Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study examined the combination of calcium and vitamin D3 ("500 g calcium and 10 microg vitamin D3", twice daily), administered to postmenopausal women to prevent osteoporotic hip fractures.

Type of intervention
Primary and secondary prevention.

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of 70-year-old women. However, the model also simulated 50- and 60-year-old women with one of several risk factors. Such risk factors included maternal family history of hip fractures, current cigarette smoking, and prior fragility fracture after the age of 50 years.

Setting
The setting was primary care. The economic study was carried out in Sweden.

Dates to which data relate
The effectiveness data were derived from studies published between 1992 and 2000. The resource use and cost data were derived from studies published in 1998 and 2001. The price year was 2000.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of published studies and the author's opinions.

Modelling
A Markov model was used to simulate the clinical and economic outcomes associated with preventive treatment versus no treatment in a hypothetical cohort of 1,000 70-year-old women free of fracture, and in different sub-populations of high-risk younger women. The model, a simplified version of which was presented in the paper, included well-defined health states. The health states were no hip fracture, current hip fracture, healed past hip fracture and death. The model tracked the occurrence and timing of specific events starting at any desired age (70 years in the base-case) to age 90 years. Women started in the "no history of fractures" state and could remain in that state or experience a fracture. After a fracture, women could heal and live in the "history of hip fracture" state or experience a subsequent fracture during the acute healing phase. General or fracture-related mortality could occur. Yearly cycles appear to have been applied.
Outcomes assessed in the review
The outcomes estimated from the literature were:

the incidence rates and relative risks (RRs) for hip fractures,

mortality data,

quality of life (QoL), and

treatment efficacy.

Study designs and other criteria for inclusion in the review
The author did not explicitly state whether a systematic review of the literature was undertaken or whether the primary studies were identified selectively. Treatment efficacy was derived from a French 3-year randomised clinical trial in which a combination of 1.2 g calcium and 20 microg vitamin D3 was used daily. The baseline rates of hip fractures (used for the no treatment strategy) came from a study based on the World Health Organization Collaboration Centre for Metabolic Bone Disease. Mortality data were extracted from the Swedish Inpatient Register and the Statistical Year Book for both the general population and for individuals who had experienced a hip fracture. The source of the QoL data was not reported.

Sources searched to identify primary studies
Not reported.

Criteria used to ensure the validity of primary studies
The author did not discuss the issue of the validity of the primary sources. However, efficacy data came from a clinical trial, which should assure high internal validity.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
Eleven primary studies provided the clinical evidence.

Methods of combining primary studies
The primary studies were not combined as each study provided a discrete series of estimates. Efficacy data in the form of RRs were superimposed on the baseline risk of hip fractures.

Investigation of differences between primary studies
Not reported.

Results of the review
The RR for hip fractures associated with osteoporosis declined from 4.8 at age 50 to 1.6 by age 84. The RR for hip fractures associated with osteopenia (a milder form of bone loss) decreased from 1.9 at age 50 to 1.1 by age 84. Osteopenia was defined as a bone mineral density (BMD) value falling between 1 and 2.5 standard deviations below the average peak BMD seen in young adults.

In terms of risk factors, women with a maternal family history of hip fracture faced a 100% greater risk of hip fracture.
than women without a maternal family history. Current cigarette smokers had a 70% greater risk of hip fractures than non-smokers. Women who had experienced a prior fragility fracture after the age of 50 had an 80% greater risk than those who had not.

Based on a 10% rate of maternal family history of hip fracture, the adjusted RR was 1.82. Based upon age-specific 1999 female smoking rates, the RRs associated with current smoking were 1.45 for 50- to 64-year-olds, 1.55 for 65- to 74-year-olds, and 1.63 for women aged 75 or older. Adjusted only for age, the RR of prior fracture versus average was 1.39.

The RRs for death 2 to 5 years after a hip fracture were 2.2 for women aged 50 to 74 years at the time of the injury, 1.3 for women aged 75 to 84 years at the time of the injury, and 1.5 for women aged 85 or older at the time of the injury.

With respect to QoL, individuals between the ages of 50 and 64 were assigned a value of 0.90 if they were free of fracture, 0.70 for the first year following a fracture, and 0.80 for the second year following a fracture. The corresponding figures were 0.79, 0.59 and 0.69 for individuals aged between 65 and 74 years old, and 0.63, 0.43 and 0.53 for individuals aged 75 or older.

In terms of treatment efficacy, the clinical trial showed a 13.5% reduction in the risk of hip fracture during the initial year of treatment in a 70-year-old woman, followed by a 27% reduction each year thereafter.

**Methods used to derive estimates of effectiveness**
The author made some assumptions that were used in the decision model.

