethnicity were associated with higher age\textsuperscript{103}. In a Finnish study, the median age of menopause was 50 years in 1997 and 51 years in 2007. Current smoking was associated with lower age at menopause, and the difference between smokers and no-smokers was larger in 2007 than ten years earlier. Lower education was associated with lower age at menopause, and physical activity with higher age\textsuperscript{104}.

\textbf{Treatment of the menopause.}

\textbf{Medicalisation.}

The term “medicalisation” was originally put forward by sociologists, such as Irving Zola and Peter Conrad, and the psychoanalyst Thomas Szasz\textsuperscript{105,106}. Although controversial, it has gradually become accepted also by the medical profession, as a notion describing underlying trends in the relation between medicine and the culture and society. The definition from Wikipedia is useful to describe the concept:

\textit{“Medicalisation is the process by which human conditions and problems come to be defined and treated as medical conditions and problems, and thus come under the authority of doctors and other health professionals to study, diagnose, prevent or treat.”} (16.01.2012.)

The philosopher Ivan Illich brought the concept forward in his famous criticism of modern medicine "\textit{Limits to medicine: Medical nemesis}" (1975)\textsuperscript{107}. He argues that medicine actually harm people through the process of iatrogenesis: the doctor-caused disease or harm. He sees medicalisation on three levels: A clinical level (the doctor’s treatment cause side effects – often more harmful than the disease), a societal level (leaving the general public in the hands of the medical expertise to cope with life) and in a cultural (structural) context, where medical understanding of life processes take over for the traditional cultural explanations and beliefs.

The modern treatment of menopause can be seen as a large-scale – may be the most extensive ever – example of medicalisation and doctor-driven iatrogenesis, rendering all the three levels of medicalisation:

1) The clinical level: Treatment with HT has caused hundred of thousands breast cancers in the western societies, and hundreds of thousands cases of thrombosis and cardiovascular disease.
2) The societal level: With the introduction of HT, menopausal symptoms should be treated by doctors, and not by the women themselves.
3) The cultural/structural level: The medical profession (or at least influential parts of the profession) described the menopause and the aging of women as a “hormone deficiency disorder” – not a natural phase in a woman’s life.

**History of hormone (replacement) therapy**

The subheading illustrates the point: In the start of the HT era of the 1960s, the therapy was called hormone replacement therapy (HRT), simply because the intention was to replace the hormone which was gone lost. Recently, the notion has been changed to hormone therapy (HT), to take away the concept of deficiency and focus on treatment of symptoms.

Medical treatment of menopausal symptoms started in the 1930’ies, when estrogens was isolated from the urine of pregnant women and became commercially available. But it did not become in widespread use before it was introduced by the American gynecologist Robert A Wilson. His bestseller “Feminine forever” started the era of hormone replacement therapy (HRT) in the Western world. In Norway, the gynecologist Eivind Myhre wrote a Norwegian version, “Er overgangsalderen en mangelsykdom?” [Is menopause a defiency disorder?]

In the 1970s and onward, this and other phenomena led to a feminist critique of the therapy. The Norwegian GP Kirsti Malterud raised a debate on the principle of giving medical treatment to a phenomenon which is basically a natural process of the body. However, the feminist critique of the therapy gradually vanished, and was more or less absent in the second half of the 1990s.

During these years, more positive attitudes towards hormone therapy (HT) during and after the menopause were seen among doctors, in particular gynecologists, but also among GPs. The most important reason was epidemiological evidence reporting that HT had positive preventive effect on several chronic health problems: osteoporosis, lower urinary tract infection, urinary incontinence and cardiovascular disease, besides the positive effect on the menopausal symptoms. The prospects for the future of HT were light: “Fortunately for humanity and the health care of women, knowledge about the hormonal deficiency aspects of menopause has increased strongly in the last three decades.” (Editorial: 25 years of hormonal replacement therapy, Maturitas 1990).

Other benefits of using HT were many, more or less documented: enhancing sex life,
increasing libido, preventing aging of the skin, preventing dementia and loss of cognitive function – the most enthusiastic promoters virtually argued that use of HT preserved feminity and prevented aging. The literature regarding many of these effects are very sparse, and among clinicians presumed effects based on biological explanations, case histories and more anecdotic evidence was circulating. Most female gynecologists in this age used HT themselves\textsuperscript{112}. The previous criticism of HT use as a medicalisation of a biologically natural phase of women’s life was more or less absent. It was therefore – in the medical community – a dramatic and more or less paradigmatic change that took place in 2002, when the first report from the large, randomized controlled Women’s Health Initiative (WHI) study was published\textsuperscript{20}. The WHI study showed that HT use led to a slight increase of risk for cardiovascular disease, contrary to the common belief, and also to an increase in breast cancer and thrombosis. Before that, the HERS I study (1998)\textsuperscript{120} did not find the postulated preventive effect of HT on CVD, and this had already led to some cautions not to prescribe HT in order to prevent CVD. Later, the findings were confirmed in other studies, like HERS II\textsuperscript{121}, and the oestrogen arm of WHI\textsuperscript{122}. Large-scale observational studies published in the same period substantiated the magnitude of the increased breast cancer risk with different regimens and treatment duration, like the British Million Women Study (MWS)\textsuperscript{123} and the Women and Cancer Study from Tromsø, Norway\textsuperscript{124}. Also, a Danish observational study published in the same period failed to prove a preventive effect of HT on death and ischemic heart disease\textsuperscript{125}. The same researchers found that early menopause was a risk factor for CVD, but that HT did not have a protective effect in these women\textsuperscript{126}. A Cochrane meta-analysis from 2005 summarizing the association between HT and stroke in 28 RCT’s (39 769 subjects) concluded that HT was associated with an increased risk of ischemic stroke\textsuperscript{127}. Among subjects who had a stroke, those who took HT seemed to have worse outcome. Following these results, most national and international guidelines for HT have been changed\textsuperscript{128,129}. The purchased volume (DDD) in Norway has been more than halved since the top years of 1999-2000\textsuperscript{130}.

Important research based knowledge before 2000 was under-communicated and did not get the necessary attention. Several observational studies had reported an increasing risk for breast cancer following long term use of HT among healthy women, and a meta-analysis from 1997 summarized this\textsuperscript{131}. For many doctors, the information regarding breast cancer risk was somewhat confusing, since several studies did not find
an increased risk for relapse of breast cancer following HT, and there are still
controversies on the issue of oestrogen treatment following breast cancer surgery\textsuperscript{132}.

After these publications, the HT of menopause has been more or less reduced to a
treatment of bothering symptoms, and the search for alternatives has started. It can
definitely be argued that Illich (and Malterud) was right: It is quite possible to cause more
harm than good when the medical profession takes over and prescribe treatment. David L.
Sackett characterized HT in an editorial in Canadian Medical Journal entitled “The
arrogance of preventive medicine”\textsuperscript{133}. He argued that the epidemiological evidence used
for advocating HT as a preventive drug in the 1980s and onward was incomplete and
partly erroneous, and that this was not understood and not taken care of by the profession:
“I place the blame directly on the medical “experts” who, to gain private profit (from
their industry affiliations), to satisfy a narcissistic need for public acclaim or in a
misguided attempt to do good, advocate “preventive” maneuvers that have never been
validated in rigorous randomized trials.”

The story of HRT (which is now HT) is an outstanding example of medicalisation,
of lack of evidence and lack of critical appraisal of the evidence which actually was there,
and an important lesson to learn for the most involved disciplines: gynecology and
preventive medicine, and also general practice, since we deal with both arenas\textsuperscript{134}. It
shows us the fallacies of epidemiology, but also – at the same time – the wonderful
benefits of science, in the context of a well designed, randomly selected and controlled
intervention trial.

But then: the doctors are left with their patients. Menopausal women continue to
seek help for bothersome symptoms and concerns about their health and the various
problems connected to menopause and aging.

\textbf{Use of HT – International and national recommendations}

Following the publications of the randomized trials (HERS I and II, and WHI)
guidelines were changed both in USA and Europe\textsuperscript{134,135}. In Norway, the Norwegian Drug
Agency [Legemiddelverket] arranged an expert meeting in 2003 to discuss the results and
give recommendations for practice\textsuperscript{128}. The statements from NDA were (summarized):
- HT should not be used to prevent cardiovascular disease.
- HT is associated with an increased risk for breast cancer and the risk increase with
  the duration of treatment.
- The risk for venous thrombosis and stroke is increased.
- The risk/benefit ratio has been changed towards greater risk and reduced benefit with HT, and practice should be more restrictive. Every woman should be carefully advised with respect to benefits and risks with the treatment.
- HT is effective against hot flushes. The lowest possible dose should be used, and the treatment should be revised annually. After 3-5 years a more rigorous evaluation should be performed, and discontinuation should be tested to assess the need.
- Vaginal discomfort due to hormonal changes (dyspareunia, small bleedings, and discharge) should be treated with local applications of estrogen. HT should not be used for bleeding disturbances or urinary incontinence.
- Osteoporosis can be treated or prevented with HT, but other strategies should be used before HT.

The U.S. Preventive Task Force have recently (2013) issued a statement regarding menopausal hormone therapy for the primary prevention of chronic conditions\textsuperscript{136}. This is an update of the 2005 statement, and is based upon a review of the literature about the benefits and harms of using HT for prevention of chronic disorders. The conclusion is a recommendation against the use of combined estrogen and progestogen for prevention of chronic conditions in postmenopausal women, and also against the use of estrogen alone among postmenopausal women who have had a hysterectomy.

The recommendation does not apply to the use of HT for treatment of vasomotor symptoms among menopausal women, and not for women below 50 who have had surgical menopause.

The North American Menopause Society have recently issued an updated position statement\textsuperscript{134}. The need for individualized treatment is underscored, in contrast to the recommendations of the 1990s. The decision to use HT should incorporate women’s health and quality of life priorities, and assess personal risk factors such as risk for venous thrombosis, breast cancer, stroke and CHD. HT should not be used for prevention of CHD or dementia, the society further states.

The American Academy of Family Physicians (AAFP) also recommends against the use of HT for prevention of chronic diseases among women. In Europe, the College of GPs in Holland has issued detailed recommendations which are even more restrictive.
against HT, recommending treatment cessation after the shortest possible time (6-12 months)\textsuperscript{137}.

Oral HT is highly effective in reducing vasomotor symptoms. The effect of HT to reduce the frequency and burden of hot flushes is demonstrated in a number of studies, and in a Cochrane Review from 2004 the reduction in weekly HF frequency compared to placebo was estimated to 75 \% (64.3-82.3)\textsuperscript{138}. Noteworthy, in women who were randomized to placebo, a 57 \% reduction in HF was observed between baseline and end of study.

\textbf{Risk of HT – current evidence and controversies. The timing hypothesis.}

The WHI study is by far the most extensive clinical trial of the effects and risk of HT. In the WHI study, 16 608 women aged 50 – 79 years were randomized to conjugated equine estrogens plus medroxyprogesterone acetate, or placebo\textsuperscript{20}. In the estrogen only study, 10 739 post-hysterectomy women of the same age were randomized to conjugated equine estrogen alone, or placebo\textsuperscript{122}. The first study was stopped early because of increased risks for breast cancer, coronary heart disease, stroke and pulmonary embolism, and the estrogen alone study was stopped because an increased risk of stroke was found. The results are summarized in Table 3. In later publications from WHI which included intervention and post-intervention phases (up to 8.6 years), the risk for CHD in the combined estrogen – progesterone study persisted (HR 1.22, CI 0.99 – 1.50)\textsuperscript{139} and in the estrogen alone no effect was shown (HR 0.95, CI 0.82 – 1.11)\textsuperscript{140}.

In the debate after WHI, arguments against the findings have been that many women were older than those usually treated in Norway. Subgroup analysis from WHI has revealed potential lower incidence of CHD in the younger age group treated with HT (50-59 years, HR 0.59, CI 0.38 - 0.90) but not in the older age groups (60-69 years and 70-79 years)\textsuperscript{140}. The \(P\) values for interaction by age were 0.05 and 0.007 respectively for CHD and myocardial infarction in the estrogen only arm, and were also apparent but less pronounced in the estrogen + progestogen arm. These findings have led to the launching of a “timing hypothesis”: If HT is started early (close to the FMP, early postmenopausal), it may in fact have a cardio protective effect. A weakness with the hypothesis is that no prospective RCT has been designed to study the timing of initiation of HT. Recently, the publication of the Danish DOPS study (Danish Osteoporosis Prevention Study) has led to a new outburst of the HT debate\textsuperscript{141-143}. The Danish researchers found that HT given to postmenopausal women during the first years after FMP reduced the risk for a combined
end point of death, myocardial infarction and heart failure, and did not increase breast
cancer risk or stroke among women who used it for more than 10 years. From 1990 to
1993, 1006 women aged 45 to 58 years, with last menstruation 3-24 months before, were
enrolled in DOPS and randomly assigned to HT or placebo. Women with an intact uterus
got 2 mg of 17-β-estradiol 12 days per month and combination with norethisterone
acetate 1 mg 10 days followed by 1 mg of 17-β-estradiol in 6 days per month.
Hysterectomized women received 2 mg of 17-β-estradiol daily. The study was planned
for 20 years, but after 10 years the investigators advised women on HT to discontinue
treatment due to the WHI study results. At 10 years, HT had reduced the risk for the
combined CVD end point (HR 0.48, CI 0.26 – 0.87) compared with no treatment. Also,
there were no statistically significant increased risk for breast cancer (HR 0.58, CI 0.27 –
1.27), hospitalization for venous thrombosis (HR 2.01, CI 0.18 – 22.16) or stroke (HR
0.77, CI 0.35 – 1.70). The results after the subsequent 6 years were similar.

The DOPS and the follow up results from WHI lend arguments to the timing
hypothesis. An argument against is that DOPS was designed to study the prevention of
osteoporosis, and CVD or breast cancer incidence was not the primary end points. The
composite end point was a combination of death and hospitalization for myocardial
infarction and heart failure, and was based on registration by clinicians in the Danish
Hospitalization Register. Since there are few numbers for each end point, the CI’s are
wide and few missing numbers in the registers may cause different results. Also, since
DOPS was an open-label study, the doctors and the participants knew if they were taking
HT or not. This may lead to different use of health service and different advice on life
style, other treatment and diagnostic efforts done by doctors and patients, in favor of a
positive outcome.

The use of a composite end point is problematic, and may lead to exaggeration of
positive outcomes. This composite end point is not described in the original protocol,
and the authors of the latest update of the Cochrane report on long term HT did not
include the DOPS study. The DOPS researchers argue that the end point is mortality-
driven, i.e. that CVD deaths are captured even though “softer” end points like angina or
PCI may not be captured. Since the study participants are young, the number of deaths is
few and this may imply bias in the favor of fewer CVD events.
A conclusion may be that the DOPS results support the timing hypothesis. However, the study is not sufficient to alter the recommendation that HT should not be used to prevent chronic diseases among post-menopausal women.

Table 3. Results from the WHI study, estrogen + progestogen arm, 16 608 women aged 50-79 at enrollment. Intervention group 8506 women, control group 8101 women. Primary end point: Events of CHD (not fatal myocardial infarction + any CHD death). Negative end point: Invasive breast cancer. Secondary end points: stroke, pulmonary embolism, uterine cancer, colorectal cancer, hip fracture, death of other causes. Mean follow up: 5.4 years. The study was stopped May 31st 2002 because of increased risk for breast cancer. Figures are calculations based on the published results.

<table>
<thead>
<tr>
<th>End point</th>
<th>HR (95% CI)</th>
<th>Intervention group</th>
<th>Control group</th>
<th>Events / 10 000 person year</th>
<th>NNH, per year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of events</td>
<td>AR per 10 years</td>
<td>Number of events</td>
<td>AR per 10 years</td>
<td></td>
</tr>
<tr>
<td>CHD</td>
<td>1.29 (1.02, 1.63)</td>
<td>164</td>
<td>3.74</td>
<td>122</td>
<td>2.90</td>
</tr>
<tr>
<td>Invasive breast cancer</td>
<td>1.25 (1.07, 1.46)</td>
<td>166</td>
<td>3.54</td>
<td>124</td>
<td>2.83</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.41 (1.07, 1.85)</td>
<td>127</td>
<td>2.74</td>
<td>85</td>
<td>1.94</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>0.63 (0.43, 0.92)</td>
<td>45</td>
<td>0.96</td>
<td>67</td>
<td>1.53</td>
</tr>
<tr>
<td>Uterine cancer</td>
<td>0.83 (0.47, 1.4)</td>
<td>22</td>
<td>0.47</td>
<td>25</td>
<td>0.57</td>
</tr>
<tr>
<td>Hip fractures</td>
<td>0.60 (0.45, 0.98)</td>
<td>44</td>
<td>0.85</td>
<td>62</td>
<td>1.42</td>
</tr>
<tr>
<td>Death – other causes</td>
<td>0.92 (0.74, 1.1)</td>
<td>165</td>
<td>3.49</td>
<td>166</td>
<td>3.79</td>
</tr>
<tr>
<td>Total death</td>
<td>0.98 (0.82, 1.1)</td>
<td>231</td>
<td>4.88</td>
<td>218</td>
<td>4.98</td>
</tr>
</tbody>
</table>
Table 4. Event rates, relative risk reduction and NNT in the DOPS study.\textsuperscript{146} Reprinted from the journal.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Event rates</th>
<th>After 10 y of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HRT</td>
<td>No HRT</td>
</tr>
<tr>
<td>Death, MI, or HF\textsuperscript{‡}</td>
<td>3.2 %</td>
<td>6.5 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death, MI, or HF\textsuperscript{§}</td>
<td>6.6 %</td>
<td>11 %</td>
</tr>
</tbody>
</table>

\textsuperscript{†}HF = heart failure; MI = myocardial infarction; other abbreviations defined in Glossary. RRR, NNT, and CI calculated from event rates and hazard ratios in article. Hazard ratio for the composite outcome was adjusted for age.

\textsuperscript{‡}Death (3.0\% vs. 5.2\%, \(P = 0.08\)), MI (0.2\% vs. 0.8\%, \(P = 0.21\)), HF (0.2\% vs. 1.4\%, \(P = 0.07\)).

\textsuperscript{§}Death (5.4\% vs. 7.9\%, \(P = 0.10\)), MI (1.0\% vs. 2.2\%, \(P = 0.14\)), HF (0.6\% vs. 1.6\%, \(P = 0.15\)).

Discussing the treatment options: The GP as advisor.

The risks and benefits of HT use is a challenge for the doctor who is supposed to give women information and for the women to take the decision to use it or not. The role of the GP when giving advice and prescribe treatment is a part of the thesis and is explored in the GP survey.

During the last 3 decades, the knowledge about decision making in medicine and questions regarding treatment options and informed choices for patients have undergone great changes. The doctor’s role has changed from a paternalistic teacher to a source of information for patients who ideally take their own informed decisions, with many grey zones in the intermediate space. The patients’ rights are reflected both in the legislation and in ethical considerations.

The ideas of patient centered medicine and patient empowerment are central in modern medicine, and have been studied in general practice settings\textsuperscript{147,148}. McWhinney describes the patient-centered approach as one where “the physician tries to enter the patient’s world, to see the illness through the patient’s eyes”\textsuperscript{149}. Patient centered medicine can be described as the process where the doctor actively explores the patient’s perspective: the needs, fears, feelings and wishes expressed by the patient in the
consultation. The doctor integrates this knowledge with her own medical knowledge and skills, and discusses the further investigation and possible interventions with the patient. During this process, the patient is empowered to take his or her own informed choice when deciding about a treatment. The aim of the consultation is a shared understanding of the patient’s problems. A comprehensive framework of the notion of patient-centered medicine is given by Stewart et al, identifying the crucial components of the method.  

