A reassessment of the cost-effectiveness of hormone replacement therapy in Sweden – results based on the Women's Health Initiative randomised controlled trial

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Abstract

The cost-effectiveness of hormone replacement therapy (HRT) based on a societal perspective is reassessed 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 50-60 year old women with menopausal symptoms is assessed in Sweden. The Markov 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 (CHD), Stroke, Venous thromboembolic events, breast cancer, colorectal cancer, hip fracture, vertebral fracture and wrist fracture. An intervention is modelled 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 gained QALY is compared to the value of a gained QALY, 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. The cost-effectiveness ratios are estimated at about SEK 10 000, which is far below the value of a gained QALY. Conditional on that HRT increases the quality of life weight more than 0.013 the therapy is cost-effective. 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.

Keywords: cost-effectiveness analysis; hormone replacement therapy; Markov model

JEL-classification: D61; I10; I12; I19

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1 INTRODUCTION

Women in the industrialised part of the world are today living more than one third of their life after menopause. For example, in Sweden about 1.7 million women are above the age of 50, which corresponds to 19% of the population. The women's health problem around the menopause, when the oestrogen production naturally decreases implies costs for society both in terms of quality of life losses but also in terms of costs arising within and outside the health care system. At menopause, which occurs on the average at age 51, about 75% of women experience menopausal symptoms such as hot flushes, night sweats and atrophy-related symptoms of the urogenital tract [1]. 10% of women suffer from symptoms more than 15 years after the menopause. The effect of menopausal symptoms on quality of life may be substantial, which is shown in e.g. Daly et al. [2] and Zethraeus et al. [3]. In Sweden the costs for estrogens (estrogens, progestins and combination drugs) has increased from 370 to 500 million SEK during the period 1995-2000. Restricting the sales in the year 2000 to women above the age of 45 years and with menopausal symptoms the sales are estimated at 300 – 400 million SEK. Also, if costs for physician visits are added the total intervention cost of HRT amount to 600 – 700 million SEK in the year 2000 [1].[5]

The use of hormone replacement therapy (HRT) mitigates or eliminates menopausal symptoms and leads to a major improvement in quality of life for women with menopausal symptoms [2, 3]. HRT also offers protection against osteoporosis and related fractures and was previously believed to offer a cardio protective effect as shown in observational studies [4]. However, recent randomised studies do not show any reduction in cardiovascular events neither in secondary nor in primary prevention [5-7]. Evidence of the effect of HRT on breast cancer has been inconclusive, but now the general belief is that the risk of breast cancer increases [1, 4, 6-11]. However, for hysterectomised women on oestrogen only therapy the Women's Health Initiative (WHI) study [7] shows a decreased risk of breast cancer. Results based on the WHI [6] show that HRT also changes the risk of colorectal cancer, venous thromboembolic events (VTE) and stroke. For non-hysterectomised 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 [1, 6]. Combining oestrogen with a

[5] A distinction can be made between HRT regimes for women with a hysterectomy and for women with an intact uterus. Women with a hysterectomy are given oestrogen only therapy and in Sweden (2001) the mean annual drug cost was estimated at SEK 900 for this patient group. Women with an intact uterus is treated with a combination of oestrogen and progestin, and the mean annual drug cost for this patient group in Sweden in 2001

progestin may induce uterine bleedings; however, such bleedings may reduce or vanish if a combined HRT is continuously applied although break through bleeding often occurs in the first few months [1]. Today oestrogen only therapy is given only to women with a hysterectomy while women with an intact uterus are given oestrogen combined with a progestin to eliminate the endometrial cancer risk.

Cost-effectiveness analysis (CEA) is a method for assessing costs and benefits of alternative ways of allocating resources to assist decisions aiming at improving efficiency. An efficient allocation of resources implies that no further health gains can be achieved by allocating resources differently. CEA is based on maximising health effects subject to a cost constraint, where costs are measured in monetary units and health effects in non-monetary units such as life years or quality adjusted life years (QALYs). QALYs are constructed by adjusting life years for the quality of life in which they are spent. To achieve this, the number of years in a health state is multiplied by a quality weight between 0 (dead) and 1 (full health). To be consistent with economic theory and to avoid suboptimisations a societal perspective should be carried out, which means that all costs and benefits are incorporated in the analysis no matter who pays the costs or receive the benefits. This has the consequence that e.g. costs in added years of life should be included [12]. To determine whether a treatment is cost-effective compared to an alternative the cost per gained unit of effectiveness (e.g. cost per gained QALY) must be compared with the willingness to pay (WTP) for a gained unit of effectiveness (e.g. the value gained QALY). If the price per unit increase in effectiveness exceeds the cost the programme is cost-effective. Without the information about the price per unit increase in effectiveness the CEA gives no information on whether a program is cost-effective or not, unless it is sorted out as a dominated alternative (e.g. the program has higher costs and lower effectiveness). The value of a gained QALY is usually stated to be about SEK 500 000 – 600 000 (US$ 50 000-60 000) [13, 14]. In this paper 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.[6] To assess the cost-effectiveness of HRT the costs of the intervention costs must be related to the gain in quality of life from symptom relief and to the

was estimated at 1200. Different oestrogen and progestin combination regimes exist. The group variation in mean annual drug cost is however small varying between SEK 1200 – 1300.

[6] The Swedish road authority states that the WTP per life saved is equal to SEK 16.3 million (2001 prices). 16.3 is divided by 1.53 to take account of crowding out effects of public investments. Life-years lost is equal to 20.4 with 3% discounting and 17.3 QALYs lost with a QALY weight of 0.85. WTP per QALY gained = 16 300 000/(1.53×17.3) = 600 000.

cost and health effect consequences of HRT due to changes in disease risks. If the value of the gain in effectiveness exceeds the increase in costs HRT is defined as cost-effective.

Cost-effectiveness information is recommended or even required as a base for discussions with reimbursement authorities in different countries. For example, the Swedish pharmaceutical benefits board (LFN) clearly states that cost-effectiveness information is crucial when deciding whether to reimburse a new drug or whether to keep an existing drug on the benefits scheme. Cost-effectiveness information is also of importance for the National Institute for Clinical Evidence (NICE) when providing national guidance on treatments and care in the National Health Service (NHS) in England and Wales.

To assess the cost-effectiveness of HRT modelling is required [15, 16][7], which is also confirmed in previous cost-effectiveness studies [17-30]. Modelling is necessary because clinical trials cannot provide all the information that is needed for the economic evaluation, which requires cost and effectiveness information in a long run perspective. There are several types of modelling alternatives, e.g. decision tree models, Markov models, and discrete event models. Usually a so called state transition Markov model is used, which is characterised 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 e.g. once a year.

All the cost-effectiveness studies from 1990 and onwards assumes that HRT decreases the risk of coronary heart disease, which was reflected in many observational studies at that time. Only a few of the cost-effectiveness studies are based on a societal perspective [17, 28, 29], which means that e.g. costs in added years of life are excluded from the analysis. Previous economic evaluation studies usually suggest that HRT is cost-effective for the treatment of menopausal symptoms [15, 28]. These economic evaluation studies are all based on medical evidence available before the WHI studies, which motivates a reassessment of the cost-effectiveness of HRT based on the new evidence [6, 7]. The WHI is the first randomised, primary prevention study that investigates the effects of HRT on women with and without a hysterectomy. The main new finding in these studies is that HRT does not decrease the risk of

[7] In Kim and Kwok 2003 the purpose was to estimate quality adjusted life expectancy with and without HRT for women with menopausal symptoms based on the findings in the WHI study (2002). The study is not a cost-effectiveness study because it did not include any costs. They conclude that combination HRT compared to no therapy decrease life expectancy but increases quality adjusted life expectancy.

coronary heart disease, which has been assumed in previous cost-effectiveness analysis. A new finding is also that the mid-point estimate for breast cancer showed a reduction in hysterectomised women. This infers that it is the progestin component of HRT that may increase the risk of breast cancer.

