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ORIGINAL ARTICLE

Vitamin K supplementation for the primary prevention of osteoporotic fractures: is it cost-effective and is future research warranted?

O. Gajic-Veljanoski · A. M. Bayoumi · G. Tomlinson · K. Khan · A. M. Cheung

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Abstract
Summary Lifetime supplementation with vitamin K, vitamin D_3, and calcium is likely to reduce fractures and increase survival in postmenopausal women. It would be a cost-effective intervention at commonly used thresholds, but high uncertainty around the cost-effectiveness estimates persists. Further research on the effect of vitamin K on fractures is warranted.
Introduction Vitamin K might have a role in the primary prevention of fractures, but uncertainties about its effectiveness and cost-effectiveness persist.
Methods We developed a state-transition probabilistic microsimulation model to quantify the cost-effectiveness of various interventions to prevent fractures in 50-year-old postmenopausal women without osteoporosis. We compared no supplementation, vitamin D_3 (800 IU/day) with calcium (1,200 mg/day), and vitamin K_2 (45 mg/day) with vitamin D_3 and calcium (at the same doses). An additional analysis explored replacing vitamin K_2 with vitamin K_1 (5 mg/day).
Results Adding vitamin K_2 to vitamin D_3 with calcium reduced the lifetime probability of at least one fracture by 25%, increased discounted survival by 0.7 quality-adjusted life-years (QALYs) (95% credible interval (CrI) 0.2; 1.3) and discounted costs by $8,956, yielding an incremental cost-effectiveness ratio (ICER) of $12,268/QALY. At a $50,000/QALY threshold, the probability of cost-effectiveness was 95% and the population expected value of perfect information (EVPI) was $28.9 billion. Adding vitamin K_1 to vitamin D and calcium reduced the lifetime probability of at least one fracture by 20%, increased discounted survival by 0.4 QALYs (95% CrI −1.9; 1.4) and discounted costs by $4,014, yielding an ICER of $9,557/QALY. At a $50,000/QALY threshold, the probability of cost-effectiveness was 80% while the EVPI was $414.9 billion. The efficacy of vitamin K was the most important parameter in sensitivity analyses.
Conclusions Lifetime supplementation with vitamin K, vitamin D_3, and calcium is likely to reduce fractures and increase survival in postmenopausal women. Given high uncertainty around the cost-effectiveness estimates, further research on the efficacy of vitamin K on fractures is warranted.

Keywords Cost-effectiveness · Expected value of perfect information (EVPI) · Fracture prevention · Postmenopausal · Vitamin K

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O. Gajic-Veljanoski · A. M. Bayoumi · G. Tomlinson · K. Khan · A. M. Cheung
Department of Health Policy, Management and Evaluation, University of Toronto,
Toronto, Canada

O. Gajic-Veljanoski · A. M. Cheung (✉)
Osteoporosis Program, University Health Network/Toronto, Rehabilitation Institute/Mount Sinai Hospital,
200 Elizabeth Street, 7 Eaton North—221,
Toronto, ON M5G 2C4, Canada
e-mail: angela.cheung@uhn.ca

A. M. Bayoumi · G. Tomlinson · K. Khan · A. M. Cheung
Department of Medicine, University of Toronto,
Toronto, Canada

A. M. Bayoumi · K. Khan
Centre for Research on Inner City Health, The Keenan Research Centre in the Li Ka Shing Knowledge Institute,
St. Michael's Hospital,
Toronto, ON, Canada

Introduction

Vitamin K as menaquinones (K_2) or as phylloquinone (K_1), given concurrently with vitamin D and calcium, is a potential treatment for the primary prevention of osteoporotic fractures. In a meta-analysis of seven clinical trials in elderly Japanese populations, vitamin K_2 at a dose of 45 mg/day significantly reduced vertebral (odds ratio [OR]=0.40, 95% confidence interval [95% CI] 0.25–0.65), hip (OR=0.23, 95% CI 0.12–0.47), and non-vertebral fractures (OR=0.19, 95% CI 0.11–0.35) [1]. However, the authors warned that the pooled trials were underpowered to detect fractures, had poor methodological quality and high attrition rates. Also, this meta-analysis included trials with older undernourished Japanese patients with prevalent fractures and, thus, may not be generalizable to other populations [1]. Since then, other studies have been published. In a Canadian randomized placebo-controlled trial involving healthy Caucasian postmenopausal women with osteopenia, 5 mg/day vitamin K_1 supplementation was found to reduce clinical fractures after 4 years (hazard ratio [HR]=0.45, 95% CI 0.20 to 0.98) [2]. Although this trial was of good methodological quality, it was not designed to detect fractures as fractures were a secondary endpoint [2]. In addition, several trials in predominantly Caucasian populations did not demonstrate an effect of vitamins K on bone mineral density (BMD) [2–7]. However, a recent meta-analysis published in 2011 compiled the data from all vitamin K trials and found a 1.3% increase in lumbar spine but not femoral neck BMD in patients treated with vitamin K [8]. The authors of that meta-analysis also cautioned that the observed increase in lumbar spine BMD may be biased because of between-study heterogeneity and publication bias.

Despite the lack of high quality evidence of the effects of vitamins K on fractures and the uncertainty about the size of any potential benefit, vitamin K is safe [2–7] and relatively affordable. Therefore, even a small benefit could make its use a good investment. Decision analysis can provide insights into uncertain decisions by quantifying trade-offs. By examining the relationship between expected benefits and costs and incorporating uncertainty around their estimates, economic analyses can indicate the expected value of additional research (or the expected opportunity loss) and can justify whether more research is likely to be a good investment of limited resources [9–11]. Thus, we evaluated the cost-effectiveness of lifetime supplementation with vitamin K for fracture prevention in postmenopausal women without osteoporosis using computer modeling techniques.