**Shared decision making – or informed choice?**

Ideally, shared decision making means that the patient and the doctor discuss the options (e.g. prescription or not) on a basis of mutual respect and equality, and the final decision is a consensus. Shared decision making raises many problems. If the doctor does not agree to the women’s decision, prescription or not may collide with her professional responsibility. On the other hand – an insisting doctor may override the personal preferences of the patient and which may imply a violation, thereby causing damage to the patient-doctor relationship. When it comes to HT, some data has indicated that the women maintain that they take the decision themselves, but that the doctors are important information sources. Some authors have used the notion of compliance here, which indicates a more paternalistic view of the process. When a prescription has been given to a woman, the woman’s decision of not buying the medicine (or not taking it) has been regarded as an example of non-compliance. Other perspectives for the discussion between the doctor and the concerned woman have been advocated, taking into account the risk for medicalisation and disease-making of a natural process. It is reason to believe that the nature of the decision process has changed after the WHI results, since the risks of HT has been described and quantified, and the risk-benefit balance has tipped against HT use. In a dissertation from Sweden, Hoffmann has discussed the framework and the process of communication about risks and benefits of HT. When analyzing consultations in 5 gynecological practices in a qualitative research design, he found that discussion about risk was asymmetrical, with the physician dominating in a 4:1 ratio of spoken words. HT was introduced by the doctor in 19 out of 20 cases, and in 15 of these in a positive mood. The patient’s participation in the decision making process was modest, in 13 cases the women’s preferences were explored, but in only 2 of the cases the woman’s role in decision making was addressed. Quantification of risk was used in 5 of the 20 consultations, where absolute risk rates for breast cancer were used. The doctors used different rhetorical strategies in the consultations, including
renaming of the words (drawbacks instead of risks), simplifying calculations, framing of HT in a positive way etc. A possible conclusion from these findings is that the notion of patient-centered medicine had little impact in these gynecological practices.

Using HT (or not) should be a question of informed decision making by the woman herself, based on information from many sources: The doctor (GP and/or gynecologist), friends, husband, media, alternative channels. The challenge for the doctor is to give the woman scientific based, precise and relevant information about the benefits and risks of HT use, based on recommendations and guidelines and taking into account the patients “ideas, fears, wishes and needs”. In some circumstances, the doctor may feel that a prescription is contra-indicated, and in others she may feel that the woman will have more to gain than to lose.

**How do doctors decide?**

Traditionally, the decision framework in medicine has two main roots: biomedical science and “humanistic tradition/philosophy”. Several underlying components are derived from this framework. Often, the road to a decision is visualized by means of a decision tree. In the clinical situation, however, doctors seldom use these algorithms. There may be several reasons for this: using algorithms and decision tools are time-consuming, and do not exactly cover the situation in case. Experiments and research from other disciplines (psychology, economy) has led to new insight in decision making, which may be applicable for how to understand clinicians.

The term *heuristics* denotes mental shortcuts, often used in complicated questions when a quick decision must be taken. Different ways to interpret risks (side effects) are also important in this respect, and will be further discussed below.

**How do doctors interpret probabilities and risk?**

Often, risk or risk reduction is communicated by means of differences between a treatment group and a control group – the *relative risk* reduction. As an example: treatment with a statin reduces the risk for CHD by 30 %, compared to a group not receiving this treatment. The statement is easy to understand, and sells well.

But this information gives us no idea regarding *how big* the risk (and the risk reduction) is: What is the *absolute risk reduction* for my patient? For how long time should he or her be treated? And what are the side effects? What is the “real benefit” for my patient? We obviously need more information. When we talk about HT, there are
benefits and risks, and we must assume that both doctors and patients calculate them differently.

In Table 3, a more detailed presentation of the WHI results are given. These results can be interpreted in different ways:

1. **Relative risk**: Treatment with HT increases the risk of coronary heart disease with 29%.

2. **Absolute risk**: The mean 10 year risk for coronary heart disease increase with 0.8% - from 2.9% to 3.7%.

3. **Absolute risk**: When treating 1000 women in 10 year, 8 more will get CHD (with 95% probability: at least one, at most 16).

4. **Absolute risk, number needed to harm**: If 1200 women is treated with HT in one year, one more will get CHD.

Based on the MWS results, the authors calculated 20,000 additional cases of invasive breast cancer in Great Britain during the 10 year period 1990-2000\textsuperscript{123}. In a Norwegian setting, the number has been calculated up to 150 – 250 additional cases per year\textsuperscript{124}, which is even greater burden than what was found in GB.

For patients, and even doctors, it is difficult to interpret these results. What do they actually mean? Is the risk difference big or small for the individual women? It becomes even more demanding when more complicated calculations come up. How many life years without disease will I loose? 3 months? 3 years? The answer will depend on other risk factors and other treatment, and we know little about how doctors and patients deal with these calculations.

Because the knowledge of risks and benefits has been changed and the scientific evidence is diverging and partly unknown, the perceptions of the magnitude of risk among both the doctors and the women probably are diverging. There is a need to explore how the doctors interpret the evidence, their role as information and discussion partners and how they will advise their patients. This was a theme for the GP study. At the same time, both the women and the doctors need updated and reliable information regarding the usual menopausal symptoms, how they relate to age and menopausal status, the duration of symptoms and factors associated with burden of symptoms. These are among the questions elucidated in the HWC study.
Research questions.

**Overall research questions:**

1. What are the attitudes and knowledge of HT among Norwegian GPs after the changing of the evidence?
2. What is the symptom burden and use of HT during the menopausal transition among healthy Norwegian women?

**GP study**

In the papers, research question 1 has been further developed into:

1. What are GPs’ views regarding effects, indications, contraindications, risks and duration of HT treatment, and are these views in line with the Norwegian recommendations? (Paper I)
2. Do the GPs regard that use of HT imply medicalisation of the menopause? (Paper I)
3. Are there differences between the GPs regarding views and attitudes to HT, and if so - which factors are associated with these differences? (Paper I)
4. Do female GPs use HT themselves, or (for younger GPs) do they consider to use HT? (Paper I)
5. What is the GPs’ perception of role when giving advice regarding HT? (Paper II)
6. Do GPs give different advice to women regarding HT, and if so - does perception of effects and risk of HT, attitude to treatment or other factors influence the advice given? (Paper II)

**HWC study:**

In the papers, research question 2 has been further developed into:

1. What are the symptom prevalences and symptom burden over time during the natural menopausal transition? (Paper III)
2. Are health factors, life style or sociodemographic factors associated with degree of symptoms? (Paper III)
3. Are the symptoms associated with self-rated health? (Paper III)
4. What is estimated age at menopause? Are there possible factors associated with this age? (Paper III)

5. How is the characteristics of HT use among healthy Norwegian women during the menopausal transition, and which factors are associated with HT use? (Paper IV)

6. Do the vasomotor symptoms reappear after discontinuation of HT? (Paper IV)
Material

This thesis is based on two sets of data:

1. The GP study: a cross-sectional survey conducted in 2004 among 400 Norwegian GPs, randomly selected from the Norwegian Medical Association’s list of GPs with contract with the municipalities. The results of this study were originally published in two Norwegian papers, later translated to English and available at the Journal’s web site (Paper I and II).

2. The HWC study: The Hordaland Women’s Cohort study - a longitudinal cohort study from western Norway. The Cohort was established in 1999, and has baseline data from Hordaland County Health Survey (HUSK) 1997-98. The Cohort consisted of 2229 women aged 40-44 at baseline, and the women have received almost identical questionnaires approximately every second year. The material is based on seven questionnaires (1999 - 2010). The first paper regarding menopausal symptoms (Paper III) has been published in Maturitas. The second paper from the cohort (Paper IV) has been submitted and follows as an attachment.

The GP Study.

In 2001, a reform took place in the Norwegian Health system, when a list system for General Practitioners (The Regular GP Scheme) was formed. Every Norwegian citizen was given the right to join the list of a GP. The system is run by the local authorities (municipalities), and almost every GP and 99.5 % of the population joined the system\textsuperscript{159}.

In 2004, the Norwegian Medical Association kept a list of approximately 3600 doctors who were registered as Regular GPs in the membership database. The number of GPs in the NMA register was a little less than the number in the Norwegian Health Directorate database\textsuperscript{160} (3600 vs. 3755), since not all GPs are members of NMA. 400 GPs (approximately 11 % of the GPs) were randomly drawn from the NMA database to form the GP panel in the survey.

After reminders, 289 responders (72.3 %) were included for analysis. 29.8 % of the respondents were women, the same as in the Norwegian Health Directorate database. The mean age of all respondents was 45.4 years (range 26–69 years), two years younger than the mean in the total GP population. The distribution of patients on the lists could not be
compared directly, since the response alternatives in the questionnaire was a grouping of the list length. The average number of years in practice was 14 years (range 1–37 years). Recorded characteristics of the responders are shown in Table 5.

Table 5. Characteristics of the GP sample 2004 and the GPs in Norway. Proportion of female GPs, mean age (with 95 % CI), age distribution, number of patients on list, years in practice and practice region (part of the country).

<table>
<thead>
<tr>
<th>GP Sample 2004</th>
<th>GPs in Norway 2004*</th>
</tr>
</thead>
<tbody>
<tr>
<td>N %</td>
<td>%</td>
</tr>
<tr>
<td>Number</td>
<td>289 29.8</td>
</tr>
<tr>
<td>Proportion female (%)</td>
<td>86 29.8</td>
</tr>
<tr>
<td>Mean age (years)**</td>
<td>287 45.4 (44.4 - 46.4)</td>
</tr>
<tr>
<td>Mean age male GPs</td>
<td>202 46.9 (45.7 - 48.0)</td>
</tr>
<tr>
<td>Mean age female GPs</td>
<td>42.0 (40.4 - 43.6)</td>
</tr>
<tr>
<td>&lt; 30 year</td>
<td>5 1.7</td>
</tr>
<tr>
<td>30-39 year</td>
<td>69 23.9</td>
</tr>
<tr>
<td>40-54 year</td>
<td>174 60.2</td>
</tr>
<tr>
<td>55-66 year</td>
<td>38 13.1</td>
</tr>
<tr>
<td>67 year</td>
<td>1 .3</td>
</tr>
<tr>
<td>No of patients on list</td>
<td>&lt; 500 3.1</td>
</tr>
<tr>
<td>1001-1500</td>
<td>154 53.3</td>
</tr>
<tr>
<td>≥ 1501</td>
<td>57 19.7</td>
</tr>
<tr>
<td>Years in practice (mean)</td>
<td>14 14.0</td>
</tr>
<tr>
<td>Practice region**</td>
<td>Eastern Norway 46.0</td>
</tr>
<tr>
<td>Southern Norway</td>
<td>17 6.0</td>
</tr>
<tr>
<td>West Norway</td>
<td>76 26.7</td>
</tr>
<tr>
<td>Mid Norway (Trøndelag)</td>
<td>24 8.4</td>
</tr>
<tr>
<td>North Norway</td>
<td>37 13.0</td>
</tr>
</tbody>
</table>


**Mean age and Practice region (part of the country) was reported from NMA database.

The Hordaland Women’s Cohort (HWC)

The Hordaland County Health Survey (HUSK) was a joint epidemiological research project carried out by the National Health Screening System of Norway (now: Norwegian Institute of Public Health) and the University of Bergen. It is a part of the national database for epidemiological research in Norway – the Cohort of Norway (CONOR). The CONOR questions cover the following main topics: self-reported
HUSK is a county based health survey in Hordaland County in Western Norway, and include the city of Bergen which is Norway’s second biggest city. HUSK consists of a baseline registration obtained in 1997-1999, including all inhabitants in the county of Hordaland born 1953-57, then in ages 40-44 years (29,335). A total of 18,851 (63 %) invited persons met at the screening stations. Baseline measurements from HUSK included body height and weight, and blood pressure. A non-fasting blood sample was also collected. The self-administrated baseline questionnaires in HUSK included open-ended questions on occupation, income, use of medicines, various health behaviors, and some self-reported diseases (among others diabetes, cardiovascular disease, asthma/allergy).

**Forming of Hordaland Women’s Cohort (HWC).**

Women who came to the screening station in HUSK received information about the Cohort. They eventually agreed to take part in the HWC by signing an informed consent form. For random sampling, the last digit of the personal ID number was used. For the necessary sample size a preliminary power calculation, based on a 70% response rate at inclusion and 5% annual attrition rates was used. With this calculation, at least 2,150 women should be asked to join at the baseline if at least 900 women should remain in the cohort after 10 years.

From the female participants in the HUSK study (N=14,349), a random sample of 3,453 was invited to participate in the Hordaland Women’s Cohort (HWC) study, and 2,331 (67.5%) of them met. After oral and written information, 2,230 (95.7%) women aged 40-44 years at the date of inclusion consented to take part in the study. One woman died before the first questionnaire was registered, so the final number in the Cohort was 2,229. A written consent form, including declaration of willingness to participate in follow-up questionnaires at regular intervals during the next 15 years, was signed by the
participants. More details regarding the recruitment and the Cohort participants are described elsewhere\textsuperscript{163}.

The baseline characteristics of HWC are summarized in Table 6. There were no significant differences between the Cohort and the rest of the female participants in HUSK, except for education and annual family income, which were slightly higher among females in the Cohort\textsuperscript{163}.

Fig.2. Forming of the Hordaland Women’s Cohort (HWC). Baseline registration in the HUSK study, sampling and recruitment procedure.
Table 6. Comparison of baseline socio-demographic characteristics between the HWC and the rest of the women in the Hordaland Health Study (HUSK).^{163}

<table>
<thead>
<tr>
<th></th>
<th>HUSK minus the Cohort (N = 7746)</th>
<th>The Cohort (N = 2230)</th>
<th>P values</th>
</tr>
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<td><strong>Age at inclusion (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>1465 (18.9)</td>
<td>481 (21.6)</td>
<td></td>
</tr>
<tr>
<td>41</td>
<td>1518 (19.6)</td>
<td>478 (21.8)</td>
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<td>42</td>
<td>1578 (20.4)</td>
<td>456 (20.4)</td>
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<td>43</td>
<td>1521 (19.6)</td>
<td>500 (22.4)</td>
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<td>44</td>
<td>1664 (21.5)</td>
<td>315 (14.1)</td>
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<tr>
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<td>230 (10.3)</td>
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<tr>
<td>Married</td>
<td>5800 (74.9)</td>
<td>1676 (75.2)</td>
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<tr>
<td>Single</td>
<td>82 (1.1)</td>
<td>23 (1.0)</td>
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</tr>
<tr>
<td>Divorced</td>
<td>861 (2.7)</td>
<td>248 (2.4)</td>
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<tr>
<td>Separated</td>
<td>212 (2.7)</td>
<td>53 (2.4)</td>
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<tr>
<td>Registered partnerships</td>
<td>3 (0.03)</td>
<td>0 (0)</td>
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<tr>
<td><strong>Education</strong></td>
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<tr>
<td>The lower secondary</td>
<td>2687 (34.7)</td>
<td>749 (33.6)</td>
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<tr>
<td>The upper secondary</td>
<td>755 (9.8)</td>
<td>284 (12.7)</td>
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<td>1371 (17.7)</td>
<td>410 (18.4)</td>
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<tr>
<td><strong>Annual family income, NOK 1000</strong></td>
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<td>&gt; 400</td>
<td>2810 (36.3)</td>
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<td>166 (7.4)</td>
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<td>731 (9.4)</td>
<td>211 (9.5)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2596 (33.5)</td>
<td>803 (36.0)</td>
<td></td>
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<tr>
<td>3+</td>
<td>2802 (36.1)</td>
<td>794 (35.6)</td>
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<td>1073 (13.9)</td>
<td>265 (11.9)</td>
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<tr>
<td><strong>Body mass index (kg/m2)</strong></td>
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<td>0.328</td>
</tr>
<tr>
<td>Category</td>
<td>Count</td>
<td>%</td>
<td>Mean</td>
</tr>
<tr>
<td>--------------------------------</td>
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</tr>
<tr>
<td>Under-weight (&lt; 18.5)</td>
<td>96</td>
<td>1.2</td>
<td>27</td>
</tr>
<tr>
<td>Normal (18.5-24.9)</td>
<td>4582</td>
<td>59.2</td>
<td>1357</td>
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<tr>
<td>Overweight (25-29.9)</td>
<td>2247</td>
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<tr>
<td>Obesity</td>
<td>797</td>
<td>10.4</td>
<td>216</td>
</tr>
<tr>
<td>Missing</td>
<td>24</td>
<td>0.3</td>
<td>2</td>
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</table>

Self-rated health

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<th>Count</th>
<th>%</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bad</td>
<td>91</td>
<td>1.2</td>
<td>18</td>
<td>0.8</td>
</tr>
<tr>
<td>Not very good</td>
<td>1120</td>
<td>14.5</td>
<td>294</td>
<td>13.2</td>
</tr>
<tr>
<td>Good</td>
<td>4791</td>
<td>61.7</td>
<td>1407</td>
<td>63.1</td>
</tr>
<tr>
<td>Very good</td>
<td>1665</td>
<td>21.5</td>
<td>497</td>
<td>22.3</td>
</tr>
<tr>
<td>Missing</td>
<td>79</td>
<td>1.0</td>
<td>14</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Lifestyle and medical conditions

<table>
<thead>
<tr>
<th>Category</th>
<th>Count</th>
<th>%</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular exercise</td>
<td>4519</td>
<td>58.4</td>
<td>1342</td>
<td>60.2</td>
</tr>
<tr>
<td>Daily smoking</td>
<td>2727</td>
<td>35.2</td>
<td>757</td>
<td>33.9</td>
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<tr>
<td>Asthma</td>
<td>503</td>
<td>6.5</td>
<td>155</td>
<td>7.0</td>
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<tr>
<td>Diabetes</td>
<td>87</td>
<td>1.1</td>
<td>23</td>
<td>1.0</td>
</tr>
<tr>
<td>Alcohol intake &gt; 6 times/month</td>
<td>1417</td>
<td>18.3</td>
<td>418</td>
<td>18.8</td>
</tr>
<tr>
<td>Psychiatric problem/condition</td>
<td>1144</td>
<td>14.8</td>
<td>314</td>
<td>14.1</td>
</tr>
</tbody>
</table>

Methods

Study design

The GP study was a cross-sectional observational study based on a random sample of Norwegian GPs.

The Hordaland Women’s Cohort is a longitudinal cohort study, based on a randomly selected, representative group of women and followed with questionnaires approximately every second year. The cohort will be followed for 15 years. The material included in the papers contains data collected at baseline (from the HUSK study) and the first seven waves up to 2010. The eighth wave was performed in 2012.

Questionnaires

GP Study

A questionnaire with a total of six background variables and 17 main questions was used in the survey, and is attached (in Norwegian) as Appendix A. The questionnaire was developed by the author (B.G), in collaboration with the co-authors of Paper I, and included questions about the role of the doctor when giving advice, the knowledge about and adherence to guidelines, assumed effects of HT, indications and contraindications, conceptions about risks and attitudes to HT prescription. 3 clinical examples (cases) concluded the questionnaire. Some of the questions regarding indications and contraindications had been used previously in a survey of Norwegian gynaecologists. Since the prevalence of consultations regarding HT could influence knowledge and attitudes, we asked the GP to indicate how often HT was a theme: How often do you discuss HT with patients? The response alternatives were: Less than once per month, 1-4 times per month, 1-3 times per week, or almost every day. Also, the changing of the evidence base could have led to confusion or difficulties when giving advice among the doctors. The question Do you experience that it is difficult to give advice (to consider benefits and risks) regarding HT? intended to explore this theme. The response alternatives for the question were divided in five categories: No, never – Seldom – Occasionally – Often – Yes, always. Question about the role of the physician was To which extent do you as doctor or the patient take the initiative to start (and in the next
The adherence to recommendations regarding revision of treatment and treatment duration was asked for with the question *Do you have a main rule for duration of HT when treating menopausal symptoms?* The response alternatives were yes or no, and if yes: for how long time: shorter than one year - one up to three years - three to five years - more than five years.