The purpose of the paper is to assess 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 the clinical findings in the WHI studies [6, 7]. The cost-effectiveness of HRT is calculated in 6 independent patient groups dependent on age (50, 55 or 60 years) and uterus status (intact uterus or hysterectomised). Women with an intact uterus are supposed to be given combined therapy while hysterectomised women are supposed to be given oestrogen 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 e.g. the effects of HRT, remaining effects of HRT, size of the quality of life improvement, treatment duration and intervention cost is varied.

The paper unfolds as follows: Section 2 introduces the model and defines the design and structure of the model. Section 3 specifies the data required for the model valid for Sweden. Section 4 presents the cost-effectiveness results based on the model described in Section 2 and data presented in Section 3. Finally, section 5 concludes the paper.

2 MODEL

The cost-effectiveness model used in this study is based on a previously developed model [17, 28, 29]. The model used has gone through some alteration compared to older versions. To capture all relevant effects of HRT found in the WHI the following disease states had to be included in the model: Coronary Heart Disease (CHD), Stroke, Venous thromboembolic events (VTE), breast cancer, colorectal cancer, hip fracture, vertebral fracture and wrist fracture.

The preceding model versions have not considered stroke, colorectal cancer and VTE. The previous model that was based on Markov cohort methodology explicitly included the long-term effects of diseases as health states, in all, the model comprised 14 health states. Continuing on the same model structure when including the new diseases would lead to a model with more than 20 health states. The larger a model is the less transparent it becomes. Also, by having too many health states with competing risks and restrictions on the transitions paths for having multiple diseases (e.g. not possible to have further disease events after having a CHD event) there is a potential risk of underestimating the risk of diseases in the model simulations, which might have an impact on the cost-effectiveness results. One way to solve this is to introduce individual based simulations instead of Markov cohort simulation. Instead of letting a patient cohort be distributed according to the given transition probabilities at the same time it is possible to let patients individually pass through the model, giving different transition paths for each patient. With this simulation method (sometimes-called first order simulation) it is possible to track the patient's transition history, i.e. how and when certain events occurred throughout the simulation. One of the assumptions in Markov modelling is that no memory is allowed. Therefore this type of simulation method is better to be called an individual state transition based model than a Markov based model. The advantage with an individual state transition approach is that by keeping track of the patient disease history it is possible to reduce the number of health states by only implicitly model the long term (beyond the first year after the disease event) costs and effects of diseases. One disadvantage is that the simulations are more time consuming because by evaluating only one patient at a time, instead of the whole group as in Markov cohort simulation, there will be random variation in individual outcomes (called first-order uncertainty). To achieve stable results a large number of trials (a trial is one individual going through the model) have to be carried out. In order to use the most transparent model structure and avoid underestimating the number of disease events we chose the individual state transition approach. The final structure of the model that was used is shown in *Figure 1*. The arrows show all the allowed transitions in the model. There is always a possibility of dying or stay in the same health state, however, these arrows are excluded to simplify the figure. CHD consists of three different health states: acute myocardial infarction (AMI), angina pectoris and coronary insufficiency. The fracture-state consists of a hip fracture, vertebral fracture and a wrist fracture state (Figure 1 in here).

A patient starts a model simulation in the *Well/No event* state and passes through the model in yearly cycles between the different health states until 100 years of age or dead. Through the simulation the number and time of events for each patient is recorded. In each cycle it is possible to incur any disease event. The transitions are approximated to occur in the middle of each cycle, i.e. the model is half-cycle corrected.

The main output from the model is costs and quality adjusted life years (QALYs), which allows for the computation of the incremental cost-effectiveness ratio of different treatment alternatives, e.g. using HRT compared to not using HRT. Some of the diseases have related costs and effects that stretch longer than one year. These could be accounted for by the memory functionality. In each cycle the model evaluates whether the patient have had any prior events and if they are related to any long term consequences (in costs and quality of life). If so, these consequences are accounted for when costs and quality of life is calculated. If the patient have had more than one disease event, then only the disease, which is related to the highest cost and quality of life reduction is used. The reason is that there are no available data on the cost and effect interrelationship between the diseases included in the model.

An intervention is modelled by its impact on the disease risks during therapy and possible also after the cessation of therapy, which is a so-called remaining effect during an offset time period. In *Figure 2*, an example on how the effect of HRT on the risk of a disease can be modelled is shown. E.g to achieve a 40% decrease in the risk of fracture the base case risk of fracture (without intervention) is multiplied by 0.6 during the intervention period, which is set to 5 years. If there is a remaining effect of HRT on the fracture risk after the treatment period this is modelled as a linearly decline in the effect for a given “offset time” period. In *Figure 2* the remaining effect has vanished 5 years after the cessation of therapy. The model is flexible and allows for different assumptions of risk changes, lengths of treatment and offset time periods (Figure 2 in here).

3 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. All the data used in the model are presented in the Appendix (*Tables A1 – A24*).

3.1 The effect of HRT

The effects of HRT on disease risks during therapy are taken from the WHI studies [6, 7]. WHI focuses on defining the benefits and risks of different strategies that could potentially reduce the risk of e.g. heart disease and breast cancer. Both women with an intact uterus (treated with estrogens combined with progestins) and women hysterectomised (treated with estrogens alone) are followed.

In the base case assumption a remaining effect of five years is assumed for fractures. There is a great deal of evidence that the offset of effect on the skeleton after stopping HRT is slow [31]. Thus, when HRT is stopped, some skeletal benefits continue. No other remaining effects are assumed to exist. In the case of breast cancer, the million women study [11] and other studies indicate that the risk is more or less immediately reversible once treatment is stopped. The same is also true for cardiovascular risk.

In WHI [6] the objective was to assess major health benefits and risks of the most commonly used combination therapy (estrogens combined with progestins) in the US. The study, with an average follow-up of 5.2 years, reported the following significant relative risks (RR): 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).

In WHI [7] the effects of oestrogen only therapy in postmenopausal women with a hysterectomy was presented. The study, with an average follow-up of 6.8 years, reported the following relative risks (RR): 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). Oestrogen only therapy significantly increased the risk of stroke and significantly reduced the risk of hip, vertebral and other total osteoporotic fractures. The relative risk of HRT used in this study is summarised in Table A1.

3.2 Disease risks

The target patient groups in the analysis were assumed to be at the same risk of fracture as the general population. Age specific population risks of hip, vertebral and wrist fracture for Swedish females used in the model were derived from a population based study from Malmö [32] (Table A2). Risks were given in 5-year intervals up to the age of 89 years. Interpolation was used to obtain age-specific fractures risks. To estimate the risk above the age of 89, which were not given in the referred article, logistic regression was fitted to the observational data and extrapolated beyond the observed ages in the data. For each age group, the middle age of the 5-year interval was used in the regression.