Methods

We constructed a state-transition probabilistic microsimulation model evaluating treatment options for a hypothetical cohort of 50-year-old postmenopausal women with a BMD T-score greater than −2. We used a health care payer perspective and compared three strategies: (1) no supplementation, (2) vitamin D_3 (800 IU/day) with calcium (1,200 mg/day), and (3) vitamin K_2 (45 mg/day) concurrent with vitamin D_3 and calcium (at the same doses). The "no supplementation" strategy was included to compare and calibrate the fracture rates from the model to the rates identified in observational studies. It also served as a comparator for other strategies. In an additional analysis, we replaced vitamin K_2 with vitamin K_1 (5 mg/day). Finally, we performed an analysis examining the use of vitamin K_2 (45 mg/day) as a single agent. Costs and benefits were discounted at an annual rate of 3% [12]. Complete details regarding the methods are presented in the Appendix. Our study was approved by the Research Ethics Boards of University Health Network and the University of Toronto.

Model structure

The model simulated the clinical course of osteoporosis in each of the 1,000 hypothetical healthy 50-year-old postmenopausal women without osteoporosis or previous fractures (Fig. 1). We tracked survival, quality of life, and costs over a woman's lifetime or until age 100. Each month, a woman had a chance of dying or experiencing a clinical vertebral, morphometric vertebral, hip, or wrist fracture. We modeled hip, vertebral, and wrist fractures since these types of fractures account for 70–95% of all fractures in women with osteoporosis [13, 14]. We assumed that morphometric vertebral fractures were clinically unrecognized [15] and did not affect quality of life or result in costs but did increase the risk of subsequent fractures. After a first clinically recognized fracture, we assumed that a woman would take alendronate (70 mg/week) for 5 years [16–18]. The model was constructed using TreeAge Pro (TreeAge Software Inc., Williamstown, MA, USA, 2009).

Fractures and mortality

We modeled fracture risks as increasing with age and with each prior fracture (Table 1). We assumed that each woman could sustain a lifetime maximum of two hip, four clinical vertebral, eight morphometric vertebral, and two wrist fractures. Although we did not model more than one fracture for the same woman in the same month, a woman could have multiple fractures over a short time frame (in the next month).

Age- and site-specific fracture probabilities were estimated from the Swedish Malmö Registry which provides the most complete population-based estimates of fracture risks across a range of BMD scores [15, 19]. We assumed that fracture rates were similar between Sweden, the USA, and Canada [13]. We

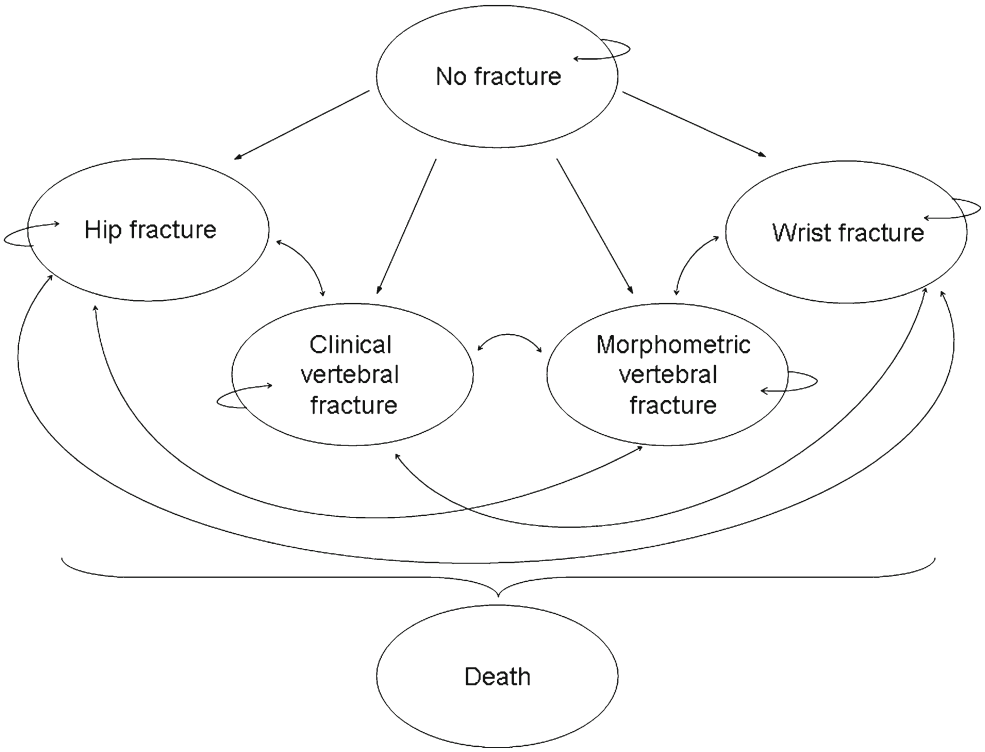

Fig. 1 Model schematic. The figure depicts an individual level Markov state-transition model that includes six health states, each represented by an *oval*. The simulation starts with a healthy 50-year-old postmenopausal woman without a fracture. At each 1-month cycle, a woman has a chance to move between health states. The model tracks the number, type, and timing of fractures over a lifetime and modifies the risk of future fractures accordingly

modeled the risks of successive fractures using data from a meta-analysis [20] and assumed that morphometric and clinical vertebral fractures increased the risk of subsequent fractures to a similar degree. Relative risks of various fractures with multiple prior fractures were calculated by multiplying risks associated with each individual fracture risk, with the constraint that the final relative risk (compared to women with no fracture) never exceeded 4; this constraint was derived from model calibration and from observations in a population-based study that the maximum relative risk of fracture among women with prior fractures was 3.9 [21].

