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Reassessment of the cost-effectiveness of hormone replacement therapy in Sweden: Results based on the Women's Health Initiative randomized controlled trial

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Objectives: The purpose of the study is to reassess the cost-effectiveness of hormone replacement therapy (HRT) based on new medical evidence found in the Women's Health Initiative (WHI). Within a model framework using an individual state transition model, the cost-effectiveness of 50- to 60-year-old women with menopausal symptoms is assessed based on a societal perspective in Sweden.
Methods: The model has a 50-year time horizon divided into a cycle length of 1 year. The model consists of the following disease states: coronary heart disease, stroke, venous thromboembolic events, breast cancer, colorectal cancer, hip fracture, vertebral fracture, and wrist fracture. An intervention is modeled by its impact on the disease risks during and after the cessation of therapy. The model calculates costs and quality-adjusted life years (QALYs) with and without intervention. The resulting cost per QALY gained is compared with the value of a QALY gained, which is set to SEK 600,000. The model requires data on clinical effects, risks, mortality rates, quality of life weights, and costs valid for Sweden.
Results: The cost-effectiveness ratios are estimated at approximately SEK 10,000, which is below the threshold value of cost-effectiveness. On the condition that HRT increases the quality of life weight more than 0.013 units, the therapy is cost-effective.
Conclusions: In conclusion, given the new evidence in WHI, there is still a high probability that HRT is a cost-effective strategy for women with menopausal symptoms.

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Keywords: Cost-effectiveness analysis, Hormone replacement therapy, Markov model

Women in the industrialized part of the world today are living more than one third of their life after menopause. For example, in Sweden, approximately 1.7 million women are above the age of 50 years, which corresponds to 19 percent of the population. At menopause, which occurs on the average at age 51, approximately 75 percent of women experience menopausal symptoms such as hot flushes, night sweats, and atrophy-related symptoms of the urogenital tract (41). Ten percent of women suffer from symptoms more than 15 years after the menopause. The effect of menopausal symptoms on quality of life may be substantial, as shown by, for example, Daly et al. (12) and Zethraeus et al. (57). In Sweden, the costs for estrogens (estrogens, progestins, and combination drugs) increased from 370 to 500 million SEK during the period 1995–2000. In the year 2000, sales were restricted to women above the age of 45 years and with menopausal symptoms and were estimated to be 300 to 400 million SEK. Also, if costs for physician visits are added, the total intervention cost of hormone replacement therapy (HRT) amounts to 600 to 700 million SEK in the year 2000 (41).

The use of HRT mitigates or eliminates menopausal symptoms and leads to a major improvement in quality of life for women with menopausal symptoms (12;57). HRT also offers protection against osteoporosis and related fractures and previously was believed to offer a cardioprotective effect as shown in observational studies (40). However, recent randomized studies do not show any reduction in cardiovascular events in secondary or in primary prevention (1;20;39). Evidence of the effect of HRT on breast cancer had been inconclusive, but now the general belief is that the risk of breast cancer increases with the use of HRT (1;4;9;10;39;40–42). For hysterectomized women on estrogen-only therapy, however, the Women's Health Initiative (WHI) study (1) shows a decreased risk of breast cancer. Results based on the WHI (39) show that HRT also changes the risk of colorectal cancer, venous thromboembolic events (VTE), and stroke. For non-hysterectomized women taking estrogens only, an increased risk of endometrial cancer is evident. The increased risk of endometrial cancer is eliminated by the addition of a progestin (39;41). Combining estrogen with a progestin may induce uterine bleeding; however, such bleeding may reduce or vanish if a combined HRT is continuously applied, although break-through bleeding often occurs in the first few months (41). Today, estrogen-only therapy is most frequently given only to women with a hysterectomy, whereas women with an intact uterus are given estrogen combined with a progestin to eliminate the endometrial cancer risk.

Cost-effectiveness analysis is a method for assessing costs and benefits of alternative ways of allocating resources to assist decisions aimed at improving efficiency. To determine whether a treatment is cost-effective compared with an alternative, the cost per gained unit of effectiveness (e.g., cost per gained quality-adjusted life year [QALY]) must be compared with the willingness to pay for a gained unit of effectiveness (e.g., the value-gained QALY). If the price per unit increase in effectiveness exceeds the cost, the program is cost-effective. The value of a gained QALY is usually stated to be approximately SEK 500,000–600,000 (US$ 50,000–60,000) (18;23). In this study, we use a value of SEK 600,000 per QALY gained, which also can be derived from the value that the Swedish road authorities put on a statistical life.