To estimate the age specific incidence of non-skeletal events that was included in the model (breast cancer, colorectal cancer, CHD, Stroke, VTE) data was extracted from the Swedish national inpatient register administered by Centre for Epidemiology at the National Board of Health and Welfare. It covers all public inpatient care since 1987 and covers the reasons for hospitalisation and procedures undertaken (by ICD code) as well as date of admission and discharge. Registration is mandatory and is administrated by the county councils. All female patients that were diagnosed with one of the defined events (see Table A3 for a definition of the disease events in terms of ICD-10 identification codes) anytime 1998-01-01 to 2001-12-31 was identified. All these patients' inpatient stays from 1997-01-01 were extracted from the register. Using these data combined with Swedish population [33] data for the corresponding years the age differentiated incidence could be calculated for the different disease events included in the model (Table A2). The incidence is the average risk of an event in the population. Only the patient's first event each year was included in the risk calculation and no division in risk between patients with and without previous disease event was made because the prevalence of the disease events in the population was not available.

3.3 Mortality rates

The age-specific annual mortality rates for the general population in Sweden are based on the years 1998-2001 (Table A4) [33]. To fit the model structure normal mortality rates had to be adjusted to not include the risk of dying from disease events included in the model [17]. This adjusted normal mortality was calculated as normal mortality multiplied by the share of all causes of death [34] that was not explained by CHD, stroke, breast cancer and colorectal cancer (Table A5). The adjusted mortality rate (Table A6) is slightly overestimated since the number of deaths related to fractures and VTE were not available. This leads to an

overestimation of the number of deaths in the target patient group. To see, whether this slight overestimation of deaths might have an impact on the cost-effectiveness the normal population mortality was down adjusted by 50% in a sensitivity analysis.

Patients with hip fractures and clinical vertebral fractures have a higher mortality compared to the normal population [35-40]. In a study by Johnell et al. [41] age differentiated mortality the first and following years after a hip fracture was calculated (Table A7 and Table A9). Age differentiated mortality risks (first and following years) after clinical vertebral fractures was derived from Johnell et al. [41] (Table A10 and Table A12). A part of the excess mortality after fracture compared to normal mortality cannot entirely be ascribed the fracture event but also to other co morbid conditions [42]. In Parker and Anand [42] it was estimated that 33% of the deaths one year after hip fracture were totally unrelated to the hip fracture, 42% possibly related and 25% directly related. In another study on Swedish hip fracture patients only 17%- 32% of all deaths were found to be causally related to the fracture [43]. Kanis et al. [39] estimated that approximately 30% of the excess mortality after vertebral fracture was related to the fracture event. Along with these findings we assumed that 30% of the observed excess mortality after a hip or vertebral fracture could be associated to the fracture event. The adjusted mortality rates the first year after events are shown in Table A8 and Table A11. Wrist fracture was assumed not to be associated with any excess mortality [36, 41].

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. Data on death events were available up to 2001-12-31. The yearly mortality rates were estimated using parametric Weibull survival regression [44]. The Weibull distribution is suitable for modelling data with hazard rates that increase or decrease over time and allows for the estimation of probability of an event in different time intervals after the starting point, e.g. the probability of dying the third year after an event. These types of calculations are not possible with other non-parametric survival analysis methods (e.g. Kaplan-Meier functions). The cost-effectiveness model follows patients at yearly risks of different events over a longer time period. The Weibull survival regression was therefore the most appropriate survival function to use for the estimation of the yearly mortality risk based on the available data. Assume that the length of time an individual lives ($T \geq 0$) follows a Weibull distribution. For

t, a particular value of *T*, the Weibull survivor *S*(*t*) and hazard function $\lambda(t)$ are defined according to:

$$S(t) = e^{-(\gamma t^{p})} \quad (1)$$

$$\lambda(t) = \gamma p t^{p-1} \quad (2)$$

where p and γ are non-negative parameters to be estimated. When p = 1, the Weibull distribution reduces to the exponential with a constant hazard and if $p > 1$ ($p < 1$) the hazard is monotonically increasing (decreasing) in *t*. To introduce covariates in the model, γ in (1,2) is replaced by $e^{(\alpha+\beta\times age)}$, where α and β are parameters and age defines the age at the occurrence of the event. This results in the following expressions:

$$\lambda(t) = e^{(\alpha+\beta\times age)} p t^{p-1} \quad (3)$$

$$S(t) = e^{-(e^{(\alpha+\beta\times age)} t^{p})} \quad (4)$$

The estimated parameter values in the Weibull survivor and hazard functions are given in *Table A13*. To estimate the mortality risk (*r*) for a certain year (*t*=1,2,3 etc) after the event the following formula was used:

$$r = 1 - \frac{\hat{S}(t)}{\hat{S}(t-1)} = 1 - \frac{e^{-(e^{(\hat{\alpha}+\hat{\beta}\times age)} t^{\hat{p}})}}{e^{-(e^{(\hat{\alpha}+\hat{\beta}\times age)} (t-1)^{\hat{p}})}} \quad (5)$$

where the ratio between the survivor functions is equal to the hazard function integrated between *t*-1 and *t*. Table A14 to Table A20 show the estimated mortality risks, using the formula in (5), for the first year after CHD, stroke, VTE, breast cancer and colorectal cancer.

In all the estimated functions the mortality rate decreases for each year that passes after the event (i.e. $p < 1$). The estimated mortality risk decreases with time after the event. In some instances, when many years has passed, it is actually possible that the mortality is estimated to

be lower than population mortality, which is not reasonable. To avoid this, the mortality rate was assumed not to be lower than the population mortality. That is, if the estimated mortality risk according to the Weibull regression model was lower than population mortality, the population mortality was used.

The use of Weibull functions allow for a more detailed modelling of the mortality compared to previous model versions [17] , which have used one mortality rate the first year and one mortality rate for second and all the subsequent years after event. As long as the used mortality rate for the subsequent years after an event is a good measure of the average mortality for all subsequent years the two modelling approaches should not lead to any major differences in the cost-effectiveness estimations.

3.4 Quality of life weights

The estimation of the gain in quality of life from HRT is based on a Swedish empirical study [3]. The increase in the QALY weight due to HRT for women with mild symptoms was 0.18 according to the TTO method. For women with severe symptoms, the QALY weight increased by 0.42 according to the TTO method. In the base case analysis we assume that the loss in quality of life is equal to 0.29 corresponding to an average woman with menopausal symptoms. E.g. to estimate the quality weight for an average woman with menopausal symptoms 0.29 is subtracted from the QALY weight for a healthy women.

The impact on quality of life the first year after a fracture (hip, vertebral and wrist) was based on a study conducted at the orthopaedic department at the Malmö University Hospital in the south of Sweden [45]. Participating patients filled out a EuroQol-5D questionnaire 2 weeks, 6, 9 and 12 months after the fracture event. Since the quality of life before fracture was not collected, quality of life values for the population [46] were used as proxies for the patient quality of life before fracture. Accounting for the gender distribution in the study sample the disutility the first year after fracture was calculated [47]. The quality of life in subsequent years after a hip fracture was assumed to be 90% of that of a healthy individual [48]. Wrist fracture was not assumed to be associated with any utility loss the second or the second and following years after fracture. A multi-centre multi-national study showed that the quality of life was reduced by approximately 9% when the clinical vertebral fracture may have occurred

at a previously unknown time [49]. Based on these findings, it was conservatively assumed that the loss of utility the second and following years for a clinical vertebral fracture was 0.05.

The utility loss after CHD, based on previous studies [50-52], was assumed to be 0.1 for all years after disease event and for all ages. Data on the utility loss after breast cancer, colorectal cancer, stroke and VTE are scarce. As in Zethraeus et al. [17, 28, 29] 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. Age differentiated quality of life weights for all diseases are summarised in Table A21.