A group of questions explored the attitudes to statements regarding effects of HT, indications and contraindications: *What is your opinion regarding the following statements?* Response alternatives mostly agree - somewhat agree - neither agree nor disagree - somewhat disagree - mostly disagree. The statements are described in more details in the *Dependent variables* paragraph. The purpose of these questions was to explore to which extent other factors than the burden of vasomotor symptoms was significant as possible reasons to prescribe HT. e.g. preventive effects or more speculative effects on sex life, aging of the skin, or making women more attractive and counteract signs of ageing. Although the medicalisation debate regarding HT had taken place some years ago in Norway, we also suggested that the attitude to this question was relevant for some of the doctors. The attitudes were explored with the statement: *HT implies an undesirable medicalisation of a natural life phase in women.* The response alternatives were the same as indicated for the other statements.

To explore the attitudes to the risks of HT and possible influence on attitudes to prescription, we also asked the following questions: *In your everyday practice: Do you feel that it is important to know how high the risk for side effects of HT is?* Following this, three different ways of displaying the risk estimates were given, and the doctors were asked which one they preferred:

- **When using HT in five years, the risk for breast cancer increases with approximately 30%**.
- **The absolute risk for breast cancer after five years of HT increase from approximately 0.25 % per year to 0.31 % per year.**
- When 1000 women are treated with HT in 10 years, 8 more women will get breast cancer.

Following the risk estimates, the doctors were asked to assign the significance of these risk estimates in the clinical situation: small/minimal, some or great significance, and also tick for to which extent they have changed their practice: much more restrictive - somewhat more - about the same - somewhat more - much more liberal.

Finally, three clinical examples were given. The purpose was to illustrate the options (prescription or not) by cases recognizable in a general practitioner’s everyday situation, in order to study possible factors associated with a positive or negative attitude to treatment. The cases were meant to illustrate different clinical situations, and are given in the Dependent variables section. The first was a woman without obvious indications for treatment (bothersome vasomotor symptoms), the second an older women where long term treatment should not be recommended, and the third a situation when other options (prescription of gestagen only) probably was the best choice. Four options were given, supplemented by a commentary field for personal responses:

Tick for the advice you will give to the patient:
- I will recommend HT
- I will neither recommend nor advise against HT
- I will not recommend HT
- I will strongly advise against HT.

For the last case, the options yes - no - do not know were given.

In the questionnaire, the last question was for female doctors only. The purpose was to explore the attitude to HS use by the female GP’s themselves. We also discussed to include a question to the male GP’s whether they would prescribe HT for their partners, but decided not to include it since it could be regarded mal practice to prescribe medication to partners. If before menopause: Would you consider using HT during the menopausal transition? The response alternatives were Yes - No - Do not know. For those in the transition or after menopause: Do you use HT? (yes – no- used earlier). If use or used before: What is the name of the medication? For how many years have you used HT? If used earlier: How many years did you use HT?
Pilot study

The questionnaire including the cases was tested on two different panels of GPs. The first group consisted of eight experienced doctors in a CME group and the second group consisted of eight younger doctors in an education group for specialization in General Practice. Thus, the pilot groups contained both young and inexperienced and older and more experienced GPs. In these group settings, the doctors knew each other and were experienced discussion partners. In both groups, the questions were discussed in detail to ensure a common understanding and interpretation of the statements and questions. The panels agreed that the questions and statements were relevant for GPs giving advice to women in the menopausal transition. The clinical examples were also presented on a larger CME course regarding women’s health arranged by NSAM in March 2004. The discussions following the presentation of the cases led to minor adjustments to ensure a common understanding.

HWC Study questionnaire

Since 1999, a two-paged questionnaire has been sent approximately every second year to the HWC-participants. The questionnaires have been almost identical each time, and consist of 4 main parts. The questionnaire used in Wave 7 is printed in Appendix B (Norwegian version).

The first part (health and lifestyle) contained questions regarding age, self-rated overall health, visits to doctor/hospital, weight, pelvic exercise, physical exercise and smoking. This part also contained questions regarding complementary treatments such as acupuncture and homeopathy. In Wave 7, the women were asked to fill in the date for completing the questionnaire and their present age.

The second part (menstruation, menopausal symptoms and contraception) contained questions regarding menstrual pattern and last menstrual period, vasomotor and vaginal symptoms, use of HT and contraception use. In Waves 1 and 4, the women were asked if they had the ovaries and/or the uterus removed. The wording of the questions regarding menstruation and menopausal symptoms were formulated after discussions with the investigators who had performed the Norwegian Menopause Project (1985-1989), and are shown in Box 1 below.
Box 1. Questions regarding menstrual periods and menopausal symptoms in HWC.

The wording of questions regarding HT use was: Do you use hormones against menopausal complaints? Response alternatives in the different waves were:

- Wave 1: yes – no. In Wave 2, the question was omitted.
- Wave 3 – 6: yes – no – used before.
- Wave 7: yes – no, never used – used before; how long: ___ year ___ months. How old were you when you started HT? ___ year.

Why did you stop HT? Response alternatives: I had side effects - I was worried about possible side effects - No longer needed - Other reasons:……

The third part contained questions about urinary conditions: voiding (bladder function) and incontinence which has not been used in this thesis.

The last part of the questionnaire contained questions about medication and/or complementary drugs used the day before. In the introduction to the question, “medicine” was explained as any drug with or without prescription, in any form. In a chart, the name of the medicine, if it was a daily (regular) intake, and the reason to use it could be indicated. The data from this part has been analyzed for the HT users in Wave 7.
Data collection

**GP Study**

In May 2004, the questionnaire was sent to these 400 Norwegian GPs. Every questionnaire had a unique number on the answer envelope connected to the name and address of the GP, so it was possible to send out reminders. The responses (answers) were processed anonymously. After a postal reminder in June, 204 responses (51%) had been returned. In August, 108 non-responders were contacted by phone, and additional reminders were posted. In November 2004, 304 responders (76%) were registered. 15 of these denied to participate or had stopped practice and was excluded from analysis. The remaining 289 responders (72.3%) were included for analysis (Table 7).

<table>
<thead>
<tr>
<th>Sample</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invited</td>
<td>400</td>
<td>100</td>
</tr>
<tr>
<td>Questionnaires returned</td>
<td>304</td>
<td>76</td>
</tr>
<tr>
<td>Denied, stopped practice</td>
<td>15</td>
<td>3.7</td>
</tr>
<tr>
<td>Included in analyses</td>
<td>289</td>
<td>72.3</td>
</tr>
</tbody>
</table>

**HWC Study**

The data collection in HUSK (1997-99) for the HWC-participants formed the baseline data in the Cohort. The first wave was performed in 1999 and the second wave in 2000. From year 2000, a questionnaire was sent to members of the HWC every second year. In order to maintain the lowest possible attrition rate in the Cohort, non-responders received up to three postal reminders. In 2010, the Cohort had completed seven questionnaires (waves) and the age range of the participants had reached 53-57 years. The response rates in waves 1-6 varied between 87% and 93%. In Wave 7, the number of remaining participants in HWC was 2157 and the response rate was 82%.
Fig 3. Time flow in the cohort. The seven waves in HWC. Age span.

Preparation of the material

**GP Study**

The returned questionnaires were processed anonymously into an SPSS worksheet. Written comments were collected in a separate file and checked manually by the author.

**HWC study**

Because our primary aim was to describe the menopausal transition, symptom distribution, and HT use in healthy women, we excluded data from 174 women who had undergone bilateral oopherectomy and/or hysterectomy. Also, members of the Cohort who had not answered questions regarding last menstrual period in any of the seven waves (n= 53) were excluded from analysis. The remaining responders (n=2002, 89.8 %) made up the dataset used in most of the analyses (Table 8). There were no significant differences with respect to baseline characteristics between the dataset analyzed and the Cohort as a whole (Table 9). The excluded individuals (n=227), however, were slightly
older, had lower income, were more obese and less physically active than those in the dataset analyzed.

Table 8. *Samples in the HWC study.*

<table>
<thead>
<tr>
<th>Sample Description</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort at baseline</td>
<td>2229</td>
<td>100</td>
</tr>
<tr>
<td>Oopher- and/or hysterectomized*</td>
<td>174</td>
<td>7.8</td>
</tr>
<tr>
<td>Missing menstrual data in all waves</td>
<td>53</td>
<td>2.4</td>
</tr>
<tr>
<td>Dataset 1, used in most analyses</td>
<td>2002</td>
<td>89.8</td>
</tr>
<tr>
<td>Hormone IUD users, Wave 1</td>
<td>274</td>
<td>12.3</td>
</tr>
<tr>
<td>Dataset 2 (hormone IUD users W 1 excluded)**</td>
<td>1728</td>
<td>77.5</td>
</tr>
</tbody>
</table>

*According to responses given in Wave 1 and Wave 4.
** Used in analyses of factors associated with Age at FMP, Paper III.

Table 8b. Missing values in the sample (Dataset 1).

<table>
<thead>
<tr>
<th>Wave no</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menstrual data missing (%)</td>
<td>7.4</td>
<td>18.5</td>
<td>7.6</td>
<td>12.1</td>
<td>14.1</td>
<td>16.6</td>
<td>23.9</td>
</tr>
<tr>
<td>Use of HT missing (%)</td>
<td>13.3</td>
<td>-*</td>
<td>9.5</td>
<td>13.8</td>
<td>15.9</td>
<td>17.2</td>
<td>21.4</td>
</tr>
<tr>
<td>Frequency of hot flushes missing</td>
<td>14.1</td>
<td>24.1</td>
<td>11.7</td>
<td>14.2</td>
<td>17.6</td>
<td>18.4</td>
<td>22.7</td>
</tr>
</tbody>
</table>

*In wave 2, this question was omitted.

The use of gestagen containing hormonal intrauterine device (IUD) often leads to more sparsely bleeding or absence of normal menstrual bleeding. This may lead to uncertainty as to reporting of FMP. In the analysis of factors influencing FMP, 274 hormone IUD users (reported in wave 1) were excluded. The remaining dataset (Dataset 2) included 1728 respondents and were used to analyze factors associated with age at FMP (Table 8).
Table 9. Baseline characteristics of women in the complete Cohort and the part of the Cohort left to analysis. Data at inclusion in HUSK 1997-99.

<table>
<thead>
<tr>
<th></th>
<th>The complete Cohort (N=2229)</th>
<th>Respondents analyzed (N=2002)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Age at inclusion (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>481</td>
<td>21.6</td>
</tr>
<tr>
<td>41</td>
<td>478</td>
<td>21.8</td>
</tr>
<tr>
<td>42</td>
<td>455</td>
<td>20.4</td>
</tr>
<tr>
<td>43</td>
<td>500</td>
<td>22.4</td>
</tr>
<tr>
<td>44</td>
<td>315</td>
<td>14.1</td>
</tr>
<tr>
<td>Self-rated health at inclusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bad</td>
<td>18</td>
<td>0.8</td>
</tr>
<tr>
<td>Not very good</td>
<td>294</td>
<td>13.3</td>
</tr>
<tr>
<td>Good</td>
<td>1406</td>
<td>63.5</td>
</tr>
<tr>
<td>Very good</td>
<td>497</td>
<td>22.4</td>
</tr>
<tr>
<td>Lifestyle and medical conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physically inactive#</td>
<td>863</td>
<td>38.7</td>
</tr>
<tr>
<td>Daily smoking</td>
<td>757</td>
<td>33.9</td>
</tr>
<tr>
<td>Asthma</td>
<td>155</td>
<td>7.0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>23</td>
<td>1.0</td>
</tr>
<tr>
<td>Alcohol intake &gt;6 times/m</td>
<td>234</td>
<td>11.0</td>
</tr>
<tr>
<td>Body Mass Index (kg/m2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Under-weight (&lt;18.5)</td>
<td>27</td>
<td>1.2</td>
</tr>
<tr>
<td>Normal (18.5-24.9)</td>
<td>1357</td>
<td>60.9</td>
</tr>
<tr>
<td>Overweight (25-29.9)</td>
<td>628</td>
<td>28.2</td>
</tr>
<tr>
<td>Obesity (&gt;30)</td>
<td>216</td>
<td>9.6</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>172</td>
<td>7.9</td>
</tr>
<tr>
<td>1</td>
<td>237</td>
<td>10.8</td>
</tr>
<tr>
<td>2</td>
<td>907</td>
<td>41.4</td>
</tr>
<tr>
<td>3+</td>
<td>873</td>
<td>39.9</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/partnership</td>
<td>1675</td>
<td>75.1</td>
</tr>
<tr>
<td>Single/widow</td>
<td>253</td>
<td>11.4</td>
</tr>
<tr>
<td>Separated/divorced</td>
<td>301</td>
<td>13.5</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elementary school</td>
<td>408</td>
<td>18.5</td>
</tr>
<tr>
<td>The lower secondary school</td>
<td>749</td>
<td>33.6</td>
</tr>
<tr>
<td>The upper secondary school</td>
<td>283</td>
<td>12.7</td>
</tr>
<tr>
<td>College, bachelor degree (&lt; 4 years)</td>
<td>410</td>
<td>18.4</td>
</tr>
<tr>
<td>University, master degree (=&gt;4 years)</td>
<td>365</td>
<td>16.4</td>
</tr>
<tr>
<td>Annual family income 1997 NOK</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1000 Low: 0-199</td>
<td>271</td>
<td>14.3</td>
</tr>
<tr>
<td>Middle: 200-399</td>
<td>702</td>
<td>37.0</td>
</tr>
<tr>
<td>High: &gt;400</td>
<td>924</td>
<td>48.7</td>
</tr>
</tbody>
</table>

*Respondents not oopher- and/or hysterectomized, not missing menstruation data in the observation period.

# < 1 hour hard activity (being warm, sweating) and/or < 3 hour light activity, per week, valid per cent.
Because recorded data in the first six waves did not include an exact date for when the questionnaire was filled in, we allocated the month following the distribution of the questionnaire as the response month. This was adjusted according to the schedule for the postal reminders. Since up to three postal reminders were sent, the allocation of FMP in the cohort became complicated and time-consuming.

To study the associations between symptoms and age, the questionnaire responses were reorganized according to two-year age groups. Each woman will thus appear in seven groups, in which will depend on her age at baseline. Each age group had data from up to three different waves, and a woman could not deliver data more than once in each age group. The number of participants in the 41-42 years age group, the 43-44, the 55-56, and the 57 year group, respectively, were 877, 1728, 1125 and 274. These figures are all lower than the total of the dataset, 2002, since no women covered the whole age range during the study period.

Many cases had missing values for HT use in some of the waves (Table 8b). In Wave 7, 190 women completed their age when starting HT and the duration of use. Thus, valid values for HT use during previous waves were inferred for 177 cases based on these data. This inference resulted in fewer missing values for HT use in the different waves and 35 more women were categorized as HT users. In Wave 7, 16 additional women reported previous HT use for three months or less. These women were categorized as nonusers. Besides obtaining more accurate count of HT users, an important reason for the inference was to obtain fewer missing values in the case-control substudy, since missing values would reduce the number of cases in the analyses.

**Dependent variables.**

The dependent variables used in statistical analyses in the different papers are shown in table 10 below. In addition, a number of variables were reported only in descriptive statistics.
Table 10. Dependent variables used in different papers.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>N</th>
<th>Dependent variables</th>
<th>Paper number</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP study</td>
<td>Norwegian general practitioners</td>
<td>289</td>
<td>Statements of treatment effects, medicalisation</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Assessment of indications and contraindications</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rule for treatment duration</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Assessment of role in prescription of HT</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Advice, clinical examples</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>Hordaland, born 1953-57</td>
<td>2002</td>
<td>Frequency and burden of VMS and vaginal dryness</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Age at menopause</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Self-rated health</td>
<td>x x</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Use of HT</td>
<td>x x</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Short-term vs. long term HT use</td>
<td>x x</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Start of HT before vs. after FMP</td>
<td>x</td>
</tr>
</tbody>
</table>

**GP Study**

**Statements regarding effects of HT**

A group of questions explored the attitudes to statements regarding effects of HT: *What is your opinion regarding the following statements?* Response alternatives *mostly agree - somewhat agree - neither agree nor disagree - somewhat disagree - mostly disagree*. To analyse the perception of the effects and attitude to treatment, those who responded “mostly agree” and “somewhat agree” were combined and tested against the combined group that responded “somewhat disagree” and “mostly disagree”, with and without those who responded “neither agree nor disagree”.

Hormone therapy:

- Increases risk of breast cancer
- Prevents Alzheimer’s disease
- Delays skin aging
- Improves sex life
- Makes women more attractive
- Protects against cardiac infarction
- Protects against colon cancer
- Increase life expectancy for women
- Implies an undesirable medicalisation of a natural life phase in women

**Indications and contraindications**

A second group of questions explored the doctor’s attitude to indications and contraindications: *How great emphasis would you place on these indications or contraindications to prescribe HT?* The response alternatives were *great emphasis - less emphasis - no emphasis - don’t know*. In the analyses, the response alternatives were grouped in two alternatives: Those who put “great emphasis” vs. those who put “less” or “no emphasis” on the indication or contraindication. In the *Methods* section of Paper I, the description given is by accident not correct. Here, it says that “great emphasis” and “less emphasis” were grouped together and tested against “no emphasis”. Both alternatives were tested, and the description given in the table (Table 4, Paper I) is correct. These dichotomised response categories were used and the associations for each indication or contraindication listed below were assessed by means of logistic regression:

- Hot flushes and/or sweats (disturbing)
- Genetic predisposition for osteoporosis
- Mood swings
- Discomfort due to dry mucous membranes
- Reduced libido
- Aging of the skin
- Breast cancer (previously, treatment completed)
- Breast cancer in first degree relatives
- Cardiovascular disease with symptoms
- Thromboembolic disease among close relatives

**Rule for treatment duration**

The 2003 recommendations advised that treatment should be revised annually, and a more extensive evaluation and discontinuation attempts should be carried out after 3-5 years. We asked the doctors if they had a general rule for treatment duration, and if so – how many years. The response alternatives were *less than one year, 1 up to 3 years, 3 up...*
to 5 years, 5 years or more. In the analyses, those who answered “yes” were compared to those who answered “no” to this question.

**Clinical examples**

Three of the questions in the questionnaire were formulated as clinical examples where doctors were requested to give an opinion about whether they would advise using HT or not, and they could also give their own comments. Responses regarding Clinical examples 1 and 2 were used as dependent variables in the analyses:

Clinical example 1:
Woman, 55 years old, has not used HT previously. Last menstruation about 2 years ago. She has experienced some hot flushes at night but has not been unduly affected by these. She has felt more depressed recently, feels her skin is ageing fast and that sexual relations with her husband have become more and more sporadic. She has talked to several friends who use HT and they say that they believe that hormones improve their quality of life. She wonders if she should try this therapy.

Tick for the advice you will give to the patient:
- I would recommend therapy
- I would neither recommend nor advise against therapy
- I would not recommend therapy
- I would strongly advise against therapy.

The response variable was recalculated into two categories, so that doctors who recommended treatment were compared to those who advised against or were neutral.

Clinical example 2:
Woman, 60 years old, no special risk factors, has used HT for about 5 years and wishes to continue because she feels that the therapy improves her quality of life.

Tick for the advice you will give to the patient:
- I would recommend continued therapy
- I would neither recommend nor advice against therapy
- I would not recommend continued therapy
- I would strongly advise against continued therapy.

The response variable was recalculated so that doctors who recommended therapy were compared to those who advised against or were neutral.
**HWC study**

The dependent variables in the HWC were partly composite and partly derived variables, based on the preparation of the data described earlier. The questions regarding menstruation and menopausal symptoms are given in section *Questionnaires* (Box 1).