Age-specific background mortality was estimated from Canadian life tables [22]. The model incorporated an increased risk of death for 12 months after a hip fracture (Table 1) [23], but we assumed that there was no excess mortality associated with clinical vertebral fractures [24].

Treatment effects

We modeled the effect of treatments as a relative reduction in fracture hazard rates (Table 1). The efficacy of vitamin D_3 (400–800 IU/day) with calcium (1,000 mg/day) was based on a meta-analysis of three randomized-controlled trials (Table 1). Estimates of hip and wrist fracture risk reductions were obtained from studies on populations without prior fractures [25–27], while the estimates of vertebral fracture reduction were from trials that combined populations with and without prior fractures [26, 27].

The efficacy of vitamin K_2 (45 mg/day) in reducing hip and clinical vertebral fractures was estimated from a meta-analysis [1] using data of 442 Japanese elderly women with osteoporosis [28–31], but excluding those with stroke, Parkinson's, or Alzheimer's disease [32–34]. We estimated the wrist fracture reduction from a single study in 241 female Japanese patients with osteoporosis [28]. Fracture reductions with vitamin K_1 (5 mg/day) were calculated from a single randomized placebo-controlled trial in 440 postmenopausal Canadian women [2].

We modeled the efficacy of alendronate using estimates from a meta-analysis in women with severe osteoporosis, osteoporosis, or ostepenia [35]. We assumed that the relative hazard declined linearly over time after stopping the drug until there was no residual effect after 5 years [36, 37].

Quality of life

We assigned each health state a quality-of-life weight or utility and calculated quality-adjusted life-years (QALYs) by multiplying the utility weight of the health state by its duration. For fractures, we used reported utility weights from the literature, subject to the constraint that hip fracture had the lowest utility weight of all fracture states (Table 1). We assumed that hip and clinical vertebral fractures had the greatest effects on quality of life in the first year after a fracture but had persistent effects thereafter over a woman's lifetime [35, 38–40]. In contrast, we assumed that wrist fractures affected quality of life for the first post-fracture year only [35, 38–40]. The utility of the no-fracture state

Table 1 Input parameters: risks, costs and utilities

Model parameters	Base case values (95% CI/SE)	Source
Risks		
Subsequent fracture following		
Hip fracture	2.40 (1.90–3.20)	[20]
Vertebral clinical/morphometric fracture	2.00 (1.70–2.40)	[20]
Wrist fracture	1.90 (1.70–2.30)	[20]
Death, first year following a hip fracture	1.37 (1.10–1.50)	[23]
Fracture risk with alendronate (70 mg/week)		
Hip fracture	0.62 (0.40–0.98)	[35]
Vertebral fracture	0.56 (0.46–0.68)	[35]
Wrist fracture	0.64 (0.30–1.35)	[35]
Fracture risk with vitamin D_3 plus calcium		
Hip fracture	0.68 (0.50–0.92)	Meta-analysis
Vertebral fracture	0.87 (0.65–1.14)	Meta-analysis
Wrist fracture	0.69 (0.18–2.54)	Meta-analysis
Fracture risk with vitamin K_2 (45 mg/day)		
Hip fracture	0.30 (0.05–1.74)	[1][a]
Vertebral fracture	0.40 (0.25–0.65)	[1][a]
Wrist fracture	0.54 (0.20–0.85)	[28]
Fracture risk with vitamin K_1 (5 mg/day)		
Hip fracture	0.34 (0.01–8.42)	ECKO, [2]
Vertebral fracture	0.45 (0.14–1.47)	ECKO
Wrist fracture	0.33 (0.09–1.25)	ECKO
Utilities		
Hip fracture, first year	0.890 (0.043)	[38]
Hip fracture, subsequent years	0.925 (0.048)	[35]
Clinical vertebral fracture, first year	0.900 (0.031)	[38]
Clinical vertebral fracture, subsequent years	0.930 (0.008)	[35]
Wrist fracture, first year	0.980 (0.005)	[35]
No fracture, age 50	0.985 (0.010)	[41]
Costs (USD)[b]		
Hip fracture, first year	51,139.20	[42]
Hip fracture, 2–5 years	3,639.90	[42]
Clinical vertebral fracture, first year	1,659.40	[42]
Clinical vertebral fracture, 2–5 years	371.90	[42]
Wrist fracture	1,030.30	[42]
Alendronate, 70 mg/week (generic)	131.04	[17]
Vitamin K_2, 45 mg/day	865.20	[46]
Vitamin K_1, 5 mg/day	199.80	[44]
Vitamin D_3 with calcium, 800 IU+1,200 mg/day	89.90	[17]

ECKO the ECKO trial (Evaluation of the Clinical use of vitamin K supplementation in postmenopausal women with Osteopenia) [2], *SE* standard error

[a]Subgroup analysis excluding the Sato studies [32–34]

[b]Adjusted for inflation using the US 2009 Consumer Price Index (medical component)

was taken from a general Swedish population [41] (Table 1). For women with multiple fractures, the utility weights for each sustained fracture were multiplied together.

Costs

We included direct medical costs obtained from a published model of short- and long-term fracture-specific costs for US Caucasian women aged 50–64 years [42] (Table 1). We included inpatient costs (hospital, physician services, and short-stay inpatient rehabilitation hospital care), outpatient costs (home care, outpatient physician services, non-medical home care, outpatient hospital, and others), and long-term care costs (nursing home care, disability, and dependency care) [42]. The total costs of multiple fracture states were the sums of costs of contributing fractures. This assumption

potentially overestimated the direct medical costs. As there are no published data on the cost of multiple fractures, we varied the fracture costs from 25% to 75% of the base cost in sensitivity analyses so as to examine the robustness of our cost-effectiveness estimates.