3.5 Costs

In the case of preventive programs, e.g. HRT, it is useful to make a distinction between intervention costs, morbidity costs and costs in added years of life. Intervention costs are inputs that go into a health care program and consist of direct costs (e.g. costs for drugs and physician visits) and indirect costs which depict production losses (or losses in leisure time) due to the treatment participation. Morbidity costs are resource consequences due to changes in morbidity (e.g. changes in fracture and breast cancer risks) and consist of direct and indirect costs caused by the disease. Costs in added life years are the resource consequences due to changes in mortality and are estimated as the change in consumption (medical and non-medical) minus the change in production due to the change in mortality. All costs are expressed in the prices of 2003. When needed the costs were inflated using the Consumer Price Index from Statistics Sweden [34].

The annual intervention cost for women on combination therapy (with an intact uterus) is estimated at SEK 2 972. This consist of drug costs (SEK 1220 [1]), 1.5 physician visits per year at a price of SEK 1 168 per visit. The corresponding annual intervention cost for women on oestrogen only therapy (with a hysterectomy) is estimated at SEK 2 078. This consist of drug costs (SEK 910 [1]), 1 physician visit per year at a price of SEK 1 168.

Costs of a fracture can be divided into acute costs, which occur the first year following the fracture, and long-term costs, which can persist several years after fracture or even for the remainder of the lifetime of the patient. Direct and indirect fracture costs in Sweden during the first year after a hip, clinical vertebral and wrist fracture were derived from Zethraeus et al. [45]. Hip fracture costs the second and following years were based on the assumption that

10% of all patients remain at a nursing home for the rest of their lives [48] at a weekly cost of 1 486 SEK [53]. There are currently no empirical estimates on the fracture-related cost of vertebral and wrist fracture beyond the first year after fracture event in Sweden, therefore it was conservatively assumed that these fractures were associated with costs only the first year after fracture. *Table A22* and *Table A23* summarises the fracture-related costs that were used in the analysis.

Direct and indirect costs related to CHD (AMI, coronary insufficiency and Angina pectoris) the first year and subsequent years after event and first year costs (direct and indirect) of stroke were based on estimates given in Zethraeus et al. [29]. Indirect costs related to breast cancer come from Liljegren et al. [54]. Direct costs associated to breast cancer, colorectal cancer and VTE were estimated from the patient sample extracted from the national inpatient register. Direct costs the second and following years after stroke, was also derived from this sample. The cost of the patient's hospital stays was assessed using the Diagnosis Related Groups (DRG) costing system. To estimate the potential cost saving of avoiding an event the patients were used as his or her own control [55]. The costs related to an event were estimated as the difference 1 year after and 1 year before the event. Event related costs the second and following years were estimated as the difference the second year after event and 1 year before the event. Only patients with sufficient observation time, from incident date to end date (2001-12-31), were included in the calculations. That is at least 1 year for the estimation of first year costs and 2 years for estimation of costs the second year after event. Patients that died within the observation time were also included in the cost estimates. That is, for the first year cost estimates, all patients that died during the first year were included. For the cost estimates subsequent years patients that died the first year was excluded but patients that died during the second year were included. This is in line with the structure of the model. The starting incident event date was the first identified diagnoses each year. To be in concordance with the risk of events that was used in the model the costs were based on all female patients irrespective of inpatient history (i.e. patients with and without prior events). The calculated mean costs based on the inpatient sample are shown in *Table A22*. It should be noted that the inpatient cost estimates do not reflect the full potential direct cost savings because outpatient care and pharmaceutical costs based on prescriptions are not included. However, since such information is not available we made the conservative assumption of only including cost of inpatient care.

Costs in added years of life, defined as the difference between annual production and consumption in different age groups, are based on Ekman [56] (*Table A24*). The figures are adjusted to the price level of 2003 according to the consumer price index of Sweden [34].

4 RESULTS

The results from the health effect, cost and cost-effectiveness results of a five-year HRT are presented in *Tables 1-4*. The calculations are based on the data described in section 3 above and assess the health and cost consequences of HRT for a 50-60 year old female population with average disease risk and menopausal symptoms. The results are separated for women with an intact uterus and for women with a hysterectomy. Women with an intact uterus are given a combination therapy while women with a hysterectomy are treated with oestrogen only therapy.

4.1 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 implies 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 0.04-0.05, 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 to no therapy in all the age groups. The increase in the number of QALYs (with and without discounting) is between 1.2 and 1.3.

For women with a hysterectomy on oestrogen only therapy, HRT implies 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 0.006-0.03 years. HRT will increase the number of expected QALYs compared to 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 in here).

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 is explained by that the value of production decreases, which implies that the costs of (consumption-production) will increase and result in a total higher costs (Table 2 in here).

4.2 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 gained QALY varies between SEK 9000 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 implies more QALYs and lower costs (Table 3 in here).

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 aged women and SEK 11 000 for a 60-year aged 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, this implies that 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 in here).

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.

5 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 [6, 7]. The cost per gained QALY varies for 50-60 year old women between SEK 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 patientgroup, 60-year old hysterectomised women on oestrogen 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 [2, 3]. Thus, given the new evidence in WHI, there is still a high 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 [16, 57] that assess the health effects of HRT based on the WHI [6]. The purpose of the study by Col et al. [57] was, by exploring the trade-off between symptomatic relief and risk of disease, to determine which women might benefit from HRT. In a Markov model they included the following health states: breast, colorectal, ovarian, and endometrial cancer, CHD, stroke, hip fracture and pulmonary embolism. A cohort of healthy women was analysed that each year could develop any one or a combination of the included diseases or die of other causes. The study purpose was to calculate the effects of HRT on life years and QALYs for 50-year old menopausal women on a 2-year combination therapy. The utility scores were derived from the literature. It was assumed that HRT decreased the loss in quality by 80%. The quality of life with and without menopausal symptoms was based on a study by Zethraeus et al. [3] and Daly et al. [2]. The results showed that HRT was associated with losses in (undiscounted) expected survival but gains in QALYs. For an average 50-year old women a two-year HRT implied 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). On the other hand HRT implied a gain in (undiscounted) QALYs for 50-year old women with a low risk of CHD and stroke estimated at 0.36 and 0.69 for women with mild and severe symptoms respectively. In our report the corresponding (undiscounted) gain in QALYs amounted to 1.26. The corresponding adjusted (undiscounted) gain in QALYs for a 2-year treatment amounted to 0.42, which is very close to the results presented in Col et al. [57]. Col et al. [57] further showed in a threshold analysis that if the effect of HRT on menopausal symptoms for women with an average risk of CHD and stroke is equal to or exceeds 0.04 HRT will increase the number of (undiscounted) QALYs. This can be compared with the corresponding figure of 0.01 found in this report (for a treatment period of 2 years).

The findings in this report are also close to the results presented in Kim & Kwok [16]. 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 [6]). The analysis is based on a Markov state transition including the following disease states: breast cancer, CHD, stroke pulmonary embolism, colon cancer, and hip fracture. Endometrial cancer was excluded, because HRT did not increase the risk of endometrial cancer in the WHI for women with an intact uterus on combination therapy. Three cohorts of 50-year old women with menopausal symptoms were analysed: The first cohort consisted of healthy women at low risk of breast cancer and CHD; the second cohort consisted of women with a high risk of osteoporosis; the third cohort consisted of women with high risk for adverse events. Each year the cohort was subject to risks of any or a combination of the included disease events. For each cohort no HRT, HRT for five years and HRT for 15 years were evaluated. The time horizon for the model was 20 years. The results were both undiscounted and discounted by a rate of 3%. The authors assumed a quality of life weight equal to 1 with HRT (and without menopausal symptoms) and then determined the required improvement in quality of life that was necessary to obtain an increase in QALYs with HRT. Menopausal symptoms were assumed to last the same length as the treatment duration. The results showed that a five-year HRT reduced the expected life length by 0.01 years using a 3% discount rate for women at low risk of breast cancer and CHD. This is very similar to the results found in this report, which shows a decrease in expected (discounted at 3%) life length of 0.02 years for 50-year old women with intact uterus on combination therapy. Kim and Kwok [16] finally showed that the required improvement in the quality of life to obtain an increase in the number of QALYs, equalled 0.004, which can be compared with 0.015 found in this report.