**Estimates of effectiveness and key assumptions**
The author assumed that only one fracture could occur every year. The relative mortality risk for women aged 85 years or older that have a history of hip fracture was set to one. Treatment efficacy in sub-populations of high-risk women was the same as that in the base case population (27%).

**Measure of benefits used in the economic analysis**
The summary benefit measures that were combined with the costs were the life-years (LYs) and quality-adjusted life-years (QALYs). These were estimated using a modelling approach. The cumulative incidence of hip fractures was also reported. An annual discount rate of 3% was applied in the base-case to the LYs and QALYs.

**Direct costs**
The analysis of the costs was carried out from the perspective of the national health care and social welfare system. Although the costs of supplements and hip fracture (acute phase and subsequent years) were included in the analysis, the cost items included were not reported. The unit costs and the quantities of resource use were not presented separately. The estimation of hip fracture-related costs relied on two published cost analyses. One of the two sources was a study of more than 1,000 women who were hospitalised in Stockholm with a diagnosis of hip fracture. The cost of supplements came from Swedish prices for medications (the cheapest product was selected). Discounting was relevant, as the costs were incurred during a long timeframe, and an annual rate of 3% was used. The price year was 2000.

**Statistical analysis of costs**
The costs were treated deterministically.

**Indirect Costs**
The indirect costs were not included. The author stated that, in the base-case, the population had already reached retirement age and that hip fractures in younger women are likely to occur after 65 years of age.
Currency
Swedish kroner (SEK). The exchange rate from SEK to US dollars ($) was SEK 10 = $1.

Sensitivity analysis
Univariate sensitivity analyses were carried out to deal with the uncertainty surrounding some estimates used in the decision model. For example, the price of supplements (an alternative value was based on the weighted average of all available products), other costs, excess mortality risk two or more years following hip fractures, and discount rate (QALYs were reported both undiscounted and discounted at 5%). Alternative values were mainly derived from published sources. The analysis was replicated in different sub-populations at high-risk of hip fracture (maternal family history of hip fractures, current smokers and prior fragility fractures after 50 years). Two alternative scenarios (i.e. 20% and 15%) for treatment efficacy were considered beside the 27% rate used in the base-case analysis.

Estimated benefits used in the economic analysis
In a cohort of 70-year-old women, with treatment efficacy set at 27% (base-case), the cumulative incidence was 21.5% in the untreated population and 15.8% in the treated cohort (difference -5.7%). The expected LYs were 12.51 in the untreated group and 12.53 in the treated group (difference 0.02), while the expected QALYs were 8.52 in the untreated group and 8.56 in the treated group (difference 0.04).

In a cohort of 70-year-old women, with treatment efficacy set at 20%, the cumulative incidence in the treated cohort was 17.3% (difference -4.2%), the expected LYs were 12.53 (difference 0.02) and the expected QALYs were 8.55 (difference 0.03).

In a cohort of 70-year-old women, with treatment efficacy set at 15%, the cumulative incidence in the treated group was 18.4% (difference -3.1%), the expected LYs were 12.52 (difference 0.01) and the expected QALYs were 8.54 (difference 0.02).

Cost results
In a cohort of 70-year-old women, with treatment efficacy set at 27% (base-case), the total costs per woman were SEK 60,779 in the untreated cohort and SEK 55,171 in the treated cohort (difference -SEK 5,608).

The higher cost of treatment (SEK 11,004) was more than offset by the reduction in costs associated with hip fractures (savings of SEK 16,612).

The total cost of preventive treatment per woman was SEK 59,480 (difference -SEK 1,299) with treatment efficacy set at 20% and SEK 62,555 (difference SEK 1,776) with treatment efficacy at 15%.

Synthesis of costs and benefits
Incremental cost-effectiveness and cost-utility ratios were calculated in order to combine the costs and benefits of preventive treatment over no treatment. However, in the base-case, incremental ratios were not calculated as the preventive strategy dominated the comparator, which was both less effective and more expensive. Similar results were achieved with efficacy at 20%. With efficacy at 15%, the incremental cost per LY gained with preventive treatment was SEK 177,600, while the incremental cost per QALY gained with preventive treatment was SEK 74,000 (SEK 13,200 undiscounted, SEK 116,950 when discounted at 5%).

The sub-population analysis showed that the "break-even" efficacy rate, namely the rate at which the estimated costs of the treated and untreated cohorts are equal, was 18% under base-case assumptions. Assuming that efficacy is the same for 60-year-old women as for 70-year-old women, the break-even age at which to initiate lifetime therapy was 61 years for a 27% risk reduction, 68 years for a 20% risk reduction and 73 years for a 15% risk reduction.

The intervention was dominant in 60-year-old women with osteoporosis, regardless of treatment efficacy. In 50-year-
old women with osteoporosis, the intervention was dominant when 27% or 20% efficacy was assumed. However, with a 15% efficacy rate, the incremental cost was SEK 103,400 per LY and SEK 68,933 per QALY.