We used a US generic cost of oral alendronate (70 mg/week) of $105 per year [17] and a dispensing cost of $26 per year [43] (Table 1). The yearly cost of vitamin D_3 (800 IU/day) with calcium (1,200 mg/day) was estimated at $89.9 [17]; no dispensing costs were assumed as vitamin D and calcium are available over-the-counter. We used Internet sources to estimate costs of vitamins K_2 and K_1 including their within-US shipping cost [44–46] (Appendix). Retail daily costs for vitamin K_2 (45 mg/day) varied from $1.7 to $9.9 (Appendix). We assumed a daily cost of vitamin K_2 of $2.07 (as compared to the daily costs of vitamin K_1 and vitamin D with calcium), yielding an annual cost of $865.2 [46]. The annual cost of vitamin K_1 was estimated to be $199.8 [44]. All costs were adjusted for inflation and expressed in 2009 US dollars using the medical component of the Consumer Price Index [47].

Model calibration

We calibrated the model by comparing our estimates of fracture risks at 10 years among women who did not receive supplementation to epidemiologic data from the Malmö Registry for women aged 50 and older without osteoporosis [15, 19]. We considered our model to be well calibrated because its 10-year fracture probabilities were within a 2% range of observational data.

Cost-effectiveness analysis

The incremental cost-effectiveness ratio was calculated by dividing the incremental cost by the incremental effectiveness (life-years or QALYs). A strategy was deemed cost-effective if this ratio was below the maximum amount a decision-maker would be willing to pay to yield one unit of benefit [48]. We used a willingness-to-pay threshold of $50,000/QALY gained [49] but also examined a threshold of $100,000/QALY. A strategy was dominated by another if it was associated with lower (or equal) expected benefits for higher (or equal) expected costs [50]. A strategy could also be eliminated by extended dominance if its costs and benefits are improved by a mixed strategy of two other alternatives [50].

Sensitivity analyses

We explored the effect of parameter uncertainty on model outcomes by varying all input parameters across plausible ranges. We also tested several base case assumptions: (1) duration of the mortality risk increase after hip and vertebral fractures (from 1 [base case] to 5 years) [51, 52]; (2) an increase in risk of subsequent fractures (0.01- to 8-fold increase [base case 4-fold increase]); (3) duration of benefit from alendronate (from 10 years [base case] to lifetime); (4) level of adherence (from 50% to 100%[base case]); (5) model time horizon (from 10 to 50 years [base case]); and (6) the base case age at the beginning of a simulation (50 [base case] to 80). We explored our assumptions about total utility loss due to multiple fractures of the same skeletal site: in one analysis, we assumed no decrease of utility weights with multiple fractures; in another, we exponentiated the total utility weight by the total number of fractures. We also examined changes in utilities over time by shortening the duration of utility loss after hip or vertebral fractures from lifetime (base case) to the first 2 years.

We used probabilistic sensitivity analysis to calculate incremental cost-effectiveness ratios. We specified distributions for input parameters and repeatedly sampled from those distributions [11]. The choice of distribution depended on the nature of the parameter (Appendix). For example, costs have a lower bound at zero but no upper bound, making a gamma distribution a reasonable choice. We calculated distribution parameters using the method of moments. The cost of alendronate was modeled as fixed and the probabilities of fractures or death were modeled as age dependent. We simulated 1,000 trials, each of which included 1,000 women, to obtain the expected mean lifetime costs and benefits of each strategy.

We used cost-effectiveness acceptability curves to graph the probability that an intervention was cost-effective across a range of willingness-to-pay thresholds ($0–$100,000/QALY) [48]. To evaluate the decision of adopting vitamin K as the optimal treatment, we calculated the expected value of perfect information (EVPI) which is the monetary value of removing all uncertainty. The EVPI establishes an upper bound of the value for future research, such that if the anticipated costs of additional research exceed the EVPI, further data collection would not be considered worthwhile [10, 11]. We also calculated the budget impact as a product of incremental direct medical costs and prevalence. The prevalence of low bone density was based on the US data for women age 50 [53].

Results

Model calibration

Our model estimated 10-year probabilities of hip, morphometric vertebral, clinical vertebral, and wrist fractures of 1.9%, 11.6%, 2.3%, and 5.8%, respectively, for 50-year-old women without osteoporosis (Appendix: Fig. A1). Epidemiological data indicated rates of 1.1%, 11.8%, 1.9%, and 5.1%,

respectively [15, 19]. For 50-year-old postmenopausal women at low risk of osteoporotic fractures, our model predicted a 40% lifetime probability for a first clinical fracture with probabilities at specific sites of 11.5% (hip), 35.8% (morphometric vertebral), 10% (clinical vertebral), and 17.2% (wrist fracture).

In our modeled cohort, 74% of women who did not receive supplementation during their lifetime sustained at least one fracture, 16% had one fracture, and 58% had multiple fractures (Appendix: Fig. A2). With vitamin D and calcium, 69% sustained at least one fracture (18% single, 51% multiple). With vitamin K_2, vitamin D and calcium, 44% sustained at least one fracture (23% single, 21% multiple), while with vitamin K_1, vitamin D, and calcium, 49% sustained at least one fracture (20% single, 29% multiple).

Survival gains and cost-effectiveness

Vitamin K_2

Compared to no supplementation, vitamin D with calcium increased survival by 1.1 years. Addition of vitamin K_2 increased survival by a further 0.8 years, yielding an overall survival gain of 1.9 years (95% credible interval (CrI) 0.5 to 3.4). After discounting and adjustment for quality of life, vitamin D with calcium increased survival compared to no supplementation by 0.43 QALYs (Table 2). The addition of vitamin K_2 increased discounted survival by a further 0.30 QALYs, yielding an overall survival gain of 0.73 QALYs (95% CrI 0.19 to 1.31) (Table 2). Compared to no supplementation, vitamin D with calcium decreased discounted costs by $4,196. Vitamin D with calcium dominated no supplementation since it was associated with lower costs and greater survival; thus, it became the relevant comparator for alternative therapies. Compared to vitamin D with calcium alone, the addition of vitamin K_2 increased discounted lifetime costs by $8,956, yielding an incremental cost-effectiveness ratio of $12,268/QALY (Table 2).