A majority of previous cost-effectiveness studies (before the WHI) have based their estimations of the quality of life weights before and after HRT on assumptions, rather than based on empirical data [19, 21, 23, 27, 58]. E.g. Weinstein assumed that the loss of quality of life due to menopausal symptoms was 0.01. The first empirical study to estimate the quality of life weight related to menopausal symptoms was carried out in a British setting and indicated that the previous assumptions underestimated the negative effect of menopausal symptoms. Daly's results showed that menopausal symptoms seem to have a much more severe impact on quality of life than assumed in analyses of cost-effectiveness, and that HRT causes a much greater improvement in quality of life than previously assumed. These findings were confirmed in a later Swedish study by Zethraeus et al. [3], which assessed the quality of

life before and after HRT for a group of Swedish women with menopausal symptoms. The results found in Zethraeus et al. [3] using the RS method are very similar to those of Daly et al. [2]. In Daly et al [2] the quality of life weight increased from 0.61 to 0.79 with HRT for women with mild symptoms and from 0.29 to 0.85 for women with severe symptoms, compared with increases from 0.60 to 0.86 for women with mild symptoms and 0.32 to 0.82 for women with severe symptoms in Zethraeus et al. [3]. The results of both studies indicate that the effect of menopausal symptoms on the quality of life has been underestimated. It should be pointed out that the RS method tends to exaggerate the gain in quality of life compared to other methods [59, 60]. However, in Zethraeus et al. [3] the gain in the quality of life was also measured by the TTO method. The TTO method gives a significantly lower gain in quality of life than the RS. The increase in the quality of life weight of 0.18 for women with mild symptoms and 0.42 for women with severe symptoms are, however, clinically significant. This indicates that the gains in quality of life are much higher than previously assumed and also shows the importance of carrying out empirical studies on quality of life rather than making arbitrary assumptions. 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 UK and that the sub-groups may not be representative of all women with mild and severe menopausal symptoms in Sweden and the UK. The results of these studies therefore may not be general. To investigate the real effect of menopausal symptoms and HRT on the quality of life further randomised studies are required.

The model used to estimate the cost-effectiveness with HRT is based on a previously model that has been well-validated and published in the literature [17, 28, 29]. The purpose of the model is to represent the current state of the art and to reflect the best knowledge available today. In line with this the model is filled with high quality cost, mortality, quality of life and risk data. The model also produces similar results on the health effect measures compared with the results found in two recent published studies [16, 57], which validates the findings in this report. Still some of the data in the model is based on assumptions. In particular there is a lack of empirical based quality of life estimates related to non-skeletal 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 e.g. women with high risk of fracture (osteoporotic women). The WHI focused on a healthy women 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% 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). To investigate the cost-effectiveness of HRT in this population group and for other indications further clinical studies are requested which is a subject for future research.

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FIGURES AND TABLES

Figure 1. The structure of the model.

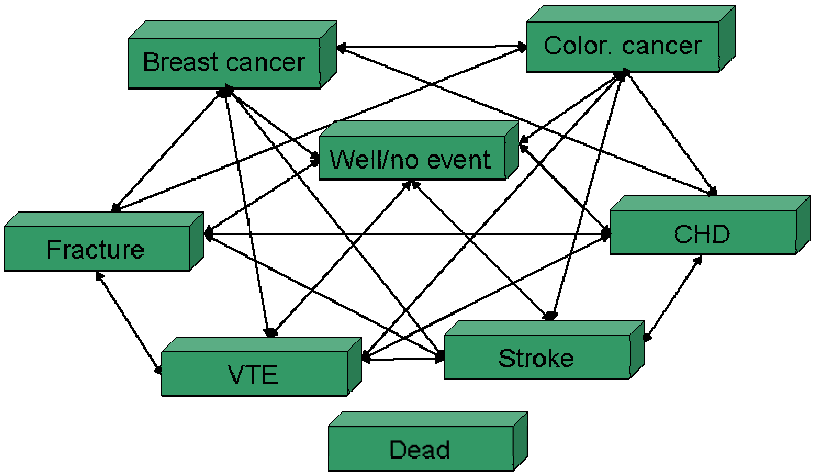

Figure 2. Modelling an intervention.

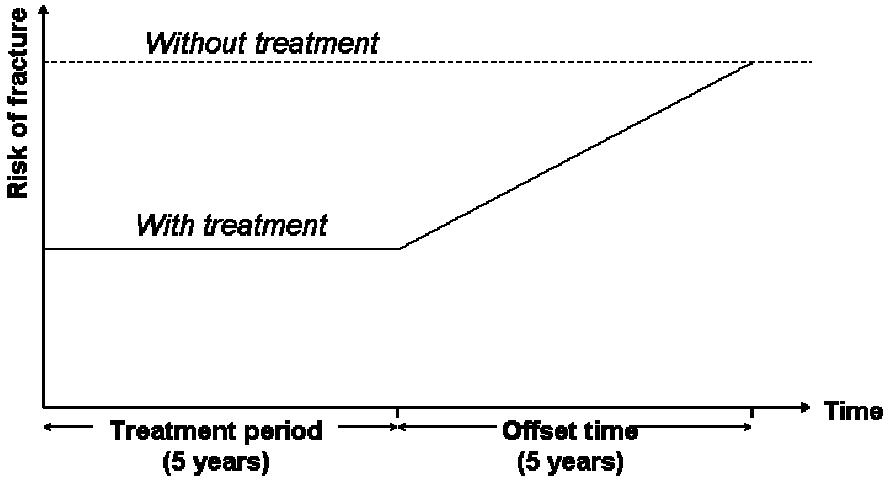

Table 1. Life years (LYs) and quality adjusted life years (QALYs) with and without HRT for 50-60 year-old women with intact uterus or hysterectomised. Discount rate=3%. (Health effects undiscounted are shown within parenthesis).

			Intact uterus	**Hysterectomised**
50 years	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 years	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 years	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)

Table 2. Costs (SEK, year 2003) with and without HRT for women with intact uterus or hysterectomised 50-60 years. Discount rate=3%.

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

Table 3. Cost (SEK) per gained quality adjusted life year (QALY) for women with an intact uterus on combination therapy compared with no therapy.

	50	***55***	***60***
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 non-skeletal 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

Table 4. Cost (SEK) per gained quality adjusted life year (QALY) for hysterectomised women on oestrogen only therapy compared with no therapy.

	50	***55***	***60***
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 non-skeletal 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

APPENDIX - DATA IN THE MODEL

Table A1. Relative risk of hormone replacement therapy.

Event	***Estrogen plus progestin*** (mean, 95% CI)	***Estrogen only*** (mean, 95% CI)
Hip	0.66 (0.45-0.98)	0.61 (0.41-0.91)
Vertebral	0.66 (0.44-0.98)	0.62 (0.42-0.93)
Wrist	0.77 (0.69-0.86)	0.70 (0.63-0.79)
Breast cancer	1.26 (1.00-1.59)	0.77 (0.59-1.01)
Colorectal cancer	0.63 (0.43-0.92)	1.08 (0.75-1.55)
CHD	1.29 (1.02-1.63)	0.91 (0.75-1.12)
Stroke	1.41 (1.07-1.85)	1.39 (1.10-1.77)
VTE	2.11 (1.58-2.82)	1.33 (0.99-1.79)

Source: [61, 62]

Table A2. Annual risk of disease event, per 1000.