**Age of menopause and menopausal status**

Based on the indication of regularity of menstruation (yes or no) and last menstruation, an algorithm was constructed to identify the wave for FMP for the individual women who had reached menopause, and censoring date or year for those who had not reached menopause. The algorithm defined a retrospective period of 12 months or more for the establishment of an FMP wave. Doing this, six cases had given no indications of last period and were processed manually. Following this, the menopausal status for the participants in the specific wave was established (pre- or perimenopausal or postmenopausal).

**Menopausal symptoms**

The vasomotor symptoms (hot flushes and sweats/night sweats) were given both as frequency and burden of symptoms. Vaginal dryness was also given in these two modalities. Frequencies were reported as “daily”, “weekly”, “monthly” or “never/almost never”. Burden of symptoms was reported as “very much”, “considerably”, “a little” or “not bothered” (Box 1).

In the logistic regression analyses of symptoms, a secondary variable of hot flushes frequency was used (Paper III). Here, the maximum frequency of HF reported in any wave was recorded and given in three categories: daily, 1-4 times per month, or never/seldom. Thus, women who had reported daily HF any time during the observation period could be compared with women who had reported HF only 1-4 times per month or never/almost never during the same time span.

**Use of HT**

The dependent variable in the HT analysis (Paper IV) was based on the response to the question: *Do you use hormones to prevent menopausal symptoms?* The response alternatives Wave 1: *yes – no*. Wave 3 – 6: *yes – no – used before*. Wave 7: *yes – no, never used – used before*; how long: ___year ___months.

How old were you when you started HT? ___year.
In Wave 7: (If stopped) Why did you stop HT? Response alternatives:

I had side effects
I was worried about possible side effects
No longer needed
Other reasons: ......

In the analysis of factors associated with HT, use of HT was either constructed as an ever vs. never use variable (registered in any wave) or used simply as a wave-specific variable. In order to stratify the HT users in different categories, two new variables were constructed on the basis of the registration of HT use during the time span. The duration of HT variable had three categories: Long-term use (HT in two or more waves), short-term use (HT in one wave only), and no-use of HT. Because we had recordings of HT use at two years interval and had no indication of HT use between the waves, it was not possible to allocate these values to an exact number of years of HT use. Use in one wave could indicate at least one month and up to four years of HT, while use in two waves indicated more than two years of HT. Based on the responses of HT start and duration of HT given in Wave 7, we have assumed that HT in one wave usually indicate 1-3 years of HT and that HT in two waves or more indicate 3 years or more of HT use as a rule, and that the long term users on average use HT longer than the one-wave users.

The second constructed variable related start of HT to the menopausal status, and was constructed on the basis of reported start of HT and the menopausal status allocated for each woman according to the algorithm described earlier. We decided to compare women who started pre- or perimenopausal (from premenopause and up to one year after FMP) with women who started postmenopausal, i.e. more than one year after FMP.
**Independent variables**

The independent variables used in the different papers are shown in Table 11.

Table 11. *Independent variables used in the studies.*

<table>
<thead>
<tr>
<th>Study</th>
<th>Domain</th>
<th>Independent variables</th>
<th>Paper number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>I</td>
</tr>
<tr>
<td>GP study</td>
<td>Demographics</td>
<td>Age, Gender, Years in practice, List size, Community type, Part of country</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>Practice patterns and attitudes</td>
<td>How often discuss HT with patients, Difficult to give advice, Having a rule for treatment duration, HT implies medicalisation, More/less restrictive, HT improves sex life, HT protects against myocardial infarction</td>
<td>x</td>
</tr>
<tr>
<td>HWC study</td>
<td></td>
<td></td>
<td>III</td>
</tr>
<tr>
<td></td>
<td>Demographics</td>
<td>Age, Civil (marital) status, Education, Family income, Community type</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>Health factors</td>
<td>Self-rated health, Body mass index, Physical activity, Daily smoking, Alcohol consumption</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>Menopausal and reproductive</td>
<td>Menopausal status, Hot flushes, Menarche age, Parity</td>
<td>x</td>
</tr>
</tbody>
</table>

**GP study**

Independent variables that were integrated in the models were: gender, age, if the GP had a general rule for treatment duration, changes in practice attitude, attitude to: whether HT implies medicalisation; whether HT leads to improvement of sex life;
whether HT gives protection against myocardial infarction. All variables were included in the multivariate models and are shown in the tables.

**Age**

The doctor’s age was used as a continuous variable in the logistic regression analysis of attitudes to indications and contraindications (Paper I, Table 4) and attitudes to treatment (Paper II, Table 4 and 5). We also tested the significance of age (both as continuous variable and in age groups) in the other logistic regressions analysis.

**Experience as GP**

The doctor’s experience as a GP was included in the questionnaire. Experience was measured as number of years in general practice (part-time or full time).

**Size of patient list**

Many GPs work part time, and a full time list is supposed to have 1500 patients. The size of the patient list was fixed in four groups: less than 500, 501 – 1000, 1001-1500 and greater than 1500.

**Community size and location**

The size of the community was preset in three categories: City (> 20 000 inhabitants), small town (tettsted) (5-20 000 inhabitants) or rural practice (< 5000 inhabitants). Norway has traditionally been divided in 5 parts: Eastern, Southern (Sørlandet), Western, Mid-Norway (Trøndelag) and Northern Norway and this were followed also in our survey.

**Practice patterns and attitudes**

In the first question, we asked the physician to indicate how frequently HT was discussed: *How often do you discuss HT with patients?* The response alternatives were: *Less than once per month, 1-4 times per month, 1-3 times per week, or almost every day.* Here, the response alternatives were divided in two categories in the analyses: Almost every day vs. weekly or less. Second, we asked the doctors to think about the task of giving advice: *Do you experience that it is difficult to give advice (consider benefits and risks) regarding HT?* The response alternatives for the second question were divided in five categories: *No, never – Seldom – Occasionally – Often – Yes, always.* In the analysis,
the response was grouped in three categories: *Never and seldom, occasionally and Often/always*.

Regarding treatment duration, the question *do you have a main rule for duration of HT when treating menopausal symptoms?* With the response alternatives *yes* or *no* was used in the analysis.

Three of the attitudes to HT questions were used in the regression analysis. The attitude to the medicalisation statement was used in the analysis of factors influencing some of the indications and contraindications, and when the doctors gave advice in the clinical examples. Also, the attitude to the statement that HT improves sex life and HT protects against myocardial infarction were used similarly. The response categories were grouped in three alternatives in the analyses: *Agree* (mostly+somewhat), *disagree* (mostly + somewhat) and *neutral*.

At last, the question “*Have you changed your practice when prescribing HT the last 1-2 years?* ” was used in the analyses. The response alternatives were grouped in “*as previously*” and “*more restrictive*”.

**HWC study**

**The baseline data in HUSK** 1997-98 consist of these variables used in the analyses:
- Sociodemographic: Age, civil status, family income, education level, dwelling community.
- Self-rated health (overall feeling of health): Excellent, good, not so good, bad.
- Age at first menstruation (menarche age).
- Number of children (parity)
- Life style (habits): Smoking, alcohol consumption, physical activity.

**Age**

The women in HWC were born 1953-1957, so the age span of the respondents was five years. They were 40-44 years at baseline, and 53-57 years in Wave 7. The variable was treated as a continuous variable in the analyses.

**Civil status**

In HUSK, the response alternatives were married, living in partnership, living single, being widow, being separated or divorced. This was not asked for in the HWC, so
we do not have information about changing of the civil status during the time span. In the analysis, the variable was grouped in three categories: married/partnership, single/widow, separated/divorced.

**Family income (per year)**

This was based on self report, and not asked for later in the cohort. The HUSK recording was very detailed, with nine intervals starting with NOK 0-50 000. In the analyses, the women were grouped in three categories: low (≤ NOK 200 000), medium (NOK 200 000 – 399 000) and high (≥ NOK 400 000).

**Education**

The question in HUSK was rather detailed, with 7 categories. In the analysis, the variable was recoded to contain three categories: Low (elementary school or less), medium (lower and upper secondary school) and high (bachelor or master degree).

**Community type**

The HWC participants were registered with a code for the dwelling municipality. Based on a definition of centralization used in the Norwegian Central Bureau of Statistics, the municipalities were divided into rural or central.

**Self-rated health**

The question “How is your health status now?” is widely used in Norwegian population based health surveys, and is a reliable predictor of mortality in the population. The response alternatives were bad, not so good, good, excellent. In the analyses, the response alternatives have been dichotomized in bad/not so good and good/excellent. In Paper III, the variable has also been used as a dependent variable in a two-way correlation test ($\chi^2$ test).

**Age at first menstruation (menarche age)**

This was reported at HUSK baseline, and is of course subject to recall bias, being reported some 30 years after the event. On the other side, as a significant event in most women’s life, we can assume that it is often remembered quite exact. In the analysis, the ages have been grouped in three categories: Early (< 12 years), medium (13-14 years) and late (≥ 15 years).
Parity

The women stated the number of children in HUSK, and this was not asked for later. Some of the women may have given birth at a later stage. In the analysis, the variable has been grouped into zero (no children), one child, two children, and three or more children.

Alcohol consumption

In HUSK, the women were asked if they used alcohol or not, the type of alcohol mostly used (beer, wine or liquor), and to quantify the consumed amount in alcohol units (1 unit = 1 glass of wine). We used the quantified amounts given, grouped in four categories: no use, 1-2 units per month, 3-7 units per months, ≥ 8 units per month.

Physical activity

In HUSK and HWC, physical activity was registered both in a light activity variable and a hard activity variable. Physical activity was specified for activity in the last year (outside work, but activity during travelling to and from the job included), estimated as a mean per week the last year. Both questions should be answered:

- Light activity (not sweating/out of breath): none - < 1 hour – 1-2 hours – 3 or more hours.
- Hard activity (sweating/out of breath): none - < 1 hour – 1-2 hours – 3 or more hours.

In the logistic regression analysis of the frequency of symptoms (Paper 3), the hard activity variable was used and dichotomized into more or less than 3 hours.

In addition, HUSK contained a composite physical activity variable which was used in the regression analysis of HT use (Paper 4). Here, regular physical activity was divided in two groups: no regular activity or regular activity with ≥3 h light activity and ≥1 h intense activity per week.

Daily smoking

This was asked for both at baseline and in every wave of the HWC. The response alternatives were yes or no, and for those who answered yes, we also asked for the number of cigarettes daily. The latter variable was not used in the analyses. Updated smoking information was used to get more valid data regarding smoking. In Wave 1, a number of respondents were missing and we assumed that if some of these respondents
later reported to be daily smokers they had probably smoked also at baseline. We also found that a number of the respondents reporting not daily smoking in Wave 1 later reported daily smoking in some of the other waves. Since the prevalence of daily smoking has been falling the last 10-15 years in Norway, we assume that these responders had been previous smokers, reporting not daily smoking in Wave 1 but starting again later. As a result of this, the prevalence of daily smoking in wave 1 or later was 39.9 %, contrasting the prevalence in wave 1 only of 33.4 %.

**Menopausal status**

Menopausal status was used as an independent variable in the logistic regression analyses of HT use in Wave 1, 4 and 7 (Paper IV, Table 4). The variable has been described earlier (section *Dependent variables*).

**Menopausal symptoms**

Frequency of hot flushes (both wave-specific and the secondary calculated variable described earlier - section *Dependent variables*) was used in the HT analyses on Paper IV (Tables 2-4).

**GP Study statistics**

Summary statistics were used to describe proportion of doctors who agreed or disagreed to the statements regarding effects, indications and contraindications. Analysis of correlations was conducted using correlation tests (Pearson, Spearman). Variables that were associated with response categories for the statements and indications and contraindications were further analyzed using logistical regression, and the answer categories were dichotomized as described in the previous chapter (dependent variables). In the analysis, the following significant and/or clinical relevant variables were included: age, gender, number of patients on list, municipality type, region, how often the doctor discussed HT with patients, whether the doctor thought it was difficult to give advice, whether the doctor had a general rule for duration of treatment, and the doctor’s stance on the question of medicalisation. We also performed analysis where the outcome variable was grouped in “no emphasis” vs. “great emphasis” and “less emphasis” combined.

To analyze attitudes to HT in the clinical examples, the «Would recommend HT» group was tested against the «Would not recommend HT» group on its own and together
with the «Would neither recommend nor advise against HT» group. An analysis of those who did not recommend HT was carried out and this was tested vis-à-vis the other two groups combined.

The level of significance was set at $p < 0.05$. The data were processed using Version 12 and 14 of the SPSS statistical package.

**HWC statistics**

**Symptoms and age at menopause**

Summary statistics and frequencies were used to describe point prevalence and distribution of vasomotor symptoms and vaginal dryness as reported in the seven questionnaires.

The mean and median age of menopause (FMP) was estimated by Kaplan-Meier survival analysis. Cox regression was used to test the influence of independent variables (smoking, menarche age and parity) on FMP.

In order to identify the number and distribution of women with different degrees of symptoms during the observation period, we also performed a longitudinal analysis of women reporting frequent (daily and weekly) hot flushes. Onset and duration of hot flushes, and relation to FMP were analyzed.

To analyze independent variables associated with the frequency of hot flushes, we used multinomial logistic regression. Each woman’s maximum value of hot flushes during the observation period was obtained and recoded into: daily, 1-4 times per month, and never/seldom. Factors known from the literature as potential predictors of vasovagal symptoms, or that from a clinical point of view might influence the degree of symptoms, were considered for inclusion in the model: age in last wave, daily smoking at baseline or during the observation period, body mass index groups (kg/m$^2$), alcohol consumption, level of exercise, self-rated health at baseline, menarche age, marital status, parity, family income and educational level. Furthermore, the model was successively reduced by removal of non-significant variables, previously excluded variables were reconsidered as possible confounders, and some hypothesized interaction effects were tested for, all according to Hosmer’s methodology$^{166}$. The final model included clinically relevant non-significant variables and is shown in Paper III, Table 4.
The association between symptoms and self-rated health in each wave was evaluated using Spearman’s correlation coefficient (rho). The statistical package used was SPSS (v.18).

**Use of HT and factors associated with HT use.**

In the prospective, longitudinal analysis, the frequency of current users (prevalence) and the frequency of new users (two-year incidence) were determined for each wave (Paper III, Table 1). The incidence of new users was defined as HT users who did not use HT in the preceding wave, which was divided by the number of women “at risk,” i.e., the number of respondents minus the HT users in the preceding wave. Thus, some of the women “at risk” (in the denominator) might have used HT in one or more of the other previous waves. The duration of HT treatment was based on the responses to the questions related to the start of HT and the treatment duration (years and/or months) in Wave 7. We determined the mean age of starting HT, the distribution of the starting age, and the relationship to FMP by calculating these values based on the responses given in the different waves. The values were adjusted accordingly if respondents answered the question (in Wave 7) related to their age when starting HT.

To check for possible responder misinterpretations of the HT questions (systemic HT use or not) in the questionnaire, we also performed a manual comparison of these responses and the medication list (the last question in the questionnaire) in Wave 7. We analyzed independent variables that were possibly associated with HT use during the observation period by applying binary and multinomial logistic regression. In the binary logistic regression, the dependent variable was HT use during the observation period or in a specific wave, i.e., ever vs. never using HT. In the multinomial analysis, the HT users were grouped into two categories: short-term use (HT reported in one wave only) and long-term use (HT reported in more than one wave). Also, HT users who started in pre- or perimenopause (before FMP or less than one year after FMP) were compared to those who started in post-menopause (one year or more after FMP). The analyses also included factors reported in the literature as possible predictors of use, as well as the participant’s background (socioeconomic) and clinically plausible factors. These factors are listed in Tables 2 and 3 in Paper IV. Possible confounding variables and interactions were examined using the methodology described earlier. We also performed separate analyses of three different waves (Waves 1, 4, and 7) to examine trends over time and possible variations in the contributions of different predictors. For time trend analyses
(Paper IV, Table 1, Fig 1) and differences by wave (Table 4), we applied McNemar’s test and formal tests of interactions by time to provide statistical evidence of secular trends.

**Case-control substudy based on propensity scores**

We studied the frequency of the reappearance of menopausal symptoms after HT discontinuation using a sub cohort where the HT users in Wave 4 were matched with nonusers in the same wave based on their propensity scores, which were calculated with the SPSS propensity score syntax produced by Levesque and Painter\(^{169}\). The propensity score was the propensity (from 0 to 1) of receiving a treatment given a set of known variables. The method is used to adjust for potential selection bias, confounding, and differences between treatment groups in observational studies\(^{170}\). The HT propensity scores in Wave 4 were estimated for each woman using binary logistic regression with the following variables as predictors: menopausal stage (Wave 4, categorized in quintiles); HT use in the previous wave (Wave 3); summed score for symptoms in the previous wave (Wave 3); and the two-way interactions between menopausal stage and HT use, menopausal stage and symptoms, and HT use in Wave 3 and symptoms. Comparisons of symptoms in later waves between the users in Wave 4 and their matched controls were performed using Wilcoxon non-parametric signed rank test. A small number of the controls started using HT in later waves, which could have blurred the differences. Thus, we conducted the analyses with and without these pairs.

The means, proportions, and odds ratios (OR) are given with 95% confidence intervals (CI), as appropriate. SPSS version 20 was used to perform all of the statistical analyses.

**Ethics and approvals**

The Norwegian Data Directorate and the Regional Committee for Medical Research Ethics approved the HWC cohort. All participants provided written informed consent to their participation in the study.

Since the GP study consisted of a questionnaire survey obtained and treated anonymously and no patients were involved, it was not necessary to obtain approval from the Research Ethics Committee or the Data Directorate for this study.
Synopsis of the Papers

Paper I
Bjørn Gjelsvik, Elisabeth Swensen, Per Hjortdahl.

The general practitioner’s view on hormone replacement therapy during and after menopause. [Allmennlegenes syn på hormonbehandling i og etter overgangsalderen.]

Background. The publication of the US-based WHI study and other studies in 2002-2003 profoundly changed the evidence base for treatment, and as a result also Norwegian recommendations for treatment were altered in 2003.

Objectives. The aim of the study was to investigate Norwegian GPs’ attitude to hormone replacement treatment in menopause, their knowledge of current guidelines, effects and indications, the risk of side effects, and the personal use of hormone treatment by female GPs.

Material and methods. A questionnaire was sent to 400 Norwegian GPs, randomly drawn from the membership list of GPs in the Norwegian Medical Association, in May 2004. Perception of treatment effect of HT was evaluated by means of a scale of 1 to 5 to show the extent of agreement or disagreement with a given statement. Response to these statements was studied with logistic regression, and doctors who answered “mostly” or “somewhat agree” were compared to those who answered “disagree” or were neutral. Emphasis on factors that could indicate or contraindicate HT was evaluated by a scale with three grades: Great emphasis, less emphasis, no emphasis or don’t know. The doctors who placed great emphasis on the indication or contraindication were compared with the doctors who placed little or no emphasis on it. The response categories were dichotomized and the associations assessed by means of logistic regression.

Results. We received answers from 72 %. 30% of the respondents were women. The average age of all respondents was 46 years (range 26–69 years), the average number of years in practice 14 years (range 1–37 years). 96 % of the doctors agreed that HT increase the risk of breast cancer.

72% agreed with the statement that HT improves sex life and 40 % agreed that it delays aging of the skin. 67% disagreed that HT provide protection against cardiac infarction. 33 % of the doctors agreed to the statement that HT lead to an unfortunate medicalisation of a natural phase in
women’s life, while 44 % disagreed and 24 % had a neutral position on this statement. The attitude to this question was not related to age or gender.

One out of four GPs did not have a general rule for treatment duration. The majority would treat for less than 5 years. Female doctors had higher odds for having a rule, compared to male.