In 990 of 1,000 simulations, vitamin K_2 was associated with better clinical outcomes than vitamin D with calcium (Fig. 2a). Vitamin K_2 was dominant (i.e., associated with greater health benefits and lower costs than vitamin D with calcium alone) in 67 simulations and was associated with increased costs but at an incremental cost-effectiveness ratio below $50,000/QALY in 880 simulations (Fig. 2a). The probability of cost-effectiveness of lifetime supplementation with vitamin K_2, vitamin D, and calcium over vitamin D with calcium alone was 74.3% at a $20,000/QALY threshold, 94.7% at a $50,000/QALY threshold, and 100% at a $100,000/QALY threshold (Fig. 3a). Based on a US prevalence of 26 million women with low bone mass [53], we estimated the budget impact of adding vitamin K_2 supplementation to be $232.9 billion. The maximum expected population cost of additional research or EVPI for vitamin K_2 with vitamin D and calcium was $28.9 billion ($1,112/woman) at a $50,000/QALY threshold and $30.1 billion ($1,157/woman) at a $100,000/QALY threshold (Appendix: Fig. A5).

In a separate analysis, vitamin K_2 as a single agent was associated with higher expected costs and lower expected benefits and was strongly dominated by vitamin K_2 with vitamin D and calcium (Table 2). Compared to vitamin D with calcium alone, the addition of vitamin K_2 yielded an incremental cost-effectiveness ratio of $12,896/QALY. The probability of lifetime supplementation with vitamin K_2, vitamin D, and calcium being cost-effective at a $50,000/QALY threshold was 82.4%.

Vitamin K_1

Compared to vitamin D with calcium alone, the addition of vitamin K_1 increased survival by 1.1 years (95% CrI −6.9 to 3.8) and discounted quality-adjusted survival by 0.42 QALYs (95%CrI −1.89 to 1.41) (Table 2). The addition of vitamin K_1 increased discounted lifetime costs by $4,014, yielding an incremental cost-effectiveness ratio of $9,557/QALY. The probability of lifetime supplementation with vitamin K_1, vitamin D, and calcium being cost-effective over vitamin D with calcium alone was 76.8% at a $20,000/QALY threshold, 80.3% at a $50,000/QALY threshold, and 82.0% at a $100,000/QALY threshold (Fig. 3b). Based on a US prevalence of 26 million osteopenic women [53], we estimated the budget impact of adding vitamin K_1 supplementation to be $104.4 billion. At a threshold of $50,000/QALY, the population EVPI was $414.9 billion ($15,961/woman) (Appendix: Fig. A5).

Sensitivity analyses

Our results were most sensitive to two assumptions: the efficacy of vitamin K_2 and vitamin K_1 and their annual costs. The incremental cost-effectiveness ratio exceeded $50,000/QALY if the efficacy of vitamin K_2 on hip, vertebral, and wrist fractures all decreased by 56–65% (incremental cost-effectiveness ratio $58,895/QALY) (Fig. 4a) or the efficacy of vitamin K_1 on hip, vertebral, and wrist fractures decreased by 12–13% (incremental cost-effectiveness ratio $50,461/QALY) (Fig. 4b). The incremental cost-effectiveness ratio also exceeded $50,000/QALY if the mean annual cost of vitamin K_2 was $1,812 (base case $865) or the mean annual cost of vitamin K_1 was $1,236 (base case $200).

Conclusions

We evaluated the cost-effectiveness of supplementation with vitamin K_2 or vitamin K_1 concurrent with vitamin D_3 and

Table 2 Discounted lifetime costs and benefits (survival and QALYs): base case and additional analyses

Analysis strategies	Outcomes[a,b]			Incremental changes			Incremental cost-effectiveness ratio	
	Costs, $US[b] Mean (95% CrI)	Discounted life-years Mean (95% CrI)	QALYs Mean (95% CrI)	Costs, $US[b] Mean (95% CrI)	Discounted life-years Mean (95% CrI)	QALYs Mean (95% CrI)	Cost ($)/life-years gained	Cost ($)/QALY gained
Vitamin K_2								
No supplementation	19,190 (12,335; 28,469)	19.08 (18.76; 19.42)	18.70 (18.22; 19.17)					
Vitamin D_3 with calcium	14,994 (9,364; 23,605)	19.51 (18.71; 20.06)	19.13 (18.28; 19.81)	−4,196 (−9,015; 520)	0.42 (−0.32; 0.90)	0.43 (−0.28; 0.89)		
Vitamin K_2 with vitamin D_3 and calcium	23,950 (14,306; 38,653)	20.19 (19.62; 20.61)	19.86 (19.16; 20.45)	8,956 (−2,618; 23,752)	0.68 (0.14; 1.30)	0.73 (0.19; 1.31)	13,171	12,268
Vitamin K_1								
No supplementation	19,028 (11,976; 28,066)	19.09 (18.75; 19.43)	18.71 (18.24; 19.15)					
Vitamin D_3 with calcium	14,745 (9,269; 22,577)	19.51 (18.65; 20.07)	19.16 (18.38; 19.78)	−4,283 (−9,307; 288)	0.42 (−0.41; 0.91)	0.45 (−0.22; 0.89)		
Vitamin K_1 with vitamin D_3 and calcium	18,759 (5,138; 91,188)	19.89 (16.77; 20.62)	19.58 (17.41; 20.44)	4,014 (−13,740; 78,154)	0.38 (−2.68; 1.41)	0.42 (−1.89; 1.41)	10,563	9,557
Vitamin K_2 as a single agent								
No supplementation	18,987 (12,027; 27,719)	19.08 (18.76; 19.37)	18.71 (18.22; 19.17)					
Vitamin D_3 with calcium	14,764 (8,989; 22,726)	19.48 (18.64; 20.03)	19.14 (18.28; 19.81)	−4,223 (−9,415; 446)	0.41 (−0.39; 0.90)	0.43 (−0.39; 0.89)		
Vitamin K_2 with vitamin D_3 and calcium	24,315 (14,805; 40,554)	20.19 (19.58; 20.59)	19.85 (19.09; 20.41)	9,285 (−2,878; 25,717)	0.71 (0.19; 1.36)	0.72 (0.09; 1.37)	13,077	12,896
Vitamin K_2 alone	24,763 (13,952; 45,966)	20.07 (19.28; 20.52)	19.71 (18.79; 20.31)	448 (−7,442; 2,282)	−0.12 (−0.16; 0.47)	−0.14 (−0.13; 0.53)	D	D