Age	**Hip fracture[1]**	**Vert fracture[1]**	**Wrist fracture[1]**	**Breast cancer[2]**	**Color. Cancer[2]**	**Stroke[2]**	**AMI[2]**	**Angina[2]**	**Cor. Insuff[2].**	**VTE[2]**
50	0.63	1.62	4.01	3.13	0.22	0.97	0.62	1.15	0.46	0.72
55	0.57	1.59	4.40	3.16	0.31	1.37	1.05	1.95	0.65	0.81
60	1.38	2.45	5.23	3.83	0.57	1.98	1.75	3.11	1.19	1.22
65	2.64	3.85	6.42	3.97	0.99	3.97	2.79	4.11	1.70	1.66
70	4.56	6.42	8.19	3.47	1.38	6.62	4.64	5.95	2.27	2.44
75	10.06	9.78	9.81	3.41	1.57	11.29	7.26	7.50	2.93	3.48
80	18.17	11.42	11.38	3.35	1.93	17.34	10.26	8.35	2.87	4.67
85	30.82	14.50	13.15	3.14	2.02	24.16	14.40	9.31	2.23	5.73
90	46.24	19.28	14.94	1.76	1.52	24.47	14.17	7.89	1.54	4.79
95	61.66	24.06	16.73	1.76	1.52	24.47	14.17	7.89	1.54	4.79
100	77.08	28.84	18.52	1.76	1.52	24.47	14.17	7.89	1.54	4.79

Source: 1. [32]
2. Centre for Epidemiology at the National Board of Health and Welfare, Sweden

Table A3. Diagnostic codes used (ICD-10) for extraction from the inpatient register.

Disease event	**ICD-10**
AMI	I21
Coronary insufficiency	I20.0
Angina pectoris	I20.1,8,9
Stroke	I60-I64
Deepvein Thrombosis	I80-I82
Pulmonary embolism	I26
Breast cancer	C50
Colorectal cancer	C18.0-9

Table A4. Normal mortality rates for women in Sweden (per 1000).

50	2.35	60	5.34	70	13.98	80	47.2	90	158.5	100	347.8
51	2.33	61	6.25	71	15.88	81	52.28	91	180.1		
52	2.57	62	6.63	72	17.2	82	59.63	92	195.7		
53	2.9	63	7.11	73	19.35	83	66.99	93	212.2		
54	3.12	64	7.56	74	21.76	84	76.62	94	229.4		
55	3.51	65	8.76	75	24.26	85	87.36	95	247.4		
56	4.04	66	9.73	76	27.47	86	100.6	96	266.2		
57	4.39	67	10.24	77	30.86	87	112.9	97	285.6		
58	4.71	68	11.49	78	35.52	88	126.9	98	305.7		
59	5.12	69	12.83	79	40.65	89	142.9	99	326.4		

Source: Statistics Sweden [34]

Table A5. Dead 1996 after underlying cause of death. Number of cases.

	50-54	**55-59**	**60-64**	**65-69**	**70-74**	**75-79**	**80-84**	**85-89**	**90-**
All causes of death	897	1029	1415	2318	4141	6399	9175	10419	9414
Malign tumour in the breast	135	130	121	146	177	212	211	166	83
Malign tumour in the colon	37	50	56	85	139	161	165	127	57
Ischaemic heart disease	56	89	181	423	924	1536	2290	2559	2139
Cerebrovascular disease	47	54	79	166	417	800	1326	1658	1301
The share of women dying of ischaemic heart disease or malign tumour in the breast	0.31	0.31	0.31	0.35	0.40	0.42	0.44	0.43	0.38

Source: Statistics Sweden, Register for causes of death 1996 [34]

Table A6. Normal mortality rates for Swedish women excluding the mortality risk of CHD, stroke, breast cancer and colorectal cancer (per 1000).

50	1.63	60	3.69	70	8.39	80	26.66	90	98.26	100	215.57
51	1.62	61	4.32	71	9.53	81	29.53	91	111.61		
52	1.78	62	4.58	72	10.32	82	33.69	92	121.32		
53	2.01	63	4.91	73	11.61	83	37.84	93	131.52		
54	2.16	64	5.23	74	13.05	84	43.28	94	142.21		
55	2.41	65	5.66	75	13.99	85	49.55	95	153.37		
56	2.77	66	6.29	76	15.84	86	57.05	96	164.97		
57	3.01	67	6.62	77	17.80	87	64.04	97	177.01		
58	3.23	68	7.43	78	20.48	88	72.02	98	189.46		
59	3.51	69	8.29	79	23.44	89	81.06	99	202.32		

Source: [34] and own calculations

Table A7. Risk of mortality the year after hip fracture (per 1000).

50	31.1	60	42.9	70	73.8	80	150.7	90	293.8	100	375.2
51	32.1	61	44.3	71	79.3	81	161.5	91	278.1		
52	33.1	62	45.7	72	85.3	82	173.0	92	269.1		
53	34.2	63	47.2	73	91.7	83	185.3	93	281.7		
54	35.3	64	48.8	74	98.5	84	198.3	94	284.0		
55	36.5	65	51.2	75	105.8	85	212.1	95	319.5		
56	37.7	66	55.1	76	113.7	86	226.7	96	318.4		
57	38.9	67	59.3	77	122.0	87	242.2	97	320.1		
58	40.2	68	63.8	78	131.0	88	258.5	98	316.3		
59	41.5	69	68.6	79	140.5	89	275.7	99	352.0		

Source: [41]

Table A8. Risk of mortality the year after hip fracture adjusted for co-morbidity (per 1000).

50	11.0	60	16.61	70	31.9	80	78.3	90	199.1	100	356.0
51	11.3	61	17.67	71	34.9	81	85.0	91	209.5		
52	11.7	62	18.35	72	37.6	82	93.6	92	217.7		
53	12.3	63	19.14	73	41.1	83	102.5	93	233.1		
54	12.8	64	19.93	74	44.8	84	113.1	94	245.8		
55	13.4	65	21.49	75	48.7	85	124.8	95	269.0		
56	14.1	66	23.34	76	53.3	86	138.4	96	281.9		
57	14.7	67	24.96	77	58.2	87	151.7	97	296.0		
58	15.4	68	27.18	78	64.2	88	166.4	98	308.9		
59	16.0	69	29.56	79	70.6	89	182.8	99	334.1		

Calculated: (HipMort-NormMort)*0.3+NormMort
Source: [41]

Table A9. Risk of mortality the following years after hip fracture (per 1000).

50	14.2	60	19.6	70	37.3	80	77.9	90	158.6	100	347.8
51	14.6	61	20.3	71	40.2	81	83.7	91	180.1		
52	15.1	62	21.1	72	43.3	82	90.0	92	195.7		
53	15.6	63	22.3	73	46.6	83	96.7	93	212.2		
54	16.1	64	23.9	74	50.2	84	103.9	94	229.4		
55	16.7	65	25.7	75	54.0	85	111.5	95	247.4		
56	17.2	66	27.7	76	58.1	86	119.8	96	266.2		
57	17.8	67	29.9	77	62.5	87	128.6	97	285.6		
58	18.4	68	32.2	78	67.3	88	137.9	98	305.7		
59	19.0	69	34.7	79	72.4	89	147.9	99	326.4		

Source: [41]

Table A10. Risk of mortality the year after a clinical vertebral fracture (per 1000).