Modeling is required to assess the cost-effectiveness of HRT (31;54), which has been mentioned in many previous studies (2;7;13;14;16;46–48;50;52;53;58–60). Modeling is necessary, because clinical trials cannot provide all the information that is needed for economic evaluation, which requires cost and effectiveness information in a long-term perspective. There are several types of modeling alternatives, for example, decision tree models, Markov models, and discrete event models. Usually, a so-called state transition Markov model is used, which is characterized by a time horizon divided into equal increments of time called Markov cycles, health states, and transition probabilities, which reallocates a hypothetical population between disease states, for example, once a year.

The purpose of the study is to reassess the cost-effectiveness of HRT for an average population of Swedish women with menopausal symptoms. The cost-effectiveness analysis is carried out based on a societal perspective and on new clinical findings in the WHI studies (1;39). The cost-effectiveness of HRT is calculated in six patient groups dependent on age (50, 55, or 60 years) and uterine status (intact uterus or hysterectomized). Women with an intact uterus are given combined therapy, whereas hysterectomized women are given estrogen-only therapy. In particular, the following questions are investigated: Is it still cost-effective to use HRT for women with menopausal symptoms, given the new information in WHI? What is the minimum gain in quality of life that is required just to make the HRT cost-effective for women with menopausal symptoms? For each group, extensive one-way sensitivity analysis is carried out where, for example, the effects of HRT, remaining effects of HRT, size of the quality of life improvement, treatment duration, and intervention cost is varied.

MODEL

The cost-effectiveness model used in this study is based on a previously developed model that included coronary heart disease (CHD), breast cancer, and fracture outcomes (58–60). Some alterations have been made to capture all relevant effects of HRT found in the WHI. The following disease

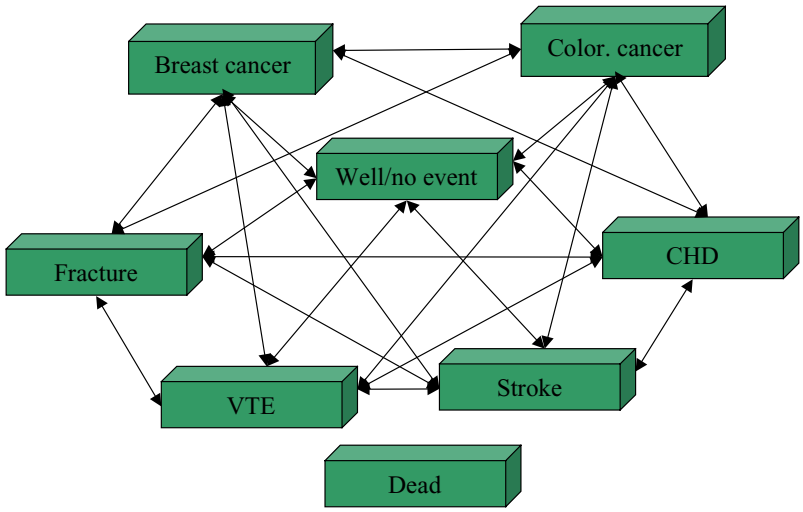

Figure 1. The structure of the model. Color., colorectal; CHD, coronary heart disease; VTE, venous thrommoboembolic events.

states were added to the model: stroke, VTE, and colorectal cancer. A detailed description of the model is available in Zethraeus et al. (56).

The structure of the model that was used is shown in Figure 1. The arrows show the allowed transitions in the model. There is always a possibility of dying or staying in the same health state. CHD consists of three different health states: acute myocardial infarction, angina pectoris, and coronary insufficiency. The fracture state consists of a hip fracture, vertebral fracture, and a wrist fracture state (Figure 1).

An intervention is modeled by its impact on the disease risks during therapy and, in some instances, effects that persist after the cessation of therapy, toward an offset time period. In Figure 2, an example on how the effect of HRT on the risk of a disease can be modeled is shown. If a remaining effect of HRT on the fracture risk after the treatment period is assumed, this is modeled as a linear decline in the effect for a given "offset time." In Figure 2, the remaining effect persists for 5 years after the cessation of therapy.