*QALY*s quality-adjusted life-years, *CrI* credible interval, *D* dominance

[a] Costs and benefits discounted at 3% per year

[b] Costs in 2009 USD

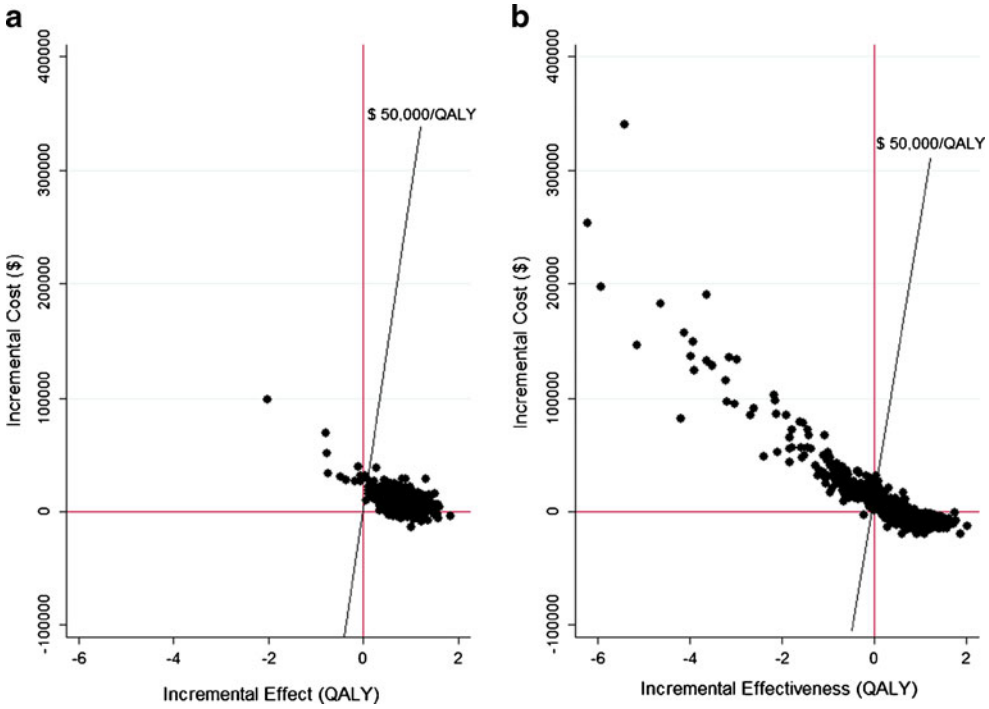

Fig. 2 Scatter plots of 1,000 simulated pairs of incremental costs and effects in the cost-effectiveness plane: vitamin K_2 and vitamin K_1 analyses. QALY denotes quality-adjusted life-year. Negative QALYs indicate that the vitamin K strategy was associated with worse quality-adjusted survival and negative costs indicate that the vitamin K strategy saved money relative to the alternative. **a** Vitamin K_2 with vitamin D and calcium compared to vitamin D with calcium. **b** Vitamin K_1 with vitamin D and calcium compared to vitamin D with calcium

calcium for the primary prevention of fractures in postmenopausal women initially at low risk of fractures. Compared to vitamin D_3 with calcium, supplementation with vitamin K_2, vitamin D, and calcium was associated with a gain in life expectancy of 1.9 years and increments in discounted survival and discounted costs of 0.7 QALYs and $8,956, respectively, and an incremental cost-effectiveness ratio of $12,270/QALY gained. This incremental cost-effectiveness ratio is less than the commonly used willingness-to-pay thresholds of $50,000/QALY and $100,000/QALY, and therefore, the addition of vitamin K_2 to vitamin D and calcium would represent good value for money.

However, the increments in the costs and benefits with vitamin K_2 are associated with large uncertainty (Table 1). For example, the discounted incremental costs could be as high as $23,752, and the discounted incremental benefits could be as low as 0.19 QALYs, yielding an incremental cost-effectiveness ratio of $125,010/QALY gained. Although