50	35.0	60	55.1	70	86.8	80	136.6	90	215.1	100	347.8
51	36.6	61	57.7	71	90.8	81	143.0	91	225.1		
52	38.3	62	60.4	72	95.0	82	149.6	92	235.5		
53	40.1	63	63.2	73	99.4	83	156.6	93	246.5		
54	42.0	64	66.1	74	104.1	84	163.8	94	257.9		
55	43.9	65	69.2	75	108.9	85	171.4	95	269.9		
56	46.0	66	72.4	76	113.9	86	179.4	96	282.4		
57	48.1	67	75.7	77	119.2	87	187.7	97	295.5		
58	50.3	68	79.3	78	124.8	88	196.4	98	309.3		
59	52.7	69	82.9	79	130.6	89	205.6	99	326.4		

Source: [41]

Table A11. Risk of mortality the year after a clinical vertebral fracture adjusted for co-morbidity (per 1000).

50	12.1	60	20.27	70	35.8	80	74.0	90	175.5	100	347.8
51	12.6	61	21.68	71	38.4	81	79.5	91	193.6		
52	13.3	62	22.75	72	40.5	82	86.6	92	207.7		
53	14.1	63	23.93	73	43.4	83	93.9	93	222.5		
54	14.8	64	25.12	74	46.4	84	102.8	94	238.0		
55	15.6	65	26.88	75	49.6	85	112.6	95	254.2		
56	16.6	66	28.52	76	53.4	86	124.2	96	271.1		
57	17.5	67	29.89	77	57.4	87	135.4	97	288.6		
58	18.4	68	31.82	78	62.3	88	147.8	98	306.8		
59	19.4	69	33.86	79	67.6	89	161.7	99	326.4		

Calculated: (VertMort-NormMort)*0.3+NormMort
Source: [41]

Table A12. Risk of mortality the following years after a clinical vertebral fracture (per 1000).

50	23.0	60	36.2	70	57.0	80	89.8	90	158.5	100	347.8
51	24.1	61	37.9	71	59.7	81	94.0	91	180.1		
52	25.2	62	39.7	72	62.5	82	98.3	92	195.7		
53	26.4	63	41.5	73	65.4	83	102.9	93	212.2		
54	27.6	64	43.4	74	68.4	84	107.7	94	229.4		
55	28.9	65	45.5	75	71.6	85	112.7	95	247.4		
56	30.2	66	47.6	76	74.9	86	117.9	96	266.2		
57	31.6	67	49.8	77	78.4	87	123.4	97	285.6		
58	33.1	68	52.1	78	82.0	88	129.1	98	305.7		
59	34.6	69	54.5	79	85.8	89	142.9	99	326.4		

Source: [41]

Table A13. Estimated parameter values in the Weibull survivor and hazard functions.

	Breast cancer	*Colorectal cancer*	*AMI*	*Stroke*	*Angina*	*Coronary insuff*	*VTE*
$\hat{\beta}$	0.043294	0.023651	0.071899	0.067963	0.097074	0.093535	0.051069
$\hat{\alpha}$	-4.80389	-2.66762	-6.69116	-6.41033	-10.0383	-9.36257	-5.31856
$\hat{p}$	0.636195	0.628465	0.415446	0.437811	0.866402	0.628174	0.542936

Table A14. Risk of mortality the year after breast cancer (per 1000).

50	68.9	60	104.27	70	156.1	80	230.3	90	332.1	100	463.2
51	71.9	61	108.62	71	162.5	81	239.2	91	343.9		
52	74.9	62	113.14	72	169.0	82	248.3	92	356.0		
53	78.1	63	117.84	73	175.8	83	257.7	93	368.4		
54	81.4	64	122.72	74	182.8	84	267.5	94	381.1		
55	84.9	65	127.79	75	190.1	85	277.5	95	394.1		
56	88.4	66	133.05	76	197.6	86	287.8	96	407.4		
57	92.2	67	138.51	77	205.4	87	298.4	97	421.0		
58	96.0	68	144.17	78	213.4	88	309.3	98	434.8		
59	100.1	69	150.05	79	221.7	89	320.5	99	448.9		

Source: Centre for Epidemiology at the National Board of Health and Welfare, Sweden

Table A15. Risk of mortality the year after colorectal cancer (per 1000).

50	202.7	60	249.42	70	304.7	80	369.0	90	441.9	100	522.4
51	207.0	61	254.56	71	310.8	81	375.9	91	449.7		
52	211.4	62	259.78	72	316.9	82	382.9	92	457.5		
53	215.8	63	265.09	73	323.1	83	390.0	93	465.4		
54	220.4	64	270.49	74	329.4	84	397.2	94	473.3		
55	225.0	65	275.98	75	335.7	85	404.4	95	481.3		
56	229.7	66	281.55	76	342.2	86	411.8	96	489.4		
57	234.5	67	287.21	77	348.8	87	419.2	97	497.6		
58	239.4	68	292.96	78	355.4	88	426.7	98	505.8		
59	244.4	69	298.81	79	362.2	89	434.3	99	514.1		

Source: Centre for Epidemiology at the National Board of Health and Welfare, Sweden

Table A16. Risk of mortality the year after AMI (per 1000).

50	44.2	60	88.63	70	173.4	80	323.6	90	551.7	100	807.3
51	47.4	61	94.92	71	185.1	81	343.0	91	577.7		
52	50.9	62	101.62	72	197.4	82	363.3	92	604.0		
53	54.6	63	108.77	73	210.5	83	384.3	93	630.5		
54	58.5	64	116.39	74	224.3	84	406.2	94	656.9		
55	62.7	65	124.50	75	238.8	85	428.8	95	683.2		
56	67.2	66	133.13	76	254.1	86	452.2	96	709.2		
57	72.1	67	142.32	77	270.3	87	476.2	97	734.8		
58	77.2	68	152.08	78	287.2	88	500.9	98	759.8		
59	82.7	69	162.44	79	305.0	89	526.1	99	784.0		

Source: Centre for Epidemiology at the National Board of Health and Welfare, Sweden

Table A17. Risk of mortality the year after stroke (per 1000).

50	48.0	60	92.49	70	174.3	80	314.7	90	525.5	100	770.3
51	51.3	61	98.66	71	185.3	81	332.6	91	549.8		
52	54.8	62	105.22	72	197.0	82	351.3	92	574.3		
53	58.5	63	112.19	73	209.3	83	370.8	93	599.1		
54	62.5	64	119.59	74	222.2	84	391.0	94	624.1		
55	66.8	65	127.44	75	235.8	85	411.8	95	649.1		
56	71.3	66	135.76	76	250.2	86	433.4	96	674.0		
57	76.1	67	144.59	77	265.2	87	455.6	97	698.7		
58	81.2	68	153.93	78	280.9	88	478.4	98	723.1		
59	86.7	69	163.82	79	297.4	89	501.7	99	747.0		

Source: Centre for Epidemiology at the National Board of Health and Welfare, Sweden

Table A18. Risk of mortality the year after angina (per 1000).

50	5.6	60	14.68	70	38.3	80	97.9	90	238.2	100	512.4
51	6.2	61	16.16	71	42.1	81	107.4	91	259.1		
52	6.8	62	17.80	72	46.3	82	117.6	92	281.4		
53	7.5	63	19.59	73	50.9	83	128.8	93	305.2		
54	8.2	64	21.57	74	55.9	84	141.0	94	330.5		
55	9.1	65	23.74	75	61.5	85	154.2	95	357.3		
56	10.0	66	26.13	76	67.5	86	168.5	96	385.6		
57	11.0	67	28.76	77	74.1	87	184.0	97	415.4		
58	12.1	68	31.64	78	81.4	88	200.7	98	446.5		
59	13.3	69	34.81	79	89.3	89	218.8	99	478.9		

Source: Centre for Epidemiology at the National Board of Health and Welfare, Sweden

Table A19. Risk of mortality the year after coronary insufficiency (per 1000).