Bothersome hot flushes were the major indication for treatment. Also risk for osteoporosis, mood variations, vaginal dryness and loss of libido was considered important indications. Of contra-indications, 98 % put great emphasis on history of breast cancer. Genetic disposition of breast cancer, thrombo-embolic disease and cardiovascular disease was also considered important contra-indications.

Female GPs seem to be better updated on some aspects of the treatment than men. 14 out of 17 (82 %) of peri- and postmenopausal female GPs were using or had used such treatment.

Interpretation. The answers imply that most Norwegian GPs knew the current evidence base regarding the effects, indications and side effects of hormone therapy. The fact that vasomotor symptoms was regarded as the dominating indication, and that most doctors had a rule for treatment duration indicate that the majority of doctors knew and applied the recommendations. Compared to female GPs, male doctors seemed less updated on the field. Given the uncertain documentation and unclear communication of some of the effects, it may appear that HT’s assumed positive and non-specific significance for «the female aspect » is assigned greater importance in the clinical decision-making process.

The proportion of menopausal female GPs who used or had used hormone treatment themselves had remained quite stable since the 1990s and was substantially higher compared to the general female population in Norway. This finding may imply that menopausal female GPs regarded the risks of treatment as low, and that most of them found the benefits of treatment greater than the risks.
Background. One aspect of prescribing HT is related to the consideration of risk and uncertainty. Increased risk of breast cancer and cardiovascular disease must be weighed against the benefit of the treatment. When the evidence base for treatment recommendations becomes more reliable, doctors may be more active in giving advice in favor of or against treatment.

Aims. The purpose of the study was to investigate Norwegian GPs’ perception of their own role with respect to prescribing HT to menopausal and post-menopausal women, and the background factors for the decisions doctors make when giving advice.

Method. A questionnaire with a total of 17 main questions and six background variables was sent to a random selection of 400 Norwegian GPs in 2004. Three of the questions in the questionnaire were formulated as clinical examples where doctors were requested to give an opinion about whether they would advise using HT or not, and they could also give their own comments. Analysis of correlations was conducted using correlation tests (Pearson, Spearman). Variables associated with recommending treatment were analyzed using logistical regression.

Results. We received answers from 72 %. 30% of the respondents were women. The average age of all respondents was 46 years (range 26–69 years), the average number of years in practice 14 years (range 1–37 years). 13% answered that it was usually the doctor who took the initiative to start HT. Those who disagreed that HT implied medicalisation had a significantly greater tendency to believe that the doctor takes the initiative to start the therapy (OR 2.5: 95% CI 1.1–6.4). 29% answered that the doctor most often took the initiative to discontinue the therapy. Doctors who agreed that HT implies medicalisation were more likely to take the initiative to discontinue the treatment (OR 2.7; 95% CI 1.3–5.4).

91% were of the opinion that it was vital to know the risks of HT. Almost two-thirds of the doctors thought that the “number needed to harm” – i.e. how many must
receive treatment in a given period of time for one person to suffer a serious side-effect – provided most information. 91% of the doctors felt that risk had considerable or some importance.

When doctors were requested to give an opinion on clinical examples, they were clearly divided when it came to giving advice. The likelihood of recommending therapy was four times higher among the doctors who did not agree that HT implied medicalisation compared with those who agreed with the statement. There was no correlation with other background variables, perception of indications or contraindications or perception of risk associated with therapy.

**Interpretation.** The study indicates that many doctors regarded themselves as active in giving advice, to a greater extent than might be anticipated beforehand; given that HT is primarily the woman’s own choice. The majority of doctors was more restrictive and believed that the therapy implies a risk of serious side-effects. It is interesting to note that the GPs’ perception of the significance of risk is not reflected in the clinical examples. This may indicate that doctors do not integrate the perception of risk indicated in this manner in their internal dialogues when giving advice on HT. The doctors’ attitude to the question of whether the treatment implies medicalisation was more crucial for the advice they gave than their perception of indications, contraindications and the effects of treatment.
Paper III

Gjelsvik B, Rosvold EO, Straand J, Dalen I, Hunskaar S.
Symptom prevalence during menopause and factors associated with symptoms and menopausal age. Results from the Norwegian Hordaland Women's Cohort study.

Background. Symptoms most consistently connected to changes in hormonal status during the menopause are the vasomotor symptoms (hot flushes and sweats/nights sweats) and vaginal dryness. Results from cross-sectional and longitudinal cohort studies vary considerably on many parameters, e.g. menopausal age and degree of symptoms. Also, factors associated with symptom prevalence and symptom burden vary in a number of studies.

Objectives. To describe symptom prevalences over time during the natural menopausal transition, to investigate factors associated with frequency of symptoms as well as their possible influence on self-rated health and to estimate age at menopause and possible factors associated with this age.

Material. 2229 women aged 40-44 years at baseline, randomly selected from a national health survey in Hordaland County, Norway, and followed with seven postal questionnaires from 1997 to 2010. Data for 2002 women (90 %) were eligible for analyses. The dependent variables were frequencies and burden of the main vasomotor menopausal symptoms: hot flushes and night sweats/cold sweats. Self-reported vaginal dryness/soreness was also included in the analysis.

Methods. Summary statistics were used to describe point prevalence and distribution of vasomotor symptoms and vaginal dryness as reported in the seven questionnaires. To analyze independent variables associated with the frequency of hot flushes, we used multinomial logistic regression. The association between symptoms and self-rated health in each wave was evaluated using Spearman’s correlation coefficient (rho). The mean and median age of menopause (FMP) was estimated by Kaplan-Meier survival analysis. Cox regression was used to test the influence of independent variables (smoking, menarche age and parity) on FMP.

Results. The proportion of women who experienced daily hot flushes increased from 2 % in the 41-42 years age group, to 22 % in the 53-54 years age group, with a slight decrease to 20 % in age group 55-57 years. The prevalence of cold sweats/night
sweats followed a similar pattern, whereas the proportion of women who reported daily vaginal dryness/soreness was considerably lower – from 1 % to 8 % during the time span.

The prevalence of bothersome symptoms showed a similar distribution over the age span: The prevalence of considerably and very much bothered reached 21 % and 19 % in the 53-54 year age group for hot flushes and sweats/night sweats respectively and 11 % in the 55-56 year old women for vaginal dryness.

In a longitudinal analysis, 36 % of the women reported daily hot flushes in one or more questionnaires, whereas 29 % did not experience hot flushes at all. The data showed a wide variation in onset, increase and decrease of symptoms.

The mean number of years between FMP and reported maximum frequency of hot flushes was 1.74 years (SD 3.37 years). Thirty-five percent reported their first top value more than two years after FMP. One out of ten women reached this degree of symptoms four or more years after menopause.

Three out of four women with daily hot flushes (20 % of the Cohort) reported this frequency of symptoms in one wave only, 8 % in two consecutive waves and 8 % in more than two waves. Twenty-eight women (1 % of the Cohort) reported daily hot flushes in 6 or 7 waves.

Odds for reporting daily hot flushes was higher for smokers compared to women who did not smoke: OR = 1.6 (1.24-2.10). Women in the lowest education group also had higher odds for reporting daily hot flushes compared to women with a university degree: OR = 1.8 (1.21-2.56).

There was no association between vasomotor symptoms and physical exercise, self-rated health, BMI, family income, parity or menarche age as recorded at baseline.

We found an association between prevalence of vasomotor symptoms and self-rated health in each wave, indicating that frequent symptoms influenced QoL.

The mean age for Final Menstruation Period (FMP) in the cohort was 51.1 (50.9-51.3) years. Smokers had a mean age of FMP 0.9 years earlier compared to the non-smokers.

**Conclusions.** About one-third of Norwegian women report frequent and bothersome vasomotor symptoms during the menopausal transition. Daily smoking and educational level were independent risk factors for experiencing daily menopausal symptoms. Degree of physical exercise, BMI, parity or menarche age did not have significant influence.
Paper IV

Gjelsvik B, Straand J, Hunkå S, Dalen I, Rosvold EO.

Use and discontinued use of menopausal hormone therapy in healthy women in Norway. The Hordaland Women’s Cohort (HWC) study.
Accepted for publication in Menopause, the Journal of the North American Menopause Society.

Background. Studies published shortly after the turn of the millennium showed that HT did not prevent cardiovascular disease, and also led to increased risk of breast cancer. According to Norwegian recommendations published in 2003, HT should only be prescribed for menopausal vasomotor symptoms with significant negative effects on a woman’s quality of life, and the treatment should be revised annually. No efforts, however, were undertaken to implement these recommendations among the physicians.

Objective. To explore HT use and possible association with self-rated health among users and no-users during the menopausal transition, to analyze the duration of HT use, its relationship to age and menopausal stage, and to identify predictors for HT use. We also examined how often menopausal symptoms reappeared in women who stopped using HT.

Material and methods. In 1997, 2229 women aged 40-44 years were selected randomly from a national health survey in Hordaland County and followed up with seven postal questionnaires during 1999-2010. Data from 2002 women (90%) were eligible for analysis. Summary statistics and multiple logistic regressions were used. We studied the reappearance of symptoms after HT discontinuation using a sub cohort based on their propensity scores, which comprised 134 matched pairs of cases (HT users) and controls (nonusers).

Results. The two-year incidence of new HT users dropped significantly from 8.2 % (95 % C.I. 7.0-9.5) in 2002 to 4.3 % (95 % C.I. 3.4-5.2) in 2004 and remained stable despite an increasing prevalence of bothering symptoms in the cohort. At the same time, the prevalence of women reporting self-rated health as bad or not so good was stable. The prevalence of HT use increased slowly from 11.5 % in 2002 (age 43-47 years) to 12.7 % in 2010 (age 53-57 years). 29.5 % (27.5-31.5) of the participants reported use of HT in one or more questionnaires.
For those who had reached menopause by 2010, FMP was the median year of starting HT. The mean duration of HT use was 4.5 years (95% CI = 4.0-5.0 years).

Odds for HT use was higher among women with daily hot flushes compared to those who never or rarely experienced them (OR = 3.2, 95% CI = 2.3-4.4). Older age at baseline, being postmenopausal, being smoker and reporting self-rated health bad or not so good in Wave 1 was also associated with higher odds for using HT.

After HT cessation, hot flushes were still present and the frequency did not differ from the untreated controls.

**Conclusion.** HT use among pre-, peri and early postmenopausal women in Norway was lower than reported in other Nordic and Western studies in the same period. The severity of vasomotor symptoms, mainly hot flushes, was the main reason for HT use and most women stopped treatment within five years. Most women experienced reappearance of symptoms after treatment cessation. The low prevalence of HT use confirms that many Norwegian women prefer to live without HT throughout the menopausal transition, despite troublesome symptoms. The use of HT was by large in line with the Norwegian recommendations, and our data do not support that the relatively low prevalence of HT use impaired the quality of life among the women in cohort.
General discussion.

Methodological considerations.

In population-based surveys, the assumptions to consider deals with the external and the internal validity of the study. The external validity has to do with the generalization of the results – that is: can the results be applied to an external, general population? In our studies: Can the results be applied to other GPs, for example in the Nordic countries or in Europe? Regarding the results from the HWC study: can the results be applied to the Norwegian female population of the same age, and to female populations in other countries? The question is: How representative is the population from which the study respondents have been selected?

Internal validity deals with the validity of the inferences in the population from which the information has been sampled. It depends on the selection of subjects, the quality of the information obtained, and confounding variables.

This study consist of a cross-sectional study (the GP study) exploring knowledge, attitudes and factors associated with prescription of HT, and a longitudinal cohort study (the HWC study) exploring symptoms, risk factors and use of HT in a female population.

In cross-sectional studies, it is in general not possible to make assumptions about causality. We therefore restrict ourselves to report correlations, e.g. between attitudes regarding the medicalisation question and the advice given. It is, however, reasonable to assume that more comprehensive attitudes predict standing when a specified case history is presented. Such attitudes can be regarded as a kind of explanatory variables in the realm of human decision making. Cross-sectional studies will often lead to hypotheses regarding risk factors or explanatory variables for a specific outcome, e.g. prescription of HT.

In a foreword in Acta Obstetricia et Gynecologica Scandinavica, Collins and Landgren pointed out that most of our knowledge of the menopause is based on women who seek medical attention for their climacteric symptoms. The authors asked for longitudinal studies drawn from the general population, allowing changes to be detected from year to year through the menopause. The design of the HWC study meets most of the demands put forward by these researchers. In order to advance from associations to causality, studies with longitudinal assessment of exposure are necessary, e.g. cohort
studies. In a cohort study, it is possible to register an exposure at a specific time point or period, register an outcome later and compare individuals with and without an exposure with respect to the outcome. In addition, the association should be biologically plausible. As an example, it is plausible that the association between daily smoking at baseline and later reporting of more hot flushes (or earlier menopause) is causal, since the time span condition is fulfilled; there is a biological plausible explanation and the regression model control for other possible explanatory variables and confounders. In a cohort study, the internal validity of the measurements usually is most important when assumptions on causality are considered.

**Internal validity in the GP Study**

In the GP study, we invited 400 doctors, approximately 11 % of the GP population in Norway. The total response rate was 76 % and the sample used represented 72 % of the invited doctors. The response rates in other cross-sectional surveys in the NMA database has been in the same range (70-73%) although some questionnaire surveys among GPs have had up to 90 % response rate. The GP sample had fewer doctors in the oldest age group (Table 7), but all taken together we regard that the proportion of important characteristics (age, gender, practice location) of the sample used is quite similar to figures in the GP database of the NMA (A. Taraldseth, NMA, personal communication). We therefore conclude that the GP sample is representative for the GP population in Norway, and the risk for systematic selection bias is neglectable.

Information bias may occur in our study due to misinterpretation of the questions in a systematic manner. We performed a pilot test of the questionnaires in two groups of GPs. Based on the experience from these groups and further discussion in the writing group of Paper I the final questionnaire was constructed. There were few missing values in the returned questionnaires, which indicate that the questions were relevant and easily understood by the doctors. Also, in the pilot testing a common comment from the GPs was that the questions were easy to understand. It was also possible for the GPs to submit comments in free text on several of the questions and the clinical examples. These comments were checked and did not reveal any evidence of systematic misinterpretation.

On this background, we regard that the knowledge and attitudes of Norwegian GPs regarding HT are reflected in the study. However, a limitation in questionnaires is
that they capture what doctors says about the statements (and the alternatives they tick off in the cases), and not necessarily what they do in the clinical situation. The measured results in the study are what the GPs declare they will do given a set of assumptions. In a clinical situation, many other factors will contribute to the final decision to prescribe or not. Among these are additional information on symptoms, evaluation of other risk factors and assessment of the woman’s preferences.

**External validity in the GP study.**

Approximately 95 % of the medical doctors in Norway are members of the NMA, so there are a number of GPs (fastleger) from which a random sample has not been drawn. The NMA register had 3654 GPs per 1.3.2004, while the number of GPs (fastleger) recorded in the Norwegian Health Directorate database per 31.12.2003 was 3713. The NMA register is updated (regarding addresses etc) and is used for several other research purposes, and we regard that the small number of GPs not included in the NMA database does not violate the representativity of the study sample. However, regarding the possibility of generalizing the inferences to GPs in other western countries is somewhat restricted. As to the Nordic GPs, there is a long tradition of scientific collaboration. The joint ownership of the Scandinavian Journal of Primary Health Care and the Nordic Conferences for GPs held biannually are examples. Also, the Norwegian and Swedish Medical Agencies have collaborated for many years with respect to guidelines for treatment in several clinical fields. On the other hand, there may be diverging traditions regarding to which extent prescription of HT is done by GPs or by organ specialists/hospital doctors in the Nordic countries. But despite some differences regarding GPs role in the health system, the clinical tasks are quite similar. It is therefore relevant to apply many of the results regarding GPs to a wider, Nordic population of GPs.

Another concern is to which extent the results, which were collected in 2004, can be regarded as valid today. In fact, there are few new scientific results regarding effects and risks of HT published after 2004. With the exception of reassessment of the WHI study139 and the debate regarding the timing hypothesis142, there has been little debate on HT in later years. It is possible that on this background, some of the assumed effects of HT which were marketed to the GPs before 2002 are unknown among younger GP’s who started their work much later. However, our results were valid in 2004, and are probably also valid among the majority of GPs today.
Medical science and treatment recommendations based on scientific research emerge rapidly from one corner of the world to another, and both journals and conferences contribute to the dissemination of results. But treatment traditions are often different, and HT is a field of medicine where differences between countries and regions of the world exists\textsuperscript{174}. On the other hand, aspects of the decision process and how doctors communicate with patients are more universal, and the results presented here concerning decision making and adherence to recommendations are relevant in many countries.

**Internal validity in the HWC study**

At baseline, the Cohort consisted of 2229 women, the characteristics of which are summarized in Table 8. There were no significant differences between the Cohort and the rest of the female participants in HUSK, except for education and annual family income, which were slightly higher among females in the Cohort.

There were no significant differences with respect to baseline characteristics between the dataset analyzed (N=2002) and the Cohort as a whole (Table 11). The excluded individuals (n=227), however, were slightly older, had lower income, were more obese and less physically active than those in the dataset analyzed.

The attrition rate in the Cohort has been low. In wave 7, the number of remaining participants in HWC comprised 93 \% of the original cohort. The response rates in the waves have varied between 82 \% and 93 \%. When the Cohort was constructed, a maximum attrition rate of 5 \% per wave was used to calculate the size of the Cohort in order to get sufficient power. The number of remaining participants in the Cohort in Wave 7 is far better, so we can conclude that the representativity and the statistical strength of the Cohort has been maintained.

Additional strengths in HWC were the long-term follow-up from before the menopausal transition to FMP and postmenopause. A particular advantage is that the observation period included observations made before and after the shift in clinical guidelines.

The questionnaire was almost identical for each wave. Thus, it was easy for the women to recognize the questions and little chance for misinterpreting the questions from one wave to the next.

Some questions had risk for memory bias. In particular, data regarding last menstrual bleeding was vulnerable. In a cross-sectional design, the impact of such
memory bias will limit the validity of the study. In the longitudinal design, every woman acts as her own control. Thus, it was possible to identify cases of possible memory bias. When these data were used to verify the FMP, it was necessary to check a number of responses manually.

The SWAN investigators found that assessing the recall of symptoms during the last 14 days had an acceptable sensitivity (78-84 %) and specificity (85-89 %) in a three year observation period\textsuperscript{175}. In our study, the symptom question was not specified to the last 14-day period. We asked the women to grade the symptoms, both how often symptoms occurred and to which degree the symptoms were bothering. When respondents are asked to grade the severity of symptoms, the prevalence is typically reduced, and this can have led to lower degree of bothering symptoms in our study\textsuperscript{176}. In clinical studies, checklist are often used to describe the symptoms. When a checklist is used for assessing symptoms instead of open-ended questions, elicitation of positive answers may represent a problem.

As concerns symptom reporting, a weakness of our study is the time span between each recording of data. It is difficult to estimate the duration of symptoms, since we do not know what happens between two waves. Also, since the oldest women in Wave 7 had reached the age of 57 years, we must expect that for some of the women in the Cohort, the duration of symptoms may be longer. Other recent studies have found that symptoms prevail for several years for some postmenopausal women\textsuperscript{49,55}.

Our set of independent variables did not include a number of variables which in the Norwegian Menopause Project were associated with symptom burden\textsuperscript{9}. These included some psychosocial variables, such as the women’s menstrual coping style, mother’s menopausal complaints, negative expectations and social network. Whether a subject report suffering from symptoms often, sometimes or never depends upon her own frame of reference. Such factors may explain some of the differences between our findings and findings from less representative samples.