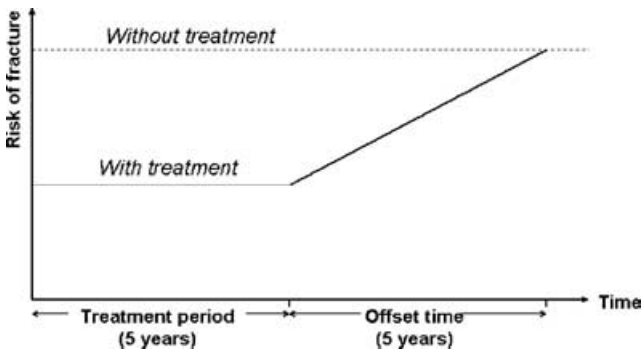

Figure 2. Modeling an intervention.

DATA

The data for the model are based on available evidence for risks, mortality rates, quality of life weights, and costs valid for Sweden. The inclusion of costs is based on a societal perspective, including intervention costs, disease related costs, and costs in added years of life. Cost and quality of life data are to a major extent based on empirical studies. Data on disease risks and mortality rates are obtained from different national registers and epidemiological studies. A detailed presentation of all data is presented in Zethraeus et al. (56).

Effect of Hormone Replacement Therapy

The effects of HRT on disease risks during therapy are taken from the WHI studies (1;39). Based on the WHI (39), the following relative risks (RR) were used for women with an intact uterus on combination therapy: CHD (RR = 1.29), stroke (RR = 1.41), VTE (RR = 2.11), breast cancer (RR = 1.26), colorectal cancer (RR = 0.63), hip fracture (RR = 0.66), vertebral fracture (RR = 0.66), and other osteoporotic fracture (RR = 0.77).

Based on the WHI (1), the following RRs were used for women with a hysterectomy on estrogen-only therapy: CHD (RR = 0.91), stroke (RR = 1.39), VTE (RR = 1.33), breast cancer (RR = 0.77), colorectal cancer (RR = 1.08), hip fracture (RR = 0.61), vertebral fracture (RR = 0.62), and total osteoporotic fractures (RR = 0.70). Estrogen-only therapy significantly increased the risk of stroke and significantly reduced the risk of hip, vertebral, and other total osteoporotic fractures. In the base case assumption, a remaining effect of 5 years is assumed for fractures (3). No other remaining effects are assumed to exist (4).

Disease Risks

Age-specific population risks of hip, vertebral, and wrist fracture for Swedish females used in the model were derived from

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a population-based study from Malmö (26). To estimate the age-specific incidence of nonskeletal events (breast cancer, colorectal cancer, CHD, stroke, VTE) data were extracted from the Swedish national inpatient register administered by the Centre for Epidemiology at the National Board of Health and Welfare.

Mortality Rates

The age-specific annual mortality rates for the general population in Sweden are based on the years 1998–2001 (43). To fit the model structure, normal mortality rates had to be adjusted to exclude the risk of dying from those disease events that were included in the model (58). This adjusted normal mortality was calculated as normal mortality multiplied by the share of all causes of death (44) that was not explained by CHD, stroke, breast cancer, and colorectal cancer.

Patients with hip fractures and clinical vertebral fractures have a higher mortality compared with the normal population (5;6;11;21;28;35). Age-differentiated mortality risks (first and following years) after clinical vertebral fractures were derived from Johnell et al. (24). A part of the excess mortality after fracture compared with normal mortality cannot entirely be ascribed to the fracture event but also to other comorbid conditions (28;29;37). Thirty percent of the observed excess mortality after a hip or vertebral fracture was assumed to be associated with the fracture event. Wrist fracture was not assumed to be associated with any excess mortality (6;24). Mortality after breast cancer, colorectal cancer, CHD, stroke, and VTE was derived by linking the inpatient sample extracted from the inpatient register with the register for causes of death also monitored by the Centre for Epidemiology at the National Board of Health and Welfare. The yearly mortality rates were estimated using parametric Weibull survival regression (30).

Quality of Life Weights

The estimation of the gain in quality of life from HRT is based on a Swedish empirical study (57). In the base case analysis, we assume that the gain in quality of life due to HRT is equal to 0.29, which corresponds to an average woman with menopausal symptoms.

The impact on quality of life the first year after a fracture was based on a study conducted at the orthopedic department at the Malmö University Hospital in the south of Sweden (55). Quality of life values for the population (33) were used as proxies for the patient quality of life without a fracture. Accounting for the gender distribution in the study sample, the disutility the first year after fracture was calculated (27). The quality of life in subsequent years after a hip fracture was assumed to be 90 percent of that of a healthy individual (25). Wrist fracture was not assumed to be associated with any utility loss the second and following years after fracture. The utility loss the second and following years after a clinical vertebral fracture was set to 0.05 (36). The utility loss after CHD, based on previous studies (17;22;49), was assumed to be 0.1 for all years after disease event and for all ages. As in Zethraeus et al. (58–60), we assumed the utility loss associated with breast cancer to be equal to the loss after CHD. The same utility loss was assumed for colorectal cancer and VTE.