In 50-year-old women with osteopenia, the incremental cost was SEK 149,000 per LY and SEK 89,400 per QALY with a 27% efficacy rate, SEK 408,150 per LY and SEK 204,075 per QALY with a 20% efficacy rate, and SEK 1,079,200 per LY and SEK 359,733 per QALY with a 15% efficacy rate.

In 60-year-old women with osteopenia, the intervention was dominant with a 27% efficacy rate. However, the incremental cost was SEK 134,400 per LY and SEK 67,200 per QALY with a 20% efficacy rate, and SEK 290,500 per LY and SEK 193,667 per QALY with a 15% efficacy rate.

When considering risk factors, with a baseline efficacy of 27%, treatment was dominant for each age group (50, 60, or 70 years) in the presence of maternal family history. Treatment was dominant for 60- and 70-year-old current smokers, and the incremental cost per QALY gained by treating 50-year-olds was SEK 7,740. Treating 60- and 70-year-old women with a history of fragility fractures after the age of 50 was also dominant at 27% treatment efficacy. Reducing treatment efficacy reduced the cost-effectiveness of the intervention for 60-year-old women, but it was still dominant for 70-year-old women. The results of the sub-population analysis were sensitive to the discount rate.

The results of the sensitivity analysis showed that the most important model input was the price of supplements, with higher prices reducing the cost-effectiveness of the intervention.

### Authors' conclusions

The administration of calcium and vitamin D3 to older women, even in the absence of other known risk factors, was cost-effective in Sweden. The intervention was dominant under most scenarios and in no case did the incremental cost-effectiveness ratios exceed the SEK 200,000 threshold commonly considered reasonable in Sweden. The intervention was also generally cost-effective in younger women with known risk factors, although an efficacy of at least 20% was required for 50-year-old women.

### CRD COMMENTARY - Selection of comparators

The rationale for the selection of the comparator (i.e. no intervention) was clear. Dosages of the preventive treatment were reported. You should decide whether they are valid comparators in your own setting.

### Validity of estimate of measure of effectiveness

The effectiveness evidence came from a synthesis of completed studies, which might have been identified selectively as no details of the methods and conduct of a systematic review of the literature were provided. The author provided some information on the characteristics of the primary studies. For example, one of the studies was a clinical trial, which has a high internal validity. The author stated that most data were derived from peer-reviewed articles. The issue of comparability between the primary studies was not addressed. Some of the clinical inputs were varied in the sensitivity analysis, in particular data on treatment efficacy. However, the author noted that the use of cross-sectional data to derive incidence might have introduced some confounding into the model.

### Validity of estimate of measure of benefit

The benefit measures used in the analysis were appropriate. QALYs capture the impact of the interventions on the most relevant dimensions of health for women at risk of hip fractures (i.e. survival and quality of life). Further, QALYs and LYS are comparable with the benefits of other health care interventions. Disease-specific measures were also used. Limited information on the approach used to derive QoL data was provided. Discounting was applied, as recommended in guidelines for economic evaluations. The impact of using an alternative discount rate or no discounting was investigated.

### Validity of estimate of costs
The costs included were consistent with the perspective adopted in the study. The author justified the exclusion of indirect costs, as the main focus of the analysis was the preventive treatment of women who had already reached retirement age. However, a detailed breakdown of the cost items was not provided as the costs were derived from published studies. In general, there was little information on the unit costs and quantities of resources used, and this might limit the possibility of replicating the analysis in other countries. The author stated that the costs were likely to have a high degree of relevance to the Swedish setting. The costs were treated deterministically in the base-case analysis, but some key cost estimates were varied in the sensitivity analysis. The price year was reported, which will facilitate reflation exercises in other time periods.

Other issues
The author did not compare the current findings with those from other studies. The issue of the generalisability of the study results to other settings was highlighted: the author pointed out that not only were the costs probably unique to the Swedish health care sector, but also that some epidemiological data used in the model may not be transferable to women in other countries because of differences, for instance, in the daily intake of calcium or vitamin D. The author stated that the analysis was carried out conservatively in order not to favour the supplement-based strategy. For example, the benefits derived from the prevention of other fractures (i.e. vertebral and forearm) were not taken into account, although the intervention with calcium and vitamin D3 will also help prevent these events. Further, no more than one fracture per year was allowed in the model, even though some patients might experience second events.

Implications of the study
The study results support the use of preventive treatment with calcium and vitamin D3 for older women. The intervention would also appear to be cost-effective in younger women, especially those with known risk factors. The initial investment associated with administering calcium vitamin D3 would be more than offset by future benefits over a short timeframe. The author noted that more clinical trials should be carried out to demonstrate the efficacy of calcium and vitamin D3 for the prevention of fractures in postmenopausal women.

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Other publications of related interest


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