A limitation in our study is that we did not exclude current or previous HT users in the analyses of factors associated with the symptom burden (Paper III). We performed a regression analysis with and without the HT users, and the exclusion of HT users did not substantially change the results. We therefore decided not to exclude the HT users in the data analysis in order to maintain the representativity of the Cohort.
Some methodological points had to be considered when we compared our HT use prevalence figures with other studies. First, we excluded women from analyses who had undergone surgical removal of the uterus and/or ovaries. The prevalence of HT use in this group was slightly higher than that among healthy women in the HWC. Second, the biennial method used for data recording in the HWC led to under-reporting of HT use. A woman could have used HT for only a short period between two waves, not reporting current HT use in our biennial questionnaires. In the last wave, 35 more women reported previous use of HT, although they had not been recorded as HT users in the preceding waves. These two factors will contribute to lower estimates of HT use in our study.

In wave 7, women who had stopped using HT also was asked for how long time they had used HT. Women who had used HT for 3 months or less (n=16) were categorized as no-users in our survey. This was an arbitrary cut-off, taking into account that we wanted to compare HT users with no-users during a time span of more than 10 years, and use in 3 months or less would represent a negligible part of the time span.

The question about HT use could have been misinterpreted, since we did not specify the meaning of systemic (per os or transdermal) treatment. Thus, topical applications or low-potency estrogen could be included. A validation of the responses was undertaken based on the responses in Wave 7. Approximately 8% of the HT users reported the use of topical or low-potency HT only when they listed their medications (last page of the questionnaire). The prevalence rate in wave 7 should then be reduced with approximately this percentage. All taken together, the possible recording bias went in opposite directions and were impossible to quantify exactly, so we decided not to do any adjustments.

The exact dates for starting treatment were not determined in our study, so the start of treatment was either estimated based on the first time HT use was reported in one of the waves or the age reported in Wave 7. This may imply a memory bias. The fact that a small proportion of the sample reported start of HT in age before forty years may imply that some women had undergone surgery (oopherectomy) without reporting it. We had no access to medical records to control for this.

When assessing self-rated health in the cohort, a standard question with grading in four categories was used. The question is widely used in other surveys carried out in Norway and many other countries, and reflects the responder’s “global” sense of present health status. However, the question is not designed to be an instrument for measuring
QoL, although there is a positive correlation between self-rated health and satisfaction with life\textsuperscript{177}. The simplicity is both an advantage and a limitation: The question is easy to interpret and has been validated as a strong predictor of mortality in several studies\textsuperscript{165,178,179}. On the other hand, it will not catch aspects and variations in QoL, which would have been possible with more detailed and sophisticated instruments. However, the impact of symptoms on QoL measurements in observational studies seems unclear, given that other surveys have demonstrated lack of correlations between vasomotor symptoms and reported QoL\textsuperscript{36,180,181}.

As concerns assessment of symptoms after HT cessation, the study design also had some limitations. When constructing the propensity score algorithm, the number of variables had to be restricted in order to get sufficient power. The design of the case control substudy has some limitations, as we cannot be sure that the treatment and control groups are identical in all other respects than HT treatment. We did not control for all the variables that had an influence in the adjusted analyses (e.g. smoking). However, they were comparable as to the most important variables: menopausal stage, sum score of symptoms in preceding wave and HT use in preceding wave. Also, the groups were smaller when analyzed in wave 5 and 6 due to the procedure per se and a number of missing values. Following this, there is a risk for loss of power and that differences between the cases and controls do not reach statistical significance in these waves (type 2 error).

A number of the controls started HT after Wave 4, which could have contributed to fewer symptoms in the control group after Wave 4 and blurred the differences between the groups. We therefore conducted the analyses with and without these pairs, and the findings did not differ significantly (data not shown).

**External validity in the HWC study**

In the HWC study, the sample was drawn from the female participants in the HUSK study 1997-98. The recruitment and characteristics of the HWC participants is discussed in another paper from the cohort\textsuperscript{163}. There are great differences in symptom prevalence and HT use reported in different parts of the world. To a large extent, these differences have been attributed to cultural differences, with different ways of describing and conceptualizing female menopause and aging\textsuperscript{1,30,182}, as well as to study design and
study sample. Although the Norwegian population gradually has become more multi-ethnic during the last 20-30 years, we suppose that in the age group represented in HWC (women born 1957-61) there are fewer inhabitants of foreign ethnic groups than in the younger generation. We do not know the ethnic background of the HWC participants, but we have no reason to believe that it differs from the average of Norway, with a predominantly white, Caucasian population with Western cultural orientation and traditions in this age group. Thus, the results will have relevance to similar populations in the other Nordic and Western societies.

The Hordaland Women’s Cohort (HWC) is community based, includes a large number of randomly selected participants, and the attrition rate was low, all factors strengthening the external validity of the study results. Compared to the US SWAN study, the women in the Cohort had a lower prevalence of surgically induced menopause. In SWAN, the overall incidence of surgically induced menopause (bilateral oopherectomy and/or hysterectomy) was 20.8 % as compared to 8 % in our population. This probably reflects different therapeutic traditions in Norway and USA, and we believe that our cohort is more representative for the general population regarding symptom burden and menopausal age. The size, the representativity, the frequency of recordings, and the low number of drop-outs make the Cohort a unique database for studying women’s health during the menopausal transition.
Discussion of the results.

Knowledge and attitudes towards HT among Norwegian GPs.

*Indications and contraindications for HT. Relief of symptoms.*

Relief of bothering hot flushes/night sweats was the overwhelming indication for HT in our survey, although other indications obviously also played an important role. The preventive effect of HT on osteoporosis and low-energy fractures was the second most important indication, and is discussed below. We found that mood variations and bothersome vaginal dryness also were important indications, along with reduced libido. Aging of the skin was not regarded important as an indication by the majority, contrary to the belief in beneficial effect. The most important finding was that along with the main indication relief of bothersome VMS, other not established indications like effect on mood swings and libido obviously were important for the doctors. The GPs have a clinical competence and work close to their patients, and assumed amelioration of such symptoms might tip the weight in the pro et contra discussion with the patient and lead to prescription. Few of the independent variables seemed to play a role when assessing the indications, with the exception that GPs who did not regard treatment as medicalisation placed greater emphasis on the indication “mood swings”. Thus, the general attitude to HT had some influence.

Regarding contra-indications, breast cancer in the medical history or among first grade relatives was the most important, but also CVD and thrombo-embolic disease among close relatives were regarded as important contra-indications. These findings are in line with results in studies among Scandinavian gynecologists after WHI\textsuperscript{183}, and indicate that the GP’s were fairly well updated on the risks and side effects of the treatment. The female doctors placed greater emphasis on “breast cancer in the immediate family” as a contraindication than their male colleagues. This effect indicate that the female GPs were more aware of the association between HT use and breast cancer, which was documented in the British MMS and the Norwegian Women and Cancer study in 2003-2004\textsuperscript{123,124}.

The attitude to HT among Norwegian GPs was examined in a survey prior to a consensus conference on HT arranged in Norway in 1990\textsuperscript{184}. A second survey was carried out after the conference to evaluate the effect of an information campaign among
Norwegian GPs\textsuperscript{185}. In general, a restrained attitude towards prescription of oestrogen was found. The intervention (an information package with recommendations from the consensus conference and information about the treatment) did not significantly alter the willingness to prescribe. However, the doctors had more patients on HT in 1992 than in 1990. From 1993 onwards, several surveys were performed in Norway and the other Scandinavian countries to explore the attitudes and use of HT among gynecologists\textsuperscript{112,186-188}. However, no GPs were included in these studies.

There are some differences between the findings in the 1990-92 GP survey and our results, although all taken together they are remarkably consistent. In our survey, the increased risk of breast cancer was very well known among the GPs. This was not asked for in the 1992 GP study. Smoking and a family history of cardiovascular disease reduced the willingness to prescribe HT in 1992. In 2004, the majority of GPs clearly disagreed with the statement that HT protects against cardiac infarction. Moreover, symptomatic cardiovascular disease and thromboembolic disease among close relatives were regarded as contraindications. Thus, it seems that GPs both in 1992 (contrary to the current evidence) as well as 12 years later (when the evidence had changed) regarded that HT could be a risk factor for CVD.

\textit{Assessment of effects of HT related to sex life and feminity}

In our study, other benefits of HT were rather controversial, and the opinions among the GPs were diverging as to many of the effects we asked them about. Approvement of the indication “bothered by vaginal discomfort” was a specific question, and the statement “HT improves sex life” intended to catch a broader aspect of the sex life, such as effect on libido (which was also asked for as a possible indication). More than 2/3 of the doctors agreed to the statement that HT improves sex life. This may be an important element in a pro- and contra discussion with the patient, not to say when a female GP considers using the treatment for herself, or when a male GP discusses the topic with his partner. A number of publications support this\textsuperscript{189-192}. However, the studies are small and the population usually selected, so the quality of this evidence can be questioned. Systemic and local application of estrogen clearly has beneficial effect on relieving dyspareunia, likely because of its impact on vulvovaginal atrophy\textsuperscript{193}. Many other factors seem more important for women when it comes to evaluate causes of impaired sexual satisfaction\textsuperscript{190}. The effect of systemic HT on libido or other aspects of
sexual desire has not been demonstrated\textsuperscript{194}. A literature review found beneficial effect on sexual desire and satisfaction when androgens was added\textsuperscript{195}.

Almost half of the GPs were of the view that HT counteracts aging of the skin, and this is probably also an important factor for the women themselves. Similar views have been found in surveys among gynaecologists\textsuperscript{196}. For many women in the target group for HT, external signs of aging are undesirable. It is particularly important to avoid wrinkles and sagging skin.

Other aspects of treatment regarding sense of well-being and quality of life seemed less important. The statement that HT makes women more attractive had few supporters.

In sum, many of the GPs had belief in beneficial effects of HT connected to the “feminine aspect” which has weak scientific evidence in the literature.

\textbf{Preventive effects of HT}

As mentioned above, the preventive effect on osteoporosis and low energy fractures is well known and was regarded as a reason to prescribe HT. However, the wording of the question was not specified in order to investigate if the doctors still had HT as a first choice for prevention of low energy fractures.

The majority of GPs had no confidence in the preventive effect against CVD, or for other preventive effects of HT. The doctors who were negative to the statement that HT implies medicalisation were most in favor of preventive effects. Also, male doctors were significantly more positive to the statement that HT could prevent heart infarction. The fact that a third of the doctors were uncertain whether HT prevents cardiac infarction or believed that it does, may indicate prevailing uncertainty and confusion about the effects and risk associated with HT. There was higher support for the statement that HT could prevent Alzheimer’s dementia. When the study was performed, positive results regarding HT effect on cognitive function had been published\textsuperscript{115,197,198}, but these studies were small. A meta-analysis published in 2001 found a decreased risk of dementia among HT users in observational studies, but found that most studies had important methodological limitations and called for further, specific research\textsuperscript{199}. The Alzheimer part of the WHI study published in 2003\textsuperscript{200} and the cognitive function part of HERS\textsuperscript{201} from 2002 found a negative effect of HT on cognitive function. Later, a study from Denmark reported positive effect of HT on cognitive function among younger women\textsuperscript{202}, and a “timing hypothesis” for a positive preventive effect if HT was started early has been
discussed. However, a recent literature review conclude that HT have a negative effect on cognitive function and do not prevent dementia\textsuperscript{203}. The 2012 US Preventive Task Force Recommendations, the latest Cochrane report and also the 2012 NAMS statements conclude that HT should not be used to prevent or treat cognitive loss in postmenopausal women\textsuperscript{136,145,204}.

**Treatment duration**

An important change in the recommendations had to do with follow-up and reconsidering the indication for treatment, and the duration of treatment. Treatment should be revised annually, and the benefits and risks for the individual woman should be discussed. Discontinuation attempts should be carried out. After 3-5 years a major revision should be done and discontinuation should be tried, since treatment longer than five years were connected to higher risk for breast cancer\textsuperscript{123}.

In our study, one in every four doctor did not have a general rule concerning the duration of treatment, so the adherence to the control and duration of treatment recommendation was modest. Among those who had a rule, only a minority would administer treatment for less than a year. Female doctors had higher odds for having a general rule for duration of treatment compared to male GPs, thus indicating that female GPs were more concerned about side effects and risks of the treatment.

**The medicalisation issue**

In our study, almost 1/3 of the GPs agreed to the statement that HT implies an undesirable medicalisation of a natural life phase of women, while 44 % disagreed. Since the medicalisation debate had taken place mainly in the 1970s, and to a large extent was initiated by a feminist critique of the treatment, we assumed that the attitude to this statement would follow age and gender. However, our study demonstrated that this was not the case. Of the independent variables, none predicted the attitude to the medicalisation statement. We must therefore assume that the position regarding the medicalisation question follows more general political or cultural attitudes. Our survey does not contain data to confirm this, or other hypotheses. The question is of interest, since we found that the attitude towards medicalisation was significantly associated with the advice given in the clinical examples (cases), and also was associated with statements about effects: Those who disagreed to the medicalisation statement, were more positive to
statements about preventive effects of HT and also put emphasis on positive effects, e.g. effects on mood swings.

To our knowledge, similar questions have not been put forward in other surveys regarding doctors’ attitudes and views on HT. Therefore, it is not possible to compare to other groups of doctors, or with doctors in other regions of the world. In Norway, the discussion among GPs about medicalisation was rather extensive during the 1970s and prevailed in other arenas of medicine during the 1980s and 1990s, e.g. treatment of hypertension and prevention of CVD\textsuperscript{10}.

Liberal prescription attitudes and several assumed effects of HT were prevalent among the gynecologists during the 1990s. In a survey among Scandinavian gynecologists published in 2001, 42\% offered HT routinely to all women provided there were no contraindications\textsuperscript{186}. Reduced libido and mood alterations were regarded as important indications for prescribing HT, along with hot flushes and osteoporosis prophylaxis. Although the attitudes to prescription among gynecologists became more restrictive after 2002\textsuperscript{205}, many of the assumed effects seem to prevail. In a recent study from Germany, prevention of osteoporosis, prevention of cognitive disorders, bleeding disorders, reduction of libido, incontinence and atrophic vaginitis leading to dyspareunia still were important indications, although relief of vasomotor symptoms was the most important indication\textsuperscript{196}.

**Perception of role**

As expected, female doctors discuss HT more often than their male colleagues. We found that about one third of the GPs regarded that they usually took the initiative to stop treatment, while fewer GPs took the initiative to start. The fact that less than half of the doctors regarded that it was usually the woman who took the initiative to start, and only one fourth that the woman took the initiative to stop treatment may indicate that the majority of doctors regarded that they were active in giving advice. The finding may reflect a traditional perception of role among many GPs to be active and take decisions, assuming that the medical knowledge shall enlighten the patient. The perception of role was associated with the standing towards the medicalisation question, as the doctors who disagreed to the statement were much more apt to give advice to start treatment, and those who agreed were much more apt to discontinue treatment. It was, however, almost half of the doctors who regarded that it was the patient just as often as the doctor who took the initiative to start or stop HT, indicating that this is a field of medicine where shared
decision making takes place to a great extent. Not surprisingly, the active “start HT” role described among gynecologists during the 90s was rare among GPs in our survey.

**To treat or not to treat – that is the question. Heuristics and biases.**

Giving advice in favor of or against HT is a matter of weighing the advantages (positive effects) against the disadvantages (side-effects or risk) for the individual patient. After WHI, the scientific basis of efficacy and risk is better documented, and the recommendations clearly state that HT should only be prescribed to women with bothersome vasomotor symptoms with a negative impact on the woman’s quality of life\textsuperscript{128}. We might then assume that the doctors would be fairly unanimous in the advice they give. However, the division of GPs into two “camps” as regards their views on hormone therapy reveals a striking divergence.

The likelihood of recommending therapy was four times higher among the doctors who did not agree that HT implied medicalisation compared with those who agreed with the statement. There was no correlation with other background variables, view of indications or contraindications or perception of risk associated with therapy. A number of those who would neither recommend nor advise against therapy (n = 129), commented that they would discuss the pros and cons and allow the patient to decide herself.

Thus, the doctor’s general attitude – “positive” or “negative” – to HT measured by the medicalisation question played an important role while the perception of risk inherent in the therapy played a lesser role when the decision to advice treatment or not was taken. Such a positive or negative attitude may represent what is termed “affect heuristics”\textsuperscript{158} in psychological research. Affect heuristics link feelings to alternative choices, and help us to make speedy decisions that are consistent with our own values and intuitive preferences. By the same token they can also result in incorrect practice in that such patterns survive attempts to change them by means of scientific or logical reasoning. In fact, there is a vast literature applying the heuristics concept in other disciplines, such as economy and psychology\textsuperscript{206}. Other examples of important heuristics are recognition heuristics and availability heuristics. Recognition heuristics is typically used in medicine when a doctor diagnoses a disease based on recognition of a typical pattern he or she has seen before, such as herpes zoster or Parkinson’s disease. Availability heuristics is used when the person limits the sources of information to what he or she already have access to or know, sorting out the other and more complicated or less available sources of information. Finally, the optimism bias is working when we take into account the positive
elements favoring a decision we want to achieve or the outcome we prefer, leaving out the “bad news”. Heuristics are significant when people make decisions in complex areas with many elements of information, such as doctors do when they make up their mind to treat or not. Although there is little discussion of the importance of this concept in medicine, these factors should be taken into consideration when new evidence-based guidelines are adopted or implemented in order to change practice.

All taken together, the GPs were fairly well updated regarding the main effects, indications and contra-indications. A proportion of the male doctors seemed less well updated regarding the results from WHI. At the same time, many assumed effects of HT that is less well documented, like preventing skin aging and enhancing sex life, also seem to play a role in the picture of reasons to use HT. Given the uncertain documentation and unclear communication of some of the effects or that they have not been grasped by the target group, it may appear that HT’s assumed positive and non-specific significance for “the female aspect” is assigned greater importance in the clinical decision-making process.

Do the female GPs use HT themselves?

In our survey, 14 out of 17 (82 %) menopausal or post-menopausal female GPs stated that they used or had used HT in connection with menopause. Because a relatively small proportion of GPs in our survey are menopausal or post-menopausal women, only a few have answered these questions, and the figures must be interpreted with caution. However, the result is in line with other studies finding that HT use among doctors is far more prevalent than in the ordinary population. No change in HT use was observed among gynaecologists between 1997 and October 2002 (after WHI). In comparison, only about a quarter of Norwegian women aged 50–69 in 2004 stated that they used or had used HT. A recent study from Germany showed a remarkably high proportion of willingness to use HT among female doctors (96.5 %) and male doctors who would prescribe HT for their partners (98 %). For some of these indications, the willingness to use it oneself was greater than the willingness to prescribe it for patients. In an Italian study from 2003, the willingness to use HT was markedly higher among gynecologists (56-59 %) than among GPs (30-31 %) or oncologists (16-30 %), and few doctors or doctor’s wives stopped using HT after the WHI trials.
The finding deserves a reflection: Why do doctors state that they have become more restrictive when prescribing HT, at the same time continuing to use it just as before? Several important factors stand out as possible explanations for the difference in consumption pattern. Doctors have ready access to drugs and are familiar with their use, and have lower thresholds against use of drugs than others\textsuperscript{208-210}. Furthermore, doctors may judge the risk for themselves associated with HT as small compared with the benefit. Indeed, for persons without additional, underlying risks, such as previous thrombosis or breast cancer, the absolute risk (and risk increase) is low. Additionally, it takes some time for knowledge to replace attitudes and practice\textsuperscript{211}. During at least one or two decades, HT has been judged beneficial and harmless. Both the “optimism bias” and the availability heuristic will lead to preservation of a practice of use and self-prescription. Included in these benefits are effects linked to sexuality and the “feminine aspect” which many doctors have confidence in. These aspects are important also for the doctors. Our survey does not say anything about the significance of these or other possible explanations.