Costs

All costs are expressed in 2003 prices. When needed, the costs were inflated using the Consumer Price Index from Statistics Sweden (44). The annual intervention cost for women on combination therapy (with an intact uterus) is estimated at SEK 2,972. This value consists of drug costs (SEK 1220 [41]) and 1.5 physician visits per year at a price of SEK 1,168 per visit. The corresponding annual intervention cost for women on estrogen-only therapy (with a hysterectomy) is estimated at SEK 2,078. This value consists of drug costs (SEK 910 [41]) and 1 physician visit per year at a price of SEK 1,168.

Direct and indirect fracture costs in Sweden during the first year after a hip, clinical vertebral, and wrist fracture was derived from Zethraeus et al. (55). Hip fracture costs the second and following years were based on the assumption that 10 percent of all patients remain at a nursing home for the rest of their lives (25) at a weekly cost of 1,486 SEK (45). It was conservatively assumed that these fractures were associated with costs only during the first year after fracture.

Costs related to CHD, stroke, breast cancer, colorectal cancer, and VTE are based on Zethraeus et al. (60), Liljegren et al. (32), and the national inpatient register. The potential savings in hospital costs were estimated as the difference 1 year after and before the event, using the patient as her own control (61). Costs in added years of life (34), defined as the difference between annual production and consumption in different age groups, are based on Ekman (15).

RESULTS

The health effect, cost, and cost-effectiveness results of a 5-year HRT are presented in Tables 1–4. The results are separated for women with an intact uterus and for women with a hysterectomy.

Health Effects and Costs

The health effect consequences of HRT in the different patient groups in terms of life years (LYs) and QALYs are presented in Table 1. HRT suggests a loss in the expected number of life years for women with an intact uterus on combination therapy. The mean decrease in expected life years is between 0.04 and 0.05, which corresponds to 15–18 days. After discounting, the mean decrease varies between 0.02 and 0.03 life years. HRT will increase the number of expected QALYs compared with no therapy in all the age groups. The increase

Table 1. Life Years (LYs) and Quality-Adjusted Life Years (QALYs) with and without HRT for 50- to 60-Year-Old Women with an Intact Uterus or Hysterectomized[a]

Age (year)			Intact uterus	Hysterectomized
50	HRT	QALYs	15.99 (24.5)	16.02 (24.57)
		LYs	20.12 (32.53)	20.15 (32.60)
	No HRT	QALYs	14.8 (23.25)	14.8 (23.26)
		LYs	20.14 (32.57)	20.14 (32.59)
	Diff.	QALYs	1.19 (1.26)	1.22 (1.31)
		LYs	− 0.02 (− 0.041)	0.006 (0.014)
55	HRT	QALYs	14.08 (20.52)	14.13 (20.59)
		LYs	18.35 (28.13)	18.39 (28.20)
	No HRT	QALYs	12.9 (19.27)	12.9 (19.28)
		LYs	18.38 (28.16)	18.38 (28.17)
	Diff.	QALYs	1.18 (1.25)	1.22 (1.31)
		LYs	− 0.02 (− 0.04)	0.0089 (0.02)
60	HRT	QALYs	11.95 (16.62)	12.01 (16.71)
		LYs	16.4 (23.82)	16.47 (23.93)
	No HRT	QALYs	10.78 (15.38)	10.78 (15.37)
		LYs	16.43 (23.87)	16.43 (23.86)
	Diff.	QALYs	1.17 (1.24)	1.24 (1.34)
		LYs	− 0.03 (− 0.049)	0.033 (0.065)

[a] Discount rate = 3%. Health effects undiscounted are shown within parentheses.
HRT, hormone replacement therapy; Diff, difference.

in the number of QALYs (with and without discounting) is between 1.2 and 1.3.

For women with a hysterectomy on estrogen-only therapy, HRT suggests a gain in life expectancy, which amounts to 0.01–0.06, which corresponds to 4–22 days. After discounting, the mean increase is between 0.006 and 0.03 years. HRT will increase the number of expected QALYs compared with no therapy in all the age groups. The increase in QALYs (with and without discounting) is estimated at between 1.2 and 1.3 (Table 1).