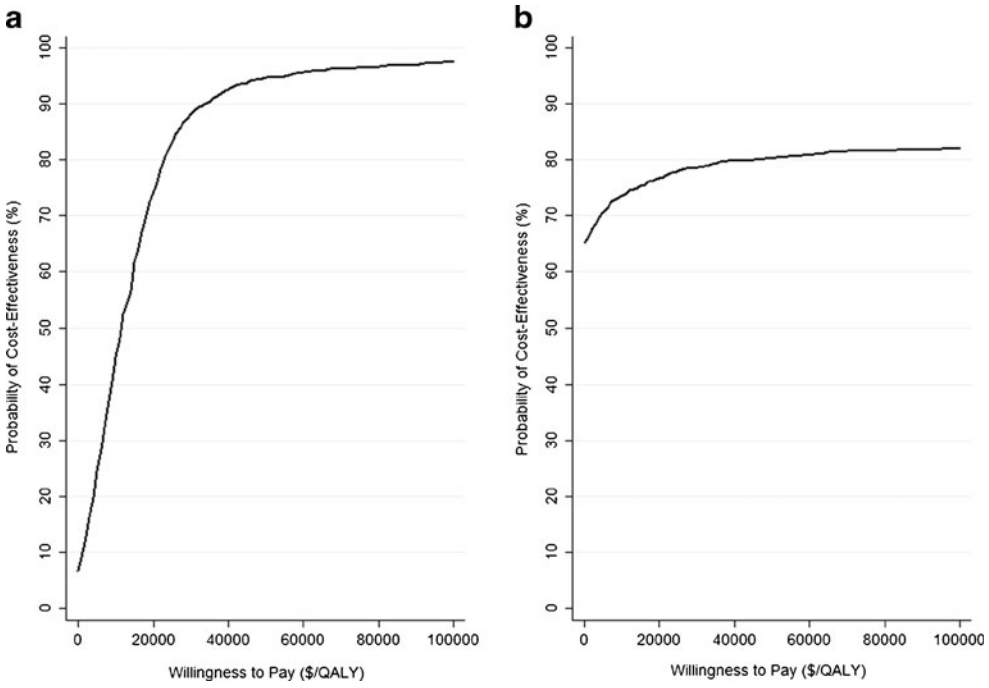

Fig. 3 Cost-effectiveness acceptability curves: vitamin K_2 and vitamin K_1 analyses. Probability of cost-effectiveness vs. willingness-to-pay thresholds ($/QALY) of lifetime supplementation with vitamin K_2 with vitamin D and calcium (**a**) and vitamin K_1 with vitamin D and calcium (**b**), both compared to vitamin D_3 with calcium

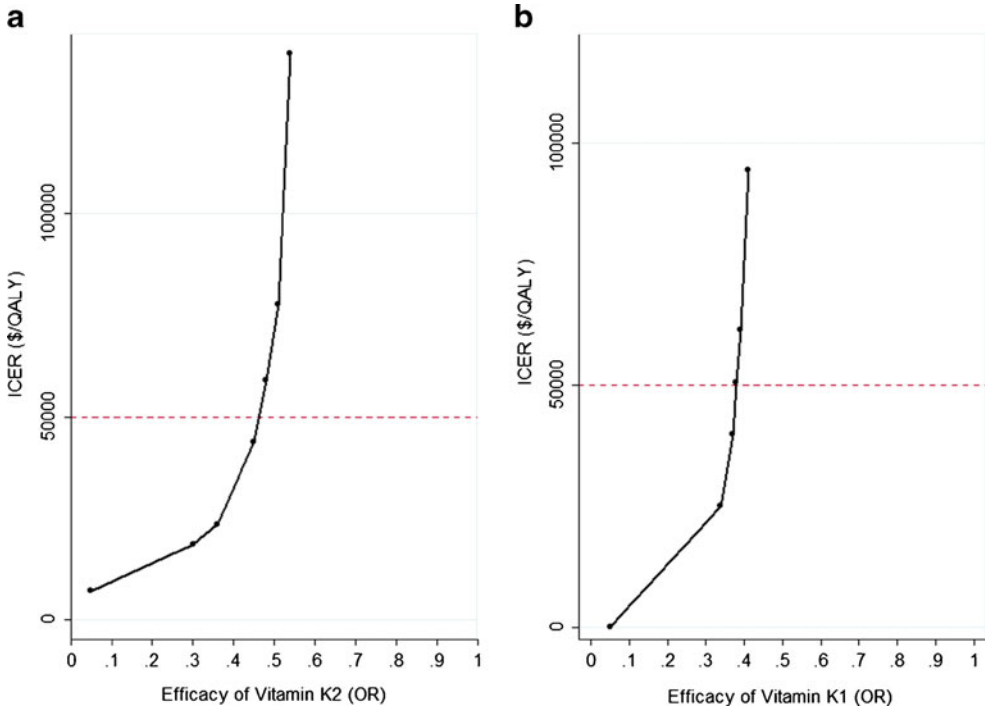

Fig. 4 Incremental cost-effectiveness ratios (ICERs) by the efficacy of vitamin K_2 and vitamin K_1. The *y*-axis represents ICERs in $/QALY (quality-adjusted life-years) and the *x*-axis represents the efficacy of vitamins K for hip fracture expressed by OR (odds ratio). The *horizontal short-dashed line* denotes a $50,000/QALY threshold. **a** Vitamin K_2 with vitamin D and calcium became less cost-effective than vitamin D with calcium if the base case ORs (Table 1) changed to 0.48 (95% CI 0.08–2.87), 0.64 (95%CI 0.41–1.07), and 0.86 (95% CI 0.32–1.36) for hip, vertebral, and wrist fractures, respectively. **b** Vitamin K_1 with vitamin D and calcium became less cost-effective than vitamin D with calcium if the base case ORs changed to 0.38 (95% CI 0.01–9.43), 0.51 (95% CI 0.13–1.65), and 0.37 (95% CI 0.1–1.4) for hip, vertebral, and wrist fractures, respectively

we did find significant increments in survival and QALYs, our estimates for the efficacy of vitamin K_2 on fractures were assumed to be unbiased. Therefore, our base case results should be interpreted with caution given the heterogeneity of methodological quality across the vitamin K_2 trials [1] and the lack of evidence regarding fracture reductions in Caucasian populations. Our sensitivity analysis also showed that the efficacy of vitamin K_2 is one of the major determinants of cost-effectiveness. We found that the population EVPI was $29 billion ($1,112/woman) at a threshold of $50,000/QALY; however, if the efficacy of vitamin K_2 on hip, vertebral, and wrist fractures decreased by 56–65% (ICER $58,895/QALY), the population EVPI would increase to 280.3 billion ($10,780/woman). Our study also found that the cost-effectiveness of vitamin K_2 was sensitive to the cost of vitamin K_2. The market price of vitamin K_2 is yet to be established in North America. At the low and high ends of the ranges we found for retail prices from Internet sources ($600 and $3,560/year), the incremental cost-effectiveness ratios were $3,902/QALY and $79,886/QALY, respectively.