**Menopausal symptoms in the HWC study**

An important finding in the HWC study was that the prevalence of frequent and bothering vasomotor symptoms and vaginal dryness were considerably lower than reported in other surveys among Western, Caucasian women\textsuperscript{53-55}. We found a peak prevalence of daily hot flushes in the 53-54 age group, when 22 % reported daily hot flushes, 17 % weekly, and 21 % was considerably or very much bothered by them. 41 % was not bothered by hot flushes in this most affected age group. When comparing with the North American Swan study\textsuperscript{73} (cross-sectional prevalence, 5 different ethnic groups, 16,075 women), the peak prevalence of combined VMS (hot flushes and/or night sweats) in the same age group (52-55 years) was 46.6 % (reported symptoms in the last two weeks). In this study, the highest prevalence was found among Afro-Americans and the lowest among the Japanese and Chinese ethnic groups. In European studies, the prevalence of symptoms is even higher (Table 1, Table 2). Our figures of bothersome hot flushes are, however, largely in line with findings in the Norwegian Menopause Project from the 1980s\textsuperscript{57}.

Our results correspond to previous findings as to the time from FMP to peak prevalence of symptoms. In a recent meta-analysis, Politi found that symptoms peak 1-2
years after FMP, when approximately half of the women experience bothersome symptoms\textsuperscript{55}.

Also, the prevalence of vaginal dryness is lower in our study compared to others. The number of studies reporting vaginal dryness is lower than for VMS and most studies report symptom prevalence in the range of 20-50 \%, highest in late postmenopause\textsuperscript{44,53,67,68}.

So – does the lower prevalence of VMS and vaginal dryness in the HWC mean that Norwegian women have less symptoms compared to other Western, Caucasian women? The strength in our study is the representativity and the long observation time, and the low attrition rate in the cohort. The design of the study seems to play a role. When comparing with other population-based longitudinal studies, such as SWAN\textsuperscript{73} or the Australian MWMHP\textsuperscript{44}, the differences are smaller. In cross-sectional studies, the prevalence is usually higher than in longitudinal studies. In our study, women with surgically induced menopause were excluded, thus contributing to somewhat lower symptom prevalence’s in HWC. Inclusion of these women raised the peak prevalence of daily hot flushes 1-2 \% across the age groups.

It is also worth noting that almost one out of three of our respondents never or almost never experienced any hot flushes or night sweats during the menopausal transition. Since our observation period is up to ages 53-57, we expect that this proportion may become lower during prolonged follow up.

In some prospective studies, attitudes to menopause (positive or negative) are associated with prevalence of symptoms. Women with negative attitudes before menopause tend to report higher frequency of symptoms when reaching the menopause\textsuperscript{212,213}. It is possible that the women in HWC (and Norwegian women as such) have more positive attitudes to menopause than other Western women. In Norway, the percentage of women working outside the home is among the highest in world\textsuperscript{214,215}. Participation in work may contribute to more positive self-evaluation during the menopause. We have, however, no data to support this hypothesis. Other cultural or socioeconomic differences may contribute to the observed differences in reported symptoms, such as differences in therapy traditions, access to specialized care and perception of the role as an elderly woman in the society. The degree of medicalisation of the menopause, that is the extent to which menopause is regarded as a medical condition,
may vary also between western-oriented countries, and contribute to the differences found.

Following the individual women across the age span also revealed a great variety in frequency and degree of bothering symptoms. Some women reported an early onset of symptoms, but a rapid decrease, others had no decrease or a two-puckled curve, and still others had late onset or very low frequency of symptoms. The youngest woman started with daily HF at age 41, and the oldest at an age of 57 years. The great variation in symptom debut, the duration of symptoms and the variation in intensity across the transition is interesting and may also be of clinical interest, since it shows the great span of normality as such.

Although the symptom burden in the HWC seems lower than in comparable populations, it is important to keep in mind that a minority of women reported very frequent and bothersome symptoms over a long time span. Twenty-eight women (1% of the Cohort) reported daily hot flushes in six or seven questionnaires, indicating more than 10 years of bothersome symptoms.

All taken together, we assume that our study shows that the prevalence of bothering symptoms among Norwegian women is among the lowest reported up to now among Western, Caucasian women.

**Factors associated with frequency of symptoms.**

Of the independent variables recorded, daily smoking was the life style factor which was most significantly associated with the intensity of symptoms. Odds for reporting daily hot flushes was 1.5 (1.2 - 1.9) for daily smokers vs. non-smokers. The finding that daily smoking was associated with more frequent hot flushes, confirms results from other surveys. Our study also showed that daily smoking was associated with lower age at FMP. The effect of smoking on symptom prevalence and FMP may reflect a biological anti-estrogenic mechanism, as mentioned earlier. We did not find that degree of physical activity or overweight (BMI) before the menopausal transition was associated with increased or less vasomotor symptoms, although women with BMI > 25 kg/m² had a slight, non-significant lower odds for reporting daily hot flushes (OR=0.8, CI 0.68-1.01, p=0.064). The finding that hard physical activity during the menopausal transition was associated with more symptoms may reflect that women with more symptoms become more physically active in this period due to a belief that physical exercise may in itself reduce vasomotor symptoms.
Our study confirms earlier findings that educational level is associated with symptom reporting\textsuperscript{71,87}. Women living single had higher odds for daily or weekly hot flushes, compared with women living in partnership or marriage. Self-reported health at baseline, family income or age at menarche recorded at baseline had no significant influence on symptom reporting. The same associations were found for women with fewer symptoms (weekly and/or monthly symptoms) compared to women without symptoms, except for educational level where no association was found. The association between symptoms and educational level is somewhat difficult to explain, since we controlled for other factors, such as income, smoking or other life style factors. It is possible that the association has to do with higher self-confidence and contention with life, and higher levels of employment outside the household, which has been found to be associated with lower reporting of symptoms\textsuperscript{72}.

**Self-rated health and association with symptoms.**

In the Cohort, overwhelming and stable proportions reported that their present health status was good or very good. From 2002 (Wave 3) onwards, only small, not significant variations in self-rated health took place. There was no indication that different values of self-rated health at baseline predicted later vasomotor symptoms. However, the analysis indicated a correlation between this perceived health status and the burden of vasomotor symptoms in the separate waves. However, the size of the effect was modest. Other studies have demonstrated that most women cope very well with the symptoms of menopause, and that there are many aspects of life that have much more influence on psychological well-being in the midlife years, such as new roles (being grandmother), becoming more experienced and competent, being better to stand up for oneself, and other factors\textsuperscript{217-219}.

We conclude that frequent hot flushes were associated with higher prevalence of reporting self-rated health as “bad” or “not so good”. The effect was not sufficient, however, to cause changes in the cohort as a whole.

**Age at menopause and factors associated with this age.**

Excluding users of hormonal IUD, mean (with 95% confidence interval, CI) and median age at FMP in the Cohort were 51.1 (50.9 to 51.3) and 51 years, respectively. Daily smoking at baseline or later was associated with lower menopausal age. In NMP, a mean age of menopause of 52.9 years was found\textsuperscript{10}, but the final sample used was small.
and the representativity of the sample is questionable. In addition, a 6-months amenorrhea
criterion was used. However, our results are largely in line with other studies\textsuperscript{103,104}. In a
recently published European cross-sectional study, higher ages for FMP and less
influence of smoking were reported\textsuperscript{102}, and the question was raised whether menopausal
age in Europe is increasing. The Finnish study\textsuperscript{104} is, like ours, a representative,
community based cohort, and this may explain the similarity in our results. A cross-
sectional design will be more vulnerable to recall bias than a longitudinal design. In
conclusion, our data does not support the hypothesis that age at menopause in Europe is
increasing.

**HT use in the cohort.**

We detected a sharp, significant decrease in the frequency of new HT users
between 2002 and 2004, despite the increasing prevalence of vasomotor symptoms in
women. This was obviously explained by the publication of the WHI results and the
following media focus on “dangerous hormones”, which were picked up by the women
themselves\textsuperscript{220}. After 2002 (Wave 3), the prevalence of HT users in the HWC was stable
throughout the observation period, although the women passed through the menopausal
transition and experienced increasingly bothersome symptoms. Obviously, many women
preferred to pass through the menopausal transition without HT, despite their bothersome
symptoms. Also, more narrow indications for HT use were followed by the women and
their doctors\textsuperscript{21,221}.

The prevalence of HT use corresponded with the findings of a Norwegian cross-
sectional study from 2005, which reported 10.1 % current use while 31.3 % of women
had used HT at some point\textsuperscript{167}. The prevalence of current HT use was lower than that
reported by two Swedish surveys where the prevalence in the corresponding age group
was 22.9-25.3 %\textsuperscript{222,223}, and also in a 2005 US study, which reported 20 % current and 50
% ever HT use among postmenopausal women\textsuperscript{224}. These observational studies were
cross-sectional rather than longitudinal like ours, which limited any comparisons.
However, our results support findings from the early 1990s, which showed that
Norwegian women were generally reluctant to use HT\textsuperscript{184,225}.

Following secondary analyses of the WHI data, some authors have argued in favor
of a “window of opportunity” for initiating HT by suggesting that HT may actually have a
cardio protective effect if it is started within 5-7 years after menopause\textsuperscript{223,226}. Our figures
do not indicate that the women or their doctors have confidence in these arguments. On
the contrary, there is no evidence for increased prescription of HT during the last years in the cohort. Instead, the incidence seems to be falling.

On the other hand – since the women reported more symptoms during this period, there is a risk for under-treatment: perhaps many women suffered reduced quality of life in this period because their bothersome symptoms were not adequately treated? In our study, self-rated health was used as a proxy for self-assessed quality of life. The proportion of women reporting self-rated health “bad” or “not so good” in the different waves was stable from 2002 onwards when the prevalence of daily hot flushes began to rise (Paper IV, Table 1, Fig 1). Our study design does not allow inference as to whether individual women have been under-treated, but the stable distribution of self-rated health categories after 2002 does not indicate systematic under-treatment in the cohort. In other words, we do not have reasons to believe that the low prevalence of use have led to reduced quality of life in this age group.

We had a long follow-up period and a significant proportion (12.7%) of the HWC still used HT when the study was completed. Thus, the proportion of long-term users and the mean duration of treatment are probably longer than those reported here. In another longitudinal Norwegian study, the mean duration of HT use among current users was 6.3 years in 2005, but the proportion of long-term users was much higher (60 %) compared with that of long-term users in our study (27 %)167.

On average, HT was initiated at FMP, although some started as many as 10-12 years before FMP. Start of VMS at an early age might have been the main reason for initiation of HT before menopause. Another possible explanation is that bleeding disturbances before FMP may have been regarded as an indication for prescribing HT22. It is also worth noting that a large proportion of the women started HT use up to four years after menopause, which reflected the wide ranges in the symptom prevalence and duration, as well as other possible reasons for using HT, such as bleeding disturbances.

The prevalence of hot flushes (daily or weekly/monthly) was the main factor associated with HT use. This association was strongest for the long-term users and for women who started pre- or perimenopausal. We suggest that this observation indicates that treatment of vasomotor symptoms was the main reason for using HT, while other reasons had less important roles. In the cross-sectional analysis in Wave 7 (Paper IV, Table 4), this association was weaker and not significant. We suppose that in this wave,
the women had used HT for a longer period and that the effect of the treatment wiped out
the difference between users and no-users.

The odds of using HT were increased by the age of women at baseline. This may
have been because a proportion of the younger women had not yet reached menopause at
the end of the observation period, although it may also reflect an increasing skepticism
about HT among the younger women. The age effect was less pronounced over time, and
was not significant in the last wave. The finding indicates that the main factor for use was
the increase in symptoms around and after FMP.

No associations were found between HT use, education, or income, which
contrasts with the findings of surveys from the 1980s and 1990s\textsuperscript{227,228}. However, our
findings are largely in agreement with more recent studies\textsuperscript{167,229}. This may reflect a shift
in medical practice from general prevention towards targeted relief of troublesome
symptoms. However, the prevalence of HT use among female GPs found in a Norwegian
survey may reflect only minor changes in doctors’ attitudes to HT use\textsuperscript{230}.

The association between HT use and smoking was somewhat paradoxical because
the increased risk of thromboembolic disease associated with HT use may be regarded as
a relative contraindication for HT use among smokers. After analyzing the symptom
prevalence and the factors that predicted symptoms in the HWC, we found a positive
association between symptom prevalence and daily smoking\textsuperscript{231}. Thus, the increased
burden of vasomotor menopausal symptoms among smoking women was probably more
important than the increased risk of thrombosis in smokers.

We found a positive association between HT use and the degree of urbanization.
An explanation might be easier access to gynecologists in the cities, but other factors
related to local cultures and attitudes are also possible.

**Reappearance of symptoms after discontinuation of HT**

We found that menopausal symptoms often reappeared after treatment cessation,
which is in line with other studies\textsuperscript{223,232}. Reappearance of symptoms is biologically
plausible and is also supported by data showing that the duration of the menopausal
transition is actually longer than previously reported\textsuperscript{55}. Hormone therapy relieves the
symptoms and is not directed at the basic mechanisms responsible for the vasomotor
symptoms. Many women restart HT after discontinuation attempts\textsuperscript{232-234}. Recent figures
from Sweden showed that 87 % experienced symptom reappearance after HT
discontinuation, irrespective of the treatment duration\textsuperscript{235}. Our finding indicate that when
HT is taken to relieve symptoms, one must expect that it is necessary to use it over several years, and may be longer than the maximum treatment period of 3-5 years that is advised in the guidelines.

The majority of former HT users in our study reported side effects, or the fear of side effects, as the most important reasons for stopping treatment. This indicates that women were aware of the possible side effects such as an increased risk of breast cancer. Our GP study also indicated that the doctors were aware of this risk and the majority of them complied with the guidelines, which recommend treatments shorter than five years\textsuperscript{230}. However, few have asked why women continue to use HT. In a study from a gynecological practice in London published in 2006, only 3% of women who used long-term HT implants wanted to discontinue their treatment\textsuperscript{236}. Depression and loss of energy and/or libido were their main concerns for HT discontinuation while few feared relapse of vasomotor symptoms.

**Concluding remarks**

An important finding in the HWC study was that the prevalence of bothersome symptoms in the cohort was lower than previously reported in other surveys in comparable populations. One third of the women experienced bothersome symptoms during the menopausal transition and early postmenopause. However, only a minority suffered from these symptoms for several years. Also, the prevalence of HT use was lower than reported from our neighborhood countries, and our data do not support that the relatively low prevalence of HT use impaired the quality of life among the women in the cohort.

Thus, we may conclude that on average, the women in the Cohort were not very bothered, and many women preferred to pass through the menopausal transition and early postmenopause without use of HT despite frequent VMS. On this background, we also conclude that *systematic* under-treatment of women was not found in our material.

The finding that bothersome hot flushes was the factor most consistently associated with HT use indicates that this was the most important indication for HT, confirming that the majority of women and prescribing doctors use HT to alleviate symptoms. Other indications, e.g. prevention of chronic disorders played a smaller role. This finding is also in accordance with the GP study. The mean duration of treatment,
reported by the women themselves was in line with the recommendations, although a proportion of women obviously had used HT for a longer period. Among the GPs the adherence to the recommended maximum treatment duration was less obvious. This should not be a surprise, since up to 8 percent of the women reported hot flushes for 8 years or more, and most women experienced reappearance of vasomotor symptoms after HT cessation.

In line with other findings, we found that symptoms reappeared in most women after HT cessation. Further research is needed to clarify in more detail how long the treatment must be for symptoms to ware off.

When analyzing factors influencing prevalence of bothersome symptoms, daily smoking was a significant risk factor, while most of the other background and health factors had little or no effect. This finding should encourage women to quit smoking.

A remarkable finding in the GP study was that the advices given in the case histories were quite diverging. The result indicates that the attitude of GPs to HT, given in the survey as agreement with the statement that HT implies an undesirable medicalisation of a natural life phase in women, was a key explanatory variable for recommending treatment when presented clinical examples. The same factor was associated with how active the doctor was in starting or stopping treatment, as was also gender and age. However, differences in other background variables, such as perception of risk or effects of the therapy showed no corresponding correlation. This finding is of interest, since several attempts have been made to encourage doctors to change practice in fields of medicine where new evidence have emerged, and there is a need for change. Traditionally, guidelines with scientific based arguments with or without treatment algorithms are used. May be it is more efficient to explore tools aimed at changing attitudes and affect heuristics? This is a field that demands further research.

Finally, the high prevalence of HT use among female GPs found in our study indicates that the doctors weigh risks and benefits differently from what their patients do, and also differently from what they do when they advise their patients. The finding is in line with other surveys. However, the reason for this striking difference regarding HT use has to my knowledge not been studied further, and represents another interesting issue that needs to be explored.
References


(14) Ekstrom H. *Keeping My Ways of Being. Middle-aged women and menopause*. Lund, Sweden: Division of Family Medicine, Department of Clinical Medical Science, Lund University, Sweden; 2005.


(22) Gjelsvik B. [General practitioners' advice on hormone replacement therapy in menopause]. Tidsskr Nor Laegeforen 2008;128:1660-1663.


(60) Archer DF, Sturdee DW, Baber R et al. Menopausal hot flushes and night sweats: where are we now? *Climacteric* 2011;14:515-528.


(63) Deecher DC, Dorries K. Understanding the pathophysiology of vasomotor symptoms (hot flushes and night sweats) that occur in perimenopause, menopause, and postmenopause life stages. *Arch Womens Mens Health* 2007;10:247-257.


(81) Sternfeld B, Quesenberry CP, Jr., Husson G. Habitual physical activity and menopausal symptoms: a case-control study. *J Womens Health* 1999;8:115-123.


(130) Statens Legemiddelverk. Estrogens used in the menopause (G03C and G03F). *Statens Legemiddelverk: www.legemiddelforbruk.no/* 2010.


(137) Boukes FS, Groeneveld FPMJ, Assendelfts WJJ. Dutch College of General Practitioners' Position on Hormone Replacement Therapy. *Dutch College of General Practitioners* [serial online] 2003; Available from: Dutch College of General Practitioners.


Hoffmann M. *Risk Talk - On Communicating Benefits and Harms in Health Care* [ Faculty of Health Sciences, Linköping University, Sweden; 2006.


Norwegian Health Directorate. GP statistics. 5-2-2013. Ref Type: Online Source


Cohort of Norway (CONOR). 2013. Oslo. 5-6-2013. Ref Type: Online Source


(170) Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983;70:41-55.


(196) Buhling KJM, von Studnitz FSG, Jantke AM, Eulenburg CP, Mueck AOM. Use of hormone therapy by female gynecologists and female partners of male gynecologists in Germany 8 years after the Women's Health Initiative study: results of a survey. [Article].


(205) Moen MH, Nilsen ST, Iversen OE. A significant change in Norwegian gynecologist's attitude to hormone therapy is observed after the results of the Women's Health Initiative Study. *Acta Obstet Gynecol Scand* 2005;84:92-93.


(207) Biglia N, Ujcic E, Kubatzki F et al. Personal use of hormone therapy by postmenopausal women doctors and male doctors' wives in Italy after the publication of WHI trial. *Maturitas* 2006;54:181-192.


(214) Skills.OECD. 2013. OECD. 6-6-2013. Ref Type: Online Source

(215) Gjelsvik M. Work Participation among women, international comparison. 28-5-2013. Ref Type: Internet Communication


Results from the Norwegian Hordaland Women's Cohort study. *Maturitas* 2011;70:383-390.


APPENDIX I

GP study Invitation letter and Questionnaire
Allmennlegen og forskrivning av hormoner til kvinner i og etter overgangsalderen. Hvordan gjør vi det?

I løpet av de siste 2 årene har det vært en økende debatt om bruken av hormonbehandling av kvinner i og etter klimakteriet. Flere undersøkelser\(^1\) har bidratt til å reise spørsmål ved kvinnens bruk av hormontilskudd og legers forskrivningspraksis.