The cost consequences are shown in Table 2. The mean difference in costs in the different age groups is estimated at between 10,000 and 15,000 SEK. In older age groups, the cost-level becomes higher. This finding is because the value of production decreases, which suggests that the costs of (consumption–production) will increase and result in a total higher cost level (Table 2).

Cost-Effectiveness

The cost-effectiveness results for women with an intact uterus are presented in Table 3. In the base case scenario, the cost per QALY gained varies between SEK 9,000 and 13,000 in the different age groups, which is below the defined threshold value of SEK 600,000. It is clear that the cost-effectiveness ratios are stable to all but one of the alternative scenarios specified in the sensitivity analysis. The results are only sensitive to whether the therapy has a positive effect on menopausal symptoms or not. If it is assumed that HRT does not increase quality of life, HRT is dominated by the no-therapy alternative, which means that the no-treatment alternative suggests more QALYs and lower costs (Table 3).

The results for women with a hysterectomy are presented in Table 4. In the base case scenario, the cost per gained QALY varies between SEK 8,000 for a 50-year-old women and SEK 11,000 for a 60-year-old women, which is also below the defined threshold value of SEK 600,000. The cost-effectiveness ratios are stable to all but one of the alternative scenarios specified in the sensitivity analysis. If it is assumed that HRT does not affect quality of life, then the cost-effectiveness ratio exceeds the threshold value of SEK 600,000 (above SEK 1 million at the ages 50 and 55). However, for a 60-year-old woman, the cost-effectiveness ratio (SEK 500,000) is still below the threshold value (Table 4).

To investigate the effect that the elimination of menopausal symptoms has on cost-effectiveness, a threshold analysis was carried out. The purpose of the threshold analysis was to determine the minimum increase in quality of life that is required just to make the treatment cost-effective. The analysis showed that HRT is cost-effective for women with or without a hysterectomy (irrespective of age) if the gain in quality of life exceeds 0.013 units.

DISCUSSION AND CONCLUDING REMARKS

This study has re-examined the cost-effectiveness of HRT for an average Swedish female population with menopausal symptoms based on a societal perspective and new evidence presented in the WHI studies (1;39). The cost per gained QALY varies for 50- to 60-year-old women between SEK

Table 2. Costs (SEK, year 2003) with and without HRT for 50- to 60-Year-Old Women with an Intact Uterus or Hysterectomized[a]

	Intact			Hysterectomized		
Age (year)	No HRT	HRT	Difference	No HRT	HRT	Difference
50	804 024	819 266	15 242	805 706	815 813	10 107
55	1 312 432	1 325 282	12 850	1 314 143	1 323 882	9 739
60	1 925 364	1 936 097	10 733	1 925 986	1 939 631	13 645

[a] Discount rate = 3%.
HRT, hormone replacement therapy.

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Table 3. Cost (SEK) per Gained Quality-Adjusted Life Year for Women with an Intact Uterus on Combination Therapy Compared with No Therapy

	50 years old	55 years old	60 years old
Base case	12,807	10,844	9,159
Sensitivity analysis:			
Excluding cost in added life years	14,494	12,933	13,369
Discount rates 5%	13,175	11,546	10,071
Discount rates: 3% costs, 0% effects	12,132	10,249	8,659
No discounting	11,373	8,900	6,974
Mild menopausal symptoms	20,907	17,724	15,054
Severe menopausal symptoms	8,759	7,428	6,277
No menopausal symptoms	HRT dominated	HRT dominated	HRT dominated
Treatment duration of 3 years	14,653	12,594	13,537
No set-time	12,689	11,130	7,103
10 years set-time	13,372	11,399	10,354
Population mortality down-adjusted by 50%	11,577	10,534	8,703
Intervention costs *1.5	17,337	16,622	14,972
Reducing utility loss of nonskeletal events by half	12,745	10,784	9,098
No effect of HRT on:			
CHD	11,080	9,717	10,991
Stroke	13,184	9,993	8,967
VTE	12,644	11,237	11,186
Colorectal cancer	12,712	10,075	6,766
Breast cancer	13,298	12,236	11,014
Fractures	12,518	10,972	4,380

HRT, hormone replacement therapy; CHD, coronary heart disease, VTE, venous thromboembolic events.