Our cost-effectiveness analysis of lifetime supplementation with vitamin K_1, vitamin D, and calcium found that the addition of vitamin K_1 was cost-effective at commonly used thresholds, with an incremental cost-effectiveness ratio of $9,557/QALY gained. Our incremental cost-effectiveness ratio was lower than the estimate of £15,240 [$24,714]/QALY gained by Stevenson et al. in the UK [54]. The difference in our incremental cost-effectiveness ratio estimates likely results from differences in study design, base case profiles, and model structures. They compared 5 mg/day vitamin K_1 to no intervention in 50-year-old women with osteoporosis over 10 years [54]. We used a longer time horizon (50 years) and modeled vitamin D with calcium in postmenopausal women initially without osteoporosis.

In our study, vitamin K_1 was associated with an extremely high population EVPI, indicating substantial uncertainty around the cost-effectiveness estimates likely because of the large uncertainty around the efficacy of vitamin K_1 (Table 1) [9, 11]. Stevenson et al. examined the uncertainty around the cost-effectiveness of vitamin K_1 vs. alendronate using expected value of sample information (EVSI) [54, 55]. EVSI is another value of information method used to estimate the expected size and expected cost of the perfect trial [11]. At a £30,000 [$48,650]/QALY threshold, Stevenson et al. estimated that a future vitamin K_1 trial would include 2,000–5,000 participants per arm (£1,111.3 [US $1,802] per participant) [54, 55]. However, as the expected net gain was not calculated and was not compared to the EVSI and actual costs

of the vitamin K_1 trial [9], the question remains whether to adopt vitamin K_1 based on current evidence or to undertake another trial. Overall, our vitamin K_2 and vitamin K_1 cost-effectiveness analyses consistently convey substantial uncertainty around the cost-effectiveness of vitamin K indicating the need for further evaluation of the efficacy of vitamin K for fracture prevention.

Our study has several limitations. First, we did not model BMD testing [16]. However, there has been a paradigm shift in osteoporosis care from focusing on BMD to focusing on absolute fracture risks or 10-year fracture probabilities [56, 57]. To make a decision about pharmacologic treatment, BMD T-scores are now evaluated together with clinical risk factors such as age and prior fractures using fracture risk assessment tools (CAROC or FRAX) [56, 58, 59]. Our model did not use these tools to evaluate fracture risk, but our base case (i.e., healthy postmenopausal women with no prior fractures and BMD T-scores above −2.0) would not qualify for pharmacologic treatment. However, we assumed that after a first clinically recognized fracture, women would be at higher risk of subsequent fracture and would take alendronate. Second, although our model was reasonably well calibrated against available data on first clinical fracture in Sweden, our predictions of lifetime cumulative fractures need further validation. Third, we assumed transferability of epidemiologic data (e.g., fracture probabilities) between Sweden, the USA, and Canada, which may not be the case. However, we showed in sensitivity analyses that the cost-effectiveness of vitamins K was robust to changes in the probabilities of fractures. Fourth, we assumed that the treatment effect of vitamin K_2 was the same in Japanese and Caucasian populations due to the lack of data on fractures for vitamin K_2 in Caucasian populations. In addition, the efficacy of vitamin K_1 was based on the results of a single randomized-controlled trial where fractures were only a secondary endpoint [2]. Therefore, the efficacy of vitamins K may be overestimated resulting in highly favorable estimates of incremental survival and incremental cost-effectiveness. However, our numerous sensitivity analyses thoroughly evaluated the influence of the efficacy of vitamins K on clinical and cost-effectiveness outcomes. A current substantial controversy around the true efficacy of vitamin K on fractures is most likely due to lack of high quality evidence [60]. Both anabolic and anti-resorptive effects on bone have been ascribed to vitamin K based on its several functions such as γ-carboxylation of 3-glutamic acid residue to enable functioning of osteocalcin [61–63], regulation of the transcription of bone-specific genes to enable the expression of osteoblastic markers [64, 65], inhibition of the nuclear factor kappa B and modulation of the expression of interleukin-6 and osteoprotegerin to modify bone turnover [60, 66, 67], and inhibition of prostaglandin E2 to reduce bone resorption [64, 68, 69]. Some authors argue that through these actions vitamin K may improve bone quality and bone strength without increasing BMD [64, 70]. Finally, we did not directly model a comparison of vitamin K_2 to vitamin K_1 because no study to date has directly compared the two vitamin K preparations for fracture outcomes.

In conclusion, we assessed the cost-effectiveness of lifetime supplementation with vitamin K, vitamin D, and calcium for the primary prevention of osteoporotic fractures. We found that the concurrent use of vitamin K, vitamin D, and calcium is likely to increase life expectancy and reduce lifetime probabilities of fractures and would be a cost-effective intervention at commonly used thresholds for long-term fracture prevention in postmenopausal women at low risk. However, there is considerable uncertainty around the cost-effectiveness estimates and further research on the efficacy of vitamin K for fracture prevention is warranted.

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Conflicts of interest None.

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