Ut fra salgstall for 2002 brukte ca 200 000 norske kvinner et hormonpreparat i eller etter overgangsalderen. De fleste (170 000) fikk systemisk behandling med tabletter eller plaster, resten brukte kun lokalbehandling. Allmennlegene står for ca halvparten av forskrivningen. Det har derfor stor interesse å kartlegge hvordan norske allmennpraktikere forholder seg til dette fagfeltet.

Undersøkelsen tar sikte på å "tegne et kart". Dette er et felt der forskrivning og indikasjonsstilling er preget av "myke verdier" – det handler bl.a. om kvinnens livskvalitet og eventuell risiko ved behandlingen, og det finnes få absolutte sannheter. Vi er ikke ute etter et "fasitsvar", men å få vite noe om holdninger til dette problemkomplekset. Likkende undersøkelser er foretatt blant gynekologer i Norge, og det vil være interessant å se om allmennlegenes holdninger og praksis skiller seg fra gynekologenes.

Vi ønsker deretter å bringe resultatene tilbake til det allmennmedisinske miljø – gjennom artikler, debatt og kanskje videre- og etterutdanningstilbud.


Med vennlig hilsen

Bjørn Gjelsvik, allmennpraktiker
Prosjektansvarlig

Per Hjordahl
Professor i allmennmedisin

Institutt for allmenn- og samfunnsmedisin
Universitetet i Oslo

PS. Svarkonvoluttene er nummererte for at vi skal kunne sende en påminnelse til dem som ikke har svart. Selve svarskjemaet behandles anonymt. Ett av spørsmålene (nr. 18) er litt mer personlig. Hvis du ikke har lyst til å svare på dette kan du droppe det. Men besvar og send inn resten av skjemaet!


University of Oslo
1. Bakgrunnsdata (Besvares av alle)

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| Antall år i praksis: |     |
|                     | (antall år i allmennpraksis i alt – hel eller deltids) |

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<td>501-1000</td>
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<th>Kommunetype:</th>
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<td>Landkommune</td>
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<td>Trøndelag</td>
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Med hormonbehandling menes i dette skjemaet systemisk behandling med østrogen, østrogen-gestagen kombinasjoner eller syntetiske analoger i eller etter klimakteriet.

2. Hvor ofte diskuterer du hormonbehandling med pasient? (sett ett kryss)

| □ Mindre enn 1 gang pr. måned | □ 1-4 ganger pr. måned | □ 1-3 ganger pr. uke | □ Nesten hver arbeiddag |

3. Opplever du at det i konsultasjoner kan være vanskelig å gi råd (vurdere nytt og risiko) om bruk av hormonbehandling i overgangsalderen? (sett ring rundt tallet)

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<th>1</th>
<th>2</th>
<th>3</th>
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<tbody>
<tr>
<td>Nei, aldri</td>
<td>Sjelden</td>
<td>Av og til</td>
<td>Ofte</td>
<td>Ja, alltid</td>
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</table>

Ved svaralternativ 1 ovenfor: Gå til spørsmål 5.

4. Hvis du opplever at det er vanskelig – hva er den viktigste grunnen? (angi eft. rangering ved 1-2-3)

□ Den medisinske kunnskapen om nytt og risiko ved behandlingen er usikker eller ufullstendig
□ Kunnskapen er vanskelig å anvende i en klinisk situasjon
□ Jeg mangler kunnskap om dette selv
□ Andre forklaringer:

5. I hvilken grad er det du som lege eller pasienten som tar initiativ til å starte hormonbehandling?

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<td>Nesten alltid meg som lege</td>
<td>Oftest meg som lege</td>
<td>Like ofte lege som pasient</td>
<td>Oftest pasienten</td>
<td>Nesten alltid pasienten</td>
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6. I hvilken grad er det du som lege eller pasienten som tar initiativ til å avslutte hormonbehandling?

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<td>Nesten alltid meg som lege</td>
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<td>Like ofte lege som pasient</td>
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7. Har du noen hovedregel for hvor lenge du anbefaler hormonsubstitusjon ved behandling for overgangsplager?

| □ Nei | □ Ja | kortere enn ett år |
|      |     | 1 år → inntil 3 år |
|      |     | 3 år → inntil 5 år |
|      |     | 5 år eller mer |
|      |     | i så fall for hvor lang tid? |

8. Hvor stor vekt vil du legge på disse forholdene for å forskrive systemisk hormonbehandling til kvinner? (kun ett kryss i hver rad)

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<thead>
<tr>
<th>Stor vekt</th>
<th>Mindre vekt</th>
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<tr>
<td>Heteoteker og/eller svette i sjenerende grad</td>
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<td>Nedsatt libido</td>
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<td>Humørsvingninger</td>
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<td>Plager fra tørre slimhinner</td>
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<td>Aldring av huden</td>
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<td>Disposisjon (arv) for beinskjøret</td>
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9. Hvor stor vekt vil du legge på disse forholdene mot å forskrive systemisk hormonbehandling til kvinner? *(kun ett kryss i hver rad)*

<table>
<thead>
<tr>
<th>Tidligere brystkreb (ferdigbehandlet)</th>
<th>Stor vekt</th>
<th>Mindre vekt</th>
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<tr>
<td>Brystkreb hos førstegrads slektninger</td>
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<th>10. Hva er din mening om følgende utsagn? <em>(kun ett kryss i hver rad)</em></th>
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<tr>
<td>Hormonbehandling øker risikoen for brystkreb</td>
</tr>
<tr>
<td>Hormonbehandling forebygger Alzheimers demens</td>
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<tr>
<td>Hormonbehandling utsetter aldring av huden</td>
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<tr>
<td>Hormonbehandling bedrer selvsivet</td>
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<tr>
<td>Hormonbehandling gjør kvinnemønster attraktiv</td>
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<td>Hormonbehandling beskytter mot hjerteinfarkt</td>
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<tr>
<td>Hormonbehandling beskytter mot tykkstammkreft</td>
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<tr>
<td>Hormonbehandling øker levealderen hos kvinner</td>
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<tr>
<td>Hormonbehandling innebærer en uheldig medikalisering av en naturlig livsfase hos kvinner</td>
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11. Opplever du i din praktiske hverdag at det er viktig å vite hvor stor risikoen for bivirkninger ved hormonbehandling er?

<table>
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</tbody>
</table>

| C | Hvis 1000 kvinner behandles i 10 år, vil 8 flere få brystkreb enn hvis ingen behandles.

13. Ut fra risikoestimatene ovenfor *(spm. 12)* – angi hvor stor betydning denne risikoen har for deg i en klinisk situasjon:

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Svært liten betydning</td>
<td>Liten betydning</td>
<td>Noe betydning</td>
<td>Stor betydning</td>
<td>Svært stor betydning</td>
</tr>
</tbody>
</table>

14. Har du i løpet av de siste 1-2 år endret din forskrivningspraksis (blitt mer restriktiv eller mer liberal) når det gjelder hormonbehandling? *(Sett et kryss på skalaen)*

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blitt more mer restriktiv</td>
<td>Blitt noe mer restriktiv</td>
<td>Omtrent som før</td>
<td>Blitt noe mer liberal</td>
<td>Blitt meget mer liberal</td>
</tr>
</tbody>
</table>

Forts. neste side
Nedenfor gis 3 kliniske eksempler som er aktuelle for allmennpraksis. Angi hva slags råd du vil gi ved å krysse av i boksene. Gi eventuelt kommentarer.

15. Klinisk eksempel I:
Kvinne, 55 år, har ikke tidligere brukt hormonbehandling. Siste menstruasjon var før ver 2 år siden. Hun har merket litt heterotakter på nittene, men det har ikke plaget henne så mye. Hun har følt seg mer nedsatt i det siste, synes huden er blitt fort eldre og samtlivet med mannen har blitt mer og mer sporadisk. Hun har snakket med flere venninner som bruker hormonbehandling og som sier de føler at hormonene bedrer deres livskvalitet. Hun lurar på om hun skal prøve behandlingen.

<table>
<thead>
<tr>
<th>Angi hva slags råd du vil gi:</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Jeg vil anbefale hormonbehandling</td>
</tr>
<tr>
<td>□ Jeg vil verken anbefale eller frarå hormonbehandling</td>
</tr>
<tr>
<td>□ Jeg vil ikke anbefale hormonbehandling</td>
</tr>
<tr>
<td>□ Jeg vil sterkt frarå hormonbehandling</td>
</tr>
</tbody>
</table>

Evt. kommentar:

16. Klinisk eksempel II:
Kvinne, 60 år, ingen spesielle risikofaktorer, har brukt hormonbehandling i ca. 5 år og ønsker å fortsette fordi hun føler behandlingen øker hennes livskvalitet.

<table>
<thead>
<tr>
<th>Angi hva slags råd du vil gi:</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Jeg vil anbefale fortsatt hormonbehandling</td>
</tr>
<tr>
<td>□ Jeg vil verken anbefale eller frarå hormonbehandling</td>
</tr>
<tr>
<td>□ Jeg vil frarå fortsatt hormonbehandling</td>
</tr>
<tr>
<td>□ Jeg vil sterkt frarå fortsatt hormonbehandling</td>
</tr>
</tbody>
</table>

Evt. kommentar:

17. Klinisk eksempel III:

| □ Ja |
| □ Nei |
| □ Vet ikke |

Evt. kommentar:

18. Besvares kun av kvinnelige leger:
Hvor befinner du deg i forhold til menopausen (enten a eller b)?

<table>
<thead>
<tr>
<th>□ A. Før menopause:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kan du tenke deg å bruke hormoner i forbindelse med overgangsalderen?</td>
</tr>
<tr>
<td>□ Ja</td>
</tr>
<tr>
<td>□ Nei</td>
</tr>
<tr>
<td>□ Vet ikke</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>□ B. I eller etter menopause:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruker du hormonbehandling?</td>
</tr>
<tr>
<td>□ Nei</td>
</tr>
<tr>
<td>□ Ja</td>
</tr>
</tbody>
</table>

Hvilket preparat: ........................................
Hvor lenge har du brukt? ...........(antall år)
□ Har brukt tidligere
Hvor lenge brukte du? ..........(antall år)

TAKK FOR INTERESSEN!
SEND INN SKJEMAET IDAG!

4
APPENDIX II

HWC study

Invitation letter and Questionnaire, Wave 7
Prosjekt om vanlige kvinneplager
Helseundersøkelsen i Hordaland

Bergen, november 2009

Kjære deltaker i kvinneveresjektet i Helseundersøkelsen i Hordaland

Vi henvender oss igjen til deg som en av de to tusen kvinnene som sa ja til tilbudet om å delta i denne undersøkelsen, og som har bidratt til dette viktige forskningsprosjektet gjennom 10 år. Spørreskjemaer har hatt en formidabel oppslutning, som har vakt internasjonal oppsikt, nå sist på en kongress i USA der innlegget om undersøkelsen vår ble kåret til et av de 50 beste blant mer enn 1000 innlegg fra 2500 deltakere!


Vi håper derfor at du også denne gangen vil fylle ut skjemaet og sende det til oss innen noen få dager i den ferdig frankerte konvolutten. Spørreskjemaet er merket med et 4-sifret referansenummer for å kunne vite hvem som har svart, og bare en person (som har taushetsplikt) skal arbeide med skjema der navnet viser. Forskerne arbeider bare med anonyme datafiler. Dersom du ønsker det, kan du klippe bort navnet med et referansenummer.

De fleste av spørsmålene svarte du også på sist. Mye av verdien av denne undersøkelsen ligger nettopp i å følge utviklingen hos de samme personene i mange år. Den observante deltaker vil se at vi har et par nye spørsmål, blant annet om vekten din som ung! Det er fordi ny utenlandsk forskning har vist at ungdomsvekten kan ha betydning for senere symptomer, og vi ønsker å sjekke om dette stemmer også i Norge. Vi spør denne gangen også om litt flere detaljer når det gjelder hormonbehandling.

På baksiden viser vi noen glimt av resultatene fra forrige runde.

Vi er takknemlige for at du hjelper oss, og at du er med videre. Noen av dere har flyttet ut av Hordaland. Vi vil gjerne ha også dere med videre, fordi dere bodde her da undersøkelsen startet. Vi regner med at det nå går 2 år før neste skjemarunde. I Hordaland er det like mange som bruker nynorsk som bokmål. Denne gangen er det bokmålsbrukerne som får skjema i sin målform!

Vennlig hilsen

Steinar Hunskår
Professor

Gateadresse: Postadresse: Telefon: Telefaks:
Kalfarveien 31 5018 BERGEN 55 58 61 00 55 58 61 30
Glimt fra resultatene i forrige runde

Hormoner og hormonbehandling

Figuren viser svarfordelingen i forrige runde på spørsmålet **Bruker du hormoner mot plager i overgangsalderen?**

Vi er spent på om det er endringer etter to år!

Alternativ behandling
Vi vet at mange personer bruker alternative behandlere i tillegg til sin vanlige lege. Det synes vi er interessant å få kartlagt. Gjennom undersøkelsen kan vi se hvilke plager man går til lege for og får medisiner mot, og hvilke alternative medisiner man bruker istedenfor, eller i tillegg. Dessuten har vi flere ganger spurt om dere har vært til alternativ behandler siste året. Det har mange av dere vært! En firedel av dere svarte positivt på spørsmålet forrige gang, og her er fordelingen over hvem denne firedelen har hatt kontakt med:
Dato for utfylling: ____/____-20____ Hva er alderen din nå? ____ år

Hvordan er helsen din nå? (Sett bare ett kryss)

- Dårlig
- Ikke helt god
- God
- Svært god

Har du vært hos lege eller ligget på sykehus det siste året? JA NEI

Dersom ja, gi stikkord for grunnene (diagnose, problem)

1. grunn _________________________________________
2. grunn _________________________________________
3. grunn _________________________________________
4. grunn _________________________________________

Har du vært hos "alternativ" behandler siste året? JA NEI

dersom ja, har du vært hos:

- Akupunktør
- Fotsoneterapeut
- Kinesolog
- Urtemedisiner
- Andre; spesifiser ________________


<table>
<thead>
<tr>
<th>Timer pr uke</th>
<th>Ingen</th>
<th>Under 1</th>
<th>1-2</th>
<th>3 og mer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Løtt aktivitet (ikke svett/andpusten)</td>
<td>JA</td>
<td>NEI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hard fysisk aktivitet (svett/andpusten)</td>
<td>JA</td>
<td>NEI</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hva er vekten din nå? _____kg Hva er høyden din nå? ______cm

Hva var vekten din ved ca 20-års alder? _____kg

Trener du bekkenbunnen (knipøvinger) en gang i uken eller oftere? JA NEI

Røyker du sigaretter daglig? JA NEI

Hvilke(n) prevensjonsmetode(r) bruker du? (Flere kryss mulig).

- Minipille
- P-pillar
- Hormonspiral
- P-plaster på huden
- Vanlig spiral
- Kondom hos partner
- P-sprog
- Pessar
- Sædrepende krem
- P-stav under huden
- Jeg er sterilisert
- Partner er sterilisert
- Hvis du bruker spiral eller prevensjonsmiddel på resept, hvem går du vanligvis til for dette?

- Fastlegen
- Gynekolog
- Annen lege

Bla om!
VANNLATING

Hvor ofte har du vanligvis vannlating?

_________ antall ganger i døgnet

Må du vanligvis opp om natten på grunn av vannlating?

Nei  1 gang  2 ganger  3 ganger  Mer enn 3 ganger

Har du de siste 12 månedene hatt episoder med akutt svie, smerte eller ubehag ved vannlatingen?

Nei  1-2 ganger  3-5 ganger  Mer enn 5 ganger

Var du plaget med sengevætning/nattevætning som barn etter 5-6 års-alderen? ..................................

Synes du at du som oftest får tømt blæren skikkelig ved vannlating? .......................................

Er du ofte plaget av sterk og brå vannlatingstrang? .................................................................

Opplever du urinlekkasje når du hoster, nyser, ler eller løfter tungt? ..........................................

Opplever du urinlekkasje i forbindelse med sterk og brå trang til vannlating? ..........................

Opplever du urinlekkasje i andre sammenhenger? ......................................................................

Hvor ofte har du urinlekkasje? (Sett bare ett kryss)

Aldri eller nesten aldri..................................................

Sjeldnere enn en gang i måneden..................................

En eller flere ganger i måneden..................................

En eller flere ganger i uken........................................

Hver dag og/eller natt..................................................

Hvor mye urin lekker vanligvis hver gang? (Sett bare ett kryss)

Har ikke lekkasje ............................................................

Dråper eller lite ..............................................................

Små skvetter .................................................................

Større mengder ............................................................

De neste spørsmålene gjelder bare hvis du har eller har hatt lekkasjeplager:

Er du operert for urinlekkasje?.................................

Har du tidligere hatt urinlekkasje og blitt bra uten behandling?..................................................

Hvilket hjelpemiddel eller behandling bruker du eller har du brukt for lekkasjeplager?

Ikke  Prøvd før  Bruker nå

Medisiner .................................................................

Mensbind, trusseinlegg..............................................

Spesialbleier ..............................................................

Knipøvinger ..............................................................

Elektrostimulator ....................................................... 

Hvordan opplever du lekkasjeplagene?

Ikke noe problem........................................................

Lite plaget.................................................................

En del plaget ............................................................

Mye plaget............................................................... 

Har du noen gang søkt legehjelp for lekkasjeplagene? .........................................................

BRUK AV MEDISIN, NATURLEGGEMIDDEL m.m.

Tok du noen medisin for helsen I GÅR? ....................

Med medisin mener vi her alle typer, både:
• med og uten resept, naturmedisin, vitamin og mineral
• medisin som skal svelges, innhaleres eller injiseres, stikkpiller, salver, kremer eller dropper.

Dersom JA:

Hvilken medisin tok du I GÅR? Hva var grunnen til at du tok medisinen (diagnose, sykdom, symptom, helseeffekt)?

Sett svarene inn i skjemaet nedenfor, en linje for hver medisin. Kryss av for ja hvis du bruker medisinen daglig eller nesten daglig.

<table>
<thead>
<tr>
<th>Navn på medisinen (ett navn pr. linje):</th>
<th>Grunn til bruk av medisinen I GÅR var:</th>
<th>Daglig</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>JA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NEI</td>
</tr>
</tbody>
</table>

Kryss av etter medisinen:

Dersom det ikke er plass nok her, kan du fortsette på et eget ark som du legger ved skjemaet.

Dersom vi har brutt feil adresse, eller du vet at du skal endre adresse, skriv den nye adressen i ruten. Du kan gi oss melding i et eget brev eller på telefon.

Send svarskjemaet i den frankerte konvolutten i dag.
Takk for hjelpen!
Errata

Paper I

Page 1500, Material and method, Paragraph 2, line 8:

The correct sentence shall read: The doctors’ assessment of indications and contraindications was analysed by testing the response category “great emphasis” against the response categories “less emphasis” and “no emphasis” added together. (not .. was analysed by adding together the response categories “great emphasis” and “less emphasis” and testing them against “no emphasis”.)

Paper II

Page 1662, Table 4: Figures in Column heading, Univariate analysis shall read:

Recommend therapy (n=90-93, not 89) vs advice against + no advice given (n=193-196 not 186)

Figures in Column heading, Multivariate analysis shall read:

Recommend therapy (n=86 not 89) vs advice against + no advice given (n=189 not 186)

Page 1662, Table 5: Figures in Column heading, Univariate analysis shall read:

Recommend therapy (n=60-63, not 89) vs advice against + no advice given (n=220-225 not 186)

Figures in Column heading, Multivariate analysis shall read:

Recommend therapy (n=60 not 89) vs advice against + no advice given (n=217 not 186)