Table 4. Cost (SEK) per Gained Quality-Adjusted Life Year for Hysterectomized Women on Estrogen-Only Therapy Compared with No Therapy

	50 years old	55 years old	60 years old
Base case	8,266	7,960	11,043
Sensitivity analysis:			
Excluding cost in added life years	7,532	6,563	5,588
Discount rates 5%	7,934	7,529	9,543
Discount rates: 3% costs, 0% effects	7,712	7,413	10,201
No discounting	9,412	9,557	15,263
Mild menopausal symptoms	13,274	12,763	17,556
Severe menopausal symptoms	5,717	5,510	7,677
No menopausal symptoms	1,510,111	1,000,772	503,160
Treatment duration of 3 years	9,147	9,946	12,072
No set-time	8,081	8,330	9,577
10 years set-time	8,870	8,507	11,078
Population mortality down-adjusted by 50%	8,172	7,956	11,388
Intervention costs × 1.5	12,190	11,875	14,896
Reducing utility loss of nonskeletal events by half	8,255	7,949	11,014
No effect of HRT on:			
Stroke	8,569	8,422	10,027
Fractures	7,900	7,730	9,475

HRT, hormone replacement therapy.

8,000 for women with a hysterectomy and SEK 13,000 for women with an intact uterus, which is far below the defined threshold value of SEK 600,000. The results show that the value of the positive effects for women with menopausal symptoms in terms of symptom relief clearly outweighs the negative effects of HRT. Given that HRT increases the quality of life more than 0.013 units, HRT becomes cost-effective in all the studied patient groups. In one patient group, 60-year-old hysterectomized women on estrogen-only therapy, HRT is cost-effective irrespectively of any symptom relief. The threshold value of 0.013 can be compared with empirical findings that shows that HRT on average increases quality of life with 0.29 and with 0.18 for women with mild menopausal symptoms, which clearly exceeds the required increase in quality of life that makes HRT cost-effective (12;57). Thus given the new evidence in WHI, there is still a high

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probability that HRT is a cost-effective strategy for women with menopausal symptoms.

The results in this report are similar to the findings presented in two recent published studies (8;31) that assess the health effects of HRT based on the WHI (39). The purpose of the study by Col et al. (8) was to determine, by exploring the trade-off between symptomatic relief and risk of disease, which women might benefit from HRT. For an average 50-year-old woman, a 2-year HRT treatment time suggested a loss in expected survival of 12 days, which can be compared with 15 days found in this report (or 4 days if assessing a treatment time of 2 years). The findings in this report are also close to the results presented in Kim and Kwok (31). The purpose of that study was to estimate quality-adjusted life expectancy with and without HRT for women with an intact uterus on combination therapy (based on the treatment in WHI [39]). The results showed that a 5-year treatment time reduced the expected life length by 0.01 years, using a 3 percent discount rate for women at low risk of breast cancer and CHD. This finding is very similar to the results found in this report, which shows a decrease in expected (discounted at 3 percent) life length of 0.02 years for 50-year-old women with an intact uterus on combination therapy.

A majority of previous cost-effectiveness studies have based the estimations of the quality of life weights before and after HRT on assumptions, rather than based on empirical data (7;13;46;51;52). Empirical studies carried out in the United Kingdom and Sweden, however, indicate that the effect of menopausal symptoms on the quality of life, either measured by the rating scale or the time-trade off method, has been underestimated (12;19;38;57). For example, in Zethraeus et al. (57), the gain in the quality of life measured by the time-trade off method was estimated at 0.18 for women with mild symptoms and 0.42 for women with severe symptoms, respectively. A limitation of the above empirical studies is that they include few patients and may not be representative of all women receiving HRT in Sweden and the United Kingdom. To investigate the real effect of menopausal symptoms and HRT on the quality of life, further randomized studies are required.

The model used to estimate the cost-effectiveness with HRT is based on a previous model that has been well validated and published in the literature (58–60). The model also produces similar results on the health effect measures compared with the results found in two recent published studies (8;31), which further validates the findings in this study. Nevertheless, some of the data in the model have to be based on assumptions. In particular, there is a lack of empirically based quality of life estimates related to nonskeletal disease events. To take this into account, extensive sensitivity analysis has been carried out, where the base case assumptions are changed. The results from the sensitivity analysis show that the conclusions are stable to variations in these variables.

It is not evident whether the results found in the WHI are valid for other populations, for example, women with high risk of fracture (osteoporotic women). The WHI focused on a healthy female population and the extent to which benefits on the skeletal system in individuals at high risk outweigh adverse effects requires re-examination in this context. Epidemiological information indicates that the baseline risk for breast cancer is approximately 30 percent lower in individuals with osteoporosis, possibly related to more marked gonadal hormone deficiency in individuals with low bone mineral density (and low body mass index). Further studies are required to investigate the cost-effectiveness of HRT in this population group.

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