50	9.2	60	23.23	70	58.1	80	141.5	90	322.2	100	628.8
51	10.1	61	25.48	71	63.7	81	154.3	91	347.6		
52	11.1	62	27.94	72	69.7	82	168.1	92	374.3		
53	12.1	63	30.64	73	76.2	83	183.0	93	402.4		
54	13.3	64	33.60	74	83.4	84	199.0	94	431.9		
55	14.6	65	36.83	75	91.2	85	216.2	95	462.5		
56	16.0	66	40.37	76	99.7	86	234.7	96	494.2		
57	17.6	67	44.23	77	108.9	87	254.5	97	526.9		
58	19.3	68	48.46	78	118.9	88	275.7	98	560.4		
59	21.2	69	53.09	79	129.8	89	298.3	99	594.4		

Source: Centre for Epidemiology at the National Board of Health and Welfare, Sweden

Table A20. Risk of mortality the year after VTE (per 1000).

50	61.0	60	99.62	70	160.4	80	252.8	90	384.7	100	554.8
51	64.1	61	104.55	71	168.1	81	264.1	91	400.1		
52	67.4	62	109.72	72	176.1	82	275.8	92	416.0		
53	70.8	63	115.13	73	184.4	83	288.0	93	432.2		
54	74.3	64	120.78	74	193.1	84	300.5	94	448.8		
55	78.1	65	126.69	75	202.1	85	313.5	95	465.7		
56	82.0	66	132.86	76	211.5	86	326.9	96	483.0		
57	86.1	67	139.32	77	221.2	87	340.7	97	500.6		
58	90.4	68	146.06	78	231.3	88	355.0	98	518.4		
59	94.9	69	153.09	79	241.9	89	369.6	99	536.5		

Source: Centre for Epidemiology at the National Board of Health and Welfare, Sweden

Table A21. Quality of life weights in different health states.

	50-59	60-69	70-79	80-89
Well[1]	0.91	0.87	0.70	0.60
1st year				
Hip fracture[2]	0.72	0.69	0.55	0.48
Vertebral fracture[2]	0.57	0.54	0.44	0.38
Wrist fracture[2]	0.89	0.85	0.68	0.59
Breast cancer[4]	0.81	0.77	0.60	0.50
Colorectal cancer[4]	0.81	0.77	0.60	0.50
AMI[3]	0.81	0.77	0.60	0.50
Stroke[3]	0.81	0.77	0.60	0.50
Angina[3]	0.81	0.77	0.60	0.50
Coronary insuff[3]	0.81	0.77	0.60	0.50
VTE[4]	0.81	0.77	0.60	0.50
2nd year and following				
Hip fracture[2]	0.82	0.78	0.63	0.54
Vertebral fracture[2]	0.85	0.81	0.65	0.56
Wrist fracture[2]	0.91	0.87	0.70	0.60
Breast cancer[4]	0.81	0.77	0.60	0.50
Colorectal cancer[4]	0.81	0.77	0.60	0.50
AMI [3]	0.81	0.77	0.60	0.50
Stroke[3]	0.81	0.77	0.60	0.50
Angina[3]	0.81	0.77	0.60	0.50
Coronary insuff[3]	0.81	0.77	0.60	0.50

Source: 1. [45-47]
2. [50]
3. [17]
4. Assumed to be equal the quality of life associated with CHD and stroke [50]

Table A22. Direct morbidity costs (SEK) in different health states.

	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85-89	90-
1st year									
Hip fracture[1]	85 748	85 748	85 748	93 353	93 353	164 861	164 861	230 433	230 433
Vertebral fracture[2]	32 504	32 504	32 504	32 504	32 504	32 504	32 504	32 504	32 504
Wrist fracture[2]	20 654	20 654	20 654	20 654	20 654	20 654	20 654	20 654	20 654
Breast cancer[3]	65 156	73 207	64 931	65 287	75 797	65 143	69 373	54 533	54 548
Colorectal cancer[3]	121 825	115 629	124 580	109 985	117 666	112 846	108 490	103 253	100 072
AMI[4]	52 290	52 290	52 290	52 290	52 290	52 290	52 290	52 290	52 290
Stroke[4]	100 682	100 682	100 682	100 682	100 682	100 682	100 682	100 682	100 682
Angina[4]	50 752	50 752	50 752	50 752	50 752	50 752	50 752	50 752	50 752
Coronary insuff[4]	101 964	101 964	101 964	101 964	101 964	101 964	101 964	101 964	101 964
VTE[3]	35 685	35 685	35 685	35 685	35 685	35 685	35 685	35 685	35 685
2nd year and following									
Hip fracture[5]	55 293	55 293	55 293	55 293	55 293	55 293	55 293	55 293	55 293
Breast cancer[3]	6 281	6 281	6 281	6 281	6 281	6 281	6 281	6 281	6 281
Colorectal cancer[3]	27 742	21 066	13 264	11 441	13 825	6 561	2 404	1 037	1 037
AMI [4]	11 595	11 595	11 595	11 595	11 595	11 595	11 595	11 595	11 595
Stroke[4]	1 655	1 655	1 655	1 655	1 655	1 655	1 655	1 655	1 655
Angina[4]	7 839	7 839	7 839	7 839	7 839	7 839	7 839	7 839	7 839
Coronary insuff[4]	7 839	7 839	7 839	7 839	7 839	7 839	7 839	7 839	7 839

Source: 1. [45]
2. [63]
3. Centre for Epidemiology at the National Board of Health and Welfare, Sweden
4. [53]
5. Based on assumption that 10% of the patients is at nursing home for the rest of their lives and [45]

Table A23. Indirect morbidity costs (SEK) in different health states.

	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85-89	90-
1st year									
Hip fracture	0	0	0	0	0	0	0	0	0
Vertebral fracture[1]	32 352	32 352	32 352	0	0	0	0	0	0
Wrist fracture[1]	3 451	3 451	3 451	0	0	0	0	0	0
Breast cancer[2]	92 953	92 953	92 953	0	0	0	0	0	0
Colorectal cancer	0	0	0	0	0	0	0	0	0
AMI[3]	100 792	100 792	100 792	0	0	0	0	0	0
Stroke[3]	83 702	83 702	83 702	0	0	0	0	0	0
Angina[3]	100 792	100 792	100 792	0	0	0	0	0	0
Coronary insuff[3]	100 792	100 792	100 792	0	0	0	0	0	0
VTE	0	0	0	0	0	0	0	0	0
2nd year and following									
Hip fracture	0	0	0	0	0	0	0	0	0
Breast cancer[2]	1 568	1 568	1 568	0	0	0	0	0	0
Colorectal cancer	0	0	0	0	0	0	0	0	0
AMI[3]	61 596	61 596	61 596	0	0	0	0	0	0
Stroke	0	0	0	0	0	0	0	0	0
Angina[3]	61 596	61 596	61 596	0	0	0	0	0	0
Coronary insuff[3]	61 596	61 596	61 596	0	0	0	0	0	0

Source: 1. [54]
2. [63]
3. [45, 47]

Table A24. Costs (SEK) in added years of life.

Age	
50-64	68115
65-74	-146838
75-84	-177364
85-	-265227

Source